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Abstracts

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RECHERCHE, FORMATION, ORGANISATION ET SYSTÈME DE SANTÉ I / FORSCHUNG, FORTBILDUNG, ORGANISATION UND GESUNDHEITSSYSTEM I

FM228

Rates, delays and completeness of general practitioners' responses to a postal versus web-based survey: a randomized trial

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Background: Web-based surveys became a new and popular method for collecting data, but only few studies directly compared postal and web-based surveys among physicians, and none to our knowledge among general practitioners (GPs).
Objective: To compare two modes of survey delivery (postal and web-based) in terms of participation rates, response times and completeness of questionnaires in a study assessing GPs' preventive practices.
Methods: This randomized study was conducted in Western Switzerland (Geneva and Vaud) and in France (Alsace and Pays de la Loire) in 2015. A random selection of community-based GPs (1000 GPs in Switzerland and 2400 GPs in France) were randomly allocated to receive a questionnaire about preventive care activities either by post (n = 700 in Switzerland, n = 400 in France) or by e-mail (n = 300 in Switzerland, n = 2000 in France). Reminder messages were sent once in the postal and twice in the web-based group. GPs practicing only complementary and alternative medicine (CAM) were excluded from the study.
Results: Overall, 764 GPs (22.5%) returned the questionnaire. Compared to the postal group, participation rate in the web-based group was more than four times lower (10.7% vs 47.1%), but median response time was much shorter (1 day vs. 1–3 weeks) and the number of GPs having fully completed the questionnaire was twice as high (63.8% vs. 34.6%).
Conclusions: Web-based surveys offer many advantages such as reduced response time, higher completeness of data and large cost savings, but our findings suggest that postal surveys can be still considered for GP research. The use of mixed-mode approaches is probably a good strategy to increase GPs' participation to surveys whilst reducing costs.

FM229

Faculty development program for clinical supervision: comparison of two training formats

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Introduction: The Swiss Institute of postgraduate and continuous training (ISFM/SIWF) now requires residents' performance to be assessed in clinical practice through the use of mini-CEX and DOPS. However, junior clinical supervisors often feel uncomfortable in supervising and giving feedback to residents by lack of effective teaching skills, especially in domains such as clinical reasoning, professionalism, communication or interprofessional collaboration. The aim of the project was to evaluate whether a discipline-related and personalized coaching faculty development program was more effective than a more traditional program on supervisors' teaching skills in such domains.
Methods: We conducted a randomized, controlled, intervention study. Clinical supervisors from 5 departments (including hospital and ambulatory general internal medicine) were invited to attend a 6-month faculty development program at the Geneva University Hospitals. They were randomly assigned to one of two formats: (1) traditional with 3 workshops (7 hrs); (2) experiential with 2 workshops and 3 individualized one-hour video-based coaching (8 hrs). Outcome measures were self-perceptions of participants' motivation (6 item questionnaire; 1–7 Likert scale) and self-efficacy (13 item questionnaire; 1–10 Likert scale) and objective analysis of participants' teaching skills during 4 objective structured teaching encounters conducted before and after the training.
Results: 86 clinical supervisors finished the training (participation rate 95%). Preliminary results show that participants' satisfaction with the training was similar in both groups. There was no change in motivation to teach or give feedback after training among both groups (sum of means – traditional: pre 37.97 (SD 3.64) vs post 37.19 (SD 4.73) p = 0.28; experiential: pre 37.8 (SD 4.19) vs post 37.8 (SD 3.18) p = 1.00). Both groups expressed higher self-efficacy regarding their ability to teach or give feedback in the post-intervention phase (sum of means – traditional: pre 94.86 (SD 17.44) vs 106.71 (14.27) p <0.001; experiential: 90.85 (SD 19.92) vs 103.94 (SD 10.33), p <0.001). Objective analysis of participants' teaching skills is still ongoing and the final results will be presented at the conference.
Discussion: Training junior clinical supervisors on how to supervise and give feedback is effective. The additional impact of individual coaching versus simple workshops is still uncertain.

FM230

Do early handoffs in internal medicine wards affect the quality and cost of care?

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Introduction: Continuity of care is a key feature for high quality of care. To maintain the continuity of care of patients in the hospital, physicians conduct clinical handoffs to transfer both patient information and accountability from one provider or team to another. Prior studies show that handoffs are associated with an increased risk of complications and an increased length of stay. We were interested in studying the association between *early handoffs* (handoffs occurring between residents within the first 72 hours of a patient's admission) and *length of stay* (LOS), use of *resources* (number of blood tests and procedures) and incidence of *serious adverse events* (transfers to ICU/ intermediate care unit or death).
Methods: This is a retrospective cohort study of adult patients admitted to the General Internal Medicine Ward of Geneva University Hospital between 2012 and 2014, with a LOS >72 hours. We compared patients admitted by physicians other than the usual day team with patients who were admitted by the primary day team in univariate and multivariate linear and logistic regression models. Our outcomes were LOS, use of resources and incidence of serious adverse events. We adjusted the models for potential cofounders.
Results: We included 11'948 patients, 38% of whom were in the early handoff group. Our preliminary analyses show that an early handoff, in particular with a change of attending, is independently associated with an increase of LOS (+6.4%, 3.5–9.5, p <0.01 and +17.9, 14.6–21.2, p <0.01 respectively). Although early handoffs are not significantly associated with a higher use of resources, it was associated with more serious adverse events (OR = 1.3, 1.1–1.7, p <0.5) in the early handoffs group. Our subgroup analyses show that the association between early handoff and LOS loses significance when the patients are admitted on a public holiday.
Conclusion: Early handoffs affected the quality of care, especially the length of stay for patients admitted during weekdays. This emphasizes the importance of identifying and handing off pertinent and essential key information to enable care continuity when the medical team in charge of the patient changes. As restricting the number of handoffs is unrealistic, we should aim to improve the handoff training for both residents and supervisors, by standardizing the process and content, to maintain the continuity, safety and effectiveness of care for hospitalized patients.

FM231

Should we stop to care about the transition because it's not cost-effective?

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Background: Patients hospitalized with heart failure (HF) present the highest rate of readmission within 30 days, above 20%. Reduction of early readmission is a major concern as quality and cost control indicator. Parts of these are potentially avoidable (PARE) and algorithms can estimate an adjusted expected range based on

medical-administrative data. To reduce readmission, a multidisciplinary transition plan is more effective than any single intervention. We aimed to assess the effectiveness of a transition plan to reduce early readmission among HF-patients.
Methods: We conducted a before-and-after study in a tertiary general internal medicine department. We included all consecutive HF-patients discharged to home during the 13 months of intervention (2013–2014) and compared them to medical records from 2011 to 2013. The transition plan consisted of 11 interventions performed by a nurse, a pharmacist and a physician. Outcomes were rate of days spent for 30-days readmission, rate of days spent for PARE according to SQLape®, and rate of readmission.
Results: We included 1'441 records in the pre-intervention period and 431 in the intervention period. 138 patients (mean age 77.8 years old, SD 10.7) received the transition plan while 293 were non-completers (mean age 78.32 years old, SD 11.8). 130 were diagnosed for HF after screening; 111 were discharged before enrolment; and 52 refused to give consent. On average, a transition plan needed 3:16 hours per patient. The medication reconciliation was the most time-consuming task. Moreover, overhead time like administration or screening accounted for 5–6 hours per day. Despite efforts to fulfill a complex transition plan, we did not observed a significant reduction of outcomes. Readmission rate even increased between pre-intervention and intervention periods (19.2% vs 21.1%, *p*-value 0.368). Conclusive results were seen in a sensitivity analysis: patients who received transition plan had lower rate of days spent for readmission and PARE compared to non-completers (19.2% vs 16.1%, *p*-value 0.002).
Conclusion: Our multidisciplinary transition plan got positive feedback of patients and stakeholders but failed to reduce readmission rate. It could be applied only to 32% of patients. However, this kind of intervention is time- and money-consuming. Further studies about transition care should look for benefit in other quality indicators like adverse drugs event, communication issue, or adherence to treatment.

MÉDECINE DE FAMILLE / HAUSARZTMEDIZIN

FM232

Prescription of homeopathy in outpatient care: what physicians believe and what they intend

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Background: Homeopathy is a highly controversial topic. Postulated mechanisms explaining homeopathy's mode of action remain unconvincing for natural scientist and non-surprisingly, the aggregated evidence from rigorous randomized controlled trials suggests that homeopathy is merely a placebo. Still, homeopathy continues to be prescribed also by physicians educated in academic medicine. Whether prescribing physicians believe in specific effects despite their education in natural sciences or whether they knowingly prescribe homeopathy to exploit non-specific/placebo effects and what might cause such homeopathy prescriptions is largely unknown. These issues, however, have important educational and ethical implications.
Methods: In 2015, we performed a cross-sectional survey among all physicians working in outpatient care in the Swiss Canton of Zurich. We assessed their prescription behaviour; believes in mode of action and accordable intentions behind the prescriptions. Furthermore, associations with prescribing homeopathy were investigated.
Results: From 4072 approached physicians in outpatient care 1531 responded (response rate 38%). Homeopathy was prescribed by 345 (23%) of the physicians. Prescribers' believed modes of action were "the law of similars" (42%), placebo effect- and other interpersonal effects (up to 35%), "Water memory" (19%) and "quantum physics" (19%). Unambiguously accordable intentions behind prescriptions were achievement of specific effects in 50% and non-specific/placebo effects in 21%. Among all physicians (prescribers and non-prescribers included) only 55% thought that the available evidence rather disproves efficacy of homeopathy. Perception of patient requests for homeopathy and certain medical specializations were among factors strongly associated with prescribing homeopathy.
Conclusion: One in five physicians in outpatient care prescribed homeopathic remedies. Half of the homeopathy prescribing physicians intended specific effects, questioning the sustainability of their education in natural sciences. One in five prescribing physicians made use of homeopathy as a non-specific/placebo treatment and are therefore transgressing ethical directives. To explain why physicians prescribe homeopathy we need to better understand social and educational factors as well as homeopathy's attractiveness in different medical specializations.

FM233

Informed decision making in colorectal cancer screening: influence of decision Aids and primary care physician on participants' intention to screen and preference for colonoscopy or faecal immunochemical tests (FIT)

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Introduction: Colorectal cancer (CRC) screening reduces CRC mortality and incidence. Faecal immunochemical tests (FIT) and colonoscopy are both recommended but vary greatly in their attributes. Primary care physicians (PCP) were shown to favour colonoscopy as a screening test for their patients in a recent study conducted in the French-speaking region of Switzerland. In the perspective of a CRC screening programme in the canton of Geneva (Switzerland) that would offer both tests through informed decision via the PCP, we aimed to investigate the *a priori* influence of written and visual decision aids and PCP counselling in the choices of individuals regarding CRC screening.
Method: We conducted a population-based survey using a self-reported questionnaire sent in 2016 to 4500 randomly selected Geneva residents aged between 50 and 69. Participants were provided with written and visual decision aid tools used in the ongoing CRC screening programme of the adjacent canton (Vaud) illustrating the potential benefit of CRC screening and the *pros* and *cons* of FIT and colonoscopy. Intention to screen and choice of screening test after the consideration of the aids was assessed. Influence of the PCP on the decision of the participant was also evaluated.
Results: Overall, 1517 participants were included in the analyses. A majority of participants (73%) considered that the decision aids clearly illustrated the benefit of CRC screening, and 53% were incited by the latter to undertake CRC screening. Based on the decision aids provided, 41% of the participants chose FIT as the preferred screening test, 46% favoured colonoscopy and 13% were undecided. A large proportion of participants (84%) stated that their decision to undertake CRC screening would be influenced by their PCP, and 85% reported that their choice of the test would be influenced by what their PCP would recommend.
Conclusion: Written and visual aid tools provide useful information for CRC screening decision-making. The participants were quite balanced in their preference for colonoscopy and FIT after considering the decision aids. This should be considered by PCPs when counselling patients about CRC screening, given their significant influence on screening decisions, in order to avoid a shift towards colonoscopy.

FM234

From practice employee to (co-)owner: young general practitioners predict their future careers. A cross-sectional survey

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Introduction: In Switzerland, the mean age of general practitioners (GPs) in 1993 was 46. In 2015, it had increased to 55, and GPs over 65 made up 15% of the workforce. As more and more older, self-employed GPs retire, young doctors will be needed to fill their positions and eventually take over their practices. Some stakeholders blamed the increasing shortage of GPs on the feminisation of the medical profession, arguing women preferred part-time work. We set out to determine what employment status young GPs wanted, if their preference would change over time, and which working conditions and factors were most important in their choice of practice.
Methods: We administered a cross-sectional online survey to members of the Swiss Young General Practitioners Association (JHaS). Our survey captured participants' characteristics, and their preferred type of practice and working conditions by closed questions, ratings of attractiveness of fictional job ads, and an open question.


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Figure: One of the eight ads shown in the survey. Participants had to rate its attractiveness on a 10-point Likert Scale

Results: Surveys were returned by 270 JHaS members (61%). Women made up 71% of respondents. Overall mean age was 32.9. Most participants were GPs or residents; less than 10% were medical students. Most wanted to work in the suburbs or countryside in small GP-owned group practices, with up to five colleagues. French-speaking participants preferred larger practices. Most respondents intended to work part-time: mean desired workload was 78% for men and 66% for women. Positive working climate was a major factor in choosing a GP practice. Dispensing medications made a practice more attractive for over a third of respondents. Most respondents intended to make house calls outside regular on-call hours. A large majority wanted to be employees in their *first* GP job. But most wanted to become owners or co-owners of a practice within five years; only 7–9% preferred to remain employees.
Conclusion: Young and future GPs in Switzerland prefer to work in small, GP-owned group practices. Feminisation of the GP profession explains only part of the increase in desire for part-time work, as both genders want to work part-time. Our study demonstrates that the large majority of young GPs project a career arc that begins as an employee, but transitions to self-employment within five years. Future practice models should take these wishes of young GPs into account if they want to attract them as employees and potential future (co-) owners.

FM235

Use of corticosteroids for subacute cough in primary care

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Introduction: Subacute cough (lasting 3–8 weeks) as a symptom of upper respiratory tract infections is very common in primary care consultations. Many colleagues reported that they often prescribe corticosteroids for subacute cough. However, the basis for an evidence-based decision for or against corticosteroids is weak. We aimed to determine the proportion of general practitioners (GPs) using corticosteroids for subacute cough.
Methods: All GPs registered with the Institutes of Primary Care Basel or Lucerne could participate in an online survey. They received an invite by e-mail containing the case vignette of a 32-year old, healthy non-smoker without asthma, who has had dry cough for 4 weeks. They were then asked if they would prescribe steroids, followed up by six (if yes) or two (if no) questions.
Results: 183 of 472 (39%) GPs replied. 141 of 183 (77%) prescribed steroids for subacute cough. 99% of those GPs replying to the follow-up questions used inhaled steroids, 18% used oral steroids. Symbicort 200/6µg twice per day for 2 weeks was the most common inhaled steroid, Prednisone 20 mg per day for 5 days was the most common oral steroid. 42% and 21% also prescribed codeine and dextromethorphan, respectively. These proportions were similar among those GPs who did not prescribe steroids (43% and 16%). Overall, 94 GPs would like to participate in an intervention study on the efficacy of corticosteroids on subacute cough.
Conclusion: Despite weak evidence corticosteroids are frequently used for subacute cough in the course of upper respiratory tract infections in primary care. An intervention study on the efficacy of corticosteroids for subacute cough should be planned.

FM236

Association between alcohol and caffeine consumption and nocturnal leg cramps in patients over 60 years old: a case-control study

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Introduction: Nocturnal leg cramps are a specific kind of cramps affecting almost half of patients over 60 years old. They reduce patients' quality of sleep and have a negative impact on their quality of life. The aim of this study was to evaluate the association between nocturnal leg cramps and the consumption of alcoholic beverages and caffeine in patients over 60 years old attending general practices.
Methods: Case-control study with a Bayesian approach for sensitivity analysis. Participants were volontary ambulatory patients over 60 years old consulting their family doctor. Cases, i.e. patients suffering from cramps, were matched with controls (free from cramps) for age, sex, medical history and medications known to trigger cramps. Alcohol and caffeine consumption were assessed through the E3N Food frequency questionnaire.
Results: We found an association between the global consumption of alcoholic beverages and nocturnal leg cramps (OR 6.5 95% credibility interval [1.68; 38.05], posterior probability 99.82%). Caffeine consumption was not significantly associated with nocturnal leg cramps.
Conclusion: We identified an association between alcohol consumption and nocturnal leg cramps among patients over 60 years old attending general practices. These findings have implication for the prevention of cramps. They also open new avenues for the further exploration of the as yet uncertain pathophysiology of cramps, considering effects of ageing and alcohol on muscular fibres.

MÉDECINE INTERNE GÉNÉRALE HOSPITALIÈRE / STATIONÄRE ALLGEMEINE INNERE MEDIZIN

FM237

Performance of the quick SOFA score in the emergency department

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Introduction: Sepsis, according to the new definition, is a life-threatening organ dysfunction with high mortality. In order to promptly identify septic patients with the worst prognosis outside the intensive care unit (ICU), a new bedside score was proposed: the quick SOFA score (qSOFA). It remains relatively untested in emergency settings. We measured the performance of the qSOFA and 2 other clinical scores at the emergency department's triage to identify the most severely infected patients among a population of patients transported by emergency medical services (EMS) to our emergency department (ED).
Methods: We performed a retrospective study of all patients transported to the Lausanne University Hospital, from January 1st to December 31st 2012. All patients with a suspected or proven infection through the ED stay were included. qSOFA, SIRS and Sepsis scores were retrospectively calculated upon arrival to the ED. End points were: ICU admission, ICU stay >3 days and mortality at 48 hours. *Definitions:* **qSOFA score:** ≥ two of the following criteria: systolic blood pressure (SBP) ≤100 mm Hg, respiratory rate (RR) ≥22/min, and altered mental status (Glasgow Coma Scale (GCS) <15). **SIRS score:** ≥ two of the following criteria: heart rate >90/min, RR >20/min, temperature <36 °C or ≥38.3 °C). **Sepsis score:** SIRS score plus one sign of organ dysfunction or hypoperfusion (GCS <15, oxygen saturation <90% or SBP <90 mm Hg).
Results: Among the 11'411 patients transported to the University hospital, 890 patients fulfilled the criteria of a final diagnosis of infection; four had missing data and were excluded. 886 (7.8%) patients were included; 454 had an infection without organ failure after the ED stay, and 442 had a sepsis with organ failure. Sensitivity of the qSOFA and sepsis scores for mortality at 48h reached 60%, and 80% for the SIRS score. For ICU admission, the sensitivity of the qSOFA score was 31.3%, 42.5% for the sepsis score, and 58.8% for the SIRS score. The sensitivities were practically identical for the stay in ICU ≥3 days: 30.5 % for the qSOFA score, 42.4% for the sepsis score, and 57.6% for the SIRS score.
Conclusion: The qSOFA score, as well as existing clinical scores, perform poorly to early identify upon arrival to the ED, the most seriously infected patients.

FM238

"Smarter Medicine" implementation: a single centre retrospective analysis

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Introduction: Inspired by the US Choosing Wisely® campaign, the Swiss Society of General Internal Medicine (SSGIM) released in May 2016 a list of 5 treatments or diagnostic tests frequently used in the Hospital and considered as unnecessary, since not improving patient care and increasing health care costs. The Swiss initiative was called "smarter medicine". "Smarter medicine" recommendations were implemented on our Department on August 9th 2016. They were supported by lectures to the physicians, weekly emails communications and were discussed during every Chief and Consultant visit. We retrospectively analysed the count of blood draws before and after implementation of the recommendation aiming at reducing unnecessary blood tests.
Methods: Retrospective single centre analysis conducted on the Department of Internal Medicine, Uster Hospital, Switzerland. Patient hospitalized in the three months before and after recommendation implementation (May to November 2016) were analysed. Data were anonymous and retrieved from a quality data base.
Results: Of the 2023 patients included in the analysis, 997 patients were hospitalized before and 1026 after "smarter medicine" was implemented. There was a significant decrease in the count of blood draws after recommendation implementation (median count of blood draws per patient in the first group 4 (interquartile range (IQR) 2–7), median count in the group after recommendation 4 (IQR 2–6), $P = 0.002$) (fig. 1). Indeed, since 46% of the patients in the 1st group had >4 blood tests, this ratio decreased to 39% after "smarter medicine". Volume of blood drawn was also significant lower in the three months after (median blood volume drawn per patient 56 mL, IQR 27–99) than before recommendation (median 65 mL, IQR 68–108, $P = 0.01$) (fig. 2).
Conclusions: Inappropriate blood draws may lead to anemia, patient discomfort and false positive results. The simple and low-cost interventions used to implement the "smarter medicine" seem to have changed physician behaviour by reducing the count of blood orders. These results are promising and we need a wide implementation of the "smarter medicine" recommendation to reduce resource wasting. Whether the "smarter medicine" will impact patient and clinical outcome remains however unknown and further studies are needed to clarify this issue.

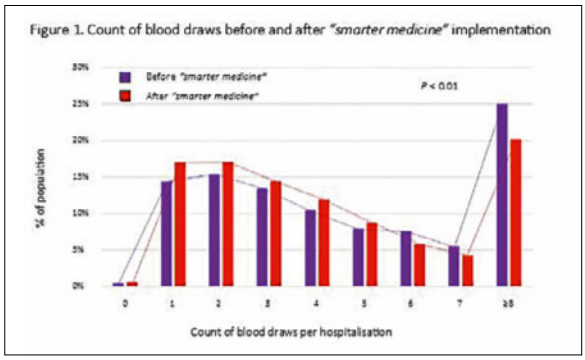

Figure 1

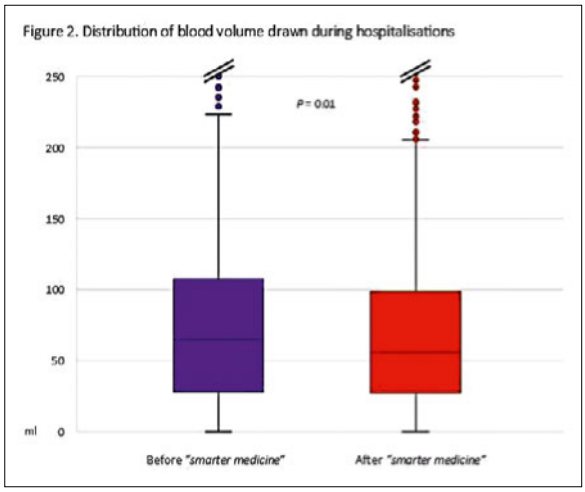

Figure 2

FM239

Association between computed tomography obstruction index and mortality in elderly patients with acute pulmonary embolism: a prospective validation study

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Introduction: Computed tomography pulmonary angiography (CTPA) has not only become the method of choice for diagnosing acute pulmonary embolism (PE), it also allows for risk stratification of patients with PE. To date, no study has specifically examined the predictive value of CTPA findings to assess short-term prognosis in

elderly patients with acute PE who are particularly vulnerable to adverse outcomes.
Methods: We aimed to evaluate the prognostic performance of the computed tomography obstruction index (CTOI) and right ventricular dysfunction (right ventricular [RV] to left ventricular [LV] diameter ratio >0.9) in elderly patients with PE. We studied 291 patients aged ≥65 years with acute symptomatic PE in a prospective multicenter Swiss cohort study. CTPA was performed at each participating study center and then anonymously sent to Lausanne University Hospital, where the images were independently evaluated by two board-certified radiologists. Outcomes were 90-day overall and PE-related mortality, and recurrent venous thromboembolism (VTE) during the whole follow-up period. We examined associations of the CTOI and the RV/LV diameter ratio with mortality and VTE recurrence using survival analysis, adjusting for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation as a time-varying covariate.
Results: Overall, 15 patients died within 90 days (6 from definite or possible PE). While the CTOI was not associated with 90-day overall mortality (adjusted hazard ratio [HR] per 10% CTOI increase 0.92; 95% confidence interval [CI] 0.70–1.21; *P* = 0.54), it was significantly associated with PE-related 90-day mortality (adjusted sub-hazard ratio [SHR] per 10% CTOI increase 1.36; 95% CI 1.03-1.81; *P* = 0.03). The RV/LV diameter ratio was neither associated with overall nor PE-related 90-day mortality. The CTOI (adjusted SHR per 10% CTOI increase 1.27; 95% CI 1.12-1.45; *P* <0.001) and the RV/LV diameter ratio (adjusted SHR per unit increase 2.74; 95% CI 1.26-5.95; *P* = 0.01) were both significantly associated with VTE recurrence.
Conclusion: In elderly patients with acute PE, the CTOI was associated with PE-related 90-day mortality but not with overall mortality. The RV/LV diameter ratio did not predict mortality. Both measures predicted VTE recurrence.

Association of predictors with 90-day mortality

	Crude HR or SHR (95% CI)	*P* value	Adjusted HR or SHR (95% CI)	*P* value
Overall mortality				
CTOI (per 10%)	0.90 (0.70; 1.14)	0.37	0.92 (0.70; 1.21)[a]	0.54
RV/LV diameter ratio (per unit)	0.27 (0.03; 2.16)	0.22	0.35 (0.06; 2.18)[a]	0.26
PE-related mortality				
CTOI (per 10%)	1.33 (1.00; 1.78)	0.05	1.36 (1.03; 1.81)[a]	0.03
RV/LV diameter ratio (per unit)	0.61 (0.17; 2.25)	0.46	0.69 (0.23; 2.07)[a]	0.51

[a]Adjustment was done for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation treatment as a time-varying covariate.
HR: Hazard ratio from Cox regression.
SHR: Subhazard ratio from competing risk regression accounting for non-PE-related death as a competing event.

Association of predictors with VTE recurrence

	Crude SHR (95% CI)	*P* value	Adjusted SHR (95% CI)	*P* value
VTE recurrence				
CTOI (per 10%)	1.21 (1.07; 1.38)	0.003	1.27 (1.12; 1.45)[a]	<0.001
RV/LV diameter ratio (per unit)	1.56 (0.67; 3.67)	0.31	2.74 (1.26; 5.95)[a]	0.01

[a]Adjustment was done for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation treatment as a time-varying covariate.
SHR: Subhazard ratio from competing risk regression accounting for non-PE-related death as a competing event.

FM240

In-hospital mortality associated with high N-terminal pro-brain natriuretic peptide levels

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Introduction: Elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels are associated with in-hospital morbidity and mortality. We aimed to compare in-hospital mortality in adult patients with different levels of NT-pro-BNP.
Method: We studied 3833 adult patients (median age: 72 years) hospitalized between June 2013 and April 2015 in a Swiss university hospital. All patients had at least one NT-pro-BNP measurement. Patients were categorized in quintiles (Q) according to their highest NT-pro-BNP level (Q1: 5-243; Q2: 244-819; Q3: 820-2271; Q4: 2272-6095 and Q5: ≥6096 ng/l). Mortality and length of stay (LOS) of Q5 was compared to the others (Q1-4); comparisons between all quintiles were also performed.
Results: Almost eight out of ten (79.9%) patients were hospitalized in a medical ward; 10.7% in a surgical ward and 9.4% in the intensive care unit. Approximately one out of seven (12.4%) had a main diagnosis of heart failure (HF), and 2.2% had stage 5 renal failure. Patients in the highest quintile (Q5) were older (78.3 ± 12.8 vs. 70.3 ± 16 years, respectively, p <0.001), had more frequently a main diagnosis of HF (26% vs. 9%, p <0.001), presented more frequently with stage 5 renal failure (7.6% vs. 0.8%, p <0.001), and were more likely to be admitted through emergency room (79% vs 73%, p <0.001) than patients in Q1–4. Patients in Q5 had higher in-hospital mortality than patients in Q1–4 (9.7 vs. 4.3 deaths per 1000 patients*day, respectively, p <0.001). This difference persisted after adjusting for age, gender, principal diagnoses (heart failure, other heart disease, pneumonia, chronic obstructive pulmonary disease and other), stage 5 renal failure, hospital ward and stay in emergency room: Hazard ratio and (95% confidence interval): 1.97 (1.57–2.46), p <0.001. Using individual quintiles led to similar conclusions, with a multivariate-adjusted test for trend: p <0.001.

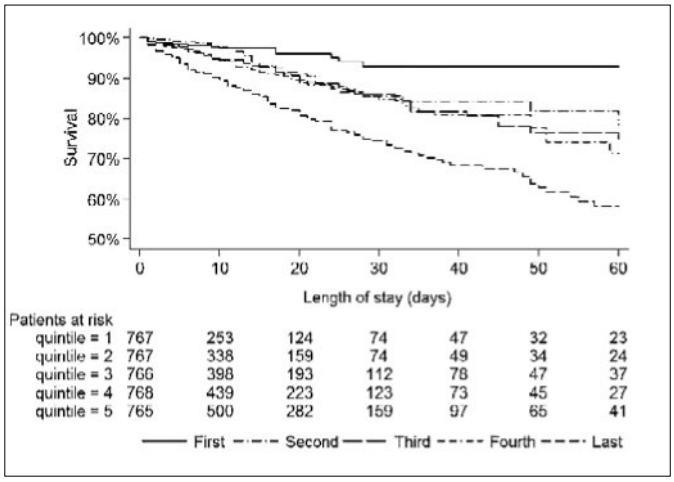

Figure 1: Kaplan-Meyer survival curves.

Patients in Q5 also had a longer LOS: median and (interquartile range): 15 (7–26) vs. 9 (2–18) days, respectively, p <0.001; this difference persisted after multivariate adjustment (p <0.001 on log-transformed data).
Conclusion: Patients with high NT-pro-BNP levels are at higher risk of in-hospital mortality and longer LOS. NT-pro-BNP levels can be a helpful tool for predicting in-hospital patient outcome.

FM241

Trends in the main classes of drugs prescribed at discharge from a university general internal medicine unit

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Background: The characteristics of patients admitted to internal medicine change with time. Patients are increasingly older and present with more comorbidities, which impacts prescription patterns. We aimed to measure the trends in the pattern of medications prescribed at discharged from a department of Internal Medicine of a university hospital.
Methods: Retrospective study including 18'075 adult patients discharged between 2009 and 2015. Drugs prescribed at discharge were coded according to the anatomical therapeutic chemical (ATC) nomenclature of the World Health Organization.
Results: The three most commonly classes of drugs prescribed were "alimentary tract and metabolism (including insulins);"; "nervous system", and A "blood and blood forming organs" (table). The five most prescribed drugs were analgesics (8.4% of all drugs prescribed); antithrombotic agents (ATC code B01, 8.0%); psycholeptics (including hypnotics and sedatives, 7.2%); drugs for constipation (7.0%) and drugs for acid related disorders (6.0%). Most prescribed groups increased during the study period, excepting ATC group B "blood and blood forming organs", "cardiovascular system", and "dermatologicals". In 2015, over eight out of ten patients discharged received at least one drug from"alimentary tract and metabolism" or "nervous system" (figure; all trends are significant at p <0.001).

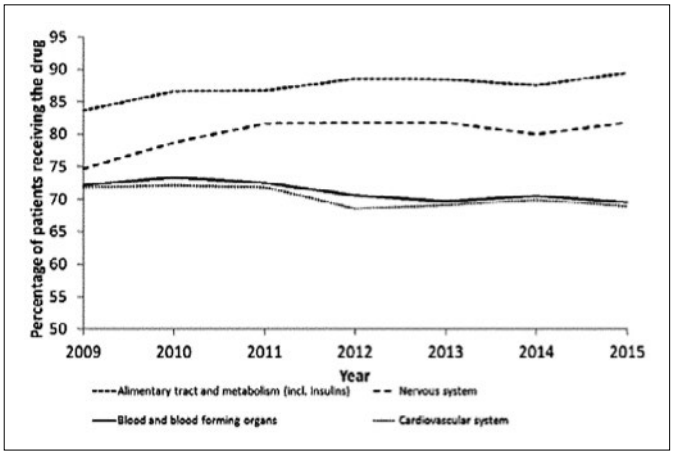

Figure 1: Trends for the major groups of drugs.

Conclusion: The pattern of drug prescription has changed, with an increase in drugs for alimentary tract and metabolism and nervous system. The reasons for and the consequences of the very high prevalence of drugs for the nervous system should be further investigated.
Keywords: Prescribed drugs; Hospital; discharge

EPIDEMIOLOGIE

FM242

Is the risk of fracture increased among participants with thyroid function within the reference range? Results of an individual participant data analysis of thirteen prospective cohorts

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Introduction: Hyperthyroidism is associated with an increased risk of osteoporosis and fractures. However, it is not clear whether high thyroid-stimulation hormone (TSH) within its reference range and low free thyroxine (FT4) levels lead to increased fracture risk. Furthermore, the target TSH to reach with levothyroxine treatment of hypothyroidism remains controversial. We aimed to evaluate the association between TSH within the reference range, FT4, and incident fractures.
Methods: We performed an individual participant data analysis of thirteen prospective cohort studies across three continents with a median follow-up of 12.1 years (interquartile range 8.5–12.9). We included adults with baseline serum TSH within the reference range (0.45–4.49 mIU/L). The primary outcome was incident hip fracture. Secondary outcomes were incident clinical vertebral, non-vertebral, and any fractures. For clinical relevance, we categorized participants' TSH as: 0.45-0.99mIU/L; 1.00–1.49 mIU/L; 1.50–2.49 mIU/L; 2.50–3.49 mIU/L; and, 3.50–4.49 mIU/L (reference group). FT4 was assessed as one standard deviation increase within each study, because FT4 assay methodology differed between cohorts. Analyses were stratified by sex and age.

Results: During a follow-up of 659,059 person-years of 61,959 participants euthyroid at baseline, 2,565 had hip fracture (4.6%; from 12 cohorts with hip fracture data). Compared with the reference group, the pooled age- and sex-adjusted hazard ratio (HR) (95%CI) for hip fractures was 1.25 (1.05–1.49) for TSH 0.45-0.99 mIU/L, 1.19 (1.01–1.41) for TSH 1.00–1.49 mIU/L, 1.09 (0.93–1.28) for TSH 1.50–2.49 mIU/L, and 1.12 (0.94–1.33) for TSH 2.50–3.49 mIU/L (*P* for trend = 0.004). The risk of hip fractures also increased according to FT4 levels (HR 1.22 [95%CI 1.11–1.35] per one standard deviation increase in FT4). FT4, but not TSH, was significantly associated with non-vertebral and any fractures, but not with vertebral fractures. Results remained similar in sensitivity analyses that excluded participants taking thyroxine at baseline, or that included only participants with TSH remaining within the reference range during follow-up, as well as in analyses stratified by sex or age (figure).
Conclusions: Lower levels of TSH within the reference range and higher levels of FT4 are associated with increased risk of hip fractures. These findings are relevant to the definition of optimal thyroid function and raise questions about treatment targets for hypothyroidism.

FM243

Changes in antidiabetic drug treatment in a Swiss population-based sample. The CoLaus study

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Background and aims: Treatment of type 2 diabetes mellitus (T2DM) evolves with time, but little information is available regarding its determinants in the general population. We aimed to assess changes and determinants associated to antidiabetic treatment in a Swiss population-based sample.
Methods: Two hundred and ten participants with T2DM from the CoLaus study. Antidiabetic drug treatment was assessed at baseline (2003–2006) and follow-up (2009–2012), and categorized into maintainers, changers and reducers/quitters.
Results: At baseline, 146 (69.5%) of the 210 participants received antidiabetic treatment. Of the 146 participants treated, 124 (84.9%) received oral antidiabetics alone, 8 (5.5%) insulin alone and 14 (9.6%) insulin and oral antidiabetics. During the 5.5 year follow-up, 108 (74.0%) patients maintained, 27 (18.5%) changed and 11 (7.5%) reduced or stopped treatment. Patients who changed therapy had higher baseline fasting plasma glucose (FPG) levels than the others (10.3 ± 3.7 vs. 7.8 ± 2.0 and 7.6 ± 2.0 mmol/L for maintainers and reducers/quitters, respectively, p <0.001) and also lower levels of FPG <7.0 mmol/L (7.4%, vs. 39.8% and 45.5% for maintainers and reducers/quitters, respectively, p = 0.002). At follow-up, patients who changed therapy had the highest prevalence of FPG decrease relative to baseline (55.6%, vs. 46.3% and 9.1% for maintainers and reducers/quitters, respectively, p = 0.025).
Conclusion: During a 5.5 year follow-up, less than one fifth of patients with T2DM had his/her drug treatment changed. Changes in T2DM treatment lead to an improvement of the unfavourable FPG status. The reasons and impact of quitting or reducing treatment should be further explored.
Keywords: Type 2 diabetes; antidiabetic drugs; treatment; epidemiology; trends

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FM244

Hip and knee replacements in Switzerland: variation in regional utilizasation patterns

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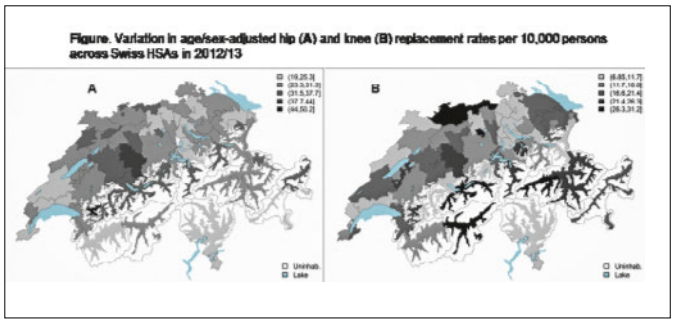
Introduction: Compared to other OECD countries, Switzerland has the highest hip replacement (HR) and one of the highest knee replacement (KR) rates. However, previous data on HR and KR use in Switzerland date back to the year 2008, and no recent data on the use of HR/KR are available. We assessed the regional variation in the use of HR/KR in Switzerland.
Methods: We conducted a population-based small area-variation analysis. We used procedure codes to identify HR/KR from routinely collected patient discharge data from all Swiss hospitals during 2012/13. We derived hospital service areas (HSAs) by analyzing patient flows to determine where the majority of residents were hospitalized, merging areas served by the same hospital into HSAs. We calculated age/sex-standardized utilization rates per 10,000 persons for each HSA. We determined 2 measures of regional variation, the extremal quotient (EQ, highest HR/KR rate divided by lowest rate) and the systemic component of variation (SCV). We estimated the reduction in variation of crude HR/KR rates in multi-level negative binomial regression models, adjusting for age/sex, socioeconomic factors (language area, urbanization, socioeconomic position), and the number of orthopedic surgeons as a proxy for care availability.
Results: Overall, 34,638 HR and 19,333 KR were electively performed in 2012/13. The age/sex-adjusted mean HR rate was 28/10,000 persons, with a range from 19 to 50/10,000 persons across HSAs (fig. A). The age/sex-adjusted mean KR rate was 16/10,000 persons, with a range from 7 to 31/10,000 persons across HSAs (fig. B). For KR, the variation was large with an EQ of 4.5 and a SCV of 17.8; age/sex-adjustment only minimally changed variation, whereas additional adjustment for socioeconomic factors and surgeon number reduced the variation by 10% and an additional 2%, respectively. For HR, the variation was low, with an EQ of 2.6 and a SCV of 2.9. While age/sex-adjustment increased variation; additional adjustment for socioeconomic factors and surgeon number reduced the variation by 9.2% and an additional 6.4%, respectively.



Conclusion: We found a substantial variation in KR rates that could not be explained by differences in age/sex, socioeconomic factors, or care availability, while the variation in HR rates was modest. The variation in KR rates is unlikely to be explained by regional differences in incidence or severity of osteoarthritis and more likely indicates regional over- and underuse.

FM245

Dietary behaviors influence inflammatory markers: results from the CoLaus study

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Introduction: Our aim is to assess the impact of dietary intake (single foods, macro and micronutrients, dietary patterns and scores) on inflammatory markers (CRP, IL-6, TNF-α and leucocyte count).
Methods: Data from 3774 participants of the population-based CoLaus study. Dietary intake was assessed using a semi-quantitative food frequency questionnaire. Single foods, nutrients, three naive (using principal components analysis) and four oriented (Mediterranean, Alternative Healthy Eating Index) dietary scores were used. Associations with inflammatory markers were assessed using spearman correlation and robust linear regression.
Results: CRP was positively associated (p <0.01, table 1) with the "meat and chips" pattern, and negatively associated with the "fruits and vegetables" pattern, the Mediterranean and the Alternative Healthy Eating Index (AHEI) scores, fruits, carrots, tofu and carotene. After adjusting for age, body mass index (BMI), gender, smoking habits, education, sedentarity, total calories intake and diabetes, the negative associations with the "fruits and vegetables" pattern, the Mediterranean and the Alternative Healthy Eating Index scores, and fruits remained significant (p <0.01, table 2). Leucocyte count was positively associated (p <0.01, table 1) with the "meat and chips" pattern and negatively associated with the "fruits and vegetables" pattern, the AHEI scores, a high intake of fiber, carotene, carrots, salad, tofu, fruits, bananas, apples and kiwis. After multivariate adjustment, only the associations with the "meat and chips" and the "fruits and vegetables" patterns remained significant (p <0.01, table 2). Conversely, no significant associations were found between all dietary markers and TNF-α and IL-6 after multivariate adjustment.

Table 1: bivariate associations between inflammatory and dietary markers

	CRP (log)	IL-6 (log)	TNF-a (log)	Leucocytes
Total energy intake	-0.008	0.057	0.018	0.012
Macronutrients				
Total protein	-0.003	0.046	0.017	0.027
Vegetable protein	-0.043	0.041	0.000	-0.030
Animal protein	0.019	0.034	0.022	0.050
Total carbohydrates	-0.034	0.037	0.012	-0.008
Monosaccharides	-0.038	0.018	0.004	-0.011
Polysaccharides	-0.020	0.038	0.012	-0.007
Total fat	0.001	**0.054**	0.016	0.019
Saturated	0.007	0.039	0.028	0.021
Monounsaturated	-0.007	0.057	0.010	0.017
Polyunsaturated	0.033	0.055	0.007	0.047
Fiber	-0.052	0.028	0.002	-0.056
Cholesterol	-0.010	0.025	-0.005	0.010
Alcohol	-0.022	0.030	0.015	0.011
Micronutrients				
Calcium	0.014	0.022	0.020	0.032
Iron	-0.024	0.051	0.005	-0.012
Retinol	0.015	0.013	0.005	0.015
Carotene	**-0.061**	0.031	-0.008	**-0.081**
Vitamin D	-0.025	0.032	0.002	-0.019
Vitamin A	-0.021	0.028	-0.009	-0.025
Patterns				
Meat and Chips	**0.072**	0.030	0.029	**0.094**
Fruits and vegs, no alcohol	**-0.090**	0.030	-0.022	**-0.131**
Pastries and fat	-0.048	-0.007	-0.017	**-0.095**
Dietary scores				
Mediterranean (Trichopoulou)	**-0.076**	0.046	-0.022	-0.032
Mediterranean (Vormund)	**-0.054**	0.027	-0.010	-0.038
AHEI [1]	**-0.111**	0.033	-0.016	**-0.072**
AHEI [2]	**-0.115**	0.032	-0.016	**-0.074**
Food Items				
Fruits	**-0.055**	0.000	-0.021	**-0.061**
Vegetables	-0.045	**0.059**	-0.002	-0.038
Fish	-0.037	0.023	-0.001	-0.016
Haricots verts	-0.015	0.016	0.011	0.019
Chou-fleur	-0.026	0.047	0.010	-0.009
Tomatoes	0.007	0.003	0.000	0.018
Carrots	**-0.068**	0.034	0.008	**-0.097**
Green salad	-0.042	0.016	-0.012	**-0.059**
Thick vegetables soup	-0.030	0.040	-0.004	0.007
Tomato sauce	0.028	0.012	0.026	0.035
Tofu	**-0.091**	0.012	-0.026	**-0.085**
Bananas, apples	-0.038	-0.004	0.004	**-0.059**
Oranges, tangerines	-0.027	-0.003	-0.028	-0.023
Peaches, nectarines	0.031	-0.038	0.045	0.028
Strawberries, blackcurrants	0.031	-0.039	-0.005	-0.021
Kiwis	-0.035	0.012	0.029	**-0.078**
Fresh fruit juice	-0.042	-0.032	-0.031	-0.003

AHEI, alternate healthy eating index. [1], original; [2], modified. Results are expressed as spearman correlations. Significant (p<0.01) correlations are indicated in bold

Table 2: multivariate associations between inflammatory and dietary markers

	CRP (log)	IL-6 (log)	Leucocytes
Total energy intake		-0.008	
Macronutrients			
Total fat		0.027	
Monounsaturated		0.031	
Polyunsaturated		0.021	
Fiber			-0.028
Micronutrients			
Carotene	-0.037		-0.044
Dietary patterns			
Meat and chips	0.011		**0.055**
Fruits and vegs, no alcohol	**-0.054**		**-0.054**
Pastries and fat			-0.015
Dietary scores			
Mediterranean (Trichopoulou)	**-0.043**		
Mediterranean (Vormund)	-0.039		
AHEI [1]	**-0.067**		-0.036
AHEI [2]	**-0.068**		-0.036
Food Items			
Fruits	**-0.043**		-0.023
Vegetables		0.031	
Carrots	-0.034		-0.034
Green salad			-0.041
Tofu	-0.017		-0.005
Bananas, apples			-0.006
Kiwis			-0.019

AHEI, alternate healthy eating index. [1], original; [2], modified. Significant (p<0.01) associations are indicated in bold

Conclusions: (un)healthy dietary behaviors have a small but significant impact on inflammatory markers in the general population. The effect of individual nutrients or foods appears to be of less clinical importance.

FM246

Legislative changes and 22-year trends in individual alcohol consumption in a Swiss adult population

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Introduction: Alcohol misuse is an important determinant of health and a major contributor to the burden of disease worldwide. With regard to alcohol use regulations, Switzerland has a long history of efforts to regulate alcohol production, sale and use, at the cantonal and federal levels. Evidence on the impact of legislative changes on individual alcohol consumption is limited. Using an observational study design, we assessed trends in individual alcohol consumption of a Swiss adult population following the public policy changes that took place between 1993 and 2014, while considering individual characteristics and secular trends.
Method: We used data from the "Bus Santé" study, an annual health survey conducted in random samples of the adult population in the State of Geneva, Switzerland. Individual alcohol intake was assessed using a validated food frequency questionnaire. Individual characteristics including education were self-reported. Seven policy changes (six about alcohol and one about tobacco) that occurred between 1993 and 2014 defined 6 different periods. We predicted alcohol intake using quantile regression with multivariate analysis for each period adjusting for participant characteristics and tested significance periods. Sensitivity analysis was performed including drinkers only, the 10th percentile of highest drinkers and smoker's status.
Results: The study included data from 18,963 participants (aged 18–75 years). Between 1992 and 2014, participants' individual alcohol intake decreased from 7.3 to 5.4 g/day (26% reduction, p <0.001). Men decreased their alcohol intake by 35% compared to 31% for women (p <0.001). The decrease in alcohol intake remained significant when considering drinkers only (30% decrease, p <0.001) and the 10th percentile highest drinkers (24% decrease, p <0.001). Consumption of all alcoholic beverages decreased between 1993 and 2014 except for the moderate consumption of beer, which increased. After adjustment for participants' characteristics and secular trends, no independent association between alcohol legislative changes and individual alcohol intake was found.
Conclusion: Between 1993 and 2014, alcohol consumption decreased in the Swiss adult population independently of policy changes.

MÉDECINE INTERNE GÉNÉRALE AMBULATOIRE / AMBULANTE ALLGEMEINE INNERE MEDIZIN

FM247

Sleep disorders are associated with trabecular bone score and osteoporotic fracture, not with bone mineral density

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Context: Sleep disorders and osteoporosis increase with age and are associated with high morbidity, mortality and economic burden. The prevalence of sleep-disordered breathing in Swiss women is 23% above 40 years and the remaining lifetime risk of osteoporotic (OP) fracture at 50 years is >50%. Poor sleep quality is associated with increased risk of fall and inconsistently with low bone mineral density (BMD), but the effect sizes were small and the mechanisms are unknown. Our study aimed to assess if sleep characteristics are associated with markers of bone health: BMD, microarchitecture assessed indirectly by trabecular bone score (TBS), and OP and non OP fractures.
Methods: OsteoLaus is a population-based cohort of 1500 randomly selected Caucasian women (50 to 80 y old) living in Lausanne, Switzerland. All women had lumbar spine BMD and TBS, hip BMD, vertebral fracture assessment, and questionnaire about OP and non OP fractures. A random selection of 660 women was included in the HypnoLaus Sleep cohort study and had a polysomnography. Total sleep time (TST), sleep onset latency (SOL), slow-wave sleep and rapid eye movement sleep (REM) quantity, apnoea-hypopnoea index (AHI), oxygen desaturation index (ODI) and sleep efficiency were evaluated.
Results: After adjustment, sleep parameters were not associated with BMD, AHI and ODI were inversely associated with TBS. All the results for fractures were adjusted for age, BMI and psychoactive drugs. Sleep onset latency was associated with OP fractures ($p < 0.001$). REM was associated with OP and non OP fractures ($p < 0.05$). We create a score of "sleep quality" including 6 parameters: total sleep time, sleep onset latency, slow-wave sleep, REM sleep, AHI, and sleep efficiency. This score was significantly lower only for women with prevalent OP fracture: women with OP fracture vs women without fracture (-0.25 ± 0.09 vs. 0.05 ± 0.04, $P < 0.03$).
Conclusion: Our study demonstrates for the first time that TBS is altered in women with high AHI or high ODI. We found however no relevant association between BMD and sleep characteristics. The sleep quality score was lower for women with OP fracture. Further studies are needed to: 1) explain how some sleep characteristics affect TBS; and 2) validate the score of "sleep quality" in other studies.

FM248

Use of polypill components in a swiss population-based study

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Background: Cardiovascular diseases (CVD) are the first cause of mortality and morbidity worldwide. Insufficient adherence to cardiovascular therapy could explain in part this finding despite tremendous progress in CVD treatment. Lack of adherence could be prevented by a fixed combined dose of efficient medications for CVD prevention, the so-called polypill. We aimed to assess the prevalence of participants in a large population-based study in Lausanne already taking simultaneously individual components of polypills approved either worldwide or in Switzerland.
Methods: Cross-sectional study conducted between 2009 and 2012 in a sample of 5064 participants aged 40–80 years. Medications taken and associated medical conditions were assessed by questionnaire and confirmed by interview. Two major types of polypill equivalents were defined based on commercially available polypills. Polypill equivalent A contains aspirin, a statin and any antihypertensive drug and equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic's approved polypills: equivalent C contains a statin and a calcium channel blocker and equivalent D a statin, a calcium channel blockers and an angiotensin-converting-enzyme inhibitors.
Results: Equivalent A was the most frequent (5.5%) and was more prevalent among men (7.8% *vs.* 3.6% in women), in the elderly (16.1% in ≥70 *vs.* 1.1% in 40–50 age group) in low educated people (6.7% *vs.* 4.2% in high educated) and in participants with a history of CVD (38.5% *vs.* 2.8% in those without). Equivalent B was taken by 5.2% of the participants and was more prevalent among men (6.1% *vs.* 4.4%) the elderly (11.1 in ≥70 *vs.* 0.9% in 40–50 age group); participants with lower education levels (6.9% *vs.* 2.3% in high educated) and participants with a history of CVD (8.9% *vs.* 4.9% in those without). Equivalent C was taken by 2.6% of the participants and equivalent D by 0.8% of the participants, both with similar distribution (table 1).
Conclusion: In the population older than 40y in Lausanne, approximately one in 38 subjects could take a Swissmedic approved polypill, instead of receiving separate drugs; and up to one in 18 subjects for worldwide approved polypills. A larger choice of polypill may increase the number of the population taking polypills. However, the potential impact of better drug adherence with a polypill prescription remains to be evaluated in randomised studies.

Table 1. Distribution of eligibility to different types of polypill according to different socio-demographic characteristics of the sample

	Polypill equivalent A: Aspirin + Statin + any antihypertensive			Polypill equivalent B: Statin + any antihypertensive			Polypill equivalent C: Statin + CCB[a]			Polypill equivalent D: Statin + CCB[a] +ACE inhibitors[b]		
	No	Yes	P-Value	No	Yes	P-Value	No	Yes	P-Value	No	Yes	P-Value
All	4783 (94.5)	281 (5.5)		4800 (94.8)	264 (5.2)		4934 (97.4)	130 (2.6)		5023 (99.2)	41 (0.8)	
			<0.001			0.008 §			<0.001			0.007§
Gender												
Man	2174 (92.2)	183 (7.8)		2213 (93.9)	144 (6.1)		2275 (96.5)	82 (3.5)		2329 (98.8)	28 (1.2)	
Woman	2609 (96.4)	98 (3.6)		2587 (95.6)	120 (4.4)		2659 (98.2)	48 (1.8)		2694 (99.5)	13 (0.5)	
Age group			<0.001			0.001 §			<0.001			<0.001
[40-50[	1415 (98.9)	16 (1.1)		1418 (99.1)	13 (0.9)		1422 (99.4)	9 (0.6)		1428 (99.8)	3 (0.2)	
[50-60[	1498 (97.1)	44 (2.9)		1492 (96.8)	50 (3.2)		1517 (98.4)	25 (1.6)		1534 (99.5)	8 (0.5)	
[60-70[	1249 (92.4)	102 (7.6)		1232 (91.2)	119 (8.8)		1306 (96.7)	45 (3.3)		1343 (99.4)	8 (0.6)	
[70+	621 (83.9)	119 (16.1)		658 (88.9)	82 (11.1)		689 (93.1)	51 (6.9)		718 (97)	22 (3)	
Education			0.001			<0.001			<0.001			0.058§
High	1034 (95.8)	45 (4.2)		1054 (97.7)	25 (2.3)		1062 (98.4)	17 (1.6)		1075 (99.6)	4 (0.4)	
Middle	1250 (95.7)	56 (4.3)		1253 (95.9)	53 (4.1)		1284 (98.3)	22 (1.7)		1298 (99.4)	8 (0.6)	
Low	2494 (93.3)	180 (6.7)		2488 (93.1)	186 (6.9)		2583 (96.6)	91 (3.4)		2645 (98.9)	29 (1.1)	
Previous history of CVD			<0.001			<0.001			<0.001			<0.001
No	4540 (97.2)	129 (2.8)		4440 (95.1)	229 (4.9)		4588 (98.3)	81 (1.7)		4647 (99.5)	22 (0.5)	
Yes	243 (61.5)	152 (38.5)		360 (91.1)	35 (8.9)		346 (87.6)	49 (12.4)		376 (95.2)	19 (4.8)	

Results are expressed as number of participants (row percentage).
Statistical analysis by Fisher's exact test (§) or chi-square test.
[a]CCB = calcium channel blockers; [b]ACE = angiotensin-converting-enzyme

FM249

Effect of thyroid hormone replacement among untreated older adults with subclinical hypothyroidism; a randomised placebo-controlled trial (TRUST)

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Background: Subclinical hypothyroidism is a common disorder among older adults, occurring in 10–15% of those over 65. Guidelines on how to treat are not precise and interpretable in various ways, leading to large variation in treatment of subclinical hypothyroidism. Underlying trial data on thyroid hormone replacement are scarce and limited. The small overall sample size (32–120 participants), the relatively young patient, the short duration of follow-up (4–12 months) and the limited quality of the included trials (three out of 12 rated as "good" by the USPSTF) yielded only limited evidence on the benefits of thyroxine replacement. To contribute to the body of evidence, we set out to a large international trial of thyroxine replacement among older adults.
Methods: We randomly assigned older adults aged ≥65 years with untreated persistent subclinical hypothyroidism into a double-blind placebo-controlled parallel group trial of levothyroxine to assess its multi-modal effects. Persistent subclinical hypothyroidism was diagnosed on the basis of persistently elevated TSH levels between 4.6 and 19.9 mU/L, measured on ≥2 occasions, at least 3 months apart, to avoid treating transient abnormal TSH based on a single TSH. Levothyroxine starting dose was 50 µg daily (or 25 µg if weight

<50 Kg or coronary heart disease), with blinded dose titration to reach a TSH <4.6 mU/L. The primary outcome was thyroid related quality of life. Secondary outcomes were general quality of life, change in muscular function with handgrip strength, measured using isometric dynamometry, change in executive cognitive function, activities of daily living and total mortality.
Results: At the close of recruitment, we enrolled 738 patients into the TRUST trial in 4 European countries. Participants were followed up for 1 to 3 years. Results are under embargo until presentation early April for meeting presentation in US, but will be fully presented at SGAIM national meeting in May.
Conclusions: This trial is by far the largest and longest RCT of treatment of subclinical hypothyroidism and is the first study which is powered to detect a meaningful change in symptoms / quality of life, over a realistic and appropriate clinical time-frame, to give definitive answers on the impact of thyroxine therapy among older adults with subclinical hypothyroidism. Results will provide the necessary evidence to properly inform best practice for treatment of subclinical hypothyroidism in older people.

FM250

Effect of vitamin D3 on self-perceived fatigue: a double-blind randomized placebo-controlled trial

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Introduction: Vitamin D deficiency is frequent and has been associated with fatigue in uncontrolled trials.
Methods: This is the first double-blind placebo-controlled clinical trial to investigate the efficacy of per os vitamin D3 (cholecalciferol) in treating fatigue among otherwise healthy persons with low serum 25-hydroxyvitamin D (25(OH)D) levels. We enrolled 120 individuals (mean age 29 ± 6 years, 53% female) presenting with fatigue and vitamin D deficiency (serum 25(OH)D <20 µg/l). Participants were randomized to a single oral dose of 100,000 units of vitamin D or placebo. The primary endpoint was intra-individual change in the Fatigue Assessment Scale (FAS) at 4 weeks after treatment.
Results: The mean age of the participants was 29 ± 6 years, 53% were female. Mean FAS decreased significantly more in the vitamin D group (–3.3 ± 5.3; 95% confidence interval for change –14.1 to 4.1) compared with placebo (–0.8 ± 5.3; 95% confidence interval for change –9.0 to 8.7); (p-value = 0.01). FAS improved significantly only in the vitamin D (p-value <0.001) but not in the placebo (p-value = 0.24) Group.

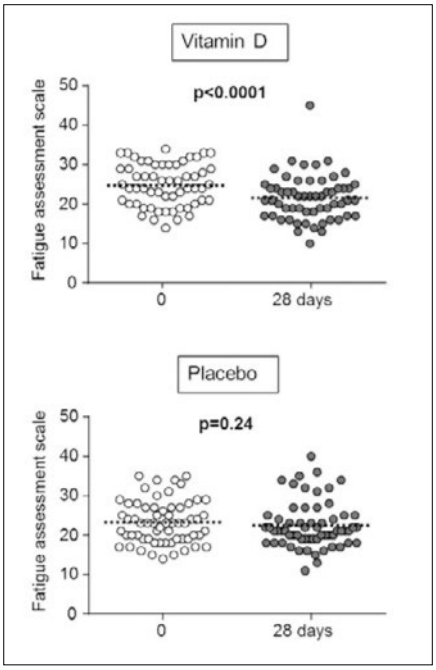

Figure 1: Fatigue before and after vitamin D treatment.

Amelioration of fatigue was reported more frequently in vitamin D than in placebo group (42 (72%) vs 31 (50%); p-value = 0.01; Odds Ratio (OR) 2.63, 95% confidence interval for OR 1.23–5.62). Among all participants, improvement in fatigue score correlated with the rise in 25(OH)D level (R = –0.22, p-value = 0.02).
Conclusion: Vitamin D treatment significantly improved fatigue in otherwise healthy persons with vitamin D deficiency.
This study was registered at the www.ClinicalTrials.gov Protocol ID NCT02022475.

FM251

Lung cancer: sex difference in the lifetime risk and 10-year risk between 1995 and 2013 in a Swiss population

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Introduction: In Switzerland, lung cancer is a leading cause of cancer death. Because smoking is the major cause of lung cancer, trends in lung cancer incidence are following trends in smoking habits in the population, with a latency time of about 30 years. In Switzerland, there was a peak in men's lung cancer incidence in the 1980s, followed by a decrease until now. Among women, the incidence has increased since the 1970s and, apparently, has not yet reached a peak. Because cancers are feared diseases, an adequate communication about the individual risk of developing cancer is important. Mortality and incidence are traditionally used to assess cancer burden. However, these metrics are difficult to interpret at the individual level. Providing the lifetime and 10-year risk of cancer could improve risk communication for patients and health professionals. Our aim was to estimate trends in the lifetime and 10-year risk of lung cancer, in men and women, between 1995 and 2013.
Methods: We used data from all lung cancer cases recorded between 1995 and 2013 by the Registre Valaisan des tumeurs (RVsT) and the Registre Vaudois des tumeurs (RVT). These two population-based registries collect data on all new cancer cases of women and men living in Valais and Vaud. Data on mortality were provided by the Federal Statistical Office. We estimated sex-specific lifetime risk and 10-year risk of lung cancer using the current probability method, which estimates cumulative risk of any condition accounting for competing risk and death.
Results: Between 1995 and 2013, 10453 cases of lung cancer were recorded. The lifetime risk of developing lung cancer decreased in men from 8.1% in 1995–1998 to 6.8% in 2009–2013 (fig. 1). During this same period, it increased in women from 2.8% to 4.1% (fig. 1). In both sexes, the 10-year risk of lung cancer increased with age until the age of 70 and decreased thereafter. Between 1995 and 2013, the 10-year risk of lung cancer decreased in men at all ages, excepted in men over 80 years of age in whom the risk increased. Among women, the 10-year risk increased in women above 50 years of age.

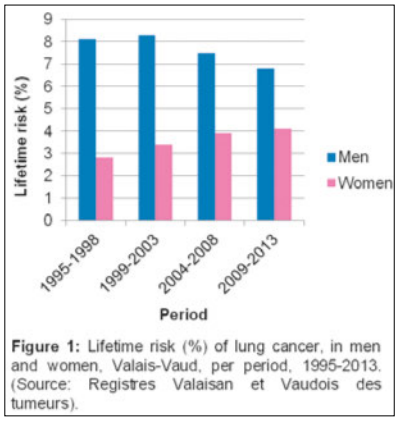

Figure 1: Lifetime risk (%) of lung cancer, in men and women, Valais-Vaud, per period, 1995-2013. (Source: Registres Valaisan et Vaudois des tumeurs).

Conclusion: Lifetime and 10-year risk of cancer can improve cancer risk communication. Between 1995 and 2013, the lifetime risk of lung cancer decreased in men and increased among women.

FUTURE RESEARCH IN EPIDEMIOLOGY

FM252

Statins and risk of Alzheimer's disease: evidence from Mendelian randomization

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Background: Observational studies suggest that statin use is inversely associated with risk of Alzheimer disease (AD). Thus, it is important to investigate whether any statin impact on risk of AD represents an on-target effect (i.e., due to a specific inhibition of the 3-hydro-3-méthylglutaryl coenzyme A reductase (HMGCR)). Since known genetic variants recapitulate the effect of statins (inhibition of HMGCR), we used single-nucleotide polymorphisms (SNPs) in/near *HMGCR* gene to estimate the association between statin use and risk of AD.
Methods: Using the properties of genetic variants (presence from conception and inalterable nature), we applied a "Mendelian randomization" (MR) approach to estimate the causal effect of HMGCR inhibition on risk of AD, a form of drug target exploratory analysis. We used 3 independent (r2 <0.25) SNPs in/near *HMGCR* (rs16872526, rs12916, rs5744707) and retrieved their association estimates with LDL-cholesterol, as reported in up to 183,465 individuals in the Global Lipids Genetic Consortium. We retrieved the same SNPs and their association estimates with AD from a large AD GWAS (including 17,008 cases and 37,154 controls). We then estimated a causal effect and a corresponding standard error (SE) for each SNP derived by the Wald and delta methods, respectively. Individual causal effect estimates were pooled using random-effects meta-analysis. Since *APOE* gene, which encodes apolipoprotein E (ApoE; found in chylomicrons and some lipoproteins), influence the odds of AD, we complemented the analysis by testing whether an ApoE-associated variant (rs7412) was related to risk of AD as a positive control. Analysis for *APOE* rs7412 was performed as described above.
Results: In Mendelian randomization analysis based on 17,008 AD cases and 37,154 controls, statin use (instrumented using HMGCR-related variants) was not associated with risk of AD (OR for AD: 1.00; 95% CI, 0.66–1.52). Using *APOE* rs7412 as a positive control, and scaling the results to the same difference in LDL-C, the odds of AD was strongly reduced (OR for AD: 0.49; 95% CI, 0.42–0.56).
Conclusions: This study shows that pharmacological inhibition of HMGCR (i.e., the on-target effect of statins) is unlikely to reduce the risk of AD. These findings provide evidence to make inferences about the clinical effect of statins and to help orientate research on any relationship between statin use and risk of AD.

FM253

Anti-apolipoprotein A-1 IgG as predictors of coronary heart disease and all-cause mortality in the general population: results from the CoLaus study

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Introduction: Autoantibodies against apolipoprotein A-1 (anti-apoA-1 IgG) have emerged as an independent biomarker for cardiovascular disease in selected settings, but their associations with incident coronary heart disease and mortality in the general population is unknown. We aimed to determine whether anti-apoA-1 IgG: a) predict incident CHD and all-cause mortality in the general population, and b) are associated with single-nucleotide polymorphisms (SNPs) in a genome-wide association study (GWAS).
Methods: Clinical, biological and genetic data were obtained from the population-based, prospective CoLaus study, including 5220 participants (mean age 52.6 years, 47.3% men) followed over a median duration of 5.6 years. The primary study outcome was adjudicated incident CHD, defined as adjudicated incident myocardial infarction, angina, percutaneous coronary revascularization or bypass grafting.
Results: In subjects positive vs. negative for anti-apoA-1 IgG, total CHD rate was 3.9% vs. 2.8% (p = 0.077), while nonfatal CHD rate was 3.6% vs. 2.3% (p = 0.018). Multivariate-adjusted Hazard ratios (aHR) and (95% confidence intervals) were 1.58 (0.96; 2.60), and 1.53 (1.03; 2.26), for total and nonfatal CHD, respectively. The association was modulated by a significant interaction between anti-apoA-1 IgG and a functional SNP in the CD14 receptor gene (rs2569190), with anti-apoA-1 IgG conferring the highest risk for CHD in non-TT rs2569190 carriers (aHRs = 1.73 (1.10; 2.73)), whereas being associated with the lowest risk in TT homozygotes (p-for-interaction = 0.015). After multivariate adjustment, anti-apoA-1 IgG positivity independently predicted all-cause mortality (aHR = 1.54, (1.11-2.13), P = 0.01), with each standard deviation of logarithmically transformed anti-apoA-1 IgG being associated with a 15% increase in mortality risk. Our GWAS yielded 9 SNPs belonging to the Fc receptor like-3 (FCRL3) gene that were significantly associated with anti-apoA-1 IgG levels, with the lead SNP (rs6427397, P = 1.54×10^{-9}) explaining 0.67% of anti-apoA-1 IgG level variation.
Conclusion: Anti-apoA-1 IgG independently predict nonfatal incident CHD in the general population, the strength of this association being dependent on a functional polymorphism of the CD14 receptor gene. Our findings further indicate that preclinical autoimmunity to anti-apoA-1 IgG is linked to FCRL3, a susceptibility gene for autoimmune diseases, and may as well represent a novel mortality risk factor in the community.

FM254

Cannabis use and risk of schizophrenia: a Mendelian randomization study

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Background: Cannabis use is observationally associated with an increased risk of schizophrenia, however whether the relationship is causal is not known. Observational studies cannot clarify causality and a randomized trial would be unethical.
Methods: We took 10 independent genetic variants previously identified to associate with cannabis use in 32,330 individuals to determine the nature of the association between cannabis use and risk of schizophrenia. Genetic variants were employed as instruments to recapitulate a randomized controlled trial involving two groups (cannabis users vs nonusers) to estimate the causal effect of cannabis use on risk of schizophrenia in 34,241 cases and 45,604 controls from predominantly European descent. Genetically-derived estimates were compared with a meta-analysis of observational studies reporting ever use of cannabis and risk of schizophrenia or related disorders. We conducted additional tests accounting for unmeasured pleiotropy of the genetic instrument and for tobacco exposure. Sensitivity analyses included exploring the influence of the causal summary estimate to individual genetic variant and restricting to putative functional variants.
Findings: Based on the genetic approach, use of cannabis was associated with increased risk of schizophrenia (OR of schizophrenia for users vs. non-users of cannabis: 1.37; 95%CI, 1.09 to 1.67; P-value = 0.007). The corresponding estimate from observational analysis was 1.43 (95% CI, 1.19 to 1.67; P-value for heterogeneity = 0.76). The genetic instrument did not show evidence of pleiotropy nor when accounting for tobacco exposure (OR of schizophrenia for users vs. non-users of cannabis, adjusted for ever vs. never smoker: 1.41; 95% CI, 1.09 to 1.83). Furthermore, the causal estimate remained robust to sensitivity analyses.
Interpretation: These findings add to the substantial evidence base that showed that association between use of cannabis and risk of schizophrenia is likely to be causal. Such robust evidence may inform public health message about the risks of cannabis use, especially regarding its potential mental health consequences.

FM255

Smartphone-app compared to standard blood pressure measurement – trial design and pilot data of the iPARR trial

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Introduction: Smartphones and smartwatches allow to measure and track vital signs traditionally assessed with dedicated equipment. As these devices and health-related apps become increasingly used by the general population, it is essential to assess the accuracy of new measuring methods. A recently developed algorithm calculates systolic blood pressure (SBP) from the pulse wave recorded with a smartphone camera. This app is the only smartphone based tool worldwide that works without calibration measurement or additional peripheral devices to estimate SBP, but works with a large database of pulse wave curves with varying data for gender, size, weight, age, tobacco use and systolic blood pressure. The iPARR trial compared the accuracy of this method with a traditional professional blood pressure monitor.
Methods: In this prospective, blind, single-center trial, 1000 adult subjects were recruited. Seven sequential blood pressure measurements were performed after five minutes of rest in a quiet room in a sitting position. The series started with a standard device (Omron HBP-1300 professional blood pressure monitor, appropriate cuff size) alternating with the tested smartphone app (Preventicus®, iPhone 4s). The photoplethysmographic signal was recorded by placing the finger on the smartphone camera for 3 minutes. Based on the pulse wave morphology and five additional parameters (age, size, weight, sex, tobacco use) the pulse wave files were analysed by Preventicus® without knowledge of the oscillometric values. Data is merged with external monitoring end of February 2017 and will be present for the SGAIM meeting.
Results: (Pilot data)In a retrospective analysis pilot data of 500 patients showed a correlation of r = 0.81 and mean error of <10 mm Hg between the SBP measured with a standard device and a smartphone. A first pilot validation cohort of 85 subjects confirms the proof of concept with a correlation of r = 0.76 and a mean error of 13.6 mm Hg

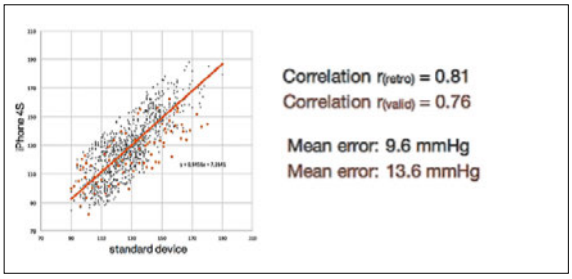

Figure 1: Repeated measurements of the same patients with a smartphone are reproducible.

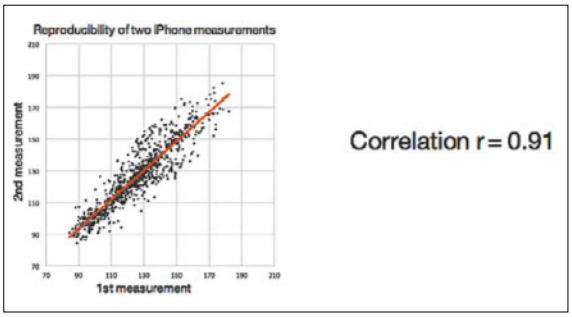

Figure 2

Conclusion: Pilot data of an ongoing prospective blinded validation trial (iPARR) shows that SBP estimation with a smartphone app is a promising innovative tool that will be tested and developed further to be implemented in a smartwatch or suitable wristband. A validation cohort following ESH criteria will follow.
The iPARR trial data will be available for the SGAIM Meeting 2017.

FM256

Education and coronary artery disease

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Introduction: Higher educational attainment is observationally associated with a lower risk of coronary artery disease, however it is not known whether this association is causal. We used Mendelian randomization, a method where genetic data are used to provide causal estimates to make inferences about the role of an exposure on the risk of a disease outcome.
Methods: We used 162 genetic variants previously associated with education to assess whether a genetic predisposition towards higher education is associated with risk of coronary artery disease in public datasets with 589,377 participants of predominantly Caucasian origin and living in developed countries. The primary outcome was combined fatal and nonfatal coronary artery disease. Genetically-derived estimates were compared with updated observational estimates of the association between education and incidence of coronary artery disease from several large observational studies. Sensitivity analyses included checking for potential pleiotropic effects of the genetic variants (i.e., when genetic variants associate directly with coronary artery disease via pathways that bypass education) and testing whether genetic liabilities for coronary artery disease is associated with educational outcomes.
Results: A one standard deviation increase in the genetic predisposition towards higher education (i.e. 3.6 years of additional schooling) lowered the risk of coronary artery disease by a third (odds ratio [OR] = 0.67, 95% confidence interval [CI], 0.59 to 0.77), consistent with observational estimates. Equivalent increases in education were also causally associated with reductions in smoking, BMI and improvements in blood lipid profiles. Genetic variants did not present pleiotropic effects based on various sensitivity approaches (Egger and weighted median Mendelian randomization analyses). The reverse investigation, of whether genetic liabilities for risk of CAD are associated with educational outcomes, showed an absence of association (standard deviation difference in education per 1-log unit increase in coronary artery disease = 0.002; 95% CI, –0.013 to 0.016).
Conclusions: Higher educational attainment is causally associated with a reduced risk of coronary artery disease. This may be partly explained by changes to smoking, BMI and blood lipids. These findings offer support for policy interventions that increase education in order to improve population health.

RECHERCHE, FORMATION, ORGANISATION ET SYSTÈME DE SANTÉ II / FORSCHUNG, FORTBILDUNG, ORGANISATION UND GESUNDHEITSSYSTEM II

FM257

What are the challenges for the management of residents in difficulty in a Swiss primary care division?

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Introduction: The prevalence of residents in difficulty is 7–15% and is a major concern in medical education. Remediation plans have shown a good efficacy, but residents in difficulty are often detected too late in their academic cursus. Difficulties concern mainly cognitive and clinical reasoning (85%), professionalism (51%), communication (49%) and collaborative problems (20%) and may occur simultaneously. Nowadays most training hospitals in Switzerland do not have specific processes to identify and manage residents in difficulty. The aim of the study was to explore the challenges perceived by physicians at different hierarchical levels (residents (R), senior residents (SR), attendings (A), physician in chief (PC)) regarding the process of identifying, diagnosing and supporting residents in difficulty in a structured and programmatic way.
Methods: We conducted an exploratory qualitative study. Participants were volunteers from the Primary Care Division of the Geneva University Hospitals. Between December 2015 and July 2016, we conducted three focus groups (with SR, A, R) and one interview with the division's PC. Focus groups and the interview were transcribed, coded, and analyzed qualitatively using a content thematic approach and Fishbein's conceptual Framework.
Results: We identified similar and divergent factors regarding the implementation of such a programmatic approach among physicians of different hierarchical levels. Major findings show: – Supervisors (SR, A, PC) usually identified correctly residents in difficulty but they did not set up systematic remediation strategies. – Supervisors (SR, A) felt concerned about residents in difficulty and the possible adverse effect on patient care, but were afraid to harm their career by writing up a poor institutional assessment. – Residents feared that sharing their own difficulties with their supervisors would impact negatively on their career. – Environmental constraints (lack of money, lack of time and resources…) were reported by the four levels.
Conclusion: We identified a lack of a programmatic approach for the management of residents in difficulty. Thus, this process depends on residents' attitudes regarding their own performance, the type of difficulties identified, and both on hierarchical involvement and institutional support. Similar and divergent factors regarding the implementation of such a programmatic approach are present at the different hierarchical levels and need to be addressed specifically.

FM258

Does patients' satisfaction change under team care in a chronic care management program instead of usual care by the family physician alone?

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Introduction: Interprofessional chronic care management (CCM) programs in teams of doctors and coaches (medical practice coordinators, specially trained medical assistants) look promising to face the lack of primary care physicians. They offer an evidence-based high quality of care. But there are still doubts about patients' acceptance. Our aim is to find, whether these evidence-based programs have an influence on patient's perception of care.
Methods: We evaluated 12 Swiss primary health care group practices offering interprofessional CCM programs by teams of doctors and coaches (medical practice coordinators, specially trained medical assistants). These programs are offered to patients with progressed arterial hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease and combinations of these conditions. Between May 2013 and December 2015, 564 consecutive patients entered the programs. 559 (99%) of them completed a patient's satisfaction questionnaire about their family physician with 9 items derived from the European Practice Assessment (EPA). Items had to be rated on a 5-point Likert scale between 1 (bad) and 5 (excellent). After a one-year program cycle, patients were asked to answer the same questionnaire regarding their team (coach **and** doctor). We collected all of these evaluation data available at January 4th, 2017. The "before-and-after" ratings were compared using paired sample t tests, applying Bonferroni correction for single item testing.

	Family doctor	CCM team			
Items	Mean (sd)	Mean (sd)	Paired-t	Degrees of freedom	p-value
Mean on all items	4.63 (0.42)	4.72 (0.41)	4.38	395	<0.001
Involving you in decisions about medical care	4.68 (0.55)	4.74 (0.51)	2.06	392	n.s.*
Listening to you	4.77 (0.49)	4.82 (0.49)	1.60	395	n.s.*
Helping to perform your normal daily activities	4.65 (0.58)	4.68 (0.58)	0.86	364	n.s.*
Offering you services for preventing	4.63 (0.62)	4.73 (0.61)	2.76	362	n.s.*
Giving informations about symptoms and/or illness	4.67 (0.59)	4.81 (0.47)	4.73	384	<0.001*
Help in dealing with emotional problems	4.53 (0.69)	4.69 (0.60)	4.20	336	<0.001*
Waiting time in the waiting room	4.30 (0.74)	4.45 (0.72)	3.31	394	0.001*
Quick services for urgent health problems	4.71 (0.49)	4.76 (0.52)	1.43	257	n.s.*
I can recommend practice to my friends	4.81 (0.48)	4.85 (0.41)	1.49	376	n.s.*

Table 1: Rating of patients' satisfaction with family doctors and CCM teams (coach and doctor) on a 5-point Likert scale (1=bad, 5= excellent).
* level of significance = 0.005

Results: 396 of the 559 patients (71%) answered the second questionnaire. There was a statistically significant difference in overall rating of family physicians alone (M = 4.63; SD = 0.42) and teams of doctors and coaches (M = 4.72; SD = 0.41); t(395) = 4.38, p <0.001. Results of single item testing are displayed in table 1.
Conclusion: In our setting, CCM programs run by teams of doctors and coaches further improved an already high satisfaction of patients with chronic conditions. Patients seem particularly better informed about symptoms and disease and feel better supported in dealing with emotional problems by this team approach.

FM259

The Swiss Resident Watch (SWATCH) study: the gold standard for working hours determination: a comparison between self-declaration and time clock

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Background: Since the subjection of residents in Swiss hospitals to the federal labour law, the worktime limit of 50 hours/week applies, but several cases became public in which the declaration of extra hours was unprecise. In 2015, the first Swiss resident time-motion study performed at the CHUV discovered that as many as 75% of extra hours were not reported with a self-declaration system. Therefore, we wanted to assess whether a time clock system prevents residents from not reporting extra hours.
Method: We compared working hours from residents working at the Cantonal Hospital Baden (KSB) and the Lausanne University Hospital (CHUV). To assess actual working time, data was extracted from the Medical Day study at each center in which trained observers followed residents during normal day shifts. To ensure comparability the same protocol, tablet software and instruction of observers was used. Actual worktime was defined as duration from entering to leaving the office. At KSB, residents registered their working hours at dedicated spots with individual badges. At CHUV, working hours were self-reported with monthly cards. Extra hours were defined as more than 660 min per day at KSB and 600 min at CHUV (including 60 respectively 30 minutes lunchbreak). Statistical testing was performed with two-sided, untailed t-test.
Results: Demographic baseline characteristics are shown in table 1.

Table 1: Baseline characteristics of residents.

	KSB		CHUV		
	mean	SD	mean	SD	p value
Age (years)	29.6	3.19	28.8	1.7	0.15
Months postgraduate	20.9	17.7	31.2	11.9	0.002
Months experience in internal medicine	16.1	11.3	27.0	10.4	<0.001
Swiss diploma	66.7%		60.70%		
Female gender	57%		63%		
SD = standard deviation					

486.4 hours of observation (43 shifts) were collected in KSB and 568.2 hours (49 shifts) in CHUV. At KSB, the length of a shift determined by time clock was very similar to observation (684.0 ± 65.6 min vs 678.6 ± 65.6 min, *p*-value 0.7). At CHUV, the length of shift determined by self-reported timecards was lower than observation (695.7 ± 80.1 min vs 635.3 ± 53.7 min, *p*-value <0.001). At KSB the difference is not significant, while at CHUV the system misses on average 60.4 minutes of daily work. Mean extra hours per shift was lower at KSB than at CHUV (18.6 ± 65.6 min vs 95.7 ± 80.1 min, *p*-value <0.001). Summarized, there were no unreported hours in KSB (–3.83h), but 49.3 hours unregistered extra hours at CHUV during observation.

	KSB		CHUV		
	mean	SD	mean	SD	p-value
number of day shift observed (n)	43		49		
mean shift duration (observed) (min)	678.6	65.6	695.7	80.1	0.26
mean shift duration (reported)* (min)	684.0	65.6	635.3	53.7	< 0.001
mean extra time (min) (observed minus official shift length)#	18.6	65.6	95.7	80.1	< 0.001
difference (observed minus reported) (min)	5.34	5.68	60.4	79.4	< 0.001

SD = standard deviation, all time displayed in minutes

* KSB: time clock, CHUV: self-declaration. # Shift length in KSB: 660 min, including 1 hour lunch break. Shift length in CHUV: 600 min, including 30 minutes lunch break.

Table 2: Shift durations depending on method of measurement.

Conclusion: 1) Using time clocks to report working hour is more precise than self-reporting. 2) Self declaration is associated with underreporting. 3) Our study may have implications for working hour reporting policies in hospitals. 4) The cold numbers must be balanced with "overall considerations" of research and education "invested" in trainees by mentors and institutions.

FM260

Effects of two job-sharing physicians versus a full timeattending physician on quality of care and coworkers' satisfactionin a Swiss hospital

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Introduction: An increasing number of physicians choose to work part-time and consider job-sharing as an alternative to the traditional hospital practice model. Whether two part-time, job-sharing physicians provide the same output as a single one working full-time has seldom been assessed. We therefore aimed to compare the effects of two job-sharing physicians versus a full time physician on quality of inpatients care and coworkers' satisfaction.
Methods: Intervention study conducted between 2014 and 2016 in an internal medicine ward of a Swiss teaching hospital. Patients (n = 549) were evaluated regarding quality of care; coworkers (30 house staff and 12 residents) were queried regarding satisfaction at work. A 6-month job-sharing period (1.6.2015–30.11.2015) with two attending physicians (Monday-Wednesday and Wednesday-Friday) was compared to a 6-month period (1.12.2014–31.5.2015) with one attending physician working full-time. Patients' outcomes were: 1) the number of biological or X-ray exams prescribed; 2) the time to send out the discharge letter, and 3) length of stay (LOS). Coworkers' outcome was self-rated satisfaction at work, assessed using validated questionnaires (COPSOQ and SAPHORA).
Results: Among the 549 patients, average LOS was shorter during the job-sharing period but a similar trend was also found for the entire hospital. Biological prescriptions were lower during the job-sharing period, X-ray prescriptions did not differ but the time needed to send out the discharge letter increased

	Full time	Job-sharing	p-value
Length of stay (days)			
Hospital	17.9 ± 19.5	13.1 ± 12.0	<0.001
Ward studied	13.2 ± 11.4	9.2 ± 7.3	<0.001
Number of prescriptions (points)			
Biological	134 ± 250	118 ± 258	0.038
X-rays	9 ± 13	9 ± 11	0.486
Time to send out the discharge letters (days)	7.9 ± 5.7	11.7 ± 9.7	<0.001

Results are expressed as average ± standard error. Comparisons performed using Kruskal-Wallis test.

Table 1: Patients' outcome after each study period.
Coworkers' satisfaction scores were similar before and after the job-sharing period.

	Full time	Job-sharing	p-value
Sample size	31	20	
COPSOQ			
Degree of freedom	57.3 ± 15.7	55.6 ± 16.6	0.626
Fulfillment at work	66.1 ± 16.8	64.4 ± 19.1	0.805
Emotional demand	50.8 ± 17.1	48.1 ± 18.3	0.759
General self rated health	39.1 ± 8.4	41.9 ± 8.4	0.242
Role of conflict	36.3 ± 30.5	42.5 ± 28.2	0.300
Exhausted	37.1 ± 23.2	38.1 ± 26.1	0.822
Stress	34.7 ± 19.0	36.9 ± 21.3	0.717
SAPHORA			
Work organization	67.4 ± 14.7	69.0 ± 17.6	0.846
Professional relationships	87.9 ± 11.7	81.8 ± 12.7	0.084
General satisfaction	79.4 ± 14.1	76.6 ± 15.7	0.575

Results are expressed as average ± standard error. Comparisons performed using Kruskal-Wallis test. Scores on a scale from 0 to 100, 100 being the best satisfaction possible.

Table 2: Coworkers' satisfaction at work.

Conclusions: Compared to a 6-month period with one full-time attending physician, a 6-months job-sharing period with two attending physicians had no effect on the number of prescriptions and LOS of the patients, and was associated with a similar coworkers' self-rated satisfaction. Conversely, it increased the delay of discharge letters.

MÉDECINE SPECIALISÉE I / FACHMEDIZIN I

FM261

Sudden cardiac death in the young: coronary smooth muscle cells of plaque and media exhibit a contractile phenotype

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Introduction: Coronary artery disease is the leading cause of sudden cardiac death (SCD) in non-athletes. The histopathologic features of atherosclerotic plaques in young SCD victims are strikingly different from those of elderly patients: plaques of young adults are characterized by extensive smooth muscle cell (SMC) hyperplasia, scanty lipid core and small inflammation (hence the misnomer "non-atheromatous atherosclerosis"). These lesions are characterized by a lower rate of acute thrombosis compared to fibroatheromatous plaques. Thus, SCD triggered by "non-atheromatous atherosclerosis" is likely not ascribable to fibrous cap rupture. Other causes, and particularly coronary artery spasm, are rather invoked. In this study we aimed at characterizing the SMC phenotype in the intima and media of coronary atherosclerotic plaques from SCD victims.

Methods: Among 652 young (<40 years old) victims in the SCD Registry of Northeast Italy, 125 (19%) were due to coronary atherosclerosis. 33 coronary artery specimens taken at autopsy were included in this study: (a) 6 "control" non-atherosclerotic coronary arteries from young patients died of cardiovascular-unrelated causes; (b) 18 atherosclerotic coronary arteries from young SCD victims (7 fibroatheromathous and 11 "non-atheromatous atherosclerosis" lesions); (c) 9 atherosclerotic coronary arteries from old cardiovascular patients. The expression of a-smooth muscle actin (a-SMA), smooth muscle myosin heavy chains (SMMHCs), heavy-caldesmon (h-CaD) and S100A4 were detected by means of immunohistochemistry and quantified morphometrically.
Results: The expression of a-SMA, SMMHCs and h-CaD was higher in the intima of non-atherosclerotic arteries from young patients and in atherosclerotic plaques from young SCD victims compared to atherosclerotic plaques from old patients. The expression of S100A4 was significantly lower in the intima of non-atherosclerotic arteries from young patients compared to atherosclerotic plaques from young SCD victims and old patients. Unlike old patients, the coronary media underlying atherosclerotic plaques from young SCD victims exhibited a strong positivity for a-SMA, SMMHCs and h-CaD.
Conclusions: Plaque and media SMCs from young SCD victims exhibit a contractile phenotype characterized by increased expression of a-SMA, SMMHCs and h-CaD. In the setting of critical stenosis, intima and media SMC contractility might contribute to coronary spasm and myocardial ischemia, precipitating SCD.

FM262

Low-dose CT for the diagnosis of pneumonia in elderly patients

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Background: Pneumonia ranks high among causes of morbimortality in the elderly. Its diagnosis is challenging because of the poor sensitivity and specificity of signs and symptoms and pittfalls in interpretation of chest x-rays (CXR). A recent study showed the value of CT in the diagnosis of pneumonia in the emergency room. Our objective was to assess whether low-dose CT modified the management of pneumonia in elderly patients and enabled discontinuation of empirical antimicrobial therapy.
Material and methods: Monocentric prospective interventional study conducted from May 2015 to April 2016, including patients more than 65 years old, hospitalized in internal medicine for a clinical diagnosis of pneumonia and who were prescribed antibiotic therapy. Patients treated for pneumonia during the last 6 months, having already undergone a CT or having received antimicrobial therapy for more than 48 hours were excluded. All patients had CXR and native low-dose CT within 72h after the hospitalization. The probability of pneumonia was assessed by the clinician on a 5 levels Likert scale before and after CT. The main outcome was the number of diagnoses that were changed after CT (upgraded or downgraded diagnosis).
Results: Among 898 screened patients, 203 were included: 98 women (48.3%), median age 84 years (65-103); 154 (75.9%) had community acquired pneumonia, 72 (35.5%) had been hospitalized during the previous 6 months. The median CURB-65 score was 2. There was an infiltrate on the CXR according to the clinician with a certain/high probability in 85 patients (41.9%). The 30-days mortality was 5.4%. Among 200 patients with available data, the probability of pneumonia before and after the CT is depicted in the table. The probability of the diagnosis was altered after CT in 134 (67%) patients: 67 were downgraded and 67 upgraded. Antibiotics were discontinued in 18 patients (9%) after CT.
Conclusions: To our knowledge, this is the first study assessing the use of thoracic CT in a geriatric population hospitalized for pneumonia. CT altered the diagnosis of pneumonia in 26% of patients and led to discontinuation of antimicrobial therapy in 9%. These results should be confirmed in a randomized clinical trial comparing usual management versus systematic CT.

Probability of the diagnosis before and after CT							
	Probability after CT						
Probability before CT	**Excluded**	**Low**	**Intermediary**	**High**	**Certain**		**Change of probability**
Excluded	0	0	0	1	0	1	1 (100%)
Low	6	4	3	1	1	15	11 (73%)
Intermediary	11	23	13	14	9	70	57 (81%)
High	3	8	11	32	38	92	60 (65%)
Certain	1	1	2	1	17	22	5 (23%)
	21	36	29	49	65	200	134 (67%)

FM263

Urinary incontinence in systemic sclerosis: results from an international multicenter study

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Introduction: Systemic sclerosis (SSc) can involve the urinary tract. However, the prevalence and disease specific risk factors for urinary incontinence (UI) are unknown. Our goal was to assess the prevalence of UI, explore the association with the main clinical and serological subsets and evaluate the impact of UI on quality of life in SSc.
Methods: 334 consecutive patients with SSc were included in five European tertiary centers. UI and quality of life were assessed through self-administered questionnaires. Logistic regressions models were performed to test the association between clinical forms, serologic status and UI. Multivariable logistic regressions were performed to adjust for confounders (age, sex, disability, diabetes, body mass index, caffeine consumption, dyspnea and pulmonary hypertension) and test further independent predefined SSc risk factors for UI.
Results: The prevalence of UI was 63% (95%CI: 60–68%). Limited cutaneous SSc (lcSSc) and anti-centromere antibodies (ACA) were both significantly associated with UI (adjusted OR 2.0; 95%CI: 1.1–3.7). Patients positive for ACA or suffering from lcSSc had frequent and heavy urinary leaks compared to other SSc patients. In multivariable model, ACA (OR 2.8; 95%CI: 1.4-5.6), lcSSc (OR 2.2; 95%CI: 1.1–4.4), female sex (OR 11.3; 95%CI: 3.6–35.1), worsening of dyspnea (OR 8.8; 95%CI: 1.6–49.3), lower HAQ-DI (OR 3.3; 95%CI: 1.6–6.6), finger-skin thickening (OR 2.0; 95%CI: 1.1–3.8), and active finger ulceration (OR 0.3; 95%CI: 0.1–0.9), were independently associated with UI. Patients suffering from UI had decreased quality of life. Failure to include the calculated number of subject and the use of a self-administered questionnaire rather than an objective measure to assess UI are the main limitations of this study.
Conclusions: Self-reported UI is frequent in SSc and disproportionally affects lcSSc and patients positive for ACA. SSc patients with UI have low quality of life.

FM264

Diagnostic accuracy of undernutrition in hospital discharge data: improvements needed

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Background and aims: Prevalence of undernutrition among hospitalized patients is high, ranging between 20 to 60%. Undernutrition is associated with increased morbidity and mortality, longer hospital stay, decreased quality of life, and increasing health care costs. Hospital administrative databases are widely used for disease monitoring and health policies planning. Hence, adequate reporting of undernourished patients is necessary and its diagnostic accuracy should be high. To our knowledge, the diagnostic accuracy of undernutrition reporting in administrative data is poorly known. We aimed to examine the diagnostic accuracy of undernutrition reporting in a Swiss university hospital.

Methods: Retrospective cross-sectional study using administrative data for years 2013-14 from the Internal medicine unit of the Lausanne university hospital (n = 2509). Two reference diagnoses were defined: 1) 'confirmed' undernutrition by a nutrition risk screening-2002 (NRS-2002) score ≥3 *plus* a body mass index (BMI) <18.5 kg/m^2, and 2) 'probable' undernutrition by a NRS-2002 ≥3 *plus* any prescription of nutritional management/support *plus* a BMI ≥18.5 and <20 kg/m^2 if age <70 years (<22 kg/m^2 if age≥70 years). Missing BMI values were imputed.
Results: Of the 2509 eligible patients, 262 (10.4%) were classified as 'confirmed' and 631 (25.2%) as 'probable' undernutrition. Sensitivity, specificity, negative and positive predictive values (and corresponding 95% confidence intervals) for undernutrition reporting using 'confirmed' undernutrition were 43.0 (37.0–49.3); 87.2 (85.8–88.6); 92.9 (91.7–94.0) and 28.2 (23.8–32.8), respectively. The corresponding values using both 'confirmed' and 'probable' undernutrition were 30.0 (27.2-32.9); 93.4 (92.0–94.6); 66.7 (64.7–68.7) and 75.1 (70.6–79.3), respectively. Similar findings were obtained after stratifying for gender or for age group, or restricting the analysis to patients with non-missing BMI data.
Conclusion: Undernutrition reporting in hospital discharge data has good specificity but its sensitivity and positive predictive values are low.

MÉDECINE SPECIALISÉE II / FACHMEDIZIN II

FM265

Evaluating thyroid disorders: should we measure both TSH and fT4 at the same time?

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Introduction: Because symptoms of thyroid dysfunction are not specific, laboratory confirmation by measuring thyroid-stimulating hormone (TSH) and free thyroxine (fT4) is essential. As small changes in fT4 result in large changes in TSH, TSH alone is a sensitive marker of thyroid dysfunction. Therefore, most guidelines for thyroid function evaluation recommend testing TSH first, with fT4 assessment only if TSH is outside the reference range (two-step) or if an abnormality of TSH secretion is suspected. However, the acceptance of these recommendations varies, even among experts and national thyroid associations, with several recommending that both TSH and fT4 should be measured simultaneously (one-step), despite the up to two-fold higher costs. We aimed to compare the diagnostic concordance of the two-step vs. the one-step approach and to assess whether fT4 testing could be reduced.
Methods: In a cross-sectional analysis of participants in the population-based Busselton Health Study in Australia, we calculated diagnostic concordance between the two-step and the one-step approach. Results were deemed concordant when normal TSH matched normal fT4, increased TSH matched decreased fT4, and decreased TSH matched increased fT4. All other combinations, as well as subclinical thyroid dysfunction, were not considered concordant. Reference ranges were defined as between 0.45 and 4.49 mU/l for TSH, and between 11.2 and 20.8 pmol/l for fT4.
Results: Of the 4471 participants (age 17–97 years, 55% women), 4156 (93%) were euthyroid, 35 (0.7%) had overt hypothyroidism, 86 (1.9%) had subclinical hypothyroidism, 170 (3.8%) had subclinical hyperthyroidism, and 23 (0.5%) had overt hyperthyroidism. Using the two-step approach, TSH alone was sufficient to correctly diagnose euthyroidism in 89.2% of individuals. Of the remaining 10.8%, 7.0% had subclinical (5.8%) or overt thyroid dysfunction (1.2%) and 3.8% had a normal TSH but a fT4 outside the reference range. In most of these cases (85%), fT4 was within 2 pmol/l of the fT4 reference range limits, consistent with healthy outliers.
Conclusions: A two-step approach (fT4 assessment only in the case of an abnormal TSH) may prevent unnecessary fT4 measurement in up to 93% individuals. Simultaneous measurement of thyroid function with TSH and fT4 does not appear to be medically justified.

FM266

Neutrophil extracellular traps in community-acquired pneumonia: effects of adjunct glucocorticoid treatment and association with adverse outcome

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Background: It has recently been discovered that Neutrophil Extracellular Traps (NETs) are formed as an antimicrobial mechanism upon activation of neutrophil granulocytes, leading to an effective entrapment and killing of a wide variety of bacteria and other microbes. Neutrophil activation plays a major role in the pathophysiological cascades of community-acquired pneumonia (CAP) which is the leading cause of infectious death worldwide. However, to date there are no clinical data on NETs in pneumonia.
Methods: This is a secondary analysis of a randomised, placebo-controlled, double-blind, multicenter trial. Patients aged >18 years with CAP were enrolled from seven tertiary care hospitals in Switzerland within 24 h of presentation. Patients were randomised (1:1 ratio) to receive either 50 mg of prednisone or placebo daily for 7 days. The primary endpoint was time-to clinical stability (TTCS); secondary endpoints were length of stay, mortality, duration of antibiotic treatment, CAP complications. NETs were assessed by measurement of cell-free nucleosomes in serum and plasma by sandwich ELISA. Multivariate regression models adjusted for severity (pneumonia severity index, age, gender, metabolic factors, cardiovascular diseases and other comorbidities) were performed in order to analyze associations with TTCS, length of hospital-stay, mortality, duration of antibiotic treatment and CAP complications.
Results: A total of 310 randomised patients were included in the analysis. Overall, levels of NETs were significantly increased at time of emergency admission and declined over 7 days (2.67 vs. 1.18 absorbance units (AU), $p = 0.01$). Baseline levels of NETs were associated with disease severity as well as reduced hazards of clinical stability [HR 0.97 (95% CI 0.94, 0.99), $p = 0.041$] and consecutive hospital discharge [HR of 0.90 (95% CI 0.82, 0.99), $p = 0.012$]. NETs were associated with a 3.81-fold odds ratio of 30-day mortality [(95% CI 1.39, 10.4), $p = 0.009$] and prolonged duration of intravenous antibiotic treatment by 0.5 days (95% CI 0.1, 0.94, $p = 0.015$). NETs were significantly increased after 5 days in the prednisone group (1.19 vs. 0.79 AU, $p < 0.0005$).
Conclusion: NETs are considerably increased in community-acquired pneumonia and represent a novel biomarker for outcome prediction, i.e. for staging of disease severity and identification of patients at risk. Effects of prednisone may partly be explained by modulation of NET formation.

FM267

Is overdiagnosis of prostate cancer leveling off? Recent changes in incidence and surgery rates in Switzerland

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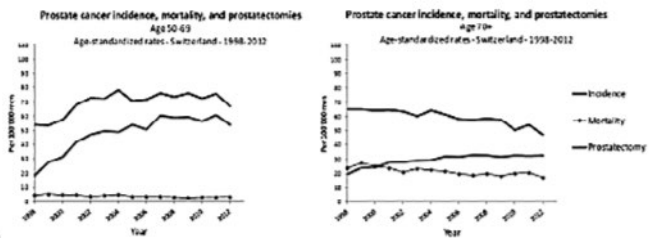
Background: Screening for prostate cancer is frequently performed in many western countries, including Switzerland. Various organizations have recently recommended against routine screening, notably due to the high risk of overdiagnosis or overtreatment. Our aim was to examine whether recent changes in secular trends in the incidence and mortality of prostate cancer, as well as prostatectomy rates have been observed in Switzerland.
Methods: We assessed all cases of invasive prostate cancer, deaths from prostate cancer, and prostatectomy from 1998 to 2012 using data from the Swiss cancer registries, the Swiss Federal Statistical Office, and the Swiss Hospital Medical Statistics. We estimated age-standardized incidence by tumor stage (early, advanced), prostate cancer-specific mortality, and prostatectomy, and stratified these rates by age group (<50 years, 50–69 years, ≥70 years). We calculated absolute and relative annual changes in rates.
Results: Figure 1 illustrates the results. The age-standardized incidence of prostate cancer increased greatly in men aged 50–69 years (absolute mean annual change +4.6/100'000 men, 95%CI: +2.9 to +6.2) between 1998 and 2002, and stabilized afterwards. In men aged ≥70 years, the incidence decreased slightly between 1998 and 2002, and more substantially since 2003. The incidence of early tumor stages increased between 1998 and 2002 in men aged 50–69 years only, then stabilized, while the incidence of advanced stages remained stable across all age strata. Since 1998, the annual age-standardized mortality rate of prostate cancer slightly declined in men aged 50–69 years (absolute mean annual change –0.1/100'000, 95%CI: –0.2 to –0.1) and in men aged ≥70 years (absolute mean annual change –0.5/100'000, 95% CI: –0.7 to –0.3). The rate of prostatectomy increased until 2008, more so among men aged 50 to 69 years old than among men aged ≥70 years; it remained stable after 2008 in both age strata.
Conclusions: The increase in the incidence of prostate cancer and in prostatectomy observed until recently in Switzerland, potentially revealing a growing frequency of overdiagnosis and overtreatment, has leveled off. This may reflect recent changes in screening and clinical workup practices.

Figure 1. Age-standardized incidence, mortality, and prostatectomy rates per 100'000 men by age group for prostate cancer in Switzerland, 1998-2012



FM268

External validation of cardiac chest pain rules including high sensitive T-Troponin assays

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Background: Acute chest pain is one of the leading causes for emergency room visits. In more than 70 percent no cardiac etiology is found. Recently derived prediction rules, the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) and the Vancouver Chest pain rule 2014 (VCP 2014) included the high sensitive Troponin T-assay (hs-Trop-T) to identify low risk patients and demonstrated good sensitivity. However, for many rules patients with a moderate to high pretest probability were included and few external validation studies exist. The aim of the study was to externally validate currently available chest pain rules in patients presenting with non-cardiac (NCCP) and cardiac chest pain (CP) to the emergency department of the Kantonsspital Winterthur.
Methods: Retrospective chart review of patient seeking care for acute chest pain of non-cardiac and cardiac origin at the emergency department between December 1, 2009 and December 31, 2011. Patients were identified using ICD-10 codes for NCCP and CP. Data was extracted in a predefined form. The quality of the data extraction was very good (<10% extraction errors). Missing values were multiply imputed. Using the cut-off of <2% Risk to miss a CP the sensitivity and specificity for the T-MACS rule and the VCP 2014 rule were calculated.
Results: In total 1467 patients were included of whom 245 (16.7%) a CP was diagnosed (104 STEMI, 125 NSTEMI, 4 ACS). The VCP 2014 correctly identified 245 (100%) CP and 578 (47%) NCCP cases, misdiagnosed 0 CP and 644 (53%) NCCP. The MACS-T rule was applied to a subset of 766 patients in whom hs-Trop-T were available. The MACS-T rule correctly identified (Risk <2% for ACS) 112 (77%) CP and 344 (55%) NCCP cases, misdiagnosed 33 CP (23%) and 277 (45%) NCCP. The sensitivity for the MACS-T rule was 71%, for the Vancouver Chest Pain Rule 100%. The specificity was 62% and 56%, respectively.
Conclusion: The external validation in a low risk population for cardiac chest pain demonstrated a high sensitivity for the VCP 2014 rule whereas the sensitivity for the MACS-T rule was poor. Both rules showed poor specificity.

MEILLEURES COMMUNICATIONS LIBRES / BESTE FREIE MITTEILUNGEN

FM269

Is subclinical thyroid dysfunction associated with dementia? Findings from a prospective cohort

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Introduction: Thyroid-stimulating hormone (TSH) measurement is recommended in etiologic dementia work-up. However, data on the association between subclinical thyroid dysfunction (SCTD) and dementia are limited, because well-performed prospective cohorts with long follow-up are lacking. We prospectively assessed the association of SCTD with incident dementia and decline in Modified Mini-Mental state (3MS) in a large cohort of older adults.
Methods: We studied participants from the Health, Aging, Body and Composition Study, with thyroid function measurement but no

dementia at baseline, and 3MS at baseline and follow-up. Dementia was adjudicated based on: 1) race-stratified 3MS change ≥1.5SD; 2) dementia diagnosis on hospital records and 3MS ≤90; 3) dementia drug. Subclinical hyperthyroidism (SHyper, TSH <0.45 mIU/L, free thyroxine [FT4] normal) and subclinical hypothyroidism (SHypo, TSH 4.50–19.99 mIU/L, FT4 normal) were compared with euthyroidism (TSH 0.45–4.49mIU/L). Dementia risk was assessed by competing-risk Cox regression and 3MS change over time by mixed-effects models, adusting for age, race, education and baseline 3MS in the main analysis, and then further for cardiovascular risk factors.
Results: Among 2558 participants, mean age was 75.1 (SD 2.8); 52% were women, 85% were euthyroid, 3% had SHyper and 12% SHypo. Over 9 years, 22% participants developed dementia. Among men, incidence of dementia was 38% for SHyper, 22% for euthyroidism and 17% for SHypo. Among women, it was 20% for SHyper, 24% for euthyroidism and 21% for SHypo. Compared to euthyroids, risk of dementia was increased in men with SHyper (adjusted HR 2.02 [95%CI 1.03;3.96]), but not in women (adjusted HR 0.73 [95%CI 0.40;1.35], $P = 0.02$ for interaction by gender). On average, men with SHyper had larger (–4.59 [95%CI –7.96; –1.22]) decline in 3MS than euthyroid men, while it did not differ in women with SHyper or SHypo participants. All results were similar after adjusting for cardiovascular risk factors. SHypo was not associated with dementia (adjusted HR 0.91 [95%CI 0.70;1.19]).
Conclusion: Among older adults, men with SHyper had increased risk of dementia and larger decrease in cognition, whereas women with SHyper and SHypo participants did not. Checking TSH among patients with dementia seems appropriate. Clinical trials are needed to assess if treating SHyper in older men reduces incidence and progression of cognitive impairment.

FM270

Derivation and validation of a clinical prediction model for the post-thrombotic syndrome

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Introduction: Not all patients carry the same risk of developing a post-thrombotic syndrome (PTS) after a first lower limb deep vein thrombosis (DVT) event. We sought to derive a clinical prediction model for prognosis to estimate the risk of PTS development within 24 months of an index DVT.
Methods: We used data from 276 patients with a first acute symptomatic DVT included in a prospective cohort as our derivation sample. We derived our prediction rule using logistic regression with backward selection, with the occurrence of the PTS within 24 months of an index DVT based on the Villalta scale as the outcome, and 12 candidate variables as predictors. We used bootstrapping methods for internal validation.
Results: Analyzed patients had a median age of 74 years, 46% were women, 32% had a concomitant PE, and 18% presented an isolated distal DVT as the initial DVT event. The majority (60%) of DVT events was unprovoked and 17% of DVTs were cancer-related. Overall, 161 patients (58.3%) developed a PTS within 24 months of an index DVT based on the Villalta scale. Our prediction rule is based on 6 clinical risk factors (age ≥75 years, presence of peripheral arterial disease, prior varicose vein surgery, multilevel thrombosis, concomitant antiplatelet or NSAID therapy, and the number of leg symptoms and signs).
Overall, 16.3%, 30.8%, and 52.9% of patients were classified as low (score 0–3), moderate (score 4–5), and high-risk (score ≥6) for developing a PTS, respectively. Within 24 months of an index DVT, 24.4% of the patients in the low-risk category developed a PTS, 38.8% in the moderate-risk category, and 80.1% in the high-risk category. Table 2 shows the predictive accuracy for risk category ≥6 points (high vs medium/low risk).
The prediction model had a good discriminatory power (AUC 0.79; 95% confidence interval 0.74–0.84) and a good fit (P = 0.12). Internal validation showed similar results.
Conclusions: This easy to use clinical prediction rule accurately identifies patients with acute symptomatic DVT who are at high risk of developing a PTS within 24 months. This particular group of patients may benefit from specific educational and therapeutical options to prevent PTS. Further validation of the score is important before its implementation into practice.

Table 1: Risk factors of PTS within 24 months.

	Odds Ratio (95%-CI)	β-Coefficient** (95%-CI)	Points assigned
Age ≥75 years	1.61 (0.91–2.85)	0.48 (-0.10–1.05)	+1
Concomitant antiplatelet/NSAID therapy	1.98 (1.05–3.70)	0.68 (0.05–1.31)	+1
Multilevel thrombosis	1.66 (0.93–2.98)	0.51 (–0.07–1.09)	+1
Peripheral arterial disease	2.50 (0.73–8.60)	0.91 (–0.32–2.15)	+1
Prior varicose vein surgery	2.81 (1.04–7.65)	1.04 (0.04–2.03)	+1
Number of signs and symptoms*	1.65 (1.40–1.95)	0.50 (0.34–0.67)	+1 each

Abbreviations: CI : confidence interval ; NSAID : non steroidal anti-inflammatory drug, *including pain, cramps, heaviness, pruritus, paresthesia, edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression. **from multivariable model

Table 2: Predictive accuracy for risk category ≥6 points.

PTS	Sensitivity % (95%-CI)	Specificity % (95%-CI)	PPV % (95%-CI)	NPV % (95%-CI)
within 3 months	76.9 (68.1–83.8)	62.5 (55.0–69.5)	56.8 (48.7–64.6)	80.8 (73.2–86.6)
within 12 months	72.9 (65.0–79.5)	67.6 (59.4–74.9)	69.9 (62.0–76.7)	70.8 (62.4–77.9)
within 24 months	72.7 (65.3–79.0)	74.8 (66.1–81.8)	80.1 (72.9–85.8)	66.2 (57.7–73.7)

Abbreviation: PTS: post-thrombotic syndrome; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval

FM271

Direct comparison of four very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I

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Objective: Four strategies for very early rule-out of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin I (hs-cTnI) have been identified. It remains unclear which strategy is most attractive for clinical application.
Methods: We prospectively enrolled unselected patients presenting to the emergency department (ED) with symptoms suggestive of AMI. The final diagnosis was adjudicated by two independent cardiologists. Hs-cTnI levels were measured at presentation and after 1h in a blinded fashion. We directly compared all four hs-cTnI-based rule-out strategies: limit of detection (LOD, hs-cTnI <2 ng/L), single cut-off (hs-cTnI <5 ng/L), 1h-algorithm (hs-cTnI <5 ng/L and 1h-change

<2 ng/L), and the 0h/1h algorithm recommended in the European Society of Cardiology guideline combining LOD and 1h-algorithm.
Results: Among 2828 enrolled patients, AMI was the final diagnosis in 451 (16%) patients. The LOD approach ruled-out 453 patients (16%) with a sensitivity of 100% (95% CI, 99.2–100%), the single cut-off 1516 patients (54%) with a sensitivity of 97.1% (95% CI, 95.1–98.3%), the 1h-algorithm 1459 patients (52%) with a sensitivity of 98.4% (95% CI, 96.8–99.2%), and the 0h/1h-algorithm 1463 patients (52%) with a sensitivity of 98.4% (95% CI, 96.8–99.2%). Predefined subgroup analysis in early presenters (≤2h) revealed significantly lower sensitivity (94.2%, interaction p = 0.03) of the single cut-off, but not the other strategies. Two-year survival was 100% with LOD and 98.1% with the other strategies (p <0.01).
Conclusions: All four rule-out strategies balance effectiveness and safety equally well. The single cut-off should not be applied in early presenters, while the three other strategies seem to perform well also in this challenging subgroup.

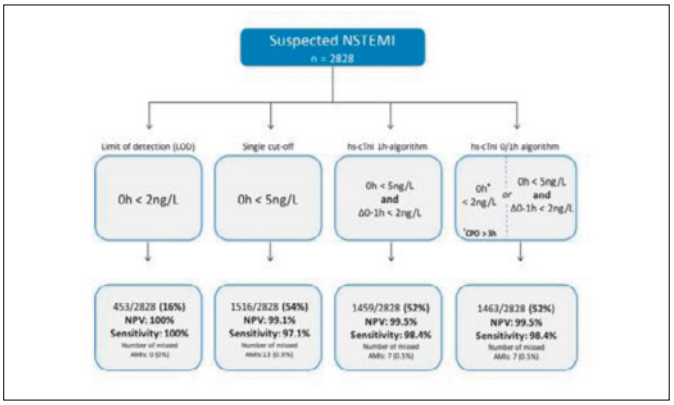

Figure 1

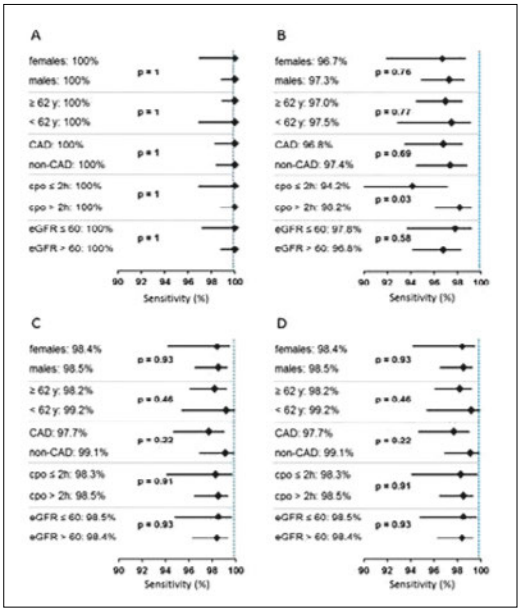

Figure 2

FM272

Improving processes of care in chronic obstructive lung disease (CAROL): a cluster randomized trial

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Background: Chronic obstructive pulmonary disease (COPD) is progressive, disabling and associated with increased mortality. Research efforts and international collaborations led to comprehensive COPD management guidelines assembling effective care elements to reduce the burden of COPD to patients and health systems. Because comprehensive care is complex shortcomings in health service delivery for COPD are common.
Objectives: To test whether a multifaceted intervention delivered to general practitioners (GPs) and their practice assistants increases adherence to recommended key elements and processes of COPD care.
Methods: Cluster-randomized pragmatic clinical trial, 1:1 randomization on the GP-level. The intervention was designed to improve knowledge but also and particularly governing professional behavior by implementation of a primary care "COPD care bundle", a tool to support evidence-based decision making and practice. Data was collected using questionnaires at GP and patient level at baseline and one year after the intervention. The primary outcome measure was the implementation of 15 individual (figure) processes of care. The primary outcome was the composite score of implemented processes measured at the patient level.
Results: Thirty-five GPs and 216 patients median age 69 years, 59% female, 69% GOLD stadium A or B were enrolled, 161 patients completed follow-up (drop-out rate 25%). After one year the composite score of implemented care processes increased from 4.7 to 6.1 (+1.4) in the intervention group and decreased from 5.3 to 4.4 (–0.9) in the control group. Linear regression model adjusting for baseline characteristics revealed a between-group difference of +2.0 (95% CI +1.2 to +2.8) implemented processes in favour of the intervention group. The effect remained statistically significant in sensitivity analyses simulating missing data due to drop-out. Detailed analyses showed that the intervention significantly increased adherence in 10 out of 15 processes of care (fig.).
Conclusion: A multifaceted intervention comprising GP education and a COPD care bundle resulted in increased implementation of recommended care processes.

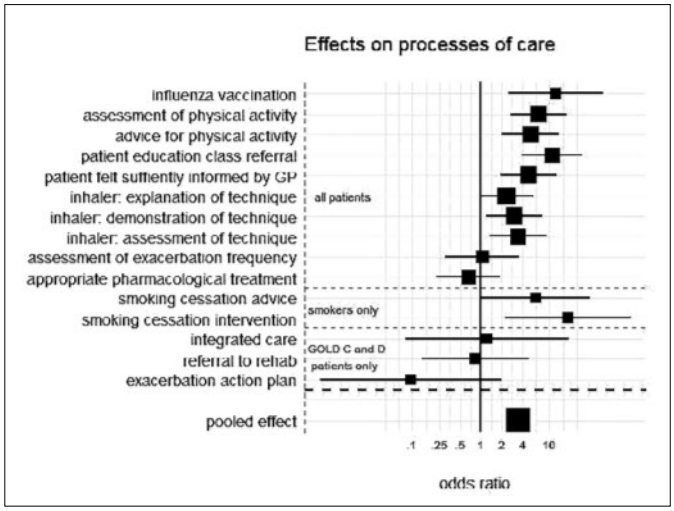

Figure: Intervention effects on processes of care.

FM273

Corticosteroids in patients hospitalised with community-acquired pneumonia: systematic review and individual patient data meta-analysis

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Introduction: The benefits and harms of adjunctive systemic corticosteroids for community-acquired pneumonia (CAP) are inconclusive. We aimed to evaluate the effects of adjunctive corticosteroids in adults hospitalised with CAP on patient-important outcomes using individual patients' data of randomised placebo-controlled trials and to explore subgroup differences.
Methods: We systematically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and trial registers plus

a hand search of conference proceedings (all through 9 June 2016) for eligible trials. Data from 1,506 individual patients in six trials were analysed using uniform outcome definitions. We investigated pre-specified effect modifiers using multivariable hierarchical regression adjusting for pneumonia severity, age, and clustering effects.
Results: Within 30 days of randomisation, 37 of 748 patients (5.0%) assigned to corticosteroids and 45 of 758 patients (5.9%) assigned to placebo died (adjusted odds ratio [OR], 0.75; 95% confidence interval [CI], 0.46–1.21, p = 0.24). Time to clinical stability and length of hospital stay were reduced by approximately one day with corticosteroids (adjusted difference, –1.03 days; 95% CI, –1.62-(–0.43), p = 0.001; and –1.15 days; 95% CI, –1.75-(–0.55), p <0.001, respectively). Patients who received corticosteroids had a higher incidence of hyperglycaemia requiring insulin treatment (160 [22.1%] vs 88 [12.0%]; adjusted OR, 2.15; 95% CI, 1.60-2.90, p <0.001; number needed to harm [NNH], 9; 95% CI 6–17) and CAP-related re-hospitalisation (33 [5·0%] vs 18 [2.7%]; adjusted OR, 1.85; 95% CI, 1.03–3.32, p = 0.04; NNH, 45; 95% CI 18–1235). There were no significant differences for other CAP-related or corticosteroid-related adverse effects between groups. We did not find significant effect modification by CAP severity or degree of inflammation.
Conclusions: Adjunct corticosteroids for patients hospitalised with CAP reduce time to clinical stability and length of hospital stay by approximately one day without a significant effect on overall mortality but with an increased risk for CAP-related rehospitalisation and hyperglycaemia.

FM274

Missed arterial hypertension by office blood pressure measured according to the NICE 2013 guidelines – results from the iPARR trial

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Objective: Standard operating procedures (SOP) for office blood pressure measurement (OBPM) vary highly between different guidelines. The NICE 2013 guidelines for arterial hypertension (AH) SOP recommends a first blood pressure measurement (BPM) after 5 minutes rest and a second BPM if blood pressure (BP) is >139 mm Hg systolic (s139) or >89 mm Hg diastolic (d89). We aimed to study how many probably hypertensive patients may be missed by this approach due to short term masked hypertension (STMH).
Design and method: In this cross-sectional, single-centre trial, 1000 adult subjects were recruited. Seven sequential BPM were performed by an operator after five minutes rest in a quiet room and in sitting position. The BPM were taken using a standard device (Omron HBP-1300 professional BP monitor, appropriate cuff size), alternating with a tested smartphone app. Standard BPM were spaced 2 minutes apart. Overall, 4 standard and 3 smartphone BPM were taken, however, only standard BPM were used for this study. Additional information about cardiovascular risk factors, concomitant disease, and medication were collected. We compared the first BPM out of four to the three following BPM. STMH was defined as first BP <s140 and <d90 mm Hg and one of the consecutive BPM >s139 or >d89 mm Hg.
Results: Complete measurements were available in 802 subjects. We identified 528 (65.8%) subjects with a BP<s140 and <d90 mm Hg in the first measurement. In 61/528(11.6%) subjects at least one consecutive BPM was >s139 or >d89 mm Hg and in 18/528 (3.4%) the mean of 2nd-4th measurement was >s139 or >d89 mm Hg. 412/802 (51.4%) subjects had no history of AH and normal first BPM. In this group STMH was present in 45/412 (10.9%). Subjects with STMH showed no differences in clinical parameters in comparison to subjects with normal BPM over all measurements.
Conclusion: By applying the SOP for OBPM suggested by NICE we found short term masked hypertension in more than 10% of all apparently normotensive subjects and especially in 11% of apparently normotensive subjects without known AH. Therefore by this SOP a significant proportion of patients may be missed for further evaluation.

GASTGESELLSCHAFT SFGG / SOCIÉTÉ CONVIÉE SPSG

COMMUNICATIONS LIBRES / FREIE MITTEILUNGEN

FM275

Effects of exercise and vitamin D on quality of life after hip fracture

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Introduction: Exercise and vitamin D supplementation are inexpensive and accessible means of aiding the recovery process after hip fracture. However, information on the benefit of these interventions on health-related quality of life (HRQL) after hip fracture is missing. We tested the effects of a simple home exercise program and vitamin D supplementation on HRQL in the first 12 months after hip fracture in an ancillary study of the Zurich Hip Fracture Trial that tested the interventions in a 2×2 factorial trial design.
Methods: We enrolled 165 of 173 acute hip fracture patients from the original trial who had baseline information on HRQL (mean age 84 years, 79% females, 77% community dwelling). We then tested the effects of the simple home exercise program (home exercise program + standard physiotherapy vs. standard physiotherapy alone) and vitamin D supplementation (800 vs. 2000 IU/day) on HRQL over time. HRQL was measured as EQ-5D index score, calculated from the EQ-5D-3L questionnaire at baseline, 6 months and 12 months. At baseline, participants were asked to estimate their pre-fracture HRQL. Effects by treatment were analyzed using multivariable repeated-measures analysis adjusted for age, gender, body mass index, comorbidities, mini-mental state examination (MMSE), living status, and baseline serum 25-hydroxyvitamin D concentration.
Results: The adjusted EQ-5D index score significantly worsened from 0.71 pre-fracture to 0.57 over time, but did not differ by treatment. However, while all other groups remained stable after the 6-month decline, the control group receiving only low dose vitamin D (800 IU/day) and no home exercise program experienced a significant further decline in the EQ-5D index score between 6 and 12 months of follow-up (p = 0.028). Notably, independent of the interventions and other covariates, patients with a better baseline MMSE score and those living in the community prior to their fracture, had a significantly lower decline in HRQL after hip fracture.
Conclusion: Based on our trial hip fractures have a long-lasting negative effect on HRQL up to 12 month after hip fracture. A simple home exercise program and high-dose vitamin D may help prevent a further decline in HRQL after the first 6 months of the index fracture.
Funding: This project was supported by the Baugarten Centre Grant for the Centre on Aging and Mobility, and by the University Research Priority Program “Dynamics of Healthy Aging”, University of Zurich.

FM276

Vitamin D status and body composition

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Introduction: Vitamin D has been linked to muscle health and insulin sensitivity. However, there is limited data on whether 25-hydroxyvitamin D (25(OH)D) status is associated with body composition. We

investigated if and to what extent 25(OH)D status is associated with body composition (muscle and fat mass), as well as insulin resistance among relatively healthy community-dwelling seniors.
Methods: We enrolled 271 seniors age 60 years and older (mean age 70.4 years, 53% women, 31.4% vitamin D deficient (<20 ng/mL)) undergoing elective surgery for unilateral knee replacement due to severe knee osteoarthritis (Baseline Exam Zurich Knee OA Trial). Analyses compared baseline body composition (percentages of total lean mass (TLM%) and total fat mass (TFM%), appendicular lean mass index (ALMI), and fat mass index (FMI)) assessed by dual-energy X-ray absorptiometry) and insulin resistance between quartiles of baseline serum 25(OH)D levels using multivariable linear regression models. Models were controlled for age, gender, smoking status and physical activity.
Results: While we did not find a difference on muscle mass, participants in the lowest 25(OH)D quartile (4.7–17.5 ng/ml) had a higher FMI than participants in the third (26.1–34.8 ng/ml; 9.3 vs. 8.4 kg/m^2; $P = 0.049$) and highest (34.9–62.5 ng/ml; 9.3 vs. 8.4 kg/m^2; $P = 0.044$) quartile. Moreover, participants of the second 25(OH)D quartile (17.6–26.0 ng/ml) had higher β-cell function (77.9% vs. 59.6%; $P = 0.018$) consistent with their lower insulin sensitivity (152.8% vs. 215.3%; $P = 0.005$) compared with participants of the highest 25(OH) D quartile. Insulin resistance was more prevalent among participants in the lowest 25(OH)D quartile compared with the highest quartile (23.8% vs. 6.3%; $P = 0.006$).
Conclusions: Our findings suggest an inverse association between serum 25(OH)D level and FMI. Consistently, prevalence of insulin resistance was higher among seniors with low serum 25(OH)D status. Thus, based on these cross-sectional analyses a replete vitamin D status may support preserving a healthy body composition and help prevent insulin resistance among seniors.

FM277

Bioimpedance-derived phase angle and mortality among older people

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Background: Phase angle measured by bioelectrical impedance analysis (BIA) may be a marker of health state.
Objective: This historical cohort study of prospectively collected BIA measurements aims to investigate the link between phase angle and mortality in older people and evaluate whether a phase angle cut-off can be defined.
Design: We included all adults aged 65 years and over who underwent a BIA measurement by the Nutriguard® device at the Geneva University Hospitals. We retrieved retrospectively the phase angle and co-morbidities at the last BIA measurement and the mortality until December 2012. We calculated phase angle standardized for sex, age, and body mass index, using reference values determined with the same brand of BIA device. Sex-specific and standardized phase angle were categorized into quartiles. The association of mortality with sex-specific or standardized phase angle was evaluated through univariate and multivariate Cox regression models, Kaplan-Meier curves, and ROC curves.
Results: We included 1307 (38% women) participants, among whom 628 (44% women) died. In a multivariate Cox regression model adjusted for co-morbidities and setting of measurement (ambulatory vs. hospitalized), the protective effect against mortality increased progressively as the standardized phase angle quartile increased (HR 0.71 (95% CI 0.58, 0.86), 0.53 (95% CI 0.42, 0.67), 0.32 (95% CI 0.23, 0.43)). The discriminative value of continuous standardized phase angle, assessed as the area under the ROC curve, was 0.72 (95%CI 0.70, 0.75). We could not define an acceptable phase angle cut-off for individual prediction of mortality (LK), based on sensibility and specificity values.
Conclusions: This study shows the association of phase angle and mortality in older patients, independently of age, sex, comorbidities, BMI categories, and setting of measurement.

FM278

Pain sites and severity, a national survey of health-related quality of life in Swiss community-dwelling older adults with pain

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Background: Regarding the epidemiology of pain in older adults, data are lacking about the association between pain severity and its impact on of health-related quality of life (HRQoL). The purpose of this study was to investigate pain prevalence and sites, its self-reported interferences with daily life activities, and the effect of pain severity on HRQoL in a Swiss community-dwelling population aged ≥65 years.
Methods: This cross-sectional national survey included a sample of individuals selected randomly from population records, stratified by age and gender. Respondents answered a face-to-face interview addressing pain location, intensity and interference with activities, and quality of life variables. Logit regression models were applied for binary outcomes, linear regression for continuous outcomes, and Poisson regression for count outcome. For each analysis, Wald Chi-square and 95% confidence intervals were used.
Results: Among the 2'995 individuals considered, 36.4 % reported pain. The results indicate that pain increases with age; more precisely, this increase concerns pain intensity from age 85 onward. Pain severity was strongly associated with HRQoL and functional impact, i.e., all scales involving physical activities were affected in those individuals reporting severe pain; it was also associated with the individuals' perception of their overall HRQoL. Pain severity had a significant effect on this perception.
Conclusions: Our results point to the importance of devoting attention to pain intensity rather than to the number of pain sites. Because of the demographic transition the management of pain problems should emphasize early referral and timely treatment in order to prevent the burden of disease and functional loss associated to pain severity.

FM279

Cognitive function in DO-HEALTH

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Introduction: Impaired cognition and impaired physical function are at the root of disability at older age and often occur together. In this study, we assess cognitive function among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study using two different screening tools (Montreal Cognitive Assessment and Mini Mental Examination). In addition, we correlated cognitive function with performance in physical function tests.
Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. Participants were required to have a Mini-Mental State Examination (MMSE) score of at least 26 to be eligible for the study. At baseline, cognitive function was additionally assessed using the Montreal Cognitive Assessment scores (MoCA). Physical function tests were conducted at the baseline clinical visit and included the short physical performance battery (SPPB) that comprises balance, gait speed and the repeated-sit-to-stand test.
Results and conclusions: First findings on baseline data from all 2157 DO-HEALTH seniors will be presented at the meeting.

FM280

Functional measures and fall status in DO-HEALTH

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Introduction: By 2030, seniors age 70 years and older will double, as will the number of seniors with falls and resulting impairments in function and mobility. In this study, we will compare functional status among fallers and non-fallers among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study.
Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. At baseline, we asked participants about their fall status in the year prior to enrollment and had a target recruitment of 40% for participants with a prior fall. In this study we will present baseline functional measures of gait speed, chair-rise test, and grip strength by fall status.
Results and conclusions: First findings on baseline functional data from all 2157 DO-HEALTH seniors from 5 European countries (Switzerland, Germany, Austria, France and Portugal) by fall status will be presented at the SGAIM Spring Meeting in May 2017.

FM281

SENIORLAB: a prospective observational lab assay survey in 1467 sedentary healthy elderly

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Reference intervals for laboratory analyses by and large are provided by analytical platform providers – provenience and preanalytics of materials for calculation of intervals often remain arcane particularly relating to age group of donors. In an observational, prospective cohort study on 1467 healthy uniracial caucasian residents >60 yrs of age, 105 frequently used lab tests were done on one blood sample/participant and reference intervals were calculated according to the CLSI-C28-A3c guideline separately with partitioning factors, e.g. age, gender and adapted exlusion criteria such as smoldering inflammation or iron deficiency; outliers were eliminated according to Dixon&Reed. With a nonrestrictive definition of health several pathological laboratory results pointing to occult disease have been found and published from SENIORLAB so far. Thus, 64.5% of the cohort showed prediabetic fasting plasma glucose and/or glycated hemoglobin (HbA1c); total serum folate levels but not red blood cell folate decreased with progressing age and 66% of 1470 evaluable study participants had insufficient levels of 25(OH) vitamin D. In a follow up enquiry on further health status of participants, SENIORLAB allowed to deduce, that the cystatin C/creatinine ratio lets survey mortality and subjective overall morbidity at follow up when computed by logistic regression. In 289 participants evaluated, serum uromodulin displayed inverse relationship with creatinine, cystatin C and urea and we now are convinced, in line with others, that serum uromodulin behaves in a manner opposite that of the different conventional renal retention markers: lower serum concentrations go along with reduced glomerular filtration rates. SENIORLAB thus not only establishes reference intervals in the elderly but also helps to elucidate physiopathological aspects of selected parameters as well as to grapple with a problem raised by WHO about the definition of health. Upon follow up evaluations of study participants years later, biomarker/risk factor status for length/quality of remaining life years might show up for certain analyses. So far carried out lab assays with this sedentary study participant cohort in the Swiss midlands, a high-income population (OECD classification) might serve as reference to study global health issues in low and middle income or poorer populations as well as in migrants; the global burden of noncommunicable diseases is at stake.

FM282

Physical Frailty in DO-HEALTH

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Introduction: Physical frailty is at the root of accelerated aging, and is an independent predictor of worse clinical outcomes among older adults in acute care. By 2030, the personal, societal, and health economic burden of frailty is expected to at least double, in parallel to the projected growth of the older segment of the population. In this study, we will assess the prevalence of frailty among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study using the Linda Fried Frailty Score.
Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. At baseline, we assessed the phenotypic model of physical frailty operationalized by five characteristic domains (fatigue, weight loss, slowness, low activity level and weakness).
Results and conclusions: First findings on baseline frailty data from all 2157 DO-HEALTH seniors from 5 European countries (Switzerland, Germany, Austria, France and Portugal) will be presented at the SGAIM Spring Meeting in May 2017.

GASTGESELLSCHAFT SGH / SOCIÉTÉ CONVIÉE SSH

PRESIDENTIAL SYMPOSIUM

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Cellular immunotherapy with multiple infusions of ex vivo expanded haploidentical natural killer cells after autologous transplantation for patients with plasma cell myelom

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Plasma cell myeloma (PCM) is currently treated with chemotherapy and autologous stem cell transplantation (ASCT) but relapse rates remain high. Adoptive transfer of mature haploidentical natural killer (NK) cells is a promising approach to provide PCM patients with highly immunocompetent effector cells with anti-myeloma function early post transplantation. Here we report on the current clinical Phase I/II trial of multiple preemptive infusions of good manufacturing practice (GMP) expanded NK cells to PCM patients. Ten patients were recruited (median age: 59y). All patients received 4 cycles of VTD chemotherapy (reaching 4xCR, 5xVGPR and 1xPR) before high dose melphalan and ASCT. NK cells from haploidentical family donors were purified from leukapheresis by T cell depletion and NK cell selection. Highly pure NK cells (mean: 4.8×10^8 cells) were obtained with a minimal T cell contamination corresponding to a 6.1 log T cell depletion. After expansion *ex vivo* for 19 days in GMP-medium containing autologous irradiated feeder cells, interleukin-2 and -15, NK cell numbers increased 54-fold (range: 38- to 76-fold). In three NK cell products T cell contents were 10x above limit of clinical trial and were successfully reduced by 2° T cell-depletion from 11 to 0.3×10^5cells/kg body weight (BW). NK cells were cryopreserved in escalating doses (1.3×10^6, 1.3×10^7 and multiple doses of maximal 1.0×10^8 cells/kg BW). The PCM patients received $65–460\times10^8$ expanded NK cells (median: 3.8×10^8 cells/kg BW, range: $0.9–5.7\times10^8$ cells/kg BW) as 3–8 infusions (median. 6 DLIs). The NK-DLIs were administered between day 2 and 21 after ASCT and were well tolerated without any acute adverse

events. No signs of acute or chronic graft-versus-host disease were observed after a total of 57 NK-DLIs. Engraftment occurred between days 13-24 (median: 16 days). Infused donor NK cells were monitored by short-tandem repeats PCR. Donor NK cells were detected in blood one and 20 hours post infusion (% donor NK of enriched blood NK cells: mean: 30%, range: 9–90%, and mean: 17%, range: 0–33%, respectively) indicating significant NK cell survival in same recipients. Clinical responses at last follow-up compared to a retrospective cohort of matched control patients will be presented. These results demonstrate the feasibility of large-scale GMP expansion and safety and tolerability of multiple high-dose infusions of human NK cells as immunotherapy after stem cell transplantation for PCM.

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CDX2 promotes leukemogenesis by modulating leukemic cell – BM niche interactions

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Objectives: The caudal-type homeobox (*CDX*) gene family regulates embryonic hematopoiesis via downstream *HOX* genes and interactions with the *WNT* signaling pathway. *CDX2* expression is not detected in healthy bone marrow (BM) cells but present in >80% of human acute myeloid (AML) and lymphoid leukemia (ALL). Ectopic activation in murine BM cells induces myeloid leukemia. Here, we explore the functional role and molecular targets of *CDX2* in human leukemia.
Methods: *CDX2* expression was modulated via lentiviral and siRNA treatment in human BM $CD34^+$ and human leukemic cell lines. *CDX2* modified and control cells were subjected to growth, colony forming (CFU), cell cycle, flow cytometry, adhesion and qRT-PCR assays and analyzed *in vivo* upon xenotransplantation in NOD/SCID/$IL2R\gamma^{null}$ (NSG) mice for bone marrow (BM) homing and leukemogenesis. DKK-1 protein levels were measured in the supernatant via ELISA and the effect of DKK-1 supplementation on leukemic versus healthy hematopoietic cells explored in *in vitro* and *in vivo* assays.
Results: *CDX2* knockdown in AML cells strongly reduced clonogenicity while leaving proliferation, apoptosis and cell cycle unaltered. Importantly, *CDX2* knockdown profoundly suppressed *in vivo* leukemogenic properties. Gene set enrichment analyses (GSEA) of microarray data collected on *CDX2* overexpressing versus control leukemic cells revealed *WNT* signaling and cell adhesion genes as the pathways most prominently regulated by *CDX2*. Surprisingly, *CDX2* overexpressing leukemic cells showed both induction of activated beta-Catenin and of secreted DKK-1, a known WNT inhibitor. In functional assays, *CDX2* was shown to positively regulate leukemic cell adhesion to stromal cells via DKK-1. Interestingly, DKK-1 showed opposite effects on healthy hematopoietic stem/progenitor cells, reducing their clonogenicity and stromal cell adhesion. These data suggest that leukemic cells might use DKK-1 secretion to confer them competitive advantage for BM niche occupation by (1) increasing their adhesion capacity to stromal cells and (2) dislocating healthy hematopoietic stem/progenitor cells from the niche. Consistently, *in vivo* DKK-1 pre-treatment promoted leukemic cell homing to the BM.
Conclusion: Our data suggest that *CDX2* plays important roles in human AML cells during *in vivo* leukemogenesis by sustaining their endogenous canonical *WNT* activity and concomitantly inducing DKK-1 secretion to alter stromal cells and healthy hematopoiesis.

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Development of a peptide macrocycle factor XII inhibitor for safe anticoagulation therapy

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Introduction: Factor XII (FXII) is a plasma serine protease that was identified as a coagulation factor. FXII has a *highly conserved* amino acid sequence *across* disparate *species*, suggesting that this molecule does have a physiologic function. Mechanistic research based on animal models indicates that FXII contributes to thrombotic disease by triggering excessive coagulation. Inhibiting FXII has been shown to reduce thrombosis without increasing the bleeding risk, a major side-effect of currently used anticoagulants. Until recently, several protein-based FXII inhibitors were developed, out of which at least one is in clinical trial, but no high affinity small molecule inhibitor has been reported.
Methods: Bicyclic peptide synthesis, protease inhibition assays for the following serine proteases: tPA, uPA, factor XIa, plasma kallikrein, thrombin, plasmin, trypsin, factor VIIa, factor Xa, trypsin and factor XIIa, structural model and structure analysis, plasma stability assays, aPTT and PT coagulant activity measurements, pharmacokinetics in mouse and rabbit, $FeCl_3$ injury thrombosis model in mesenteric arteries in mouse.
Results: We have generated a potent and highly selective FXII inhibitor based on a macrocyclic peptide format (MW <2000 kDa). Recently, we had improved the potency and stability of the inhibitor using various approaches based on unnatural amino acid incorporation. The final peptide shows high inhibitory affinity and selectivity with a high stability in plasma (K_i = 380 ± 80 pM, >200,000-fold selectivity, $t_{1/2}$ plasma >96 h). The inhibitor prolonged intrinsic coagulation in human, mouse and rabbit plasma (EC_{2X} human = 1 µM). Pharmacokinetic studies in mouse and rabbit showed that the peptide was active *in vivo* and no signs of toxicity or abnormal bleeding were observed. We then recorded thrombus formation in mesenteric arterioles by intravital microscopy in mouse, a thrombosis model sensitive to defects in the intrinsic pathway of coagulation. The peptide could substantially reduce thrombus formation (peptide: 3/9 (33%), control: 7/8 (87%), P <0.05), full occlusion (peptide: 0/9 (0%), control: 5/8 (63%), P <0.05), time to thrombus formation (peptide: 20 ± 3.6 min, control: 9.6 ± 5.7 min, P <0.05).
Conclusion: Our results suggest that FXII inhibition by a peptide macrocycle can potentially offer a safe anticoagulation therapy.

QUICK ORAL PRESENTATIONS

FM283

Thromboembolic events in patients with ITP

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Introduction: Immune thrombocytopenia (ITP) is characterized by severe thrombocytopenia due to autoantibody- and cell-mediated peripheral platelet destruction and attenuated thrombopoiesis. Despite a higher risk for bleeding, thromboembolic events (TEE) have been observed. The objective was to investigate the prevalence and type of TEE and the potential risk factors.
Method: Retrospective cohort which included all patients followed between 01/1990 and 05/2016 in our clinic. Information on gender, age, date of diagnosis, platelet count, type and clinical form, treatments, response to treatment, cardiovascular risk factors, number and type of TEE, date and cause of death, and follow up time were collected in 438 adult patients. We evaluated and compared risk factors of ITP patients with and without TEE in univariate and multivariate analysis.
Results: Of all patients, 10% (44) presented ≥1 TEE after ITP diagnosis. In total 54 TEE occurred: 34 venous (61%), 19 arterial (34%) and 3 arterial and venous (5%). The most frequent venous TEE are pulmonary embolism, deep vein thrombosis, and superficial vein

thrombosis; arterial TEE were cerebrovascular insults, myocardial infarction and peripheral artery thrombosis. At time of TEE, 43% of patients were taking corticosteroids, 14% thrombopoietin receptor agonists (TPO-ra) and 18% were off-treatment. In the univariate analysis, older age at diagnosis (≥50 years, P = 0.015), longer interval since ITP (P = 0.001), persistent/chronic ITP (versus acute, P = 0.009), ≥2 treatments (P = 0.0002), TPO-ra at time of thrombosis (P = 0.027), non-response to first treatment (P = 0.010), smoking (P = 0.011), arterial hypertension (P = 0.005), and obesity (P = 0.041) revealed to be significant. The multivariate analysis model showed that older age at diagnosis (P = 0.016), splenectomy (P = 0.021), ≥2 treatments (P = 0.006), persistent or chronic ITP (P = 0.033) were independent risk factors for TEE. The cumulative incidence of TEE at year 1, 5, 10, 15 and 20, is respectively 6.2% (95% CI, 4.1–9.3), 11.9% (95% CI, 8.3–17.0), 15.8% (95% CI, 11.1-22.4), 24.2 % (95% CI, 16.9–34.7) and 32.8% (95% CI, 22.8–47.3). Death occurred in 7/44 (16%) of patients with, and in 12/394 (3%) without TEE (P = <0001). Most frequent cause of death was infection (32%) and bleeding (21%).
Conclusion: ITP patients are at risk for TEE. Those patients who underwent splenectomy, had chronic disease, needed a higher number of treatments for ITP, and smoke were more likely to develop TEE.

FM284

Mice generated by in vitro fertilization show a reduced platelet count accompanied by a heightened response to thrombin

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Background: Children conceived by assisted reproductive technology (ART) show vascular dysfunction, increased arterial pressure and early atherosclerosis, conditions associated with a higher risk of cardiovascular morbidity. The effect of ART on the synthesis, maturation and function of platelets is unknown. Therefore, we investigated platelet production and reactivity in a murine model of in vitro fertilization (IVF).
Methods: IVF mice were generated by *in vitro* insemination of oocytes from FVB female mice, followed by transfer to pseudopregnant NMRI females 48 h later. IVF and control (naturally born, C) male mice (n = 12) were euthanized at the age of 12 weeks. Total blood cell count, mean platelet volume (MPV) and reticulated platelet analysis was performed on EDTA blood, while platelet receptor expression (GPVI and GpIb) and platelet activation were determined by flow cytometry on citrated platelets.
Results: IVF mice showed a significantly reduced platelet count compared to control mice (860.15 ± 172×10^3/ul IVF vs 1119.5 ± 243 ×10^3/µl C, p = 0.013), accompanied by a slightly reduced (albeit not significantly) mean platelet volume (MPV: 5.07 ± 0.35 µm^3 IVF vs 5.25 ± 0.6 µm^3 C, p = 0.41). Total blood leukocytes and erythrocytes counts were not different between the two groups. Newly synthesized platelets (reticulated platelets) stained by thiazole orange (TO) were significantly reduced in IVF mice (% TO positive platelets: 8.47 ± 3 C vs 4.9 ± 0.9 IVF, p = 0.003), indicating reduced production. Collagen receptor GPVI expression was unchanged (mean fluorescence intensity MFI: 2575 ± 329 C vs 2554 ± 442 IVF), and also vWF receptor GpIb levels were similar between the two groups of mice

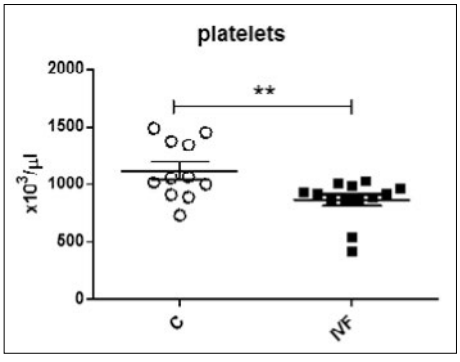

Figure 1: Platelet count C and IVF mice.

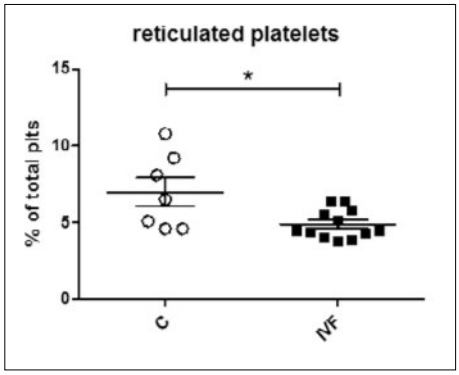

Figure 2: Reticulated plts.

(MFI: 3470 ± 508 C vs 3232 ± 591 IVF). Upon thrombin stimulation (0.1 U/ml), platelets from IVF mice exposed higher levels of P-selectin (fold increase versus resting state: 54.53 ± 37 C vs 95.64 ± 72 IVF mice, p = 0.1) and exhibited significantly more active integrin alpha$_{2b}$beta$_3$ (fold increase 21.48 ± 15 C vs 172 ± 190 IVF mice, p <0.01).
Conclusions: Mice generated by IVF display a reduced platelet count, due to a diminished platelet production. On the other hand, their circulating platelets show an increased response to thrombin as agonist. Given the key role played by platelets in thrombotic events and the fact that IVF individuals are at higher risk of cardiovascular events, these preliminary data warrant further research on to the effects of ART on platelet production, count and function.

FM285

Effects of chronic viral infections on the functional and structural integrity of bone marrow stromal networks

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Introduction: Hematopoiesis is sustained by a rare population of self-renewing, multipotent hematopoietic stem and progenitor cells (HSPCs), which reside in specialized nurturing microenvironments within bone marrow (BM) tissues. The basic tissue infrastructure of the BM is provided by stromal cellular networks of mesenchymal, neural and vascular origin, which are critically involved in the fine regulation of different stages of hematopoiesis. Viral infections act as major stressors to the hematopoietic system, inducing a massive and adaptive response in cellular output. Albeit the effects of viral infections and ensuing inflammatory responses on hematopoietic cells have been studied in detail, how viral infections can alter BM stromal scaffolds and thus shape hematopoietic responses remains poorly defined.
Methods: We here perform a detailed multidimensional analysis of the structural and functional effects of viral infections on the BM microenvironment. We combine flow cytometric analysis for detailed quantification of cellular subsets, with conventional *in vitro* and *in vivo* assays to assess cellular fitness. Finally, to analyze microarchitectural effects we employ advanced 3D confocal microscopy methods pioneered in our laboratory.
Results: Chronic LCMV infections result in a substantial loss of BM endothelial and mesenchymal stromal progenitor cell populations and a decrease in their capacity to produce HSPC-sustaining factors. Moreover, we observed that chronic LCMV infection triggers vasodilation of BM sinusoids, intense vascular remodeling and a substantial disruption of extracellular matrix networks throughout the BM cavity. Major damage to BM stromal integrity is accompanied by a profound and sustained reduction in the number of both hematopoietic multipotent progenitors as well as hematopoietic stem cells. Competitive repopulation assays reveal that remaining HSCs are also strongly impaired in their repopulation capacity for prolonged times after LCMV infection. Finally, our results indicate that the observed alterations in the composition and functionality of cells in the BM are, at least partially, mediated by activated virus-specific CD8 T cells.
Conclusion: The BM microenvironment supporting hematopoiesis suffers long-lasting alterations as a consequence of infections, which are likely to impact the hematopoietic function of the BM and HSC regulation.

FM286

Hematopoietic stem cell transplant-associated thrombotic microangiopathy and acute graft-versus-host disease

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Introduction: Steroid refractory acute graft-versus-host disease (GvHD) remains a major complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). GvHD has been associated with transplant-associated thrombotic microangiopathy (TA-TAM). Complement is thought to be a major mediator of endothelial damage. We hypothesize that a TA-TMA, related to dysregulation of the alternative complement pathway correlates with organ damage.
Methods: A retrospective analysis of 660 consecutive patients with hematological malignancies receiving an allo-HSCT at the University Hospital Basel in the period from 2003 to 2013 was performed. Data on the occurrence, risk factors and outcome of patients with TA-TMA and the correlation with acute GvHD was collected. Available biopsies of organs suspected to be affected by TAM and/or GvHD will be performed. Routine bone marrow biopsies for histological, immunohistochemical signs of TA-TAM and complement activation will be analyzed. Serum samples will be used to characterize markers of complement activation using plasma levels of C5b-9 and C5b-9 deposition in tissues biopsies.
Results: 660 patients (AML n = 260; ALL n = 152; MDS/MPN n = 93; lymphoid neoplasm n = 85; plasma cell disorder n = 53; bone marrow failure n = 17) underwent myeloablative (n = 432) and non-myeloablative (n = 228) allo-HSCT at a median age of 47 years (range 19-71 years). Forty-eight (7.3%) patients matched the established diagnostic criteria for TAM (increased LDH, platelet count <50 G/L or <50% of normal baseline, schistocytes >2 per high power field, creatinine increase). The median time to onset of TAM was 36 days post-transplant (range 22 to 67 days). Subjects with TA-TAM had significantly higher 3-year non-relapse mortality compared to those without (47.8% vs 18.2%, P <0.001). Grades 2 to 4 aGvHD and cytomegalovirus viremia were independent risk factors for TA-TAM, and serum LDH level >500 U/L as well as arterial hypertension were early signs of TA-TMA occurrence. Patients with clinically relevant aGvHD (≥ grade 2) had more TA-TAM than patients without aGvHD (45% versus 24%; p <0.001). TAM correlated with aGvHD severity; the higher the aGvHD grade, the more the patients who suffered from TAM.
Conclusions: Allo-HSCT recipients with grades 2 to 4 aGvHD or cytomegalovirus viremia should be closely monitored for the presence of TA-TMA. At the meeting first results of histological, immunohistochemical and complement activation analyses will be presented.

FM287

A model of platelets in the aging organism reveals increased numbers and enhanced activatability, possibly mediating a larger stroke burden

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Background: Age is a key risk-factor for cardiovascular disease (CVD). Platelets play a major role in CVD. Yet, little is known about age-dependent changes in their function. Thus, we used a mouse model of aging, in absence of any confounding factors, to analyze platelets in aging and their putative role in ischemia/reperfusion (I/R) brain injury.
Methods: To discern specific aging effects from confounding factors, we used young (12 weeks, young Cohort; yoC) and very old (>20-months, old Cohort; oldC) C57BL/6 wildtype mice. Blood cell count and MPV were measured in EDTA-anticoagulated blood. Reticulated platelets were determined by thiazole-orange staining. Platelet clearance was assessed on CD41-stained hepatic and splenic cryosections. Plasma glycocalicin (GC) was assayed by ELISA. Platelets were activated with thrombin or collagen I and analyzed by flow-cytometry. I/R brain injury was induced by transient middle cerebral artery occlusion for 30 mins followed by 48 h of reperfusion. Stroke size was assessed by triphenyltetrazolium chloride (TTC) staining; neurological function by RotaRod and Bederson tests.
Results: Platelet mass (number and size) was increased in the oldC. Reticulated platelet counts were higher in the yoC, suggesting decreased clearance in the oldC. This was supported by hepatic and splenic cryosection histology: areas positively covered by staining for CD41 in the yoC were larger than those in the oldC. The GC index was similar in the yoC and oldC. GP IIb/IIIa and P-selectin were increased in the oldC after activation with thrombin.

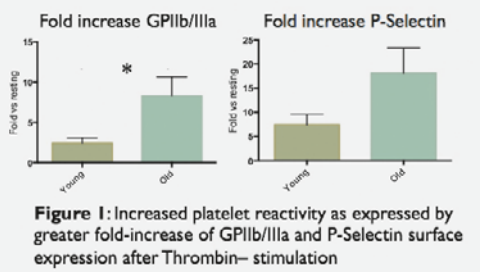

Figure 1: Increased platelet reactivity as expressed by greater fold-increase of GPIIb/IIIa and P-Selectin surface expression after Thrombin– stimulation

Figure 1

Stroke size was doubled in the oldC and related to significantly poorer neurological performance.

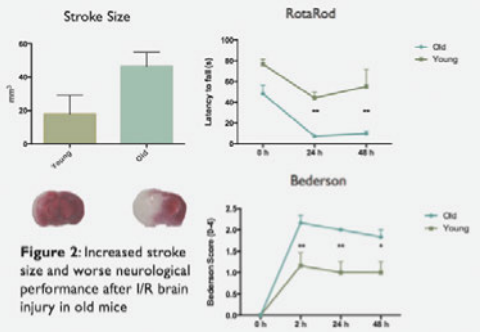

Figure 2: Increased stroke size and worse neurological performance after I/R brain injury in old mice

Figure 2

Conclusions: Our model reveals 1) higher platelet numbers and larger platelet size irrespective of reticulated platelets, 2) reduced hepatic and splenic clearance and 3) increased procoagulant and pro-inflammatory response in the oldC. These platelet changes in the oldC may be related to 4) larger stroke size and poorer functional outcome. The model may delineate the role of platelets in age-related CVD, and provide insight into the therapeutic relevance of targeting platelet changes in aging.

FM288

Autophagy pathways active during APL therapy – identification of key autophagic networks

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Introduction: Autophagy is an intracellular degradation system that ensures a dynamic recycling of cytoplasmic contents. It is required for self-renewal and cell survival under stress. There is accumulating evidence for additional functions of autophagy during myeloid development and therapy responses in acute myeloid leukemia (AML). In this study we aimed at identifying the autophagy-related network involved in AML therapy responses.
Methods: In this study, we analyzed primary APL/AML samples and cell lines to characterize the autophagy mechanisms active during all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) therapy. Techniques used were qPCR, western blotting, FACS, immunofluorescence microscopy, autophagic flux analyses, immunoprecipitation, lentiviral knockdown and overexpression systems, ChIP as well as promoter reporter analyses.
Results: In general, expression of most autophagy-related (ATG) genes was attenuated in primary AML patient samples and reactivated upon neutrophil acute promyelocytic leukemia (APL) and $CD34^+$ differentiation. Importantly, we identified several of these myeloid differentiation associated ATG genes as novel transcriptional targets of the hematopoietic transcription factor PU.1. Regarding the autophagic mechanisms, we found that ATRA-induced autophagy during APL differentiation is Beclin-1 independent. Moreover, knocking down ATG16L2 but not ATG16L1, both genes are involved in

autophagosome maturation, in APL cells significantly attenuated neutrophil differentiation clearly indicating that ATG16L2 but not L1 is needed for a successful ATRA response. Moreover, we identified a novel link from the neutrophil enhancer kinase DAPK2 to autophagy via its binding to the ATG gene ATG5 upon ATRA treatment. On the other hand, DAPK2 is dispensable for ATO-mediated induction of autophagy but not cell death. We further showed that DAPK2 stabilizes the transcription factor p73 and that *DAPK2* expression is transcriptionally regulated by p73 thereby creating a positive feedback loop during ATO induced cell death.
Conclusions: Our data provide strong evidence for a particular, non-canonical subtype of autophagy operative during neutrophil differentiation of APL cells as opposed to canonical autophagy in ATO therapy. Deciphering the particular autophagy pathway active during APL differentiation and cell death responses is a prerequisite to develop novel therapies that are based on autophagy modulation for this disease.

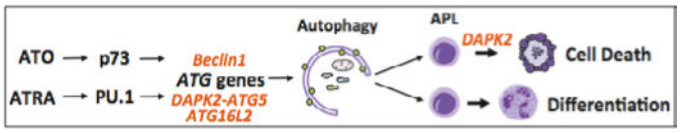

Figure: Autophagy in APL Therapy.

FM289

Effects of the sympathicomimetic agonist mirabegron on disease course, allele burden, marrow fibrosis, and nestin positive stem cell niche in patients with JAK2-mutated myeloproliferative neoplasms: a prospective multicenter phase II trial SAKK 33/14

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Introduction: Nestin+ mesenchymal stem cells (MSCs) are reduced in bone marrow of JAK2-V617F positive myeloproliferative neoplasms (MPN) patients due to damage of the sympathetic nerve fibers triggered by cytokines from the mutant cells. In a mouse model therapy with a beta-3 sympathicomimetic agonist corrected the damage inflicted by the MPN clones on their niches and ameliorated the MPN phenotype. To test the effect on disease-control in patients with MPN we performed a phase II trial with the beta-3 sympathicomimetic agonist mirabegron.
Methods: The trial consisted of mirabegron 25 mg daily during the first week, followed by 50 mg daily for at least 24 weeks. Patients with a cytohistologically confirmed diagnosis of MPN and a JAK2-V617F allele burden >20% in granulocytes at study entry were eligible, if not treated with JAK2 inhibitors or interferon. Reduction of the JAK2-V617F allele burden ≥50% was the primary end point. Secondary end points included blood count changes or MPN related symptoms. As a side study, bone marrow biopsies were quantified for nestin+ MSCs, fibrosis and CD34+ hematopoietic stem and progenitor cells.
Results: Thirty-nine patients have been accrued in 10 institutions in Switzerland: 8 (21%) had essential thrombocythemia, 22 (56%) polycythemia vera, 9 (23%) primary myelofibrosis, 27 (69%) were male and the median age was 62 (IQR 53–72). Twenty-eight (72%) patients had cytoreductive therapy, the remaining patients had antiaggregation, anticoagulation or phlebotomy. No patient reached the primary endpoint, one patient achieved a 25% reduction in allele burden by 24 weeks. Adverse events were mostly grade I or II on the CTCAE scale, 3 patients had grade III events. The mean blood counts were similar between start and end of therapy. In 20 patients bone marrow biopsy was available, showing an increase in the nestin+ MSCs cells from a median of 1.09 (IQR 0.38–3.27)/mm^2 to 3.95 (IQR 1.98–8.79)/mm^2 ($p < 0.0001$) and a slight decrease of myelofibrosis from a median grade of 1.00 (IQR 0.50–3.00) to 0.75 (IQR 0.50–2.00) ($p = 0.02$) between start and end of therapy.
Conclusion: Therapy with mirabegron for 24 weeks failed to reach the primary endpoint of reducing the JAK2-V617F allele burden ≥50% in MPN patients. However, an increase in the nestin + MSCs in bone marrow and a slight decrease of myelofibrosis were found, suggesting that mirabegron can reverse the damage inflicted by the JAK2-V617F positive MPN clone on the nestin + stem cell niche.

FM290

Utility of thromboelastometry analysis in patients with mild bleedings disorders

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Background: Viscoelastic methods are regarded as promising concept to overcome the limitations of conventional laboratory assays in patients with haemostatic disorders, particularly in the perioperative setting. Their performance regarding frequently occurring mild bleeding disorders (MBD) such as von Willebrand disease, platelet function disorder, or mild haemophilia is however unknown.
Aim: We conducted a prospective cross-sectional study to investigate the value of thromboelastometry analysis for diagnosis and prognosis of MBD.
Methods: Thromboelastometry analysis (ROTEM®) was conducted in all consecutive patients referred between January 2011 and March 2013 with a suspected bleeding disorder. Diagnostic work-up was done according to current guidelines.
Results: MBD was diagnosed in 111 out of 217 patients (52.1%), median age was 40.1 years, IQR 28.9, 59.2; 67.6% were female. Possible or definite platelet function disorder was diagnosed in 50 patients (42.7%), von Willebrand disease (vWD) in 24 patients (11.1%), mild haemophilia in 4 patients (1.8%), mild factor XI deficiency in 2 patients (0.9%), low von Willebrand factor associated with blood group 0 in 13 patients (6.0%), anticoagulation treatment in 3 patients (1.4%), and a systemic disorder in 15 patients (6.9%). Presence of MBD was not associated with a significant difference in thromboelastometry parameters (CT EXTEM, MCF EXTEM, CT INTEM, MCF INTEM, MCF FIBTEM). In addition, no significant differences were observed with regard to categories of the ISTH bleeding assessment tool. Minor differences – all within the established ROTEM reference ranges – were noted for some MBD: mild haemophilia (MCF EXTEM, MCF INTEM, MCF FIBTEM), definite vWD type 1 (MCF FIBTEM), anticoagulation treatment (CT EXTEM), and systemic disorders (CT EXTEM).
Conclusions: Our data do not support the utility of thromboelastometry analysis for diagnosis, prognosis or management in patients with mild bleeding disorders, particularly in the perioperative setting.

FM291

Establishment of a patient-derived myelofibrosis xenograft mouse model

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Introduction: A growing number of patient-derived xenograft (PDX) mouse models have been developed over the past few decades that allow engraftment of human hematopoietic stem cell (HSC) malignancies in order to study the evolution of HSC and leukemic stem cells, as well as disease heterogeneity. Myelofibrosis (MF) is a HSC disorder characterized by bone marrow fibrosis that has the potential to transform into acute myeloid leukemia. However, the engraftment of MF SCs in PDX models is poor (Wang et al., JCI 2012) presumably due to the lack of supportive factors in the bone marrow (BM) microenvironment. We hypothesized that the constitutive expression of human cytokines and growth factors in a PDX model

may promote the development of the human MF clone *in vivo*. Therefore, we used next-generation mice that express human M-CSF, IL-3, GM-CSF, TPO, and SIRPαTg (MISTRG) in order to develop a pre-clinical MF PDX model.
Methods: Purified peripheral blood stem and progenitor (CD34+) cells were collected from MF patients and intrahepatically transplanted into sublethally irradiated newborn MISTRG mice. 5–9 weeks after transplantation mice were sacrificed and analyzed for human engraftment using flow cytometry and immunohistochemistry.
Results: Engraftment was seen from four out of seven patient samples transplanted in MISTRG mice with an overall total median of 16.1% in the BM and 7.1% in the peripheral blood (PB) of human CD45+ cells. Over 60% of engrafted cells were of myeloid origin in the BM and PB, 18.55% and 50.85% were monocytes in the BM and PB respectively. In addition, a significant frequency of human CD34+ hematopoietic stem and progenitor cells (HSPCs) was observed in engrafted mice. Overall, the results suggest that the next-generation MISTRG mice support human MF engraftment.
Conclusions: MISTRG mice support unprecedented myelo-monocytic differentiation of human MF SCs in 57% of patient samples investigated so far. Immunohistochemistry will also be performed on the BM and spleen of these mice in order to check for fibrosis and megakaryocytes. In order to determine whether specific somatic mutations promote human MF engraftment in PDX models next-generation sequencing will be performed on transplanted patient samples.

FM292

Targeting the MAPK signaling pathway with Cobimetinib (GDC-0973) enhances the anti-leukemia efficacy of the MDM2-inhibitor Idasanutlin (RG-7388) in acute myeloid leukemia

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Introduction: The tumor suppressor protein p53 is inactivated in a large variety of cancer cells including acute myeloid leukemia (AML). While *TP53* gene mutations are rarely observed in AML cells at diagnosis, p53 protein function is commonly suppressed by overexpression of the cellular p53 inhibitor MDM2. In addition, other growth factor signaling pathways such as the MAPK cascade (RAS-RAF-MEK-ERK) are often active in AML cells. Consequently, combined administration of MDM2 antagonists and MEK inhibitors may present a promising anti-leukemia treatment strategy.
Methods: The aim of this study was to identify AML subgroups with particular sensitivity against the combined treatment with MDM2 antagonists and MEK inhibitors. In particular, molecular subgroups defined by the mutational status of *TP53, FLT3* and *NPM1* were screened. The MDM2 antagonist Idasanutlin and the MEK inhibitor Cobimetinib were assessed as single agents and in combination in a variety of AML cell lines and AML blast cells for their ability to induce apoptosis and cell death. AML cell lines and blast cells comprised all major morphologic and molecular AML subtypes.
Results: We found a considerably differing anti-leukemia efficacy across various AML cell types depending on the molecular background. AML cells with maximum sensitivity to single compound treatment as well as to the combined treatment with both Idasanutlin and Cobimetinib were characterized by wildtype status of the *TP53*, *FLT3* and *NPM1* genes. Remarkably, combined treatment with Idasanutlin and Cobimetinib together was more effective than single compound treatment. In contrast, AML cells with *FLT3*-ITD or with mutated *NPM1* were less sensitive. Finally, *TP53*mut cells were largely resistant to both compounds as well as to the combined treatment.
Conclusion: Our data indicate that AML cells defined by the wildtype status of the *TP53*, *FLT3* and *NPM1* genes accounting for up to 25% of AML patients emerge to be most sensitive to the combined treatment with Idasanutlin and Cobimetinib. In contrast, AML cells with mutations in *FLT3* or *NPM1* are less sensitive, whereas AML cells with mutated *TP53* are largely resistant. These results propose that the combination of an MDM2 and a MEK inhibitor may be an effective and specific treatment to target AML subtypes with wildtype status of the *TP53*, *FLT3* and *NPM1* genes.

FM293

Different anticoagulant effects despite similar Rivaroxaban plasma concentrations in individual obese patients

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Introduction: Rivaroxaban (RVX), a direct inhibitor of factor Xa, has been developed to bypass the limitations of traditional anticoagulants, such as intensive coagulation monitoring, drug-drug and drug-food interactions, or large inter-individual variations in dose-response. RVX has predictable pharmacokinetics and pharmakodynamics. Thus, there is no need for laboratory monitoring or guided dose adjustment in patients. However the “one dose fits all” concept based on randomized clinical trials might not be always adequate for individual patients in everyday clinical practice.
Objectives: The aim of this study was to assess the anticoagulant effect of similar plasma concentrations of RVX on thrombin generation (TG) in obese patients undergoing bariatric surgery and to compare individual anticoagulation profiles before and after surgery.
Methods: A total of 12 patients receiving a single dose of RVX (10 mg) before bariatric surgery and on the third postoperative day had 9 citrate whole blood samples taken during the 24 hours following drug ingestion. RVX plasma concentration was quantified at baseline and at different time points from ingestion with a calibrated automated anti-Xa chromogenic assay. RVX anticoagulant effect was assessed *ex-vivo* by monitoring tissue factor induced TG in platelet-poor-plasma (PPP) with calibrated automated thrombogram (CAT).
Results: TG measurements showed that despite similar RVX-concentrations, patient thrombograms significantly differed (fig. 1).

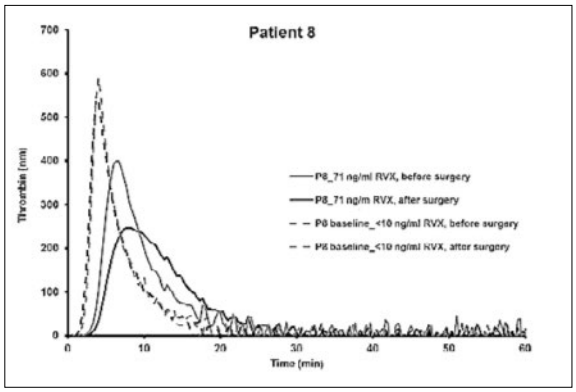

Figure 1

First, we observed large inter-individual variations among patients. Second, we also observed different TG patterns for the same individual before and after surgery. Specifically, at similar RVX concentrations, patients had higher thrombotic profiles in the post-operative phase.
Conclusions: CAT analysis shows that in obese patients, inter-individual differences exist in TG inhibition in response to a similar plasma concentration of RVX. Those differences appear to reflect the peculiar prothrombotic potential of each individual patient and suggest that the same RVX doses might not exert the same anticoagulant effect in different patients and/or in the same patient at a different point in time. This might be of particular relevance in the postoperative phase, in which the lower TG inhibition observed could indicate that the preoperative RVX dose is less efficient in providing a good prophylactic anticoagulation.

FM294

Applying 3D quantitative microscopy to study global topography and cellular interactions in the bone marrow

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Introduction: During adulthood, bone marrow (BM) cavities are the primary sites of production of vast amounts of blood cellular components from a rare population of hematopoietic stem cells (HSCs). Beyond their hematopoietic function, BM tissues host immune responses and maintain immunological memory. In addition to hematopoietic cells, the BM is populated by a heterogeneous mixture of endothelial, mesenchymal and neural stromal cells, which provide the necessary infrastructure for hematopoiesis to unfold and play essential regulatory roles. A thorough understanding of the spatial distributions, structural dynamics and interactions established by diverse cellular components within the complex landscape of the BM, is key for the generation of comprehensive models of healthy and pathological hematopoiesis.
Methods: In our laboratory we have recently developed advanced microscopy protocols that enable the 3D visualization of large volumes of BM tissues at an organ-wide level and with cellular and subcellular resolution. Here we report the generation of customized computational tools, which allow to generate quantitative spatial information in an automatic and unbiased fashion, and enable the extraction of spatial statistics for rigorous analysis of cellular interactions.
Results: We have employed this newly developed software suite to describe for the first time the spatial distribution of key components of the HSC niche, namely sinusoidal vessels and mesenchymal stromal cells. Our data demonstrate that in general the quantitative contribution of BM stromal cells to the total BM cellular asset is substantially underestimated by widely employed flow cytometric techniques. Detailed topological analysis reveals that the highly branched sinusoidal vessel network occupies on average 18% of the BM volume, subsequently constraining the space available for cells to distribute. Using rigorous spatial statistics we estimate that 95% of the BM space is contained within a distance of 22 µm from the nearest sinusoid. Nonetheless, mesenchymal stromal cells are significantly enriched in perivascular locations, pointing to a preferential interaction between these two key stromal components. Collectively our analyses provide quantitative measurements defining microarchitectural organization of BM stroma in homeostatic conditions. We anticipate that the tools developed will be instrumental to investigate the microarchitectural alterations underlying pathological hematopoiesis.

FM295

Use of first or second generation TKI for CML after allogeneic hematopoietic stem cell transplantation: a study by the CMWP of the EBMT

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Introduction: Patients (pts) relapsing with CML after allogeneic hematopoietic stem cell transplantation (alloHSCT) may be treated with TKI and/or DLI. As nowadays the majority of CML pts would have received at least imatinib prior to transplantation, we were interested in analizing a) the type of TKI used after alloHSCT, b) the indication for TKI treatment, c) the outcome of this treatment and d) the temporal relationship with DLI if given.
Patients and methods: 435 pts received TKI after first allogeneic HSCT for CML. The indications for TKI were the same as for transplantation (n = 25), for relapse/progression/persistent disease (n = 246), for prophylaxis/pre-emptive (n = 147), planned (n = 5), others (n = 8) and missing (n = 4).
Results: Median follow-up from start of TKI was 55 (1–171) months. The median time interval from transplant to TKI was 6 (0.2–165) months. It was longer for TKI given for relapse/progression with 15 (1–89) months and shorter for TKI given for prophylaxis/pre-emptive with 1.6 (0.2–43) months. It was longer for imatinib with 11 (0.2–121) months vs 3.8 (0.2–165) months for other TKI. Best response after TKI was complete molecular remission in 17.7%, cytogenetic remission in 4.4%, hematological remission in 20.2% and no response/progression/relapse in 57.7% of pts. 50% of pts treated with imatinib had a response (molecular/cytogenetic/hematological) vs 34% with nilotinib, 33% with dasatinib and 33% with bosutinib/ponatinib, p = 0.014. In univariate analysis, OS, RFS and RI were better for imatinib vs other TKI (table).

	All patients	Imatinib	Other TKIs	p value
5-yr OS	60% (55–65%)	66% (60–73%)	51% (42–60%)	0.0024
5-yr RFS	47% (42–53%)	53% (46–60%)	40% (32–48%)	0.0102
5-yr RI	25% (21–30%)	21% (16–27%)	31% (24–38%)	0.0454
5-yr NRM	27% (23–32%)	26% (20-31%)	29% (22-36%)	0.365

In multivariate analysis for OS, imatinib vs other TKI post-transplant did not show anymore an effect, HR 1.19 (0.85–1.67), p = 0.317. Factors influencing OS were time from diagnosis to transplant, HR 1.01 (1.00-1.01), p = 0.009, AP vs CP1, HR 1.80 (1.11–2.91), p = 0.017 and BC/>CP1 vs CP1, HR 2.3 (1.58–3.33), p <0.0001. In multivariate analysis for RFS imatinib vs other TKI did not have an effect. Other factors having a tendency or influencing RFS were time from diagnosis to transplant, HR 1.00 (1.00–1.01), p = 0.054, AP vs CP1, HR 1.52 (1.00-2.31), p = 0.050, BC/>CP1 vs CP1, HR 2.11 (1.55–2.88), p <0.001.
Conclusion: These data suggest that TKI after alloHSCT induce a response in about 42% of pts regardless of the type of TKI used and that time from diagnosis to transplantation as well as the phase of disease at transplant remain the main factors influencing the outcome of CML patients relapsing after alloHSCT.

FM296

Long-term clinical outcomes of patients with CYP2C9 and VKORC1 variants treated with vitamin K antagonists: a prospective, multicenter cohort study of elderly patients with venous thromboembolism

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Background: The application of individualized medicine based on genetic factors to patients requiring anticoagulant treatment is hampered by a lack of knowledge on their long-term effects on relevant clinical outcomes.
Aim: To fill this gap, we examined the association between polymorphisms of the vitamin K-epoxide reductase *(VKORC1)* as well as the cytochrome P450 enzyme gene *(CYP2C9)* and long-term clinical outcomes in a prospective, multicenter cohort study of elderly patients treated with vitamin K antagonists for venous thromboembolism (VTE).
Methods: Consecutive patients aged 65 years or older with an acute, objectively confirmed VTE were identified between 2009 and 2013 in all five university hospitals and four high-volume non-university hospitals in Switzerland. The primary outcome was the time to any clinical event, i.e. overall mortality, major- and non-major clinically relevant bleeding, or recurrent VTE.
Results: Overall, 774 patients were followed for a median duration of 30.1 months. The primary outcome occurred in 334 patients (43.2%) and 119 patients died (15.4%). Major bleeding occurred in 100 patients (12.9%), clinically relevant non-major bleeding in 167 patients (21.6%), and recurrent VTE in 100 patients (12.9%). After adjustment, the presence of *CYP2C9* variants was significantly associated with any clinical event (hazard ratio [HR] 1.34; 95% CI 1.08, 1.66), death (HR 1.74; 95% CI 1.19, 2.52), and clinically relevant non-major bleeding (sub-hazard ratio [SHR] 1.38; 95% CI 1.01, 1.55), but not with major bleeding (SHR 1.03; 95% CI: 0.69, 1.55) and recurrent VTE (SHR 0.95; 95% CI 0.62, 1.44). The presence of *VKORC1* variant was not associated with any clinical event. No relevant differences in the percentage of time spent within the therapeutic range were observed in patients with and without *CYP2C9* variants [DA1].
Conclusions: In conclusion, our results demonstrate a significant association between *CYP2C9* polymorphisms and deaths, probably because of effects independent from quality of anticoagulation and major bleeding.

FM297

Targeting the p53 inhibitor MDM2 enhances specificity and efficacy of the FLT3-inhibitor midostaurin in FLT3-ITD acute myeloid leukemia

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Introduction: Prognosis of acute myeloid leukemia (AML) patients with *FLT3*-ITD is poor, particularly in *FLT3*-ITD AML patients in relapse or refractory to conventional induction treatment or in *FLT3*-ITD AML patients unfit for intensive treatment, thus highlighting an unmet need for novel therapeutic approaches. The combined use of compounds targeted against the mutated FLT3 receptor and against cellular inhibitors of the master tumor suppressor p53 might propose an effective treatment option for this poor risk group of AML patients.
Methods: In this study, we assessed the protein kinase inhibitor Midostaurin (PKC412) and the MDM2 inhibitor HDM201 as well as cytotoxic compounds used for conventional induction treatment as single agents and in combination in AML cell lines and in AML blast cells for their ability to induce apoptosis and cell death in leukemic cells. AML cell lines and blast cells represented all major morphologic and molecular subtypes, including *FLT3*-ITD and *FLT3* wildtype, *NPM1* mutant and wildtype, as well as *TP53* mutant and wildtype cell lines.
Results: We found that Midostaurin and HDM201 appear to specifically target *FLT3*-ITD AML cells that are wildtype for *TP53* and *NPM1*. *FLT3*-ITD cells were significantly more sensitive to both compounds than *FLT3* wildtype cells whereas *TP53* mutant cells were not sensitive at all. The presence of a mutated NPM1 allele significantly reduced the susceptibility to both compounds. Moreover, the combination of Midostaurin and HDM201 was superior to single agent therapy and more specific and effective against *FLT3*-ITD cells than the combination of Midostaurin together with conventional cytotoxic induction treatment.
Conclusion: Our data indicate that AML cells with *FLT3*-ITD, *NPM1* wildtype and *TP53* wildtype accounting for up to 30% of AML patients emerge to be most sensitive to the combined treatment with Midostaurin and HDM201 whereas AML cells with wildtype *FLT3* or mutated *NPM1* are less sensitive, and *TP53* mutated cells are not sensitive at all. These results indicate that the combined use of an MDM2 and a FLT3 inhibitor may be both a promising and specific treatment option to target *FLT3*-ITD AML.

FM298

Conjoint high anti-C1q and anti-ADAMTS13 autoantibody titers mark the immune response in lupus nephritis and concurrent SLE/iTTP patients

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Introduction: Thrombotic events such as microvascular occlusions – a hallmark of immune-mediated thrombotic thrombocytopenic purpura (iTTP), are the main causes of morbidity and mortality among systemic Lupus erythematosus (SLE) patients with a prevalence of 10%. Renal thrombotic microangiopathic symptoms (TMA) are observed frequently together with an overactivated classical complement system where anti-C1q antibodies (Abs) were shown to be strongly linked to the severity of active lupus nephritis. Given the considerable overlap of clinical symptoms between SLE and iTTP, we evaluated if ADAMTS13 activity, anti-ADAMTS13 and/or anti-C1q antibodies (Abs) titers might serve as diagnostic markers to distinguish primary iTTP from conjoint (secondary) iTTP/SLE.
Method: ADAMTS13 activity (FRETS-VWF73 assay) and presence of circulating anti-ADAMTS13 and/or anti-C1q titers (commercial ADAMTS13 INH ELISA or C1q ELISA, respectively) were assessed in blood samples of a SLE cohort (n = 93; 40/93 with active lupus, 13/93 in remission and 40/93 with complement-mediated complications only) and compared to a cohort of acute iTTP (n = 92; 67 first episode, 25 with a relapse) and 41 healthy controls.
Results: ADAMTS13 activity was severely deficient (<5%) in 96% (88/92) iTTP patients and the 5 iTTP/SLE patients. Anti-ADAMTS13 Abs were found in 43% (40/93) of SLE patients (titer >15 AU/ml, range: 16–85 U/ml) compared to 95% (87/92) in iTTP patients with a median of 62.8 AU/ml (range 5 to >104 AU/ml) and only 5% (2/41; 16 and 26 AU/ml) in healthy controls. Anti-C1q Ab titers (positive 15 U/ml) were significantly increased in SLE patients (65/93, 70% with median 140 U/ml) when compared to iTTP (21% positive, median 33 U/ml) and healthy controls (19% positive, median 49 U/ml). Patients suffering from more than 1 autoimmune disease (n = 16) in both the SLE and iTTP cohort, lupus nephritis (SLE cohort, 22/40), TMA-associated nephritis (5/40) or concurrent SLE/iTTP (5) were marked by high dual positive Ab titers with median anti-C1q and anti-ADAMTS13 titers of 130 U/ml, respectively 40 AU/ml.
Conclusions: Our findings show that SLE patients presenting with a TMA-like picture (lupus nephritis) or iTTP patients with renal TMA constitute a specific subgroup marked by high anti-ADAMTS13 and anti-C1q Ab titers. Evaluation of larger patient cohorts with well documented clinical courses will allow to confirm dual Ab positivity as a marker for secondary complications in SLE and iTTP.

FM299

Trends in incidence and mortality of acute myeloid leukemia in Switzerland between 1989–2012

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Introduction: Acute Myeloid Leukemia (AML) is a rare disease with an increasing incidence in the elderly and an emerging impact on health system resources. The trends in incidence and mortality of AML have not been studied in detail in Switzerland for comparison with other countries.
Methods: This is a population-based, retrospective observational analysis of AML cases reported to the *Cantonal Cancer Registries* (CCRs) in Switzerland between 1989 and 2012 and aggregated by the *National Institute for Epidemiology and Cancer Registration* (NICER). The *Swiss Federal Statistics Office* (SFSO) provided canton-specific mid-year estimates of the general population and mortality statistics.

Results: The coverage of the Swiss population by the CCRs increased from 55.3% to 65.1% during the observation time. 3684 new AML cases were registred, corresponding to an extrapolated number of 6226 new AML cases in the Swiss population during the observation time. The extrapolated mean annual case frequency increased from 235 to 299 AML cases (+27%). Age-standardized incidence rates ranged from 3.3–3.6 in males, and 2.5-2.8 in females per 100'000 patient-years, respectively, and remained stable throughout the observation time. Median age at diagnosis was 66 years for males in all time periods and ranged from 67-70 years in females. Age-standardized mortality rates ranged from 1.1–2.4 in males, and 0.8–1.7 in females. Mortality rates were lowest in the earliest time periods, indicating a reporting bias for 1989-2000. The fraction of unclassifed AML decreased from 78% to 39% during the observation time. However, the proportion remained high (50% and 1.4%) in the older compared to younger patients in 2008–2012 (age cut-off: median age).
Discussion: AML incidence remained stable during the observation period, indicating that the 27% rise in case-frequency is related to population growth and ageing and not to an increase of age-specific risk. Elderly AML patients are more frequently not further subclassifed, suggesting that diagnostics and reporting is less accurate in elderly patients. As previously reported for MDS patients, the currently available data is also insufficient for detailed health services research in AML patients. Further collection of longitudinal data on treatment, side effects and outcomes is warranted.

TABLE 1: Characteristics of MDS cases reported to Swiss cancer registries for 1989-2012

	1989-2000		2001-2007		2008-2012		Total
	n	%	n	%	n	%	
Overall observed	1574	100	1148	100	964	100	**3684**
- coverage (%)		55.3		59.3		65.1	
- extrapolated*	2815*		1914*		1497*		**6226***
- mean annual case frequency*	235*		273*		299*		-
Sex							
female	748	47.5	529	46.2	481	49.9	**1758**
male	826	52.5	617	53.8	483	50.1	**1926**
Age							
<65	724	46.0	503	43.9	430	44.6	**1657**
65-74	340	21.6	261	22.8	233	24.2	**834**
75-84	368	23.4	286	25.0	216	22.4	**870**
85+	142	9.0	96	8.4	85	8.8	**323**
Subtypes							
Recurrent genetic alterations							***179***
- t(15;17)(q22;q11-12)	38	2.4	48	4.2	49	5.1	**135**
- 11q23 abnormalities	-	-	2	0.2	2	0.2	**4**
- t(8;21)(q22;q22)	-	-	18	1.6	22	2.3	**40**
Therapy-related							***62***
- t-AML	-	-	9	0.8	29	3.1	**38**
- t-MDS	-	-	10	0.9	14	1.5	**24**
AML-NOS							***1034***
- FAB M0	-	-	14	1.2	48	5.0	**62**
- FAB M1	-	-	54	4.7	69	7.2	**123**
- FAB M2	-	-	79	6.9	88	9.1	**167**
- FAB M4	136	8.6	88	7.7	73	7.6	**297**
- FAB M4eos	-	-	11	1.0	14	1.5	**25**
- FAB M5	109	6.9	77	6.7	58	6.0	**244**
- FAB M6	41	2.6	27	2.4	20	2.1	**88**
- FAB M7	15	1.0	8	0.7	5	0.5	**28**
Specific subtypes							***181***
- Acute basophilic leukemia	1	0.1	-	-	1	0.1	**2**
- Acute panmyelosis with myelofibrosis	3	0.2	4	0.4	9	0.9	**16**
- Myeloid sarcoma	3	0.2	4	0.4	8	0.9	**15**
- MDS-related	-	-	66	5.8	81	8.4	**147**
Unclassified							***2228***
- AML, unspecified	1125	71.5	585	51.1	364	37.8	**2074**
- AML, NOS	100	6.6	42	3.7	9	0.9	**154**

* Extrapolation to the whole Swiss population

TABLE 2: Incidence and mortality rates of AML

	1989-2000		2001-2007		2008-2012	
	crude rate [a]	age-standardized rate (95% CI) [a,b]	crude rate [a]	age-standardized rate (95% CI) [a,b]	crude rate [a]	age-standardized rate (95% CI) [a,b]
Incidence Rate						
overall	3.4	3.0 (2.7-3.2)	3.7	3.0 (2.8-3.3)	3.8	3.0 (2.7-3.3)
male	3.7	3.5 (3.2-3.7)	4.1	3.6 (3.3-3.9)	3.9	3.3 (3.0-3.6)
female	3.1	2.5 (2.3-2.6)	3.4	2.5 (2.2-2.7)	3.7	2.8 (2.5-3.0)
Mortality rate						
overall	1.1	0.9 (0.8-1.0)	2.7	2.1 (1.9-2.2)	2.6	1.9 (1.7-2.0)
male	1.2	1.1 (1.0-1.2)	2.9	2.4 (2.3-2.6)	2.8	2.2 (2.2-2.4)
female	1.1	0.8 (0.7-0.9)	2.4	1.7 (1.5-1.8)	2.4	1.5 (1.4-1.7)

a) per 100'000 habitants
b) Old European Standard

FM300

GPR56, a novel stem cell marker in CD34 negative acute myeloid leukemia?

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Objectives: Although considered a curable disease, acute myeloid leukemia (AML) leads to death in a considerable percentage of patients. The main obstacle to cure is relapse after apparent remission, which, from a cellular perspective, is thought to occur from so-called leukemic stem cells (LSCs). Several reports have documented that surface expression of the HSC marker CD34 can identify subpopulations of leukemic blasts with LSC properties and stem molecular signature within AML. However, ~30% of AML do not express CD34 on the cell surface, mainly in NPM-mutated AML that show low CD34 expression, and no other reliable marker for LSC isolation has been reported in this disease subtype. Recently, the G-coupled protein receptor 56 (GPR56), a molecule regulating cell adhesion, has been implicated as LSC marker in CD34 positive AML. Here, we aim to analyze whether surface expression of GPR56 can be used as LSC marker in CD34 negative (NPM-mutated) AML, where the LSC compartment has not yet been characterised.
Methods: CD34 negative AML patient samples were screened for GPR56 surface expression by flow cytometry using an anti-human GPR56 PE antibody, followed by subsequent FACS to separate GPR56-negative and positive leukemic blasts that were either used for *in vitro* colony forming unit (CFU) or *in vivo* xenotransplantation assays in immunosuppressed NSG mice.
Results: Flow cytometric assessment of GPR56 surface expression revealed heterogeneous but distinct GPR56 expression in each of the analysed samples (n = 6 CD34-negative AML patient blasts). Pilot data indicate that only GPR56+ (and not GPR56-) cells indeed induce CFU and *in vivo* leukemogenicity, indicating that clonogenicity and *in vivo* leukemogenesis are confined to GPR56+ cells in CD34- AML. We are currently awaiting further results from additional patient samples.
Conclusion and outlook: Our preliminary data suggests that GPR56 might indeed be used as a novel stem cell marker in CD34 negative AML. In order to solidify these results, we will perform RNA sequencing experiments to retrieve the LSC signature in GPR56+ vs. GPR56- sorted AML blasts. Since it has been recently shown that GPR56 expression promotes migration and adhesion of healthy HSCs to the BM niches, we furthermore plan to functionally characterize the role of GPR56 in CD34 negative AML by analysing the adhesion capacity of GPR56+/- cells in *in vitro* co-culture experiments with MS5 stromal cells and in *in vivo* homing assays.

FREE CONTRIBUTIONS: EXPERIMENTAL HEMATOLOGY

FM301

The bone marrow microenvironment is a target of graft-vs-host reactivity following allogeneic hematopoietic cell transplantation in mice

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Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for many malignancies of the blood. Graft T cells (Tc) are critical to control malignant cells but can also induce graft-vs-host-disease (GVHD), in which donor Tc target and destroy host tissues. Little attention has been paid to effects of alloreactive Tc on the bone marrow (BM) and how structural damage of its microenvironment affects hematopoietic recovery and function. Here, we studied in an MHC-matched, minor antigen mismatched mouse model the effects of lethal irradiation and HCT of purified hematopoietic stem cells (HSC; cKIT$^+$Sca1$^+$Lin$^-$) +/- Tc on the hematopoietic and non-hematopoietic BM compartments. At 1, 2, 3, and 4w post-HCT bones and marrow were analyzed by FACS and 3D-confocal microscopy. Post allo-HCT there was a transient weight loss in both groups (HSC and HSC+Tc), but no overt GVHD. Total BM cell counts dropped, but at 2w mice given HSC had significantly higher absolute BM counts compared with HSC+Tc recipients. Strikingly, B-cell recovery occurred promptly in HSC recipients but was severely impaired in the HSC+Tc group. Likewise, granulocyte recovery at 2, 3, and 4w was significantly better in HSC vs. HSC+Tc recipients. Regarding the non-hematopoietic compartment CD45$^-$Ter119$^-$CD31$^+$ endothelial cells (EC) were significantly reduced in both groups compared with wildtype controls (WT) at 1, 2, and 3w post-HCT but recovery was superior in the HSC vs the HSC+Tc group with significantly higher EC counts at 2+3w. The most pronounced effects were observed for CXCL12-abundant reticular (CAR) cells (CD45$^-$Ter119$^-$CD31$^-$CD140B$^+$), which were initially reduced in HSC recipients but normalized at 4w post-HCT. In HSC+Tc recipients CAR cells were significantly lower and remained reduced at w4. 3D-confocal microscopy confirmed these observations and revealed rapid recovery of extracellular matrix and vascular structures, with simultaneous disappearance of adipocytes at 2w post-HCT in the HSC group. In contrast, in recipients of HSC+Tc severe disruption of the structural integrity (Figure1) but rather occupation of space by adipocytes. In clinical HCT delayed hematopoietic reconstitution presents a major problem contributing to increased morbidity and mortality. Our data show that alloreactivity has a major impact on the non-hematopoietic compartment of the BM in terms of both damage and reconstitution of the microarchitecture and ultimately hematopoietic recovery.

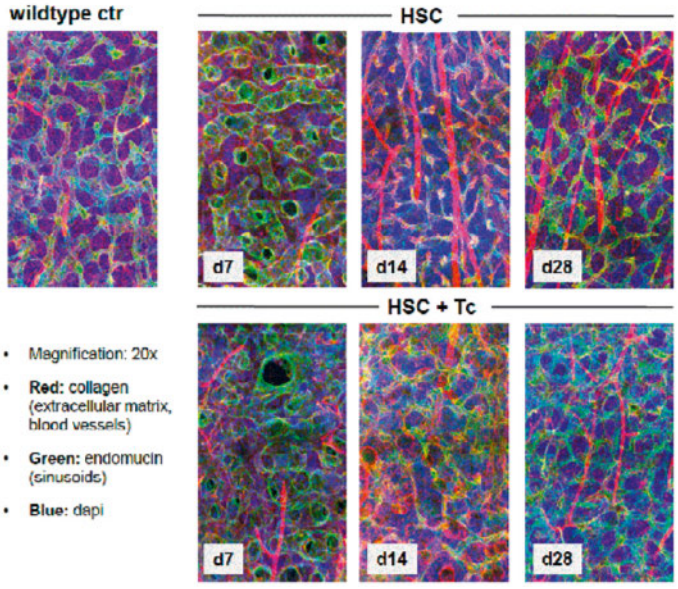

Figure 1

FM302

Functional and structural dynamics of the bone marrow stromal microenvironment after cytoreductive therapies

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Introduction: Hematopoietically active bone marrow (BM) tissues are highly sensitive to cytoreductive treatments such as ionizing irradiation and chemotherapeutic agents, which are the treatment of choice for multiple malignancies and employed as conditioning regiments in BM transplantations. The cytotoxic damage and killing of rapidly cycling hematopoietic progenitors induced by myeloablative therapies have been extensively characterized. However, it is still largely unknown whether and to what extent these treatments target BM stromal cells of endothelial and mesenchymal origin, which critically regulate hematopoiesis. Here we have analyzed the dynamics of BM stroma upon myeloablation, the resulting microarchitectural effects on BM and the kinetics of regeneration of BM tissues post-injury.
Methods: In this study we employ advanced flow cytometric protocols to analyze quantitative changes in cellular populations. Structural effects on the murine BM microenvironment are in turn visualized and quantified by using advanced 3D-confocal microscopy in combination with newly developed computational tools for image-based analysis.
Results: As previously reported, ionizing irradiation and 5-FU treatment led to a severe loss of hematopoietic stem and progenitor cells (HSPCs). Notably, a similar profound decrease in endothelial and mesenchymal stroma was observed. Decline in stromal cell numbers was apparent 7 days after treatment and encompassed a major loss of structural integrity of the BM microenvironment. 3D imaging revealed massive sinusoidal dilation followed by appearance of ruptures in vessel walls. Structural effects and cellular effects were partially reversed 14 days post treatment in a regenerative process that culminated 4 weeks after treatment. In addition, massive *de novo* differentiation of mesenchymal progenitors into adipocytes lead to adipogenic infiltration of large regions of the BM. Of note, this process was fully reversible as virtually almost all adipocytes were cleared from BM tissues 56 days after treatment. To compensate for impaired BM function, reversible extramedullary hematopoiesis was prominent at time points of maximal BM damage.
Conclusion: Our observations demonstrate that the stromal BM microenvironment is highly sensitive to myeloablative therapies. Of note, BM tissues are endowed with an intrinsic regenerative and self-organizing capacity that enables rebuilding of a fully functional tissue microenvironment after severe damage.

FM303

Intrinsic and extrinsic factors control aging of hematopoietic stem cells

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Life-long self-renewing hematopoietic stem cells (HSCs) repetitively contribute to replenishment of mature blood cells. Aged HSCs show reduced self-renewal, less efficient bone marrow (BM)-homing capacity, and myeloid-skewed differentiation. We demonstrated a cell-intrinsic drive towards dormancy in HSCs imprinted by increased divisional history (JExpMed 2011). Here, we tackle the questions what extrinsic and intrinsic factors determine HSC behaviour at the cellular and molecular level. We have established in vivo single HSC divisional tracking with CFSE (5(6)-carboxyfluorescein diacetate *N*-succinimidyl ester), and subsequent isolation of different divisional classes of HSC-containing cell fractions (LKS) based on CFSE dilution for in vivo HSC functional readout. CFSE-labeled young (8–12 week old) and aged (>2 year old) LKS were transferred into non-irradiated young or aged recipients, respectively. To test biological function of HSC with distinct divisional histories, quiescent or cycling LKS were isolated and transplanted into lethally irradiated mice. The transplanted mice were monthly bled to follow long-term donor engraftment and lineage repopulation. To dissect aging-associated extrinsic factors, we performed antibody based protein arrays and transcriptome analysis

with total BM of young versus aged animals. The effect of identified candidates on HSC behavior was further tested in vivo by employing CFSE assay. BM analysis at 8 weeks after divisional tracking showed that young LKS proliferated faster than old LKS independent of the BM environment, while both young and aged LKS were more dormant in an old environment. In secondary recipients, dormant aged HSCs, independent of environmental age, favor myelopoiesis. In contrast, cycling aged HSCs that were exposed to a young environment showed balanced lineage repopulation similar as do young HSCs. Expression levels of some inflammatory cytokines and myeloid differentiation factors were altered in aged BM. These factors drive young HSC towards proliferation and differentiation, while this effect is limited on aged HSCs, in part likely due to their increased quiescent state. These findings demonstrate that HSC proliferation and differentiation are controlled by cell-intrinsic and -extrinsic factors: extensive proliferative history imprints a quiescence program on HSCs that is associated with myeloid-biased differentiation; lineage skewing of HSC during aging can be modulated via environmental cues.

FM304

Hypoglycemia and energy crisis contribute to early lethality in JAK2 mutated models of myeloproliferative neoplasm

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Background: Myeloproliferative neoplasms (MPN) are clonal disorders of hematopoietic stem cells (HSC) driven by activation of oncogenic mutations such as JAK2-V617F. MPNs are characterized by elevated platelet and/or erythrocyte production or development of myelofibrosis. We studied several mouse models of MPN that are driven by mutant JAK2-V617F (VF) or by an activating mutation in exon 12 (Ex12). These mice exhibit all features of MPN and result in early mortality. The causes of death in these mice are largely unknown, since hemorrhagic and thrombotic complications are relatively rare and leukemic transformation is not observed. We noticed that VF and Ex12 mice display markedly decreased body fat and therefore we performed a detailed analysis of metabolism in these mice.
Results: Hematopoietic specific activation of VF or Ex12 mutations in mice caused global metabolic changes including adipose tissue atrophy due to increased adipocyte lysis in white and brown fat tissues, systemic metabolic changes, and resistance to high-fat diet (HFD) induced obesity in mice. In addition, these mice under normal dietary conditions were severely hypoglycemic and showed almost no increased glucose tolerance despite normal insulin levels. These metabolic changes were also present in recipients transplanted with bone marrow from VF or Ex12 donors, indicating that the changes are caused by the mass of mutant hematopoietic cells. Intriguingly, HFD treatment significantly ameliorated early mortality of MPN mice. This effect was not due to reduction in elevated platelet and erythrocyte numbers, implying that altered energy homeostasis likely attributable for early mortality of MPN mice. Integrated transcriptomics, and metabolomics analysis together with metabolic functional assays identified increased reliance of mutant HSPCs on fatty acid oxidation, glycolysis, and amino acid metabolism causing clonal expansion of MPN initiating HSPCs. Pharmacological targeting of JAK2 activation with classical JAK2 inhibitor, Ruxolitinib, reduced MPN associated hypoglycemia, MPN clonal expansion, and disease burden.
Conclusion: Hypoglycemia and energy crisis are likely to contribute to lethality of MPN mice. Maintaining energy homeostasis and adipose tissue depots by high fat diet improved survival of MPN mice. Targeting the metabolic dependencies of the mutant MPN clone is a novel potential strategy for MPN treatment.

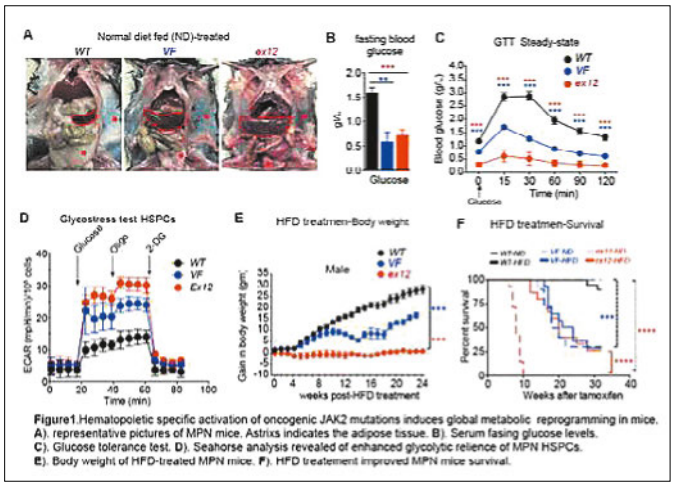

Figure1.Hematopoietic specific activation of oncogenic JAK2 mutations induces global metabolic reprogramming in mice. A). representative pictures of MPN mice. Astrixs indicates the adipose tissue. B). Serum fasing glucose levels. C). Glucose tolerance test. D). Seahorse analysis revealed of enhanced glycolytic reliance of MPN HSPCs. E). Body weight of HFD-treated MPN mice. F). HFD treatement improved MPN mice survival.

Figure 1

FM305

Genotyping of hodgkin lymphoma on the liquid biopsy

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Introduction: In classical Hodgkin lymphoma (cHL) the low representation (1–5%) of Reed-Sternberg cells (RS) challenged tumor genotyping on the diagnostic tissue biopsy. Cell free DNA (cfDNA) is shed into the blood by tumor cells undergoing apoptosis and can be used as source of tumor DNA for the identification of somatic mutations. This study aims at providing the evidence that the genetic profile of the cHL can be accurately tracked by using plasma cfDNA.
Methods: The study incudes a panel of 24 newly diagnosed cases of cHL provided with cfDNA from plasma and paired DNA from granulocytes as source of germline DNA to filter out polymorphisms and sequencing noise. Paired genomic DNA from formalin fixed paraffin embedded (FFPE) tumor tissue biopsies was available for 22 cases. A targeted resequencing panel including the coding exons and splice sites of 77 genes that are recurrently mutated in aggressive B-cell lymphomas was used for genotyping. DNA samples were analyzed by ultra-deep-next generation sequencing (NGS) on the MiSeq platform (Illumina) using the CAPP-seq strategy.
Results: Genotyping of plasma cfDNA identified 145 non-synonymous somatic mutations in 37 genes, including *STAT6* (45%) *TNFAIP3* (45%), *ITPKB* (30%) *B2M* (20%), *GNA13* (15%) *CIITA* (10%) *XPO1* (10%) and *CD58* (5%) among the most recurrently affected. The mutational profiles pointed to the involvement of PI3K/AKT signaling, cytokines signaling, NF-kB signaling and the immune escape in cHL. *ITPKB* (a negative regulator of the PI3K/AKT signaling pathway) was specifically mutated in the cHL across aggressive B cell lymphomas. By using highly sensitivity techniques, most of the mutations discovered in cfDNA were also identified in pair tumor DNA from the tissue biopsy, thus confirming their tumor origin.
Conclusions: This study provides the evidence that cHL can be genotyped using plasma cfDNA as source of tumor DNA, and identified *ITPKB* as a new gene involved in this lymphoma type.

FREE CONTRIBUTIONS: HEMOSTASIS, VASCULAR BIOLOGY, TRANSFUSION MEDICINE

FM306

Heparin-induced thrombocytopenia (HIT) diagnosis in 30 minutes! A prospective evaluation of a rapid diagnostic work-up

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Introduction: The laboratory gold standard for diagnosing HIT is a functional assay, e.g. the Heparin Induced Platelet Aggregation (HIPA) test. We assessed 3 quantitative immunoassays (IAs) detecting anti-PF4/heparin antibodies for their ability to predict the HIPA result. Our aim was to prospectively evaluate a rapid algorithm able to confirm or exclude HIT with a laboratory turn-around-time of 30 minutes.
Methods: We conducted a retrospective (05.2014–08.2015; n = 220) and a prospective (09.2015–08.2016; n = 234) study in patients with HIT suspicion. 46 plasma samples of the retrospective study and all samples of the prospective one were analyzed by 3 IAs (ELISA Zymutest HIA monostrip IgG; AcuStar HIT IgG; ID-H/PF4-PaGIA). ROC analysis let us compare the areas under the curve (AUC) and determine cut-offs with 100% negative (NPV) and positive (PPV) predictive values for a positive HIPA.
Results: HIT diagnosis was confirmed by a positive HIPA in 10% of patients (22/220) in the retrospective and in 9.4% (22/234) in the prospective study. AcuStar showed an AUC of 0.98 both in the retrospective (p = 0.02 compared to Zymutest and p = 0.59 to PaGIA) and in the prospective study (p = 0.06 compared to Zymutest and p = 0.52 to PaGIA). A 100% PPV was observed with a result >1.37 U/ml (identifying 18/22 HIPA-positive samples) and with a result >0.77 U/ml (identifying 20/22 HIPA-pos samples) in the retrospective and prospective studies, respectively. A 100% NPV was observed with a result of ≤0.12 U/ml and ≤0.18 U/ml (overall identifying 218/236 HIPA-negative samples). PaGIA showed an AUC of 0.99 and 0.97 in the two studies. A titer ≥16 had a 100% PPV and a titer < 2 had a 100% NPV (identifying 210/236 HIPA-negative cases). Applying conservative cut-off values of **≤0.12 (= negative) and ≥1.50 (= positive) for AcuStar results,** only 13% of samples (36/280) were between these values ("grey zone"). Among them, 17 (47%) were correctly solved by PaGIA. Eventually, 7% of all samples (19/280) remained unclear until HIPA result. The in house cut-off produced no false positive or negative results.
Conclusion: The sequential application of two rapid immunoassays (AcuStar HIT IgG and ID-H/PF4-PaGIA) with in-house determined cut-off values with 100% NPV and PPV enables a reliable and conclusive diagnostic work-up for ~95% of patients with clinical suspicion of HIT, in a laboratory turn-around-time of 30 minutes. We are now conducting a prospective validation of this rapid diagnostic algorithm.

FM307

Risk factors for recurrence in deep vein thrombosis patients with a tailored anticoagulant treatment based on residual vein thrombosis: contemporary data

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Background: Finding the optimal duration of anticoagulant treatment following an acute event of deep venous thrombosis (DVT) is challenging. Residual thrombosis has been identified as risk factor for recurrence, but data on management strategies based on residual thrombosis and associated recurrence rates in defined clinical care pathways (CCP) are lacking.
Objective: To investigate the long-term clinical outcomes and predictors for VTE recurrence in a contemporary cohort of patients with proximal deep vein thrombosis (DVT) managed according to the presence of residual vein thrombosis.
Methods: All patients treated at Maastricht University Medical Center within an established clinical care pathway from June 2003 through June 2013 were prospectively followed for up to 11 years. Treatment duration was tailored based on residual vein thrombosis. Recurrence rates were determined. A cox proportional hazards model employing anticoagulation treatment as time-varying covariate was used to define risk factors for recurrence.
Results: Out of 479 patients diagnosed with proximal DVT, 474 completed the two-year CCP (99%), and 457 (94.7%) the extended follow-up (2231.2 patient-years; median follow-up 4.6 years; median age 58.0 years; 50.4% females). Overall VTE recurrence was 2.9 per 100 patient-years, 1.3 if provoked by surgery, 2.1 if a non-surgical transient risk factor was present, and 4.0 if unprovoked. Residual thrombosis was present in 141 patients (29.8%). Duration of anticoagulation was 3 months in 75 patients (15.7%), 6 months in 230 (48.0%), 12 months in 95 (19.8%) and indefinite in 79 (16.5%). DVT was provoked by surgery in 95 patients (19.9%), by a transient non-surgical risk factor in 107 patients (22.3%) and unprovoked in 265 (55.3%). Significant predictors of recurrent events were unprovoked VTE (adjusted hazard ratio [HR] 4.6; 95% CI 1.7, 11.9), elevated d-dimers one month after stop treatment (HR 3.3; 1.8, 6.1), male sex (HR 2.8; 1.5, 5.1), high factor VIII (HR 2.2; 1.2, 4.0) and use of contraceptives (HR 0.1; 0.0, 0.9).
Conclusions: Patients with DVT managed within an established clinical care pathway according to the presence of residual vein thrombosis had low incidences of VTE recurrence. In accordance with other clinical settings, unprovoked VTE, male sex, elevated D-dimers one month after stop treatment, inflammation, and high FVIII were identified as major predictors for recurrent VTE.

FM308

Calcium monitoring in platelets: tool for diagnosing platelet function defects

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Introduction: Laboratory tests currently used to investigate a bleeding diathesis may fail to reveal the underlying hemostatic disorder. Flow cytometry (FC) improved our tools for exploring platelet (PLT) function and profiling defects associated with a bleeding diathesis. Our aim is to hone standard FC analysis by extending investigations to intracellular signaling. In this work, we assessed free intracellular Ca^{2+} upon PLT activation.
Method: Platelet-rich plasma was obtained from citrate-anticoagulated whole blood. PLTs were activated with increasing concentrations of thromboxane analogue U-46619, ADP, thrombin, the two selective thrombin receptor agonists TRAP6 (PAR-1 agonist) and AYPGKF (PAR-4 agonist), convulxin (agonist of the GPVI collagen receptor), and ionophore. Activation end-points were secretion of alpha-granules (detected by P-selectin expression) and activation of the fibrinogen receptor (visualized by PAC-1 binding). Intracellular free Ca^{2+} was detected by its indicator Fluo-3 AM. After measurement of a stable baseline, PLTs were activated with various agonists, and Fluo-3 fluorescence was continuously acquired over time, up to 10 minutes, on a BD Accuri C6 flow cytometer.
Results: Optimal dose-response concentrations were determined for each agonist and Ca^{2+} monitoring following PLT activation was performed. Maximal and sustained cytosolic Ca^{2+} increase was observed after PLT activation with ionophore. Very strong and sustained increase was also observed by activation with convulxin and thrombin. While convulxin was able to induce a strong Ca^{2+} spike followed by a plateau, thrombin induced an initially strong Ca^{2+} response, which subsequently declined. Both selective PAR agonists, TRAP6 and AYPGKF, demonstrated a strong increase with rapidly declining intracellular Ca^{2+}, but their combined action was not able to fully replicate thrombin effect. Finally, although a similar weak Ca^{2+} mobilization was observed with U-46619 and ADP, these agonists differently affected convulxin and thrombin responses when employed in combination.
Conclusion: The present work highlights the use of continuous calcium monitoring to complement FC analysis of PLT function. We demonstrate characteristic Ca^{2+} mobilization patterns following PLT activation with various agonists. This technique will sharpen the ability to detect PLT signaling defects in bleeding patients investigated for platelet function disorders.

FM309

Effect of complete lack of protein S on pregnancy outcome in mice

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Introduction: Complete protein S (PS) deficiency is a rare fatal thrombophilia associating purpura fulminans (PF) and disseminated intravascular coagulation (DIC). We obtained a full rescue of *Pros1*$^{-/-}$ lethality by targeting FVIII, *F8*$^{-/-}$*Pros1*$^{-/-}$ mice showing neither PF or DIC. Pregnancy loss was not observed in *Pros1*$^{+/-}$ mice. Because thrombophilias are associated with pregnancy loss, we investigated the effect of complete lack of PS on pregnancy outcome in mice.
Methods: Pregnancy monitoring in *F8*$^{-/-}$*Pros1*$^{-/-}$, *F8*$^{-/-}$*Pros1*$^{+/+}$ and *F8*$^{+/+}$*Pros1*$^{+/+}$ mice by blood cell count, coagulation tests and histology of pregnant mice and embryos.
Results: Vaginal plugs were observed in all *F8*$^{-/-}$*Pros1*$^{-/-}$ females (n = 19) but, independently of the male breeder genotype, no litters were produced. Embryos collection revealed embryonic mortality at E11.5-12.5 (58% dead embryos; n = 41/71), E13.5-16.5 (69%; n = 44/64). Most of dead embryos were macerated but some of them showed hemorrhages and thrombosis but no PF. Among embryos collected before E9.5–10.5, there was a lower number of embryos carrying the *F8*$^{-/-}$*Pros1*$^{-/-}$ genotype than expected (33% vs 50%) and no live embryos collected after E12.5 were *F8*$^{-/-}$*Pros1*$^{-/-}$. All embryos collected from *F8*$^{-/-}$*Pros1*$^{+/+}$ and *F8*$^{+/+}$*Pros1*$^{+/+}$ pregnant mice were alive. Recurrent pregnancy loss never affected *F8*$^{-/-}$*Pros1*$^{-/-}$ mice survival. Between E12-16 and in comparison to *F8*$^{-/-}$*Pros1*$^{+/+}$ gravid mice, *F8*$^{-/-}$*Pros1*$^{-/-}$ pregnant mice displayed reduced platelet count (559 ± 79 vs 829 ± 92G/L;P <0.05) and fibrinogen (1.0 ± 0.1 vs 2.4 ± 0.3g/L; P <0.001), and increased TAT complexes (25.4 ± 2.8 vs 12.6 ± 4.3 ng/L;P <0.05) whereas PT was normal in both genotypes. Moreover, placenta but not lung and liver sections showed fibrin clots. Importantly, all blood and histological analyses were comparable in *F8*$^{-/-}$*Pros1*$^{+/+}$ and *F8*$^{+/+}$*Pros1*$^{+/+}$ pregnant mice.
Treatment of *F8*$^{-/-}$*Pros1*$^{-/-}$ pregnant mice with enoxaparin prevented pregnancy loss; newborns were normal. Pregnancy outcome was also positive with low-dose aspirin. However, the litter size was slightly reduced (n = 2–4) in the aspirin group as compared to the enoxaparin group (n = 5–6).
Conclusion: Targeting FVIII did not prevent pregnancy loss due to placental thrombosis in gravid *Pros1*$^{-/-}$ mice. Although *F8*$^{-/-}$*Pros1*$^{-/-}$ pregnant mice displayed coagulation activation, there was no overt DIC. Aspirin or better enoxaparin treatment prevented pregnancy loss, indicating that thromboprophylaxis might apply to pregnancy in very severe inherited thrombophilias.

FM310

Overexpression of miR-21 involved in plasma cell myeloma-associated angiogenesis

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Introduction: Angiogenesis plays an important role in the pathophysiology of hematological malignancies including plasma cell myeloma (PCM). MicroRNA-21 (miR-21) is overexpressed and displays oncogenic activity in cancers. The aim of the present study is to examine the expression level of peripheral miR-21 in PCM patients and to determine its role in angiogenesis.

Methods: VEGF serum levels and miR-21 in PBMCs was measured in 93 patients with PCM directly before melphalan 200 mg/m^2 followed by autologous hematopoietic stem cell transplantation (auto-HSCT) and 2 months after HSCT; and 35 healthy controls. The study population was divided into two groups after therapy: responders (stringent complete response, complete response, very good partial response, partial response) and non-responders (stable disease, progressive disease). Gene expression of miR-21 was quantified by SYBR green real-time fluorescent quantitative PCR. Further tube formation of HUVECs and VEGF secretion was measured in miR-21 mimic or inhibitor transfected human plasma cell myeloma cell lines H929 and RPMI-8226.
Results: The expression level of miR-21 was significantly increased (2.7 ± 0.55 versus 0.78 ± 0.22; p <0.01) in PBMCs of PCM patients compared with healthy controls. Further, serum VEGF levels were increased in PCM patients (477 ± 145 pg/ml versus 178 ± 78 pg/ml in normal controls; p <0.01). After auto-HSCT, the expression level of miR-21 was significantly different in responders compared to non-responders. Responders had a lower expression of miR-21 compared to non-responders. Further, serum VEGF levels decreased in responders to auto-HSCT compared to non-responders. VEGF expression was increased in the supernatant from miR-21 mimic transfected human PCM cell lines H929 and RPMI-8226 compared with the negative control, while VEGF was decreased in the miR-21 inhibitor transfected cell lines. The angiogenic ability of HUVECs was increased under pretreatment with the supernatant from H929 and RPMI-8226 cells transfected with miR-21 mimic compared with negative controls and decreased when pretreated with miR-21 inhibitor transfected cells

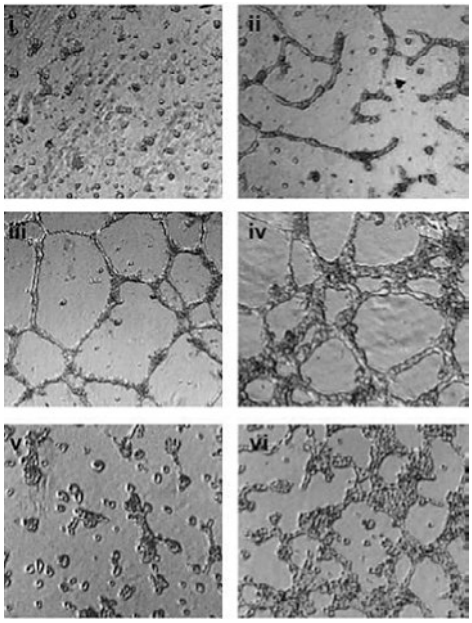

Figure 1

Conclusions: This study demonstrated that miR-21 was upregulated in PCM patients. Responders to auto-HSCT had a decrease of miR-21 expression and VEGF levels. Further, miR-21 regulated angiogenesis. Therefore inactivation of miR-21 or activation of its target gene may be a potential therapeutic approach in PCM.

FREE CONTRIBUTIONS: CLINICAL HEMATOLOGY

FM311

Dynamics of expression of Programmed cell death protein-1 (PD-1) on T cells after allogeneic hematopoietic stem cell transplantation

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Introduction: Blockade of the programmed-death 1 (PD-1) immune checkpoint represents a promising strategy to enhance anti-tumoral immune responses after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, observational studies suggest that PD-1 blockade can be complicated by the development of severe graft-versus-host disease (GvHD). A better knowledge of the dynamics of PD-1 expression by T cells after allo-HSCT is necessary in order to optimize PD-1 targeting therapies and limit toxicities.
Methods: We analyzed by flow cytometry 124 freshly drawn blood samples isolated from 98 allo-HSCT recipients. 23 healthy blood donors served as controls (HC).
Results: We observed a strong increase in PD-1 expression at the surface of CD4 and CD8 T cells isolated from allo-HSCT recipients compared with HC (Fig 1A). Importantly, we observed the significant increase of PD-1 expressing cells in all CD4 and CD8 T cell subpopulations studied (fig. 1B). We observed an inverse correlation between the time since allo-HSCT and PD-1 expression at T cell surface (fig. 1C). PD-1 expressing cells were higher than normal already at one month after allo-HSCT (fig. 1D). Thereafter, proportions of CD4 PD-1+ T cells remained higher than in HC up to more than 5 years after HSCT, while PD-1 expression on CD8 T cells started to normalize at 1 year after transplantation (fig. 1D). The stem cell source (BM vs PBSC), conditioning regimen (RIC vs MAC), use of total body irradiation and disease status at HSCT did not impact PD-1 expression. We observed higher proportions of PD-1+CD4+ but not of PD-1+CD8 T cells in patients having received *in vivo* and/or *ex vivo* T-cell depletion (TCD) compared with patient receiving T cell replete grafts (p = 0.0269). CD8 T cells from patients receiving grafts from haploidentical donors displayed higher proportions of PD-1+ cells than patients receiving grafts from matched related (p = 0.0492) or unrelated donors (p = 0.0049). No association was found between PD-1 expression on T cells and post-transplant complications, including acute or chronic GvHD, disease relapse and CMV reactivation.

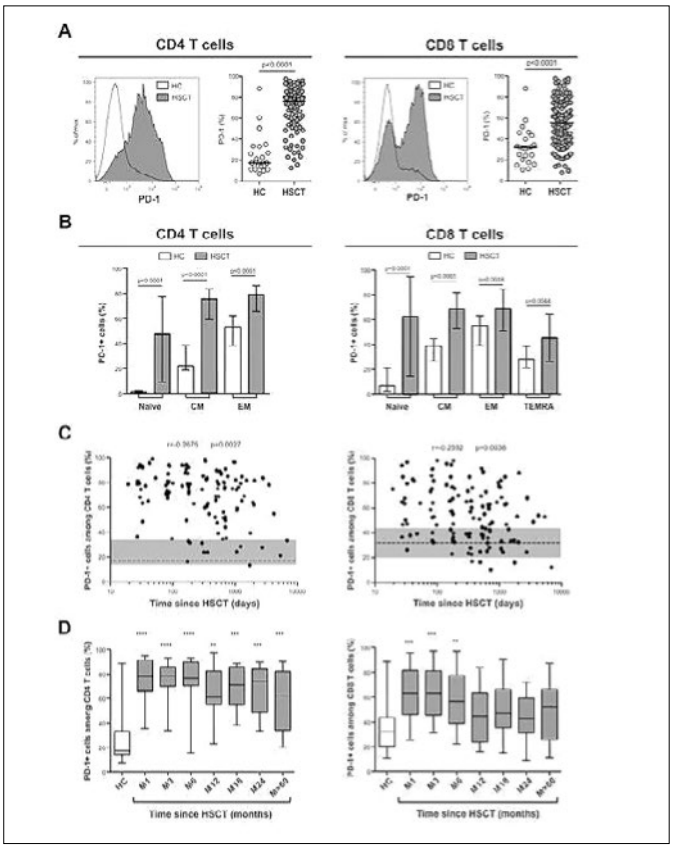

Figure 1

Conclusion: We report here an early and long lasting increase of PD-1 expression on CD4 and CD8 T cells after allo-HSCT. Several factors, including TCD and transplantation from haploidentical donors, are associated with a further increase in PD-1 expression on T cells. These results will help harnessing the potential of PD-1 blockade after allo-HSCT.

FM312

Defibrotide shows efficacy in the prevention of sinusoidal obstruction syndrome (SOS) after allogeneic hematopoietic stem cell transplantation: a retrospective study on 237 patients

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Introduction: Sinusoidal obstruction syndrome (SOS) is frequent after HSCT and may have a mortality rate of up to 85%. Defibrotide has shown efficacy not only in the treatment of established SOS but also in SOS prevention in a prospective study in children as well as in adults (several retrospective studies).
Patients and methods: Between 1999 and 2009, we gave defibrotide intravenously to 237 successive patients transplanted (248 transplantations) for hematological diseases starting at day –7 up to day +20 post-transplantation (dose range 800–2400 mg/d) in combination with heparin. The control group did not receive defibrotide as prophylaxis anymore (2011–2015, total 241 patients with 248 transplantations).
Results: Median follow-up for the study group was 10 (range 2–16) years and for the control group 2.7 (range 1–18) years. None of the 237 patients in the defibrotide group developed SOS (Baltimore criteria). The 100 day cumulative incidence (CI) of SOS was 0% in the defibrotide group as compared to 4.8% (95%CI 2.6–8%) in the control group, p = 0.00046. The day 100 event free survival (EFS) was not significantly different with 60% (95%CI 54%-66%) in the defibrotide group vs 53% (95%CI 47–59%) in the controls, p = 0.165, but the one year EFS was statistically different with 38% (95%CI 32%–44%) vs 28% (95%CI 22–34%), p = 0.00969. The 100 day CI of acute GVHD was not significantly different between the two groups [27% (95%CI 22–33%) in the defibrotide group vs 29% (95%CI 24–35%) in the control group, p = 0.707] while the 1 year acute GvHD CI was significantly reduced in the defibrotide group [31% (95%CI 25–37%)] compared with the control group [42% (95%CI 36–48%), p = 0.026]. The one year overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM) were not statistically different. Multivariate analysis, performed taking into account clinical factors known to influence the risk of SOS, confirmed the favorable impact of defibrotide on 100 day SOS CI [HR 7.5×10^{-7} (95%CI 1.8×10^{-7} –3.2×10^{-6}), p <0.00001] (table).

SOS incidence at 1 year	Hazard ratio	Lower 95%CI	Upper 95%CI	p value
Age (>50 vs <50 years)	0.147	0.032	0.685	0.01500
AST/ALT (high vs normal)	34.410	5.813	203.700	0.00010
Bilirubin (high vs normal)	31.660	1.886	531.500	0.01600
HSCT Year (>2007 vs <2007)	0.009	0.000	0.180	0.00210
Conditioning (RIC vs MAC)	0.077	0.008	0.703	0.02300
Busulfan use (Yes vs No)	22.810	6.079	85.580	<0.00001
TBI (Yes vs No)	2.758	0.564	13.490	0.21000
HSCT Number (2nd vs 1st)	2.501	0.468	13.370	0.28000
Defibrotide use (Yes vs No)	0.000	0.000	0.000	<0.00001

Conversely, multivariate analysis failed to confirm the impact of defibrotide on 1 year EFS or acute GvHD CI.
Conclusion: To the best of our knowledge, this is the largest study on SOS-prophylaxis with defibrotide and it suggests that this drug may benefit the prevention of this liver complication. Our retrospective study needs to be confirmed in a prospective randomized trial.

FM313

Reactive hemophagocytic syndrome after hematopoietic stem cell transplantation: a multicenter retrospective study on behalf of the francophone society of stem cell transplantation and cellular therapy (SFGM-TC)

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Introduction: Reactive hemophagocytic syndrome (HS) is a rare complication that may occur after both autologous and allogeneic hematopoietic stem cells transplantation (HSCT). Only about sixty cases of post-HSCT HS have been reported in the literature so far.
Methods: We performed a multicenter retrospective study on behalf of the SFGM-TC, including adult HSCT recipients diagnosed with HS after HSCT. The recently reported HScore was applied for confirmation of HS diagnosis.
Results: Among the 33 patients reported, 2 patients were excluded because of insufficient data and 4 patients for an HScore less than 169. We included in the final analysis 27 patients in which the HS diagnosis was confirmed (median HScore 218 and HS probability of 97%). Median age was 45 years. 3 patients underwent autologous HSCT for non-Hodgkin lymphoma (NHL). 24 patients received allogeneic HSCT for hematological malignancies (n = 23) or severe aplastic anemia (n = 1) from HLA-identical siblings (n = 4), HLA-matched (n = 10) or mismatched (n = 6) unrelated donors, haploidentical donors (n = 2) or cord blood (n = 2). Median time from HSCT to HS diagnosis was 66 days (range 6–326). Fever was present in almost all patients (93%) while we observed splenomegaly in 13 (48%), hepatomegaly in 11 (41%), and lymphadenopathy in 8 (30%) patients. We found pancytopenia in 14 patients (52%). All patients displayed elevated ferritin levels. 11 patients (41%) had triglyceride levels at >4 mmol/l, while only 7 patients (26%) had fibrinogen <2.5 g/L. Aminotransferases were elevated in half of the patients (n = 14). Bone marrow hemophagocytosis was found in 15 patients (56%) (fig. 1A). 20 patients (74%) had pharmacological immune suppression at time of HS diagnosis. Infections were the most frequent triggering events (48%) followed by cancer (30%) and GvHD (15%) (fig. 1B). Median survival after HS diagnosis was 58 days and the 1-year overall survival (OS) was 22% (fig. 1C). Treatments most frequently employed, either alone or in combination, were steroids (n = 16), IVIG (n = 7) and Etoposide (n = 7). Etiological anti-infectious or anti-cancer agents were employed alone in 7 patients. Three patients underwent a second allogeneic HSCT that provided long-term rescue in one patient.
Conclusion: Our study, which is to the best of our knowledge the largest series of HS following HSCT reported so far, provides a description of HS as a rare but devastating complication of HSCT associated with an extremely high mortality.

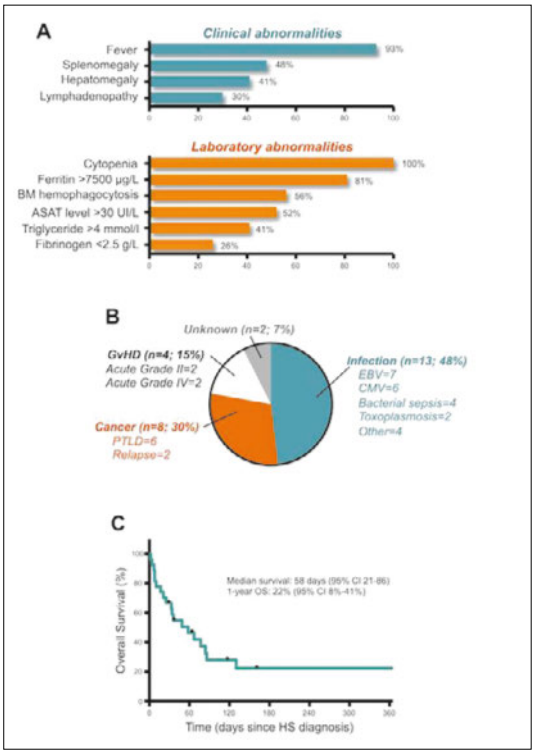

Figure 1

FM314

Changes of telomere length reflect the clonal suppression seen with the telomerase inhibitor imetelstat in patients with essential thrombocythemia

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Background and aims: Myeloproliferative neoplasms (MPN) are characterized by cellular proliferation due to a dominant clone defined by a driver mutation, with or without subclones with additional mutations and/or polyclonal hematopoiesis. Due to the loss of telomere sequences with each cell division, in neoplastic cells with a high mitotic rate telomeres are typically short. In the study with the telomerase inhibitor imetelstat (IM) we demonstrated rapid and durable hematologic and molecular responses (Baerlocher et al. N Engl J Med 2015) and suppression of clones with non-driver mutations in patients (pts) with ET. Our aims were to evaluate telomere length values (TLV) in MPN pts and in ET pts treated with IM (IM-ET) as well as correlation with hematologic and molecular responses.
Patients and methods: 17 IM-ET pts who were resistant or intolerant to prior therapies and 63 MPN pts (16 ET, 34 PV, 13 MF) untreated or treated with standard of care (SOC-MPN) were analyzed. TLV were measured by automated multicolor flow-FISH.
Results: All IM-ET pts showed low TLV at baseline, with 12 pts below the 1st percentile, and TLV of SOC-MPN pts were around the 10th percentile. The median difference in TLV to the age-related 50th percentile (dTLV) in IM-ET pts was significantly lower than in SOC-ET pts and similar to dTLV of pts with MF. In IM-ET pts with shorter baseline TL, driver mutation burden at baseline was significantly higher ($p = 0.03$) and best reduction in driver mutation burden was significantly less ($p = 0.03$). In 10/13 IM-ET pts, dTLV were higher at best response, reflecting the reduction of neoplastic clones in relation to normal hematopoietic cells. This change of dTLV correlated significantly with the maximum reduction of the JAK2V617F burden ($p = 0.0003$). Of interest, the 3 IM-ET pts with lower or steady TLV after 9 months of treatment had the highest number of additional mutations at baseline.
Conclusions: The lower TLV found in pts with MPN and especially with MF compared to healthy individuals reflect the higher mitotic history of malignant clones. In the IM-ET cohort, driver mutation burden at baseline and best response during treatment correlate significantly with baseline TL. The higher TLV observed after 9 months of treatment and the correlation with the reduction in the driver mutation burden suggests that in ET pts, IM may suppress neoplastic clones and, in the absence of a high number of additional mutations, favor recovery of normal hematopoiesis.

FM315

A prognostic tool for predicting prognosis in early stage chronic lymphocytic leukemia patients

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Introduction: The natural history of Binet A chronic lymphocytic leukemia (CLL) is highly variable, including patients showing progressive disease requiring treatment and cases with an indolent disease for whom a watch and wait approach is recommended. Recently, two prognostic scores (MDAAC-score and CLL-IPI) have been developed to predict prognosis of CLL, though they do not inform the outcome of patients with Binet A CLL. The aim of our study was to perform and validate a model retaining its prognostic value in the subgroup of Binet A patients.
Methods: 637 patients affected by Binet A CLL were included into the study. The dataset was divided into training and validation series. The training cohort included 229 patients prospectively enrolled at the University of Eastern Piedmont (UPO). The validation cohorts included 90 patients retrospectively observed at Oncology Institute of Southern Switzerland (IOSI) and 318 individual patient's data from the multicenter observational study O-CLL1.
Results: In the UPO training cohort, three independent prognostic variables predicting disease progression (PFS) were identified by the multivariate analysis: IGHV mutational status (HR = 3.6), palpable lymph nodes (H = 2.4) and lymphocyte count (H = 2.1). By recursive partitioning, patients concomitantly harboring unmutated IGHV genes and palpable lymph nodes had the highest risk of progression (median PFS, 2.5 years; 5-year PFS, 7%). The model correctly discriminated PFS in 73% of cases (c-index: 0.732) and showed a positive (PPV) and negative predictive (NPP) values for the identification of patients progressing within 5 years of 81% and 80%, respectively. The accuracy of the model was higher than that of the MDAAC-score (c-index = 0.593) and of the CLL-IPI score (c-index = 0.687). The model was validated in the IOSI (c-index = 0.712) and in the O-CLL1 (c-index = 0.660) series.
Conclusion: The presence of unmutated IGHV genes and palpable lymphadenopathy identifies Binet A CLL patients showing a high risk of progression and treatment requirement within 5-years from diagnosis. For this subset of CLL patients, enrollment into early interventional studies may be beneficial.
Disclosures: None.

GASTGESELLSCHAFT SGKPT / SOCIÉTÉ CONVIÉE SSPTC

POSTER PRESENTATION SESSION

P493

Concomitant use of ciprofloxacin and tizanidine leading to an increased risk of excessive hypotension and sedation: a retrospective Analysis of the WHO Pharmacovigilance Database

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Background or introduction: Tizanidine (TIZA) is indicated for the treatment of spasticity. The substance has antihypertensive effects 0and is extensively metabolized via cytochrome P450 (CYP) 1A2. Co-administration with potent CYP1A2 inhibitors such as ciprofloxacin (CIPRO) resulted in significant increase of TIZA plasma concentrations in healthy volunteers. The combination is contraindicated and clinical effects in patients are unknown.
Material and methods: Several adverse drug interactions with clinical reactions after concomitant use of TIZA and CIPRO were reported to the Regional Pharmacovigilance Centre of Zurich. We conducted a retrospective study of Individual Case Safety Reports (ICSRs) obtained from the World Health Organization (WHO) Global Database to analyse this drug safety issue. All ICSRs of TIZA registered in the WHO Database until August 2015 were included. Demographic data, drug administration information, the course of the adverse drug reaction (ADR), its severity and outcomes were analysed in patients with co-administration of TIZA and CIPRO. Other centrally-acting drugs (e.g. baclofen, benzodiazepines, opioids, antidepressants) or substances with hypotensive effects (e.g. calcium channel blockers, ACE-inhibitors, beta-blockers) were frequently co-administered.
Results: Concomitant use of CIPRO was reported in 64 (2.0%) of 3253 TIZA-related ICSRs. The majority of patients was female (n = 36, 56%), the median age was 53 years (range 13–83 years). Most reports were derived from the US (n = 34; 53%) followed by Switzerland (n = 11; 17%). Most of the reported ADRs were related to increased TIZA effects with hypotension and sedation. Most frequently reported terms included hypotension, asthenia, hypoventilation, somnolence, or unconsciousness. Patients who experienced ADRs had 3 other drugs when receiving TIZA daily doses ≥12 mg – or 6 other drugs when receiving TIZA daily <12 mg. One patient in each dosage group died.
Conclusions: Concomitant use of CIPRO increases the risk of dose-dependent TIZA effects, such as hypotension and sedation. This combination should be absolutely avoided. Especially combinations with high doses of TIZA ≥12 mg/day but also lower doses <12 mg/day combined with CNS- and blood pressure lowering drugs may result in serious ADRs and even fatal outcomes.

P494

Pharmacokinetics and pharmacodynamics of LSD following oral administration in healthy subjects

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Background and objective: Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. The aim of the present study was to characterize the pharmacokinetics and exposure-response relationship of oral LSD.
Methods: We analyzed pharmacokinetic data from two published placebo-controlled, double-blind, cross-over studies using oral administration of 100 and 200 µg LSD in 24 and 16 subjects, respectively. Plasma concentrations of LSD, subjective effects, and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.
Results: Geometric mean (95% confidence interval) C_{max} values of 1.3 (1.2-1.9) and 3.1 (2.6-4.0) ng/ml were reached 1.4 and 1.5 h after administration of 100 and 200 µg LSD, respectively. The plasma half-life was 2.6 h (2.2–3.4). The subjective effects lasted (mean ± SD) 8.2 ± 2.1 and 11.6 ± 1.7 h following a dose of 100 and 200 µg LSD, respectively. Subjective peak effects were reached 2.8 and 2.5 h after administration of 100 and 200 µg LSD, respectively. A close relationship was observed between the LSD Plasma concentration and subjective response within-subjects, with moderate counterclockwise hysteresis. EC_{50} values were in the range of 1 ng/ml. No correlations were found between plasma LSD levels and its effects across subjects at or near C_{max} and within dose groups.
Conclusions: The present pharmacokinetic data are important for the evaluation of clinical study findings (e.g., functional magnetic resonance imaging studies) and the interpretation of LSD intoxication. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination up to 12 h. The effects of LSD were related to changes in plasma concentrations over time, with no evidence of acute tolerance.
The studies were registered at ClinicalTrials.gov (NCT02308969, NCT01878942).

P495

$GABA_A$ subtypes-selective modulation: a novel mechanism-based approach to the treatment of neuropathic pain

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Introduction: Neuropathic pain (NP) affects about 7% of the general population in European countries. Meta-analyses indicate that only a minority of NP patients has adequate response to drug therapy and management of NP is still an unmet medical need. New insights into the contribution of defined subtypes of $GABA_A$ receptors ($GABA_A$ Rs) to the different clinical effects of benzodiazepine (BDZ)s, including analgesia, have suggested that α1-sparing selective BDZs, such as N-desmethylclobazam (NDMC), may be a new realistic alternative for the treatment of NP.
Method: Healthy volunteers, proof-of-concept RCT assessing antihyperalgesic and sedative effects of BDZs on a UVB-induced pain model of central sensitization [1]. Human cell electrophysiology (recombinant $GABA_A$ Rs) and mice behavioral experiments based on a chronic constriction injury model comparing diazepam (DZP), clobazam (CBZ) and NDMC activity profiles [2].
Results: In healthy volunteers, at the time of maximum effect, CBZ and clonazepam (CLN) antihyperalgesic effect was greater (vs. placebo) by respectively 15.7% (95% CI 0.8–30.5) and 28.6% (95% CI 4.5–52.6), p <0.05. Difference (vs. placebo) in sedation (VAS) was only significant for CLN 26.3 mm (95%CI 15.0–37.7), p <0.001 [1]. In recombinant receptors, NDMC had better α2- over α1$GABA_A$Rs activity ratio than CBZ and DZP. Unlike DZP, NDMC caused no or modest sedation at antihyperalgesic doses in two strains of wild-type mice [2].
Conclusion: NDMC α2/α1 in vitro activity profile and long term clinical experience from its marketed parent compound (CBZ) make it an advisable clinical candidate for further proof-of-concept assessments in human. Therefore the HUG has manufactured a new chemical entity and initiated a drug development program for NDMC starting with a phase-I trial comparing analgesic and sedative effects of NDMC 20 mg and 60 mg with clonazepam 1.5 mg in healthy volunteers and two phase-I single and repeated dose pharmacokinetic studies.

1. Besson M. et al, Pain, 2015.
2. Ralvenius W. T. et al, Neuropharmacol, 2016.
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P496

Method for the simultaneous quantitative analysis of nine antimalarial drugs in dried blood spot (DBS) samples using LC-tandem mass spectrometry, and relationship of lumefantrine concentrations in DBS samples and in plasma

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Introduction: Measurement of the concentration of antimalarials in blood of the general population constitutes a suitable approach for estimating population drug exposure and is used in efficacy studies. Storage and transportation conditions of blood samples are common problems for studies in areas with a high prevalence of malaria. The dried blood spot (DBS) sampling technique allows facilitating storage and transportation procedures. We present a method for the analysis of 9 antimalarial drugs in DBS and show the relationship between the concentrations of lumefantrine in DBS, plasma and whole blood.
Methods: Known concentrations of amodiaquine, desethyl-amodiaquine, quinine, chloroquine, mefloquine, sulfadoxine, pyrimethamine, lumefantrine and desbutyl-lumefantrine were added in whole human blood. A 10µl-aliquot of spiked blood was applied onto a filter paper card (Whatman FTA DMPK-B) and allowed to dry for 3 hours at room temperature. A 3 mm-punch was taken out from the DBS and extracted with 100 µl of methanol + 1% formic acid containing the stable isotopically-labeled Internal Standards for all antimalarials. Concentrations of all antimalarials were simultaneously determined by chromatography coupled to tandem mass spectrometry (LC-MS/MS) in DBS, venous blood spotted onto DBS, whole venous blood and plasma collected in 16 healthy volunteers who took a single dose of artemether-lumefantrine and were followed up to 336 hours.
Results: Lower limits of quantification were 2 ng/ml for pyrimethamine, 6 ng/ml for desethyl-amodiaquine, and 20 ng/ml for the other antimalarials. The analytical inter-day variation coefficient was 2.1–15.2%. Lumefantrine concentrations measured in plasma were twice as high as those measured in DBS and were highly correlated (r = 0.99). There were no differences in drug concentration between venous blood spotted on DBS cards and capillary blood directly spotted from volunteers' finger. Lumefantrine could be quantified in volunteers up to 336 hours after drug intake.
Conclusion: With a low volume of 10-µl of blood, our technique enables precise and sensitive measurement of antimalarials in DBS. The concentration measured in capillary blood DBS reflects the drug levels measured in venous whole blood. These relationships could contribute to define the therapeutic ranges of lumefantrine concentrations measured in DBS. DBS sampling is a confident surrogate marker of drug level in plasma and is suitable for epidemiological studies.

P497

Population pharmacokinetics analysis of dolutegravir in HIV-1 infected individuals

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Introduction: Dolutegravir (DTG), the latest integrase inhibitor (INIs) approved for HIV treatment is coformulated in a single tablet regimen with abacavir and lamivudine. DTG has demonstrated potent antiviral activity and a very good tolerability and is widely prescribed in HIV-infected patients (1). DTG is primarily metabolized via UDP-glucuronosyltransferase (UGT 1A1) with a minor component of CYP3A4 (2). The aim of this observational study was to characterize DTG pharmacokinetic profile, to quantify interpatient variability and to identify potential factors that could influence drug exposure.
Methods: All dolutegravir concentrations data were collected as part of routine therapeutic drug monitoring performed in our hospital, between June 2014 and December 2015 from HIV treatment-naive and experimented patients. A population PK analysis was performed by comparing various structural models using NONMEM®. The effect of relevant demographic factors and co-medications were on dolutegravir disposition was explored.
Results: A total of 594 plasma levels were measured in 514 HIV-positive patients under steady state regimen conditions. Plasma concentrations ranged between 31 and 7971 ng/mL. A one-compartment model with first order absorption and elimination best characterized dolutegravir pharmacokinetics. Average DTG clearance was 0.93 (L/h), volume of distribution 18.9 (L), and mean absorption time 1.27 (h^{-1}). The inter-subject variability on CL was estimated at 27%. Among the demographic covariates tested, body weight and age influenced positively and moderately DTG CL (29% and 24% respectively) as well as smoking status (17%). Coadminisation of atazanavir decreased DTG clearance by 38% and the association of darunavir increased the clearance of DTG (14%).
Conclusion: The variability in DTG pharmacokinetics appears lower than for other INIs. Several covariates were identified impacting DTG exposure however their effect appears to be relatively modest and seems not to be clinically significant except for atazanavir coadministration.

1 FDA. 2013. TIVICAY (dolutegravir) FULL PRESCRIBING INFORMATION. administration FaD, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf.
2 Castellino S, et al. Antimicrob Agents Chemother. 2013;57:3536–46.

P498

Cost-effectiveness of extended screening and treatment with sofobuvir and ledipasvir using systematic rapid antibody saliva and dried blood spot testing in custodial setting

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Introduction: HCV prevalence amongst prisoners is typically high due to the large proportion of high-risk groups. We explored the cost-effectiveness of expanding hepatitis C virus (HCV) screening and subsequent treatment in Swiss custodial settings, given the availability of rapid antibody saliva tests (Oraquick®) and dried blood spot tests (semi-quantitative viremia and viral genotype), and recent therapeutic advances which have higher cure rates and shorter treatment courses [1].
Methods: A comprehensive strategy offering screening to all detainees was compared to the current setup of screening high-risk individuals (e.g. from endemic countries, active or former injecting drug users [IDUs]). A decision tree simulated the diagnosis pathway, and results from a Markov model were included to predict treatment effects based on ledipasvir and sofosbuvir regimen, and natural progression over a lifetime time-horizon [2]. Deterministic and probabilistic sensitivity analyses were performed to explore parameter uncertainty and whether key input variations changed the cost-effectiveness of comprehensive screening.
Results: At a willingness-to-pay threshold of CHF 100,000 per quality-adjusted life-year (QALY), comprehensive screening had an 84% probability of being cost-effective, with a corresponding NMB of CHF 33,451,972 and ICER of CHF 7,168/QALY. Results were most sensitive to the respective HCV prevalence in the current and comprehensive screening populations, treatment initiation rates, and screening offer acceptance rates. Compared to the current practice of screening high-risk individuals, comprehensive screening is likely to be cost-effective due to the increase in testing rates, which were conservatively estimated in this study. Furthermore, comprehensive HCV screening of prisoners may prove more cost-effective in countries where prisoners are not routinely screened.
Conclusions: Comprehensive screening programmes could be considered in prison units with a large proportion of high-risk individuals and where detainees are incarcerated for enough time to complete a treatment course during their sentence.

References

1 McLeod A, et al. Rise in testing and dianosis associated with Scotland's Action Plan on Hepatitis C and introduction of dried blood spot testing. J Epidemiol Community Health. 2014;68(12):1182–8.
2 Dolan K, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. Lancet. 2016;388(10049):1089–102.

P499

Novel genetic variants in carboxylesterase 1 predict early-onset capecitabine-related toxicity

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Background: Capecitabine (Cp), an oral prodrug of 5-fluorouracil, is commonly prescribed to treat gastrointestinal and breast tumors. However, dose-limiting adverse effects occur in 20–35% of patients at standard doses, in particular hand-foot syndrome and diarrhea. The aim of this study was to evaluate, for the first time, the association of genetic variability in all enzymes of the Cp activation pathway with early-onset toxicity from Cp-based chemotherapy.
Patients and methods: The coding and exon-flanking regions of the cytidine deaminase gene (*CDA*) were sequenced in 144 Cp-treated patients, in whom Cp-related toxicities in the first two chemotherapy cycles were recorded. For the other investigated genes (*CES1*, *CES2*, *TYMP*, *UPP1*, and *UPP2*), sequencing of coding and exon-flanking regions was performed in a discovery subset of 48 patients (24 with severe Cp-related toxicity, 24 with no or mild toxicity), and associated candidate variants were subsequently genotyped in the full cohort.
Results: We identified a haplotype in the carboxylesterase 1 gene (*CES1*) associated with Cp-related toxicity ($OR_{additive}$=2.2, 95%CI 1.2-4.0, $P_{adjusted}$=0.012; $OR_{recessive}$=10.3, 95%CI 2.1-49.4, $P_{adjusted}$ = 0.0038). This common haplotype (frequency = 14%) encompassed five noncoding variants, including an expression quantitative trait locus (rs7187684) for *CES1*. In addition, the association of two common linked *CDA* promoter variants (c.1-451C>T: $OR_{dominant}$ = 4.3, 95% CI: 1.3-14.2, $P_{adjusted}$ = 0.017; and c.1-92A>G: $OR_{dominant}$ = 4.4; 95% CI 1.3-14.5, $P_{adjusted}$ = 0.015) with increased risk of Cp-induced diarrhea was replicated.
Conclusions: This is the first study to identify an association of genetic variation in *CES1* with Cp-related toxicity. Given that a variant (rs2244613) of the same *CES1* haplotype was previously associated with trough concentrations and bleeding from the CES1-metabolized anticoagulant dabigatran, this finding provides evidence for the existence of a common regulatory *CES1* variant with possible clinical relevance for carboxylesterase-metabolized drugs.

P500

Genetic variants of cytochrome P450 influence pharmacokinetics and pharmacodynamic effects of MDMA in healthy subjects

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Introduction: *In vivo* and *in vitro* studies respectively showed that cytochrome P450 (CYP) 2D6, CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). However, the role of genetic polymorphisms in CYP2D6, CYP2C19, CYP2B6, and CYP1A2 in the metabolism of MDMA in humans is widely unknown. Therefore, we characterized the effects of genetic variants in the involved CYP enzymes on the pharmacokinetics and pharmacodynamic effects of MDMA.
Methods: The genetic variants in these CYP enzymes were characterized in 139 healthy subjects (69 male, 70 female, aged between 18–45 years) in a prospectively designed pooled analysis of eight double-blind, placebo-controlled, crossover studies. MDMA was administered orally in a single dose of 75 or 125 mg (dose range of 0.8–2.7 mg/kg; mean = 1.7 mg/kg). Blood samples and pharmacodynamic measures were taken repeatedly up to 6 h after drug administration. Subjective effects were assessed using Visual Analogue Scales (VAS) including: "any drug effect" and "drug liking". Genomic DNA was extracted from whole blood. Genotyping was performed using TaqMan SNP genotyping assays.
Results: CYP2D6 poor metabolizers (PMs) exhibited increased maximum plasma levels of MDMA (+15%) and of its active metabolite 3,4-methylenedioxyamphetamine (MDA, +50%) compared with extensive metabolizers (EMs), and decreased levels of the inactive metabolite 4-hydroxy-3-methoxymethamphetamine (HMMA, –50%). Blood pressure and subjective drug effects increased more rapidly after MDMA administration in CYP2D6 PMs than in EMs. MDMA-MDA conversion was positively associated with genotypes known to convey higher CYP2C19 or CYP2B6 activities. Additionally, CYP2C19 PMs showed greater cardiovascular responses to MDMA compared with other CYP2C19 genotypes. Furthermore, the maximum concentration of MDA was higher in tobacco smokers that harbored the inducible CYP1A2 rs762551 A/A genotype compared with the non-inducible C-allele carriers.
Conclusion: The findings indicate that genetic polymorphisms in CYP2C19, CYP2B6, CYP1A2, but mainly CYP2D6 contribute to the metabolism of MDMA in humans. Additionally, genetic polymorphisms in CYP2D6 and CYP2C19 may moderate the pharmacodynamics effects of MDMA.

P501

Determination of plasma levels for serotonin, melatonin and their metabolites: analytical validation, normal ranges and circadian variations

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Introduction: Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine derived from tryptophan, best known as an autacoid and neurotransmitter that modulates a wide range of physiological processes. Its multi-step metabolism, including its interconversion into melatonin (involving the pineal gland), has been poorly studied. In this work we developed an analytical method to determine plasma concentrations of 5-HT and 8 of its metabolites: melatonin (Mel), N-acetylserotonin (NAS), 6-hydroxymelatonin (6-OH Mel), 5-Methoxytryptamine (5-MT), 5-Hydroxyindole acetic acid (5-HIAA),

5-Methoxyindole acetic acid (5-MIAA), 5-Hydroxytryptophol (5-HTP), 5-Methoxytryptophol (5-MTP). Additionally, these molecules can be sulfo- or/and glucuro-conjugated. Our first aim was to determine the physiological range and circadian variability of plasma levels of theses metabolites.
Methods: An LC-MS/MS assay for the measurement of free 5-HT and its 8 metabolites in plasma was developed and fully validated. The determination of conjugate forms is underway. In a preliminary study, free 5-HT and its metabolites were measured in 21 healthy volunteers (aged 20 to 54 years, 12 males), over 24 hours. Blood samples were collected every hour between 10 PM and 6 AM in complete darkness, and every 2 hours the rest of the day.
Results: A calibration curve ranging from 0.25 to 400'000 pg/ml was established for each analyte. The assay was found linear within this concentration interval. The sensitivity of the LC-MS/MS assay was dependent on the analyte investigated (0.25 to 390 pg/ml). No carryover was found. Intra- and inter-run coefficients of variation were acceptable (0.5% to 22.7%). Free 5-MT, 5-HTP and 5-MTP remained below the quantification limit. Mean values and SDs were determined for the remaining metabolites at each time point. All metabolites exhibited significant circadian variations over 24 hours, as already known for melatonin, but of less amplitude.
Conclusion: We developed and validated a robust method for measuring serotonin and 8 metabolites in human plasma. The determination of these concentrations will afford a valuable tool for our understanding of pineal and digestive physiology, effects of drugs modulating serotoninergic transmission and paraneoplasic manifestations of neuroendocrine tumors. Circadian variations preclude the definition of single normal ranges.

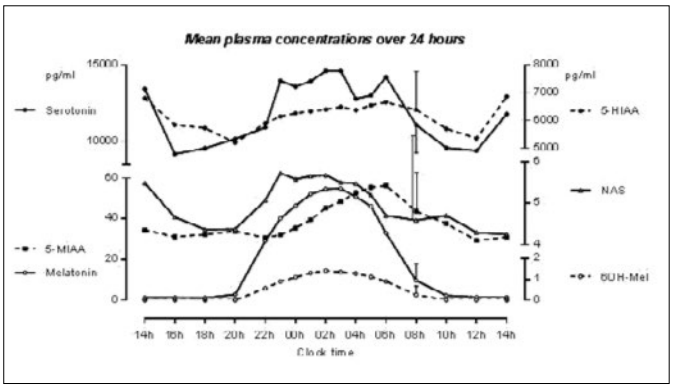

Figure 1: Mean plasma concentrations over 24 hours.

P502

Cross-species comparison study of the *in vivo* metabolism of the novel investigational anti-tuberculosis agent PBTZ169

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Introduction: PBTZ169 is a drug candidate for treating tuberculosis (TB) with a new and unique mode of action, *i.e.*, it covalently inhibits DprE1, a flavo-enzyme essential for the biosynthesis of key cell wall components of *M. tuberculosis* [1]. A remarkable *in vitro* effectiveness has been demonstrated with minimum inhibitory concentration (MIC) values below 0.0005 µg/mL, together with no general anti-bacterial activity [2]. *In vitro* metabolism studies demonstrated that PBTZ169 undergoes primarily hepatic phase I biotransformation into several metabolites. Moreover, hydroxyl- and oxo-metabolites of PBTZ169 have been shown to also possess anti-TB activity *in vitro*, with appreciable MIC values. For a comprehensive pharmacokinetic-pharmacodynamic analysis, it is therefore necessary to fully characterize the *in vivo* profiles of active (and inactive) metabolites of PBTZ169, in various human and non-human species.
Methods: A bioanalytical method employing ultra-high pressure liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS) was developed for the accurate and sensitive quantitation of PBTZ169 together with 6 currently known metabolites (5 active and 1 inactive) in biological fluids (*e.g.*, plasma) from several species (*e.g.*, rodent, dog, human, etc.). Secondly, an untargeted analysis approach using liquid chromatography hyphenated to high-resolution mass spectrometry (LC-HRMS) was applied to *in vivo* samples for the comprehensive analysis of the metabolites profile of PBTZ169.
Results: Quantitative assays highlighted distinct cross-species differences in the pattern of metabolites profiles of PBTZ169. Moreover, targeted analysis using UHPLC-MS/MS reveals additional chromatographic peaks with consistent kinetics over the dosing interval in the monitored *selected reaction monitoring* traces. These newly identified PBTZ169 metabolites are additional oxidized species which, together with phase II biotransformation products, are currently being characterized in detail by LC-HRMS.
Conclusion: Overall knowledge about the behavior of PBTZ169 is currently being expanded through this comprehensive characterization and quantification of the *in vivo* phase I and II metabolite profiles of PBTZ169, in several relevant species, by using a combination of targeted and untargeted LC-MS-based approaches.

References:
1 Makarov V, et al. Science. 2008;324:801–4.
2 Makarov V, et al. EMBO Mol Med. 2014;6:372–83.

P503

Use of antiepileptic drugs during breastfeeding: what do we tell the mother?

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Introduction: Epilepsy affects nearly one in a hundred persons. Its treatment is effective but not without side effects. Epileptic mothers are faced with the question of the possibility of breastfeeding under treatment. Knowledge about the passage of various antiepileptic drugs into breast milk and its consequences for the infant is limited. Faced with this uncertainty, breastfeeding is often discouraged for these patients. The aim of this work is to comprehensively review the available data regarding antiepileptic drugs during breastfeeding, to compare these data with the information provided by the summary of product characteristics (SmPCs), and to provide recommendations for the use of these drugs in breastfeeding women.
Methods: The 23 antiepileptic agents available in Switzerland were included in this study. We performed a systematic review of the literature using Medline and Lactmed. In Medline, the generic name of each antiepileptic drug was associated with the terms "Breastfeeding" or "Lactation" or "Milk, Human". A breastfeeding compatibility score was developed and validated (1 = compatibility established; 2 = likely; 3 = uncertain, requiring surveillance; 4 = rather discouraged; 5 = clearly contra-indicated). The estimated score based on the literature review was compared with the estimated score based on the recommendations provided by the SmPCs.

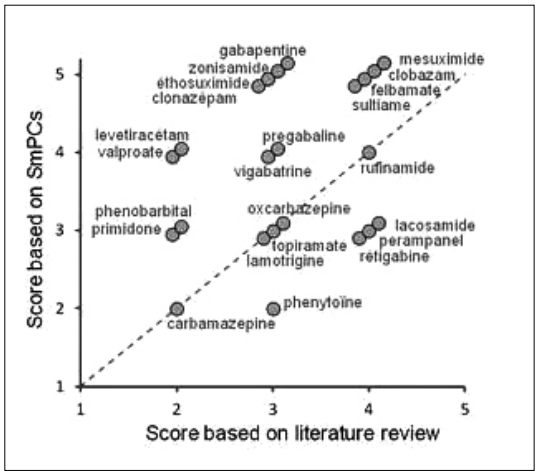

Figure 1: Comparison between the compatibility scores.

Results: 75 articles were identified as containing exposure and safety data for 15 antiepileptic agents during breastfeeding. The comparison between the score values based on the literature review and on the SmPCs revealed a very low degree of concordance (weigthed kappa: 0.08).
Conclusion: Phenobarbital, primidone, carbamazepine, valproate, and levetiracetam are probably compatible with breastfeeding. Treatment with phenytoin, ethosuximide, clonazepam, oxcarbazepine, vigabatrin, topiramate, gabapentin, pregabalin, lamotrigine, zonisamide may be authorized during breastfeeding. However, breastfed infants should be carefully monitored for side effects. Data on use of mesuximide, clobazam, rufinamide, felbamate, lacosamide, sultiame, perampanel and retigabine are insufficient to adequately assess the risk for the breastfed infant. The reliability with which the current state of knowledge is reflected in the SmPCs should be improved.

P504

A posteriori percentiles for Therapeutic Drug Concentration Monitoring (TDM)

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Introduction: A population pharmacokinetic model allows reconstructing the predictive distribution of drug concentrations in a population of patients, as a function of time and the dosing regimen. We propose to calculate *a posteriori* percentiles (i.e. percentiles from the posterior predictive distribution of concentrations) for the rendering of TDM results in a patient for whom past measurements are available. We illustrate the clinical usefulness of such *a posteriori* percentiles to:
– determine the probability that future concentrations lie within a pre-specified therapeutic range, under either the current or a modified dosing regimen
– detect significant changes in drug disposition, e.g. following drug-drug interactions or malfunction of elimination organs
– identify patient adherence issues
Methods: Considering a population pharmacokinetic model of Voriconazole (Pascual & al. Clin Infect Dis, 2012;55:381-90), a set of 1 to 10 simulated trough concentrations was generated for a fictive patient under different dosing regimens. The distribution of predicted concentrations over the next dosing interval was reconstructed using the model while taking into account past values. This enabled us to assess the expectedness of future measurements in the patient, and the probability of the next trough concentration to lie within the therapeutic range, under different dosing regimens.
Results: Based on 10'000 fictive patients, simulated TDM improved from 50% to 71% the chance of reaching the target therapeutic range of 1.5–4.5 mg/L. Using simulations, we show how the incremental consideration of historical information can reduce the width of the prediction interval for future concentrations in the patient being monitored. We also illustrate how *a posteriori* percentile curves may detect a future abnormal concentration measurement as the patient gradually becomes his own reference.
Conclusion: When past concentration measurements are available for a patient, the rendering of *a posteriori* percentile curves depicts the likelihood of future concentrations in this patient, under the current or an adapted dosing regimen. Such percentiles constitute an important piece of information that can be graphically communicated to the physician, who can then judge whether a measured concentration is both expected and appropriate for the patient. This will contribute to better informed treatment decisions, representing a further step towards individualized drug dosage adaptation.

P505

The financial incentive to market secondary patent of ritonavir

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Background: The World Intellectual Property Organization reported more than 9'750 patents of ritonavir from the discovery in December 1993. The patents aim at protecting intellectual property from the strong market competition and therefore encourage innovation as well as reward the pharmaceutical industry from their investment in the R&D of drugs. However, heatstable formulations, combinations with other chemicals, new indications might be patented and marketed at higher price and also when the original patent is about to expire, a so called evergreening strategy. We aimed to determine the financial incentive of marketing heatstable formulation using the proprietary melt-extrusion (Meltrex®) technology allowing in addition to reduce the pill count from 6 to 4 per day. The Meltrex® technology was applied to ritonavir stand alone formulation in Oktober 2010 almost 4 years after the lopinavir/ritonavir (December 2006).
Methods: Frequency of administration, dosage (in mg) and galenic form for all patients under ritonavir and lopinavir/ritonavir were collected from the Geneva Swiss HIV Cohort Study from January 2003 to June 2016. Extracosts were calculated for three different scenarios assuming the replacement with the corresponding Swiss market price de-escalation of (1) lamivudine, (2) lamivudine/zidovudine and (3) efavirenz over time. Prices were adjusted by the inflation rate.
Results: Over the study period the total cost was USD 2'805'135 for the ritonavir and USD 13'351'886 for the lopinavir/ritonavir. The increase in cost for the Meltrex® technology per patient was 17% for ritonavir 4% for lopinavir/ritonavir, leading to an extracost of USD 166'358 and USD 368'255 respectively. Theoretical savings if generic ritonavir would enter the market after original ritonavir patent termination would be USD 994'080 for lamivudine price de-escalation, USD 750'917 for lamivudine/zidovudine and USD 600'741 for efavirenz.
Conclusions: The financial incentive encourage the pharmaceutical firm to be innovative leading to negotiate higher prices and at the same time to extent of the originator patent. The consequence is a financial impact for the society by preventing competition from generic equivalent and the delay in the accessibility of innovation for the patient.

P506

Experiences and optimisation strategies of medication supply after hospital discharge

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Introduction: The hospital-to-home transition is a vulnerable stage in patient care. Patients might experience problems with medication supply, which possibly lead to therapy interruptions. The objectives of this study were to investigate medication supply after hospital discharge, and patients' and physicians' opinions about optimisations.
Methods: A telephone interview was conducted with 100 discharged patients from the surgical and internal medicine's wards from the cantonal hospital in Baden. Inclusion criteria were: ≥50 years old, discharged home with a discharge prescription. Patients were recruited by telephone between the 2nd and 6th day after discharge, and a piloted, structured interview on experiences and optimisations of the medication supply process took place. Semi-structured interviews were conducted with five physicians. Results from patient interviews and the general discharge process were discussed.
Results: Patients were 65.6 ± 17.4 years old, 39% female, and 53% from the internal medicine's ward, and 97% regularly visit the same pharmacy. At the time of the interview, 77 had their prescription filled. Of these, 78% visited the pharmacy on the day of discharge, but it took up to six days until they received all medication. Supply problems were encountered by 14 of 77 patients (18%), mainly because of medication not being on stock at the community pharmacy. Four patients experienced therapy interruptions for a maximum of three days. Patients discharged from internal medicine's wards had more supply problems compared to surgical wards (relative risk = 5.56, p = 0.007). Patients experiencing supply problems had statistically significant more daily medication intakes (8.0 ± 4.32 vs. 4.9 ± 3.04, p = 0.010). Physicians were surprised about the late prescription filling and worried about disease outcomes. However, interruptions were interpreted as rare. The strategy to transfer prescriptions from hospital to community pharmacy prior to discharge was refused by 71% of patients and not favourable for the physicians, mainly because of a questionable benefit. But both groups indicated that bridging supply would be welcome.
Conclusion: This study showed that patients discharged from a Swiss hospital encounter supply problems, but therapy interruptions are rare. Bridging supply was preferred compared to an early prescription transfer. Interventions should consider these opinions and focus on internal medicine patients with a high number of medication.

P507

Role of cytochrome P450 3A4 and 1A2 phenotyping in patients with advanced non small-cell lung cancer receiving erlotinib treatment

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Introduction: The oral EGFR tyrosine kinase inhibitor erlotinib is metabolized by cytochrome p450 (CYP) 3A and CYP1A. In this study patients with advanced non small- cell lung cancer (NSCLC) were phenotyped for CYP3A4 (midazolam) and CYP1A2 (caffeine) using plasma and dried blood spot (DBS) samples to assess the correlation between phenotype and pharmacokinetics and pharmacodynamics of erlotinib.
Methods: We prospectively included 36 patients with advanced NSCLC receiving oral erlotinib 150 mg once daily. On day 1 and after an overnight fast, 2 mg oral midazolam and 100 mg oral caffeine were administered. Plasma and DBS were collected to determine concentrations of erlotinib, midazolam, caffeine and their metabolites (OSI-420, 1-hydroxymidazolam, paraxanthine) up to 6 hours. Plasma and DBS samples were analyzed using UPLC-MS-MS, and PK data were processed using population modeling.
Results: A high correlation was found between plasma and DBS concentrations for erlotinib (R2 = 0.960, P <0.0001), OSI-420 (R2 = 0.971, P <0.0001), midazolam (R2 = 0.995, P <0.0001) and caffeine (R2 = 0.968, P <0.0001). Individual caffeine clearance was significantly correlated with erlotinib clearance (R2 = 0.33, P = 0.048), but midazolam clearance was not (R2 = -0.09, P = 0.596). There was a trend for lower erlotinib clearance in patients experiencing grade 2 or 3 skin rash as compared to patients experiencing grade 0 or 1 rash (3.15 vs. 3.93 L/hr, P = 0.086).
Conclusions: Probe drug phenotyping is unlikely to substitute therapeutic drug monitoring of erlotinib in patients with advanced NSCLC, but capillary blood sampling may replace more invasive venous blood sampling to monitor erlotinib concentrations.

P508

Cost analysis of gastrointestinal (GI) bleedings associated with adverse drug events

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Introduction: Adverse drug events (ADE) are a problem in health care systems all over the world. About 10% of the admissions to hospitals are related to ADE and are associated to considerable increases in costs. For the present study gastrointestinal (GI) bleeding was selected as it is one of the most often observed ADE. The aim of the study is to estimate the incidence of GI bleeding associated with drugs in patients admitted to a tertiary hospital and to calculate costs associated with the ADE.
Methods: In a retrospective study all hospital admissions in 2015 were screened for GI bleeding by selecting cases with relevant ICD codes in the primary diagnosis. Cases were categorized as "ADE cases" when one or more drugs from the entry medications were considered relevant for the GI bleeding. The costs due to the ADE was defined as the total cost allocated to the case and compared to patients without such drugs.
Results: Within 1 year, 86 out of 39.724 admissions (0.22%) were due to GI bleeding. Half of the patients (n = 43, 50%) agreed to retrospective data research and were included in the analysis. The majority of GI hemorrhages (n = 32, 74%) was associated with a relevant drug. Female (15, 47%) and male (17, 53%) patients were equally affected. The median age between the groups was similar (59 vs. 66 years in the ADE group). Most frequently implicated drugs were NSAIDs (59%) and oral anticoagulants (22%). Patients with vitamin-K antagonists and non-vitamin K oral anticoagulants (NOACs) were comparable (57% vs. 43%). In the ADE group the mean length of stay was longer (10.8 days, 95%CI 5.9–15.6 vs. 6.6 days, 95%CI 3.0–10.2) and total costs per patients' hospitalization were higher (23.160 CHF, 95%CI 10.363–35.958 CHF vs. 15.633 CHF, 95%CI 3.923–27.343 CHF), compared to patients in whom the bleeding episode was not drug-related. Overall, nearly half of the patients was already taking a proton-pump inhibitor (19, 44%), 16 patients (50%) had a proton pump inhibitor in the ADE group vs. only 3 (27%) in patients who experienced GI bleeding without a drug being implicated. In both groups 2 patients had fatal outcomes (6% and 18%).
Conclusions: Preliminary data suggest prolonged duration of hospitalization and increased costs incurred by patients with drug-associated gastrointestinal bleeding compared to GI bleeding not induced by a drug. Further studies are needed to confirm these differences between drug-induced and non-drug-induced GI bleeding.

P509

Enzymatic pathways metamizole metabolism in humans

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Introduction: Metamizole (dipyrone, Novalgin®) is an analgesic drug used increasingly due to its favorable gastrointestinal and renal tolerability. The major metabolites of metamizole are the non-enzymatically generated methylaminoantipyrine (MAA), aminoantipyrine (AA), formylaminoantipyrine (FAA) and acetylaminoantipyrine (AAA). It is assumed that the metabolism of metamizole takes place in the liver but the CYPs involved are not known. The only identified enzyme in this pathway is N-acetyl transferase 2, which acetylates AA to AAA. The aim of the present study was to identify the enzyme responsible for the demethylation of MAA to AA.
Methods: MAA was incubated with human liver microsomes (HLM) over 6 hours. Inhibition assays were conducted by adding selective CYP450 inhibitors. CYP substrates were used to proof specific CYP inhibition. Induction assays were performed using HepaRG cells in the basal state and after induction with rifampicin (20 µM for 2 days). Moreover, the metabolism of MAA was investigated in human liver homogenate (HLH). Additionally, MAA was incubated in buffer containing oxidizing enzymes (horseradish peroxidase (HPO), soybean lipoxidase (SLO), human myeloperoxidase (MPO)). Drug concentrations were quantified by LC-MS/MS.
Results: HLM displayed a minor formation of AA (<1%) over 2 hours. Inhibition assays did not reveal a specific CYP for the demethylation. However, the inhibition cocktail reduced the metabolic microsomal activity by half. HepaRG cells treated with rifampicin (inducing CYP2B6, CYP2C9, CYP2C19 and CYP3A4) did not show an increase in MAA metabolism compared to basal conditions. Demethylation could also be shown in HLH, whereby the calculated reaction velocity was comparable to the reaction velocity in HLM. Extrapolation of MAA metabolism in HLM or HLH to the entire liver revealed that hepatic metabolism could explain only a minor portion of metamizole metabolism in humans. Interestingly, in the presence of HPO, SLO or MPO, MAA was rapidly metabolized, depending on the peroxidase used and the hydrogen peroxide concentration. Under these conditions, approximately 20% of MAA was demethylated to AA.
Conclusions: Comparison of the *in vitro* metabolism of MAA with the *in vivo* pharmacokinetics of metamizole suggests that the liver is not the main location of metamizole metabolism in humans. Our data imply that extrahepatic peroxidases might play an important role in MAA metabolism.

10 MEILLEURS POSTERS / 10 BESTE POSTER

P316

Smarter Medicine Hospital: quantified self

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Introduction: Based on the choosing wisely initiative, corresponding top-five Smarter Medicine Recommendations SMR for Swiss hospitals were published. Nearly no data exist with regard to adherence to these key values, however. Tools like big data analytics / data mining based on clinical information systems help to quantify, understand and influence our institutions' processes and thus achieving continuous improvement.
Methods: Retrospective, anonymized, quantitative analysis of all inpatients (Internal medicine) in 2016 concerning key values linked to the top-5 list.
Results: 3'930 inpatients (41% female, average length of stay 6.6 days, mean age 71.3 years) were analyzed. Blood tests: in a cumulative amount of 20'024 inpatient days, 19'116 phlebotomies were performed. This results in 5 blood tests per patient stay (including phlebotomy on admission/ED) or an average of 0.8 blood samples per patient and day. Urinary catheter (UC): 607 (15.4%) received a UC, 41 (1%) already had it on admission. Mean duration of maintenance was 4.8 ± 3.8 days. In 1% of UC patients, nosocomial urinary tract infection was documented. Blood transfusions BT: 408 BT where performed. On average, hemoglobin level prior to transfusion was 74.0 ± 10.3 g/l and 1.6 ± 0.6 red blood cells RBC units were administered. Bed rest: in 3'505 inpatients formal assessments were performed; 159 (4.5%) were initially under bed rest, additional 128 (0.4%) during hospitalization. On average, bed rest lasted for 2.9 days regardless of causes. Benzodiazepines: 3'427 patients had at least one drug prescription, both on admission and discharge. 365 (10.7%) had benzodiazepine prescriptions on admission, 373 (10.9%) on discharge. During hospitalization, 1473 (5.3%) out 27'886 on demand prescriptions were benzodiazepines. 628 (43%) where second line prescriptions (given a first line non-benzodiazepine prescription) for sleep disorders. Only 28 (1.9%) had benzodiazepines as first-choice on demand prescription for sleeping disorders.
Conclusion: For a first time, this quantitative assessment with regard to SMR offers both, deep insight into (selectively excellent) adherence to key values as well as a launching point for benchmarking with other institutions and further quality improvements. Information management will play a key role (including correlated data, e.g. diagnoses, co-morbidities, indications) in order to achieve precise decision support, process improvements and increased quality of care at lower costs.

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The role of GPs in hospital admissions of terminally ill patients: results from a survey of Swiss GPs

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Background: Hospital admissions of palliative care patients at the end-of life are considered inappropriate and should be avoided. This study aimed to evaluate the frequency and type of GPs self-reported end-of-life hospital referrals. Further, the association between frequent hospital referrals and referral reasons, confidence in end-of-life care and regional palliative care network were assessed.
Design and setting: Cross-sectional postal survey involving a stratified random sample of 2000 GPs in Switzerland in 2014.
Methods: Main outcome measure was GPs assessment of the type and frequency of end-of-life referrals 1–3 weeks before death. The association between hospital admissions frequency and GP characteristics was tested using logistic regression models, controlling for age, gender and regional characteristics.
Results: The questionnaire was completed by 579 Swiss GPs (Response Rate 31%). Thirty-seven percent of GPs reported frequent hospital admissions shortly before death. Logistic regression analysis indicated GPs were less likely to report frequent hospitalizations shortly before death when they felt confident in crisis anticipation (OR = 0.76, 95% CI = 0.60, 0.96), in coping with patient's wish to die (OR = 0.74, 95% CI = 0.60, 0.91) and in handling spiritual needs (OR = 0.80, 95% CI = 0.68, 0.94). Furthermore, GPs were twice as likely to report frequent hospitalizations because of relatives' wish (OR = 2.39, 95% CI = 1.90, 3.05), difficult symptom control (OR =2.26, 95% CI = 1.84, 2.81), missing resources of GPs (OR = 2.16, 95%CI = 1.68, 2.80) or small or missing caring network
(OR = 2.11, 95% CI = 1.71, 2.63). Intriguingly, GPs were more likely to transfer their patients often to the hospital if GPs used palliative councils often (OR = 1.93, 95% CI = 1.22 3.10).
Conclusions: GPs reporting frequent hospital admissions of palliative care patients at the end-of life were shown to be less confident in non-somatic palliative care skills, irrespective of age, gender and regional characteristics. Thus, favoring the acquisition of these skills through continuous medical education and providing alternative options to hospitalisation might reduce hospital admissions shortly before death.

P318

Elegibility for PCSK9 inhibitors in the general population

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Introduction: PCSK9 inhibitors are new lipid-lowering drugs recommended for very high-risk patients such as those with familial hypercholesterolemia or cardiovascular disease (CVD) not reaching optimal LDL-cholesterol levels despite maximum dose of statins. Because these news drugs are 40 times more expensive than statins, the societal impact of using these drugs in the general population is unknown.
Aims: We aim to assess the proportion of patients potentially eligible for PCSK9 inhibitors in the Swiss general population according to the latest 2016 European and American guidelines.
Methods: We studied 4,905 adults aged 35–75 years from the CoLaus study, a prospective population-based cohort in Switzerland, with available lipid measurements both at baseline and at the 5-year follow-up visit. At baseline, the prevalence of patients at very-high risk of CVD was assessed. After 5-years, according to 2016 European Society of Cardiology (ESC) and 2016 American College of Cardiology (ACC) guidelines, we assessed eligibility for PCSK9 inhibitors, defined as unmet LDL-cholesterol goals despite use of rosuvastatin 20 mg, atorvastatin 40 mg or simvastatin 40 mg, assuming a 20% additional reduction of LDL-cholesterol with addition of ezetimibe.
Results: The prevalence of very high-risk patients at baseline was 16.3% (n = 715) respectively 12.3% (n = 604), and after 5 years only 1.2% (n = 58), respectively 1.8% (n = 87) reached optimal lipid target according to ESC, respectively ACC guidelines. Most of very high-risk patients would first need initiation or intensification of statins or ezetimibe, before prescription of PCSK9 inhibitors (see figure).

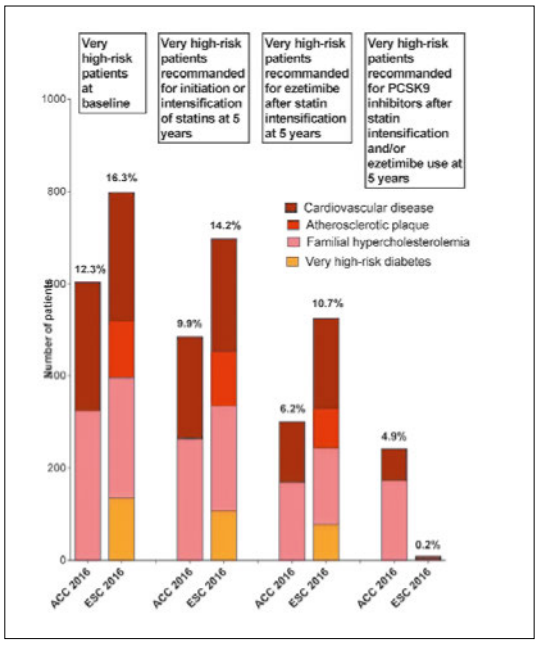

Figure 1

According to ESC respectively ACC guidelines, 0.2% (n = 9) respectively 4.9% (n = 243) of the general population would be eligible for PCSK9 inhibitors. If initiation or intensification of statins at 5-year would not be possible because of statin intolerance, 1.4% (n = 70) respectively 9.6% (n = 471) would be eligible for PCSK9 inhibitors according to ESC respectively ACC guidelines.
Conclusion: A large number of patients at very high-risk for CVD had sub-optimal statin therapy and did not reach optimal lipid targets after 5 years. Although there are large differences of eligibility between European and American guidelines, the amount of prescription of PCSK9 inhibitors in the general population will also depend on the ability to intensify statin use and dosage.

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The "Rösti"-Study: a time motion study comparing the allocation of time of internal medicine residents in two Swiss hospitals, a comparison of a Swiss German Cantonal teaching hospital with a university hospital in the French speaking part

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Background: Several factors, such as cultural habits, type of hospital (university vs. non-university), local organization and practice (number of patients per resident) and resident characteristics may influence residents' time allocation. We thus aimed to evaluate the composition of internal medicine residents' working day in two different teaching hospitals and to assess the proportion of time spent with direct patient care.
Methods: Two different time motion studies were performed in the departments of internal medicine of CHUV and KSB. Trained observers recorded residents' activities during day shifts. To ensure comparability, the same study protocol, tablet-based software and instruction manual were used. Out of 22 recorded activities, we selected for comparison: activities directly related to patients, documentation, supervision, personal time and direct patient contact. The time spent per patient per day was calculated based on patient-equivalents. One patient-equivalent was defined as the presence of a patient during the whole observed shift of an individual resident. We compared mean values using the two-sided, untailed t-test.
Results: Demographic baseline characteristics of residents are shown in table 1.

Table 1: Baseline characteristics of residents.

	KSB		CHUV		
	mean	SD	mean	SD	p value
Age (years)	29.6	3.19	28.8	1.7	0.15
Months postgraduate	20.9	17.7	31.2	11.9	0.002
Months experience in internal medicine	16.1	11.3	27	10.4	< 0.001
Swiss diploma	66.70%		60.70%		
Female gender	57%		63%		

SD = standard deviation

KSB residents had a shorter post-graduate training (21 vs 31 months, p <0.001). Residents were observed during 486.4 hours (43 shifts) in KSB vs 568.2 h (49 shifts) in CHUV.Mean shift duration were similar (11.3 ± 1.1h in KSB vs 11.6 ± 1.3h in CHUV, p = 0.19). Mean patient-equivalent was 7.4 ± 1.0 in KSB vs 7.8 ± 2.3 at CHUV (p = 0.27). Mean durations of activities are presented in table 2. In CHUV, residents dedicated more time to patients (114.7 ± 44.9 vs. 94.9 ± 31.4, p = 0.015; i.e. 14.6 vs 12.6 minutes/patient/day) and for EMR documentation, whereas in KSB, residents spent more time writing the discharge letter, performing transmission with the team and for communication with patients and families.
Conclusions: 1) Despite shorter post-graduate training for KSB residents,allocation of time was similar regarding total working hours, patient-equivalents and supervision. 2) Differences in allocation of time for documentation may be due to different computer systems favouring either discharge letter or documentation in EMR. 3) These data provide the basis for the implementation of measures to reduce resp. optimize the administrative load and to increase the time spent with patients. No major differences document an excellent Rösti-collaboration rather than a "-Graben".

Table 2: Comparison of time spent in different activities.

		KSB		CHUV		
		mean	SD	mean	SD	p value
Total Time spent with patients	min	94.9	31.4	114.7	44.9	0.015
Activities directly related to patient*	min	112.3	38.1	198.9	61.8	< 0.001
Time with communication	min	25.1	16.18	15.6	14.4	0.004
Delivery of results, decision	min	9.9	9.9	4.6	8.5	0.0067
Communication with family	min	15.19	13.79	11.0	12.78	0.14
Documentation	min	169.89	50.6	140.02	48.67	0.005
Writing in EMR	min	72.52	32.17	110.09	43.23	< 0.001
Discharge letter	min	64.55	37.35	14.08	24.54	< 0.001
Transmission	min	32.82	19.05	15.84	14.50	< 0.001
Supervision	min	60.39	37.43	60.34	34.97	1.00
Personal time†	min	69.37	24.04	31.04	18.22	< 0.001

* entry, discharge, daily round, puncture, out of unit support/emergency. SD = standard deviation.

† toilet, lunch/coffee break, personal talk

EMR: electronic medical records

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How well are Swiss French-speaking physicians prepared for independent practice in ambulatory general internal medicine?

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Introduction: Moving from training to independent practice represents a major transition in professional life. The aim of this study was to explore the extent to which Swiss general internists who recently set up private practice felt prepared to work as independent physicians.
Methods: We conducted focus groups among a sample of physicians practicing as general internists (FMH) for <5 years in different working contexts of the French-speaking part of Switzerland. Questions focused on positive and negative aspects of setting up a practice, degree of preparedness, strengths and weaknesses of postgraduate training. Transcripts were analysed according to dimensions described in organisational socialisation and work role transition frameworks.
Results: 28 physicians from 5 cantons participated in 7 focus groups: 1/3 trained exclusively in academic settings, most worked in an urban or suburban area and predominantly in small group practices. Most positive reported elements of setting up practice referred to notions of freedom, autonomy and mastery, and physician patient relationships while negative reported elements referred to feelings of stress and loneliness related to non-clinical tasks such as administrative, financial and time management as well as medico-legal issues for which all participants felt both incompetent and unprepared. Although physicians felt adequately prepared to perform most medical tasks, they reported discomfort in dealing with common problems in rheumatologic, minor traumatology, ENR, skin and psychiatric problems in all contexts and in paediatrics, gynaecology, as well as surgical skills if working in rural areas. Several participants reported not having anticipated the importance of having a network of specialists once in independent practice. They also described several practice-based ethical dilemmas opposing professional values to reality of practice (freedom, autonomy, altruism versus work-life balance, practice business management and patient accountability) which forced them to clarify their professional roles and expectations. Adjustments to these new tasks were mainly made informally.
Conclusion: Postgraduate training in ambulatory general internal medicine could be further improved to better support the reality of transition. More emphasis should be put on learning and teaching in the environment for which physicians are being prepared, especially during the last years of training.

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Undernutrition is associated with increased financial losses in hospitals

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Background and aims: Undernutrition is associated with increased hospital costs. Whether these increased costs are totally compensated by third payer systems has not been assessed. We aimed to assess the differences between actual and reimbursed hospital costs according to presence/absence of nutritional risk, defined by a Nutritional risk screening-2002 (NRS-2002) score ≥3.
Methods: Retrospective study using administrative data for years 2013 and 2014 from the department of internal medicine of the Lausanne university hospital. Total and specific costs (i.e. related to treatments, medical interventions, imaging, laboratory analyses, food, intensive care units…) were obtained. Reimbursed costs were based on the Swiss Diagnosis Related Group (DRG) system and we considered 1 DRG point = 10'500 CHF (average value for 2014). Coverage of the costs was computed as the ratio costs/reimbursements and expressed as percentage, and further categorized as complete (≥100%) or less than complete (<100%).
Results: 2200 admissions with NRS-2002 data were included (mean age 76 years, 53.9% women), 1398 (63.6%) of which were considered nutritionally 'at-risk'. After multivariate adjustment, patients nutritionally 'at-risk' had higher costs (multivariate-adjusted difference ± standard error: 34'206 ± 1246 *vs.* 22'214 ± 1666 CHF, p <0.001) and higher reimbursements (26'376 ± 1105 *vs.* 17'783 ± 1477 CHF, p <0.001) than patients 'not at risk'. Still, reimbursements failed to cover the costs, leading to an average deficit of 7831 ± 660 CHF in patients 'at-risk' vs. 4431 ± 881 in patients 'not at-risk' (p <0.003). Being nutritionally 'at-risk' also led to a lower likelihood of complete coverage of costs: multivariate-adjusted odds ratio and 95% confidence interval 0.77 (0.62–0.97), p <0.05. Patients 'at-risk' had lower percentage of total costs in medical interventions, food, imaging and "other", but the absolute differences were less than 2%.
Conclusion: Hospital costs of patients nutritionally 'at-risk' are less well reimbursed than of patients 'not at-risk'. Better reporting of undernutrition in medical records and better reimbursement of undernourished patients is needed.

P322

Should thyroid tests be performed to investigate the causes of anaemia? A large population-based study

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Introduction: A relationship between overt thyroid dysfunction and anaemia is commonly mentioned, but limited data are available on the association with subclinical thyroid dysfunction. In a large population-based cohort, we aimed to quantify the effect of thyroid function on haemoglobin concentration (Hb) and to study the association with anaemia.
Methods: We analysed participants from the EPIC-Norfolk cohort with thyroid stimulating hormone (TSH), free thyroxine (fT4) and Hb measured at baseline and follow-up. Hypothyroidism was defined as TSH >4.49 mIU/l, either subclinical (SHypo) with normal fT4 or overt (OHypo) with low fT4. Hyperthyroidism was defined as TSH <0.45 mIU/l, either subclinical (SHyper) with normal fT4 or overt (OHyper) with elevated fT4. Euthyroidism was the reference category (normal TSH/fT4). Anaemia was defined as Hb <12 g/dl for women and <13 g/dl for men. In the cross-sectional analysis, we used multiple linear regression to compare Hb across the TSH categories and logistic regression to analyse the association between thyroid dysfunction and anaemia. In the longitudinal analysis, we used multivariable Cox regression to compare the incidence of anaemia among participants with SHypo/SHyper and euthyroidism.
Results: In the cross-sectional population (n = 12,337), the mean age was 59 years and 53.1% were women. 11,174 (90.6%) participants were euthyroid and had a mean Hb of 13.9 g/dl. No relevant differences in Hb were observed among TSH categories. In multivariable analyses, Hb was 0.23 g/dl (95%CI-0.40 to-0.06) lower in OHypo, and 0.40g/dl (95%CI-0.78 to-0.01) lower in OHyper than in euthyroidism. In the logistic regression, OHypo was associated with anaemia (adjusted OR 1.89, 95%CI 1.23–2.88), OHyper showed a borderline association (adjusted OR 2.16, 95%CI 0.94–4.95) whereas no association was found in SHypo/SHyper. In the longitudinal analysis, 460 of 7,031 participants (6.5%) developed anaemia during a follow-up of 55,733 person years (median 4.7 years). When we compared SHypo/SHyper to euthyroidism, the adjusted hazard ratio of anaemia was 1.01 for SHypo (95%CI 0.68–1.51) and 0.52 for SHyper (95%CI 0.23–1.18). Results were similar in all sensitivity analyses.
Conclusion: Considering the minimal changes in Hb among the TSH categories and the lack of prospective association between thyroid dysfunction and anaemia, in our study subclinical thyroid dysfunction does not seem to be an independent risk factor for the development of anaemia.

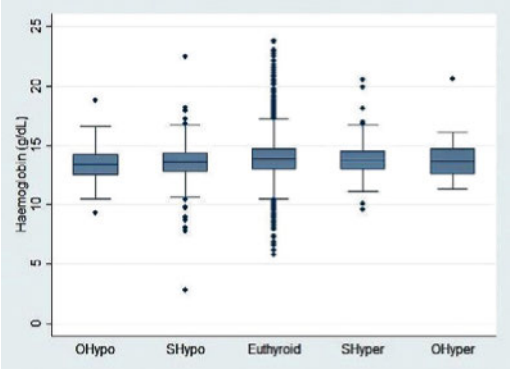

Figure 1: Haemoglobin concentrations in thyroid dysfunction.

P323

Introduction of an organised programme and social inequalities in mammography screening: a 22-year population-based study in Geneva, Switzerland

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Introduction: Generalisation of mammography screening contributed, at least in part, to the decrease in breast cancer mortality in developed countries. The implementation of an organised programme has been suggested to increase screening participation and reduce social disparities in screening access. We aimed to describe the evolution of socioeconomic inequalities in mammography screening before and after the introduction of an organised programme in Geneva, Switzerland.
Methods: We included 5345 women with no past history of breast cancer, aged 50–74 years and who participated in the cross-sectional Bus Santé study, between 1992–2014. Outcome measures were: a) never had a mammography (1992–2014) and b) never had a mammography or not in the two years before survey (for subgroup analysis, 2007–2014). We divided educational attainment in 3 groups

(primary, secondary and tertiary) and considered two periods - before the introduction of screening programme in 1999 and after. We calculated the relative (RII) and slope (SII) indexes of social inequality, which measure the relative and absolute inequalities between the different educational levels, respectively. We used Poisson models to compare screening prevalence before and after screening programme implementation.
Results: We observed a decrease in the proportion of unscreened women during the study period from 30.5% to 3.6%. Lower educated women more probably never had a mammography (RII = 2.39, p <0.001; SII = 0.10, p <0.001). Implementation of an organised screening programme coincided with a decrease in the proportion of unscreened women independently of educational attainment (prevalence ratio$_{\text{before vs. after}}$ = 4.41, p <0.001). However, both absolute and relative inequalities persisted (RII = 2.11, p = 0.01; SII = 0.04, p = 0.01).
Conclusion: Introduction of an organised programme increased participation but was not sufficient to eliminate socioeconomic disparities in breast cancer screening.

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Diagnosis of acute myocardial infarction in patients presenting with left bundle branch block

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Introduction: Patients with suspected acute myocardial infarction (AMI) in the setting of left bundle branch block (LBBB) present an important diagnostic and therapeutic challenge to the clinician, highlighted by divergent recommendations given by the respective guidelines in the United States and Europe. It is currently unknown, whether patients presenting with acute chest pain and new/presumably new LBBB should also receive immediate coronary angiography and/or thrombolysis such as those with clear ST-segment elevations.
Methods: We aimed to prospectively evaluate the incidence of AMI, and the diagnostic performance of selected ECG criteria and high-sensitivity cardiac troponin (hs-cTn) T and I among 8830 patients presenting with symptoms suggestive of AMI to the emergency department. Presence of LBBB, ECG criteria (Sgarbossa, Smith, Selvester), and final diagnoses were adjudicated by independent cardiologists. Findings of the derivation cohort (n = 4015) were validated in two external cohorts.
Results: In the derivation cohort, LBBB was present in 140 patients (3.5%). AMI was the adjudicated final diagnosis in 32% of patients with LBBB, with similar incidence in those with known LBBB versus those with presumably new LBBB (29% vs 35%, p = 0.42). ECG criteria had modest accuracy (64–71%), low sensitivity (2–18%), and high specificity (94–100%) for AMI. Diagnostic accuracy of hs-cTnT and hs-cTnI at presentation as quantified by the area under the receiver-operating characteristics curve was very high (0.91; 95%CI 0.85-0.96 and 0.89, 95% CI 0.83–0.95; fig. 1). Hs-cTnT levels ≥42 ng/l (hs-cTnI ≥45 ng/l) provided a positive predictive value of 80% for AMI and together with known coronary artery disease (odds ratio 4.6, 95%CI 2.0–10.4) predicted AMI in multivariate analysis (odds ratio 30.5, 95%CI 11.7–80.1). These findings were confirmed in both validation cohorts.

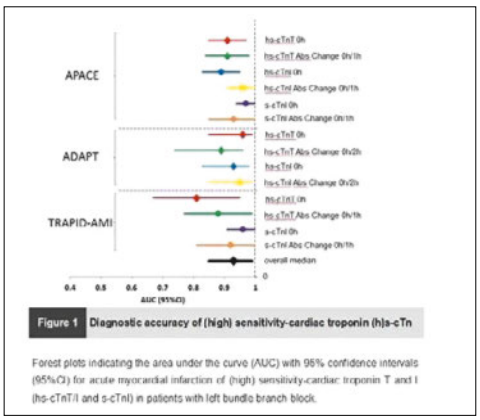

Figure 1 Diagnostic accuracy of (high) sensitivity-cardiac troponin (h)s-cTn

Forest plots indicating the area under the curve (AUC) with 96% confidence intervals (95%CI) for acute myocardial infarction of (high) sensitivity-cardiac troponin T and I (hs-cTnT/I and s-cTnI) in patients with left bundle branch block.

Figure 1

Conclusion: Guidelines calling for immediate invasive procedures in patients with LBBB should be reevaluated. Specific ECG criteria and suggested (h)s-cTn thresholds allow an accurate and immediate triage to coronary angiography in patients with LBBB and symptoms suggestive of AMI (fig. 2).

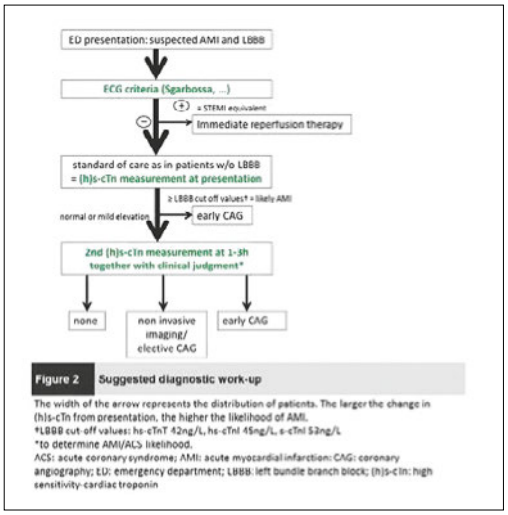

Figure 2 Suggested diagnostic work-up

The width of the arrow represents the distribution of patients. The larger the change in (h)s-cTn from presentation, the higher the likelihood of AMI.
*LBBB cut-off values: hs-cTnT 42ng/L, hs-cTnI 45ng/L, s-cTnI 52ng/L
*to determine AMI/ACS likelihood.
ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAG: coronary angiography; ED: emergency department; LBBB: left bundle branch block; (h)s-cTn: high sensitivity-cardiac troponin

Figure 2

P325

Interventions recommended to prevent, manage and treat compassion fatigue: a systematic review of the literature

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Background: In healthcare and social professions, compassion fatigue (CF) is a term used to refer to a state of advanced and profound exhaustion and distress resulting from the repeated empathic and compassionate engagement with traumatised and suffering populations. This study provides a critical appraisal and review of the existing recommendations to prevent, manage and treat CF.
Methods: Five electronic databases (Medline/Pubmed, Embase, Web of Science, CINAHL plus and PsycINFO) were consulted. Because of the conceptual ambiguity of CF, the first search strategy was to identify articles published between January 1980 to March 2016, in English or in French, using the term "CF" and the terms that were used interchangeably with it in the literature (namely "secondary traumatic stress and "vicarious traumatisation"). The second search strategy was to identify and review published articles containing suggested strategies and interventions for combating CF. The literature search was completed by hand searching reference lists. Each of the articles was analyzed in detail using an evaluation form. Duplicate papers, papers which did not provide an abstract, and papers that were not related to the topic of this study were removed (see fig. 1).

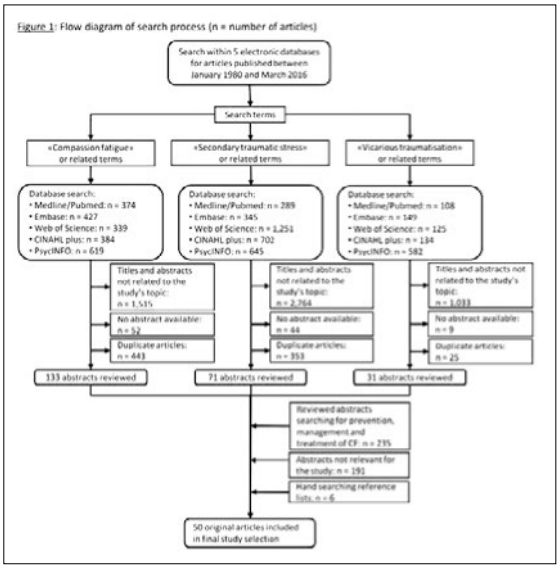

Figure 1

Results: Fifty published original articles met the inclusion criteria: three articles were systematic literature reviews, seven were experimental studies, six were descriptive studies, seven were qualitative studies, two were mixed method studies, and twenty-five were evidence based on the authors' opinion. The analysis of the articles suggested that CF can be combated among helping organisations and professionals, which requires increasing their (self-) awareness of occupational hazards through education, debriefings and supervisions, and equipping them with adequate knowledge and skills that will enhance their coping and resiliency resources. It also requires developing and nurturing self-care and self-management strategies, and promoting organisational and structural changes that will mitigate work environment constraints (see fig. 2).
Conclusions: CF can be combated among helping organisations and professionals. Additionally, combating successfully CF may also require redefining our own perceived role and missions as a helping professional, including changes in our ways and levels of expectation to fulfil them.

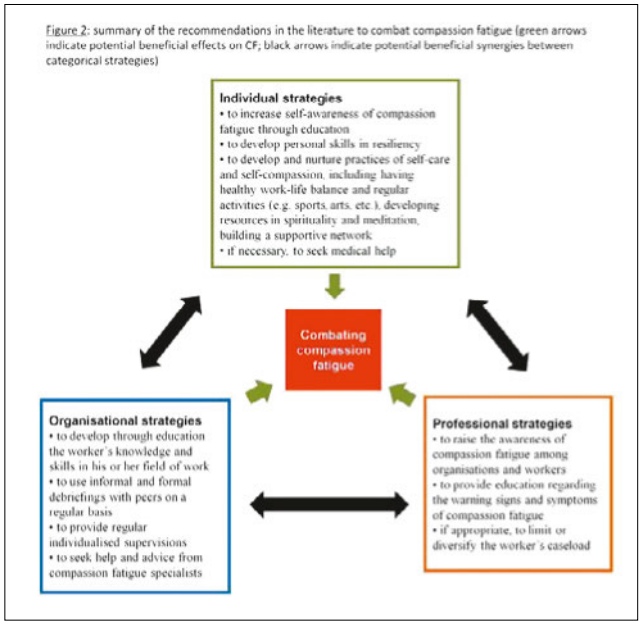

Figure 2

POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE II / ALLGEMEINE INNERE MEDIZIN II

P326

No association between grip strength and cardiovascular risk; the CoLaus population-based study

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Background: Low grip strength (GS) is predictive of cardiovascular (CV) disease but whether it improves CV risk prediction over existing CV risk scores has not been evaluated. We assessed the predictive value of low GS on incident CV events taking into account several CV risk equations in a Swiss population-based study.
Methods: 2707 adults (54.8% women, age range 50–75 years) were followed for a median time of 5.4 years. GS was assessed using a hydraulic hand dynamometer. Low GS was defined according to Fried criterion. CV absolute risk at baseline was assessed using recalibrated SCORE, Framingham and PROCAM risk equations.
Results: 188 incident CV events occurred during follow-up. The unadjusted positive association between low GS and incident CV events disappeared after adjusting for CV absolute risk (table).
Conclusion: Low GS is not predictive of incident CV events when taking into account CV absolute risk.

Table: Association grip strength and CV events.

	Hazard Ratio	[95%CI]	P value
Unadjusted	1.76	1.13–2.76	0.01
Adj. for SCORE	1.23	0.79–1.94	0.36
Adj. for Framingham 2001	1.34	0.86–2.10	0.20
Adj. for PROCAM 2007	1.47	0.94–2.31	0.09

P327

Trying hard to reconciliate the medication upon admission in a tertiary internal medicine department

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Background: Medication discrepancies largely arise due to communication issues at transition steps. Up to 70% of patients have at least one discrepancy between regularly taken drugs and hospital-prescribed drugs. A lack of accuracy in medication history is responsible for 50% of medication errors and for 20% of adverse drug effects occurring in hospitals. We aimed to assess the feasibility of a medication reconciliation process upon admission.
Methods: Within "Progress!", the national initiative of Patient Safety Switzerland, we developed our process from own expertise and literature. Interns were trained to collect two different sources of information (medical and practical) and confront them within a structured interview with the patient, which included questions about allergies and over-the-counter drugs. We developed a electronic medical record (EMR) form to support the process. The nurses provided the practical source (i.e pillbox). We included all consecutive patients admitted in two unit of the internal medicine during one year. Exclusion criteria were age <65 years and not being directly admitted from home. Interns were asked if the reconciliation would have clinical significance (yes or no) and to assess the time spent on a 5-step scale.
Results: Starting November 2015, 1'155 admitted patients were screened. 621 were excluded because of age (n = 369), not directly admitted from home (n = 243), or lost follow-up (n = 9). Of the 534 included patients, 62% were females. Average age was 80.4 (SD ± 8.0) years. Interns performed 302 reconciliations (56.9%). Average delay until completion was 37.7 (SD ± 59.2) hours after admission. Interns assessed 54% of reconciliations as useful (116 / 213 answers). Time spent for reconciliation was estimated between 15 and 30 minutes in 44% (101 / 229 answers) and over 30 and 45 minutes in 31%. Lessons learned include: 1) the difficulty to get information from partners delays the reconciliation; 2) a high rate of reconciliation needs training and support of interns; 3) a good EMR is the key tool for an efficient reconciliation.

Conclusions: Despite subjective benefit, medication reconciliation performed by the physicians alone is time-consuming and barely feasible without added resources. Wide implementation is desirable but needs to be supported by good IT tools, active participation of other caregivers, and might have to be restricted to high-risk patients.

P328

Integrative hospital treatment in older patients to benchmark and improve outcome and length of stay – the *In-HospiTOOL* study – *a quasi-experimental, multicenter comparative effectiveness health care research trial*

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Introduction: Health care costs are high and rising also due to an aging, polymorbid population, why resource allocation becomes a priority. There is lack of evidence-based tools namely for polymorbid patients to improve integrative in-hospital care and transition process in an acute care hospital setting. Also, there is no reference standard for quality benchmarking in Switzerland which is mandatory to compare quality of different institutions. To address these issues, we propose a multicenter "before-and-after" trial to study the effect of an inter-professional inpatient management tool on length of stay and other patient-centered outcomes.
Methods: In-HospiTOOL combines several patient discharge measures and was developed involving multiple professions. An electronical monitoring and reporting system enables clinical user oriented benchmarking to assess hospital processes, quality, delays in hospital transition and barriers for discharge stratified by profession. For external multicenter validation, In-HospiTOOL will be implemented in five Swiss secondary and tertiary care hospitals. We will use a quasi-experimental approach and compare length of stay before and after hospital-wide implementation of the management tool in relation to changes in length of stay in hospitals not using the tool (time-trend analysis with data from other Swiss hospitals provided by the Swiss Federal Office of Health serving as controls).
Expected results: We expect a total inclusion rate of 45'000 patients across all three 6-month study periods (observation, implementation, intervention). Based on our monocentric experience we expect the In-HospiTOOL to have a strong effect on inter-professional team work in this polymorbid setting which results in reduction in length of stay of at least 1 day. We also expect that patient outcomes are not negatively affected by the intervention (e.g. intensive care unit admission, mortality, unplanned readmission, patient satisfaction). A safe reduction of length of stay will have positive implication on overall hospital costs.
Conclusion: The trial will yield concise information on whether and how the "In-HospiTOOL" improves inter-professional team work and thereby reduces length of stay without negatively impacting subjective and objective markers of patient outcomes. The large amount of collected patient data will enable comparison of transition processes within different hospitals and establish a benchmarking for patient care quality.

P329

Students' implication in faculty development programs contributes to their development of professional identity

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Background: Medical students develop their professional identities through various activities and relationships within different settings. As students are being increasingly involved as simulated learners in objective structured teaching encounters (OSTEs) for Faculty development purposes, we explored if taking part in OSTEs influenced their actual and projected professional identity development (PID).
Methods: A Faculty development program was developed at the Geneva University Hospitals (Switzerland) to train faculty members from five departments (including hospital and ambulatory general internal medicine) in clinical teaching skills on domains such as clinical reasoning, communication, professionalism, and inter-professional collaboration. Medical students who participated in OSTEs were invited to take part into focus groups. They were asked about what they learnt and how this experience influenced their vision of being a student, resident, and supervisor. Discussions were analysed using a framework based on personality and social structure perspectives (PSSP model).
Results: Focus groups took place with 25 medical students from 4th to 6th years. PID emerged at three levels. On the institutional level, having the opportunity to take part into clinical supervisors' training helped students develop a feeling of being a professional inside the institution and allowed them to enter further into the community of practice On the interactional level, students realised they could become actors of change by actively seeking or giving feedback. On the personal level, they discovered that mistakes could become sources of learning rather than blaming and felt better prepared to cope with faculty feedback. Finally, they realised that being a medical supervisor was about mastering medical and teaching competencies.
Discussion: Taking part in OSTEs has a positive impact on students' perceptions regarding the institution as a learning environment, their role as actors of change and their own position towards mistakes. Including students' participation in OSTEs seems to be a way to support their PID while sustaining faculty development.

P330

Frequency of use and acceptability of clinical prediction rules for pulmonary embolism among Swiss general internal medicine residents

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Background: Whether the Revised Geneva Score (RGS) and the Pulmonary Embolism Severity Index (PESI), two well validated and recommended clinical prediction rules (CPRs) for pulmonary embolism, are used in daily clinical practice remains unexplored. We evaluated the frequency of use, the acceptability among clinicians, and which factors drive the use of the RGS and the PESI.
Methods: We conducted an online survey among Swiss general internal medicine residents from five university and five non-university hospitals in July 2016 to examine the frequency of use of the RGS and PESI. We assessed rule acceptability using the 12-item Ottawa Acceptability of Decision Rules Instrument (OADRI). Each item is rated on a 6-point scale, 0 points indicating a low and 6 points a high acceptability. We further explored the association between physician and educational factors and rule use using a mixed logistic regression model.
Results: The response rate was 433/859 (50.4%). Overall, 61% and 35% of the residents indicated that they always or regularly use the RGS and the PESI, respectively. The mean overall OADRI score was 4.3 points for the RGS and 4.1 points for the PESI, indicating good overall rule acceptability. Participants judged both the RGS and the PESI to be easy to use (mean score for the RGS 5.4 points; mean score for the PESI 4.7 points) and to have a clear wording (RGS 5.1; PESI 4.7), but not to be easy to remember (RGS 3.8; PESI 3.0). Rule acceptability (odds ratio [OR] 5.71 per score point, 95% confidence interval [CI] 3.34–9.76), prior training in the emergency department (OR 4.96, CI 2.09–11.76), number of years since graduation (OR 1.37 per year, CI 1.04–1.80), availability of internal guidelines recommending RGS use (OR 4.15, CI 2.05–8.38), and younger age (OR 0.83 per one-year increase, CI 0.72–0.96) increased the odds of using the RGS. Rule acceptability (OR 6.27 per score point, CI 4.04–9.73), learning of the rule during medical school (OR 2.06, CI 1.22–3.48), and younger age (OR 0.83 per one-year increase, CI 0.72–0.96) increased the odds of using the PESI.

Conclusion: Among Swiss general internal medicine residents, the RGS was more frequently used than the PESI. Both CPRs had a good acceptability. Several factors, including rule acceptability, prior training in the emergency department, availability of internal guidelines recommending rule use, learning of the rule in medical school, and younger physician age were associated with rule use.

P331

Effect of a quality improvement intervention with the implementation of an endoscopy safety checklist

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Introduction: Safety checklists might have a place in interventional procedures such as gastrointestinal (GI) endoscopy. The aim of this study was to reinforce commitment in safety culture and better communication among team members in endoscopy and to prove feasibility of successful checklist adoption before selected GI procedures.
Methods: *before-after* quality improvement (QI) study involving all consecutive patients admitted for a colonoscopy at McGill University Health Center from November 2016 to January 2017 (ongoing study). Psychometric properties of the checklist have been assessed through a validation process. A questionnaire-based survey was administered to all staff members and to a random sample of 250 patients before and after the QI intervention. Patient and team satisfaction using 5-point scale questionnaires were the primary outcome. Secondary outcomes included different per-procedure outcome and complications.
Results: During the 3-month baseline period and comparative intervention period, 1318 and 990 (still enrolling) colonoscopies were performed respectively. Out of these initial 990, 707 have completed checklists (72%). 147 of the random sample of 250 patients returned the satisfaction questionnaire (59%) before the QI intervention and 76 after (ongoing study). Mean overall scores for patient satisfaction were high at baseline and do not differ (4.66 vs 4.69, p = 0.5). However, perception of team communication and teamwork from the patient perspective (blinded to the study aim) was improved after checklist implementation (4.6 vs 4.88, p = 0.03). 57 of 76 patients noticed the use of the checklist and only 3 (4%) felt anxiety regarding its use during the procedure. Comparative analyses of team satisfaction and per-procedural outcome are pending completion of enrollment.
Conclusion: This QI study demonstrates that adoption of an endoscopic checklist before GI procedures (in this case, colonoscopy) is feasible and increases patient favourable perception of team communication and teamwork without causing anxiety. This may be one mechanism through which safety outcomes can subsequently be improved. Future research should aim to further elucidate the relationship between checklists use and safety outcomes through better communication in this specific setting using more consistent methodological approaches such that best practice guidelines can be more fully practiced.

P332

Use of strong opioids in cancer and non-cancer pain in a Swiss population

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Introduction: Globally, opioids are increasingly used for non-cancer pain. In Switzerland, the use in strong opioids more than doubled between 2006 and 2013. Studies suggest that the use of opioids in a daily morphine equivalent dose (MED) of 100 mg and more are associated with an increased risk of potential serious side effects. The objectives of this study were twofold: 1) to assess the use of opioids for cancer and non-cancer pain in a Swiss population; 2) to assess in non-cancer pain patients the proportion of opioid use at a daily MED dose of 100 mg and more.
Methods: Analysis of insurance claims for opioids between 2006 and 2014 from one of the major health insurers in Switzerland covering 1.2 million individuals (approximately one-sixth of the Swiss population). Included were persons with at least one opioid prescription claim. Strong opioids used in drug substitution programs were excluded. All opioids were converted into mg MED. Opioid use was divided into cancer and non-cancer diagnosis using the Anatomical Therapeutic Chemical (ATC) drug classification and predefined Tarmed positions. We analyzed the treatment duration and the median MED daily dose in non-cancer related opioid use. Treatment duration was categorized <90 days, 90 to <120 days, and chronic opioid use of ≥120 days. Based on the total dose and duration we calculated the median MED dose per episode categorized into less than 20, 20 to <50, 50 to <100, and ≥100 mg/day.
Results: Overall, we analyzed 597'536 episodes (94% non-cancer diagnoses, 6% cancer diagnoses) of opioid use in 376'664 patients. In 207'334 episodes (152'493 patients) more than one opioid claim was reimbursed: 90.8% of these opioids were used for non-cancer diagnosis, in 9.2% for cancer diagnoses. More than one opioid claim for strong opioids was found in 78431 episodes (66'440 patients); in 17.2 % for cancer diagnoses, 82.8% for non-cancer diagnoses. In non-cancer episodes, treatment duration was mainly less than 90 days (82%) and mostly at a dose of less than <20 mg MED. In 15% of the episodes a chronic opioid use was found. Of the patients taking opioids at a maximum dose of 100 mg and more, 56% were chronic opioid users (fig. 1).
Conclusion: The analysis of opioid use in a Swiss population showed that opioids were mainly used for non-cancer diagnoses. Further, a small population potentially at risk for opioid related serious adverse events was identified.

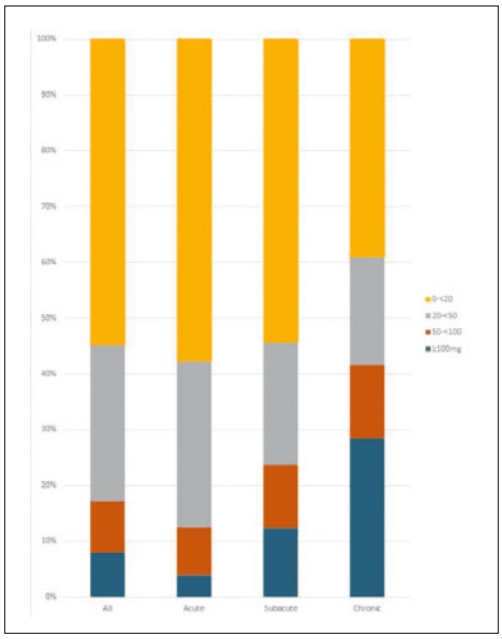

Figure 1: Treatment Duration and median Daily Dose.

P333

Comparisons of intra- and interprofessional conflicts in healthcare teams

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Introduction: Interactions between healthcare professionals range from good communication to conflict and may affect patient care. While much research has focused on interprofessional collaboration, conflict is still poorly understood. Our goal was to develop a deeper understanding of conflicts in healthcare teams by comparing intra- and interprofessional conflicts so as to inform interprofessional training programs, which are increasingly introduced in clinical settings.

Methods: We conducted 82 semi-structured interviews with randomly selected residents, fellows, nurses, nurse managers, and nursing assistants across four departments of the Geneva University Hospitals: internal medicine, family medicine, pediatrics, and surgical units. Interviews focused on sources, consequences, and responses to conflicts. Content analysis enabled us to identify features characterizing conflicts. Descriptive and inferential statistics were used to compare the features between intra- and interprofessional situations.
Results: Of the 130 situations of conflicts shared by participants, 57% were intra-professional and 43% were interprofessional. Regarding sources of conflicts, relationship difficulties caused more intra- than interprofessional conflicts (62% *vs* 41%, $P = .02$), whereas disagreements on patient-related tasks (27% *vs* 48%, $P = .02$) and general perceptions of a group vis-à-vis another group (3% *vs* 27%, $P < .001$) generated more interprofessional conflicts. There were no significant differences between intra- and interprofessional conflicts for most consequences, except for professional mobility, which tended to be affected by intra-professional conflicts (20% *vs* 9%, $P = .09$). Individuals involved in intra-professional conflicts tended towards denial and avoided actively managing conflicts (47% *vs* 30%, $P = .07$). For other responses, differences between intra- and interprofessional conflicts were not significant.
Conclusion: There are differences between intra- and interprofessional conflicts, particularly for conflict sources. These differences suggest that interprofessional education would benefit from integrating situations that focus on collaborative patient care. The similarities we observed between intra- and interprofessional conflicts in terms of consequences and responses to conflicts evidence the need to focus on a variety of situations, relationships, and professional roles that reflect clinical settings when designing educational interventions.

P334

Cardiovascular disease risk factors among male youths in Southern Switzerland: a transversal study

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Introduction: Cardiovascular diseases, first cause of death in Switzerland, are frequently attributable to risk factors already present in children and adolescents. The aim of this study was therefore to describe the prevalence of cardiovascular disease risk factors in 18- to 20-year-old males undergoing medical examination to assess fitness for recruitment into the army.
Methods: An exploratory transversal study, approved from the regional ethic commission, was conducted during the recruitment days. The analysis includes measurement of the anthropometric parameters, arterial brachial pressure, central arterial pressure and arterial stiffness (= pulse wave velocity in m/s). Moreover, a structured questionnaire addressing smoking behavior, sedentariness and familial cardiovascular risk factors, as well as blood analysis for determination of glycaemia, lipids and Vitamin D metabolism values was performed.
Results: In the period between 1/4/2014-31/12/2016, 1045 voluntary were included in our study. Following cardiovascular risk factors were present in this young male population: tobacco use (N = 449, 43%), body mass index >25.0 Kg/m^2 (N = 274, 26%); Abdominal circumference > 94.0 cm (N = 117, 11%); Arterial pressure = or >140/90 mm Hg (N = 83, 8%); 25-OH-vitamina D3 rate = or <50 nmol/L (N = 201, 19%); total cholesterol = or >5.2 mmol/L (N = 54, 5%); uricaemia >500 µmol/L (N = 61, 6%); pulse wave velocity >10m/s (N = 25, 2.5%).
Conclusion: The results of this study allow us to analyze the cardiovascular health of young males living in Southern Switzerland. These results clearly show that a high number of young male present at least one cardiovascular risk factor.

P335

Caring for chronic wounds: a pilot survey of knowledge, attitude and beliefs of internal medicine house staff

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Objective: Assess house staff (HS) knowledge, attitude and perceptions regarding chronic wounds and their treatment.
Methods: Pilot study among 171 HS in general internal medicine post-graduate training who were invited by email to complete an online web-based questionnaire in January 2017.
Results: We received 50 responses (29% participation rate). Nearly all responders (92%) had managed chronic wounds during the prior month. 64% had dealt with issues related to wounds at least 10 times since graduation and all felt this would recur in their future careers. For 56% of them, this represented a major real public health issue. 52% of responders did not feel confident managing chronic wound, specifically with regards to choice of dressing, pressure relief, debridement, probe to bone test, arterial assessment or restraint use. They were more comfortable recognizing etiology, infection and factors that may delay healing. 59% reported lack of practical training and 4% lack of interest. 92% received less than 10 hours of undergraduate teaching about chronic wounds and 89% wished for further training. 61% of HS felt that the choice of dressing was "very important" and 35% considered it to be "vital". Nearly all (98%) trusted nurses to select local treatment. 77% of HS were in favor of using a smartphone application to support wound management and 90% felt telemedicine could also be helpful. Potential wound management barriers were, by decreasing frequency: lack of training, the diversity of wounds, lack of consensus, multidisciplinary approach, the workload, the off-putting appearance of wounds and discouraging prognosis.

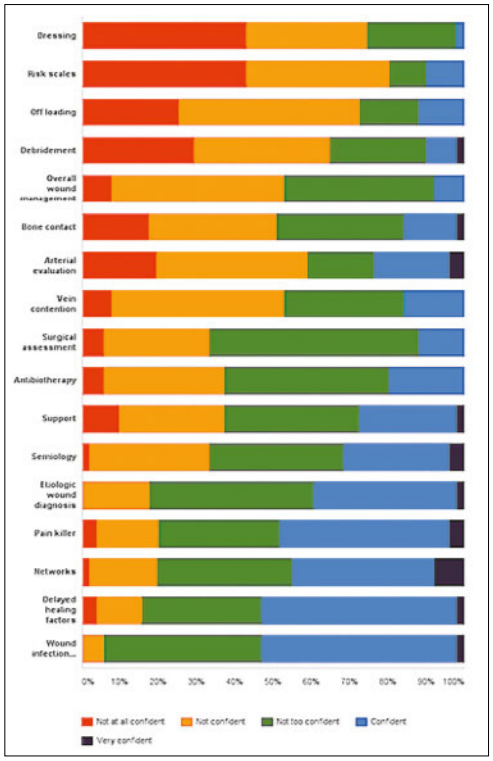

Figure 1: Confidence range regarding chronic wound.

Conclusions: Our data suggest that many junior house staff in internal medicine do not feel confident with chronic wound management and wish for more training in this area which they consider a frequent problem and a major public health issue. This statement of needs, paves the way for a larger study designed to confirm these preliminary findings and to identify ways to improve the training in chronic wound management.

POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE III / ALLGEMEINE INNERE MEDIZIN III

P336

Detection of atrial fibrillation with a smartphone-App – study design and methods of DETECT AF pro trial

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Introduction: Detection of silent atrial fibrillation (AF) is challenging but of pivotal importance particularly in stroke prevention. Recent studies confirmed the merits of long-term monitoring. Nevertheless, currently available diagnostic tools are burdened with disadvantages in that they are inconvenient, costly and/or invasive. The prospective DETECT AF pro trial aims to verify the accuracy of a new diagnostic tool using a smartphone-App (Preventicus® Heartbeats). In a predecessor study (DETECT AF) we tested the same App employing photoplethysmographic (PPG) signals of a smartphone camera to distinguish between AF and sinus rhythm (SR). In that retrospective study the App reached a sensitivity and specificity of 95% (Krivoshei et al., Europace 2016).
Study design: Prospective, blinded, multicenter, international study.
– Inclusion criteria: Subjects of legal age, with SR or AF, informed consent
– Exclusion criteria: Legally incompetent persons, pacemaker rhythm AF Group: Patients with atrial fibrillation at the time of recruitment SR Group: Age- and gender-matched patients with sinus rhythm Data is blinded to the analysing researcher and will be evaluated and monitored externally. 660 subjects will be recruited until February 2017.
Methods: The subjects place the camera of a smartphone (iPhone 4s, Apple, CA, USA) on their index finger for 5 minutes to allow the recording of a PPG signal (pulse wave). During this recording the finger is illuminated by the integrated LED-light. A single lead ECG is recorded (Kardia, AliveCor, USA) as a reference. Person-related data including comorbidities and medication are collected. The pulse wave curve data are coded with the patient´s ID and analysed by Preventicus® in a blinded fashion; files of the patients will be assigned to SR or AF. The ECG will be analysed by cardiologists other than the researcher in a blinded fashion and assigned to SR or AF as well. Results will then be aggregated, unblinded and merged under monitoring. Primary target parameters are the App's sensitivity and specificity for detecting AF compared to a standard ECG interpreted by a cardiologist. Secondary target parameters include the proportion of non-evaluable recordings in the overall study.
Conclusion: The DETECT AF pro trial provides clinical level evidence evaluating an App for automatic detection of AF with a smartphone camera. Data will be available for the SSGIM Meeting.

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Bedside mobility app: improving the bedside workflow process

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Introduction: Clinical documentation in the electronic medical records (EMR) at the bedside is suboptimal due to lack of adapted tools. The current tools used at the bedside in our hospital are paper supports (task list printouts or personal notes) and portable computers on wheels (COWs). Although the printouts can guide tasks and the personal notes can support handoffs, they are a potential source of error (e.g., prescriptions made after printing, transcription errors in delayed data entry from annotations). COWs facilitate data entry (e.g., vital signs, or clinical scores) but are not always available (two COWs per unit). Our project aims at developing a prototype of a smartphone app that can optimize the bedside workflow process to improve the efficiency, quality and safety of patient care.
Method: After studying the bedside work process of nursing teams, an interprofessional team elaborated a design for a smartphone application with nurses from internal medicine and surgery. The iterative development process also included a usability test in a lab with twelve nurses.
Results: In the specifications for the prototype, we included existing EMR or paper functionalities (e.g., task lists, clinical data entry for vitals), as well as new functionalities to support team communication (e.g., support for handoffs, team chat). After selecting one's assigned patients for the shift, the app provides an overview of patient charts to support the handoffs, as well as a multi-patient view of tasks and needed materials per room. At the bedside, scanning the patient's identity bracelet opens their chart (identito-vigilance): users can validate tasks by one swipe and/or add explanatory notes. Clinical data can be entered directly at the bedside, and is integrated in the EMR. Finally, an informal team chat can help improve team communication.
Conclusion: Our prototype was designed to fill a gap in the nursing bedside workflow process, and was developed iteratively with nurses to provide optimal usability. A proof of concept test will be conducted in two wards shortly (internal medicine and surgery) to study the app's efficiency, its integration in the workflow process, and its effect on patient safety. Based on this prototype, future mobile support tools can also be developed for physicians.

P338

How asthma, nose polyps and myorcardial infarction finally led to the diagnosis of an eosinophilic granulomatosis with polyangiitis

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Background: The eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) is a systemic vasculitis of small and medium blood vessels, characterised by asthma, nose polyps and serum eosinophilia. The most affected organ is the lung. There are three typical phases (prodromal, eosinophilic and vasculitic phase). Diagnosis is made by clinical findings and in 40–60% by positive antineutrophil cytoplasmatic antibodies (ANCA).
Case presentation: A 49-year old female presented with chest pain, dyspnea and ecg changes, suspicious for an infarction. The patient has a 4-month history of cardiac attacks, starting with an infarction caused by a spontaneous dissection. There was no significant coronary sclerosis in the angiography. Since then, the patient had 3 more attacks, once leading to reanimation. The last angiography due to a non-stemi showed vasospasm of the coronaries, reversible to local application of nitroglycerin. Under these circumstances, a single coronary etiology seemed implausible. The patient has a history of allergic asthma, well controlled until her early 30ties. Lately, the patient suffered of poor control and of nose polyps. A recent spirometry showed severe obstruction and decreased diffusion capacity with partial atelectasis of the left lower lobe in a CT-scan. The biopsy showed negative cytology and bacteriology but proliferation of the eosinophilic granulocytes, also documented in the blood analysis (with elevated total IgE). Repeated vasculitis screening was negative. During a systemic steroid therapy, the patient was asymptomatic with normal eosinophilic blood count. Two weeks later the patient suffered another cardiac attack in combination with elevated eosinophilic granulocytes. In synopsis of poorly controlled asthma, nose polyps (prodromal phase), elevated IgE, serum eosinophilia (eosinophilic phase) and cardiac vasospastic attacks (vasculitic phase), we diagnosed EGPA despite negative ANCA screening. We started a systemic therapy with steroids and cyclophosphamide. The eosinophilia normalised quickly. Follow up showed a well controlled asthma without cardiac symptoms and a high quality of life.
Conclusions: The diagnosis of a EGPA can often be missed because of diffuse symptoms, differential diagnosis and negative ANCA tests (in cardiac involvement up to 40%). Heart involvement is a leading cause of mortality in EGPA, the more important it is to think of EGPA with patients having cardiac symptoms and a history of asthma.

P339

Is total and segmental fat mass equally associated with cardiovascular risk factors? The Colaus study

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Introduction: Obesity is a risk factor for cardiovascular diseases (CD). Adipose tissue is an endocrine organ, due to the secretory activity of the visceral fat (VF) that is associated with cardiovascular risk factors (CRF). Fat mass (FM) can be evaluated by bioelectrical impedance (BIA) and dual x-ray absorptiometry (DXA). DXA measures the total FM (TFM) and the segmental FM: gynoid fat (GF), android fat (AF)

and VF. The aim of this study was to determine which method of FM measurement (TFM by BIA or DXA, GF, AF and VF) is best correlated with CRF: blood pressure (BP), cholesterol, blood glucose and other specific biological markers.
Methods: OsteoLaus, a sub-study of the cross-sectional population-based CoLaus, includes 1'500 women aged 50 to 80 years. BIA, systolic and diastolic BP (SBP, DBP) and biological markers (total cholesterol and subclasses, triglycerides, blood glucose, insulin, high-sensitivity CRP, ALAT, uric acid, leptin, adiponectin, afamin) were carried out during the CoLaus visit. DXA was performed 6 months later in a subgroup of 1158 OsteoLaus women. Spearman correlations were computed between FM markers and CRF.
Results: The mean age was 63.2 ± 6.3 y, mean BMI 25.8 ± 3.7. All correlations were significant at p <0.001. The correlation for the TFM evaluated by BIA and DXA was good (r = 0.704). Overall, the CRF parameters were better correlated with VF than with AF, and better with AF than with TFM (evaluated by BIA or DXA). Most of the CRF parameters were poorly correlated with GF. The correlation between SBP and VF, AF and TFM by DXA was 0.290, 0.219 and 0.204. Total cholesterol wasn´t correlated with any of the measures. LDL was poorly correlated with FM measures. Correlation coefficients between HDL and VF, AF and TFM were–0.465, –0.363 and –0.366; between triglycerides and VF, AF and TFM 0.453, 0.368 and 0.328. Correlation coefficients between insulin and VF, AF and TFM were 0.601, 0.565 and 0.536; between high-sensitivity CRP and VF, AF and TFM 0.601, 0.565 and 0.536. Leptin level was highly correlated with all FM measures (r from 0.563 to 0.743). Adiponectin level was negatively correlated with VF, AF ant TFM measures (–0.229, –0.185, –0.166).
Conclusion: The correlation between the TFM measured by BIA and DXA was good. We demonstrated a stronger correlation between the VF (higher as the other FM measures) and the various CRF analyzed. GF was poorly correlated with the CRF analyzed. This shows an association between the role of the VF and the CD.

P340

Nightlife Switzerland: prevalence of violence and violence-linked injuries in major cities on weekend nights

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Introduction: Observed over a week, 78% of night disturbance, 74% of verbal conflicts and 73% of violent acts and violence-linked injuries are associated to alcohol consumption, mostly on Friday and Saturday nights in neighborhoods with active nightlife. The consumption of alcohol and recreational drugs may be linked to the opening hours of bars and clubs on Friday and Saturday. Comparing the prevalence of violent acts with the amount of clubs different Swiss cities count and analyzing the number of violent incidents stratified per hour over a week could help establishing recommendations for a safer nightlife. This includes advice for teenagers and young adults, their parents, as well as public health professionals, medical teams and police corps.
Methods: Literature research concerning years 2014 to 2016 and communication with five public health institutions and research groups, as well as with three nightlife organizations. Consulting of statistical evaluations in cooperation with the Federal Statistics Office concerning the type and timeframe of violence-linked injuries and municipal and cantonal police reported violence acts. Graphical representation of nightlife offer in Switzerland 2016 and number of violent acts (yearly from 2009 to 2015) stratified per hour.
Results: Violence-linked injuries incidence increases up to over eight-fold on weekend nights compared to nights on workdays. Police reported infractions against penal code concerning violence were clearly more numerous on Friday and Saturday night compared to the other ones. Lausanne leading the list of club offer with 6.2 clubs per 100 000 inhabitants is also the Swiss city with the highest reported infractions against penal code in general and ranging in top-three position of increase of violence-linked injuries (8.6-fold increase; 8.8 in Lucerne, 8.7 in Geneva) in weekend nights compared to the remaining ones.
Conclusion: Cities presenting a broad offer of nightlife activities such as clubs are prone to sharp increases in violent act incidence on Friday and Saturday nights, be it measured on the amount of violence-linked injuries or on the amount of reported infractions against penal code. Recommendations for "high-risk" hours on weekend nights could be made through the results of this study. Public health professionals and policy makers should be aware of the issue linked to late-night violent acts, and establish and support the corresponding medical resources and safety disposures.

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The patient is always right – an unusual cause of low back pain in an immunocompetent woman

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Background: Low back pain is very common and usually does not require extensive medical work-up. However, serious medical conditions can also cause low back pain and might be challenging to diagnose.
Case: A 38 year old woman attended our hospital because of worsening low back pain since 14 days. She had a history of chronic back pain after an accident 17 years ago, which so far had been tolerable under opioid treatment. She had no neurological symptoms but fever (38.8 °C) and an elevated C-reactive protein (CRP) at 65.2mg/l and a creatinine at 129 umol/l. Spondylodiscitis was suspected, but could not be confirmed by two serial magnetic resonance imaging (MRI) scans 10 days apart, that only showed erosive transformation of the vertebral endplates L5/S1 (type Modic I).

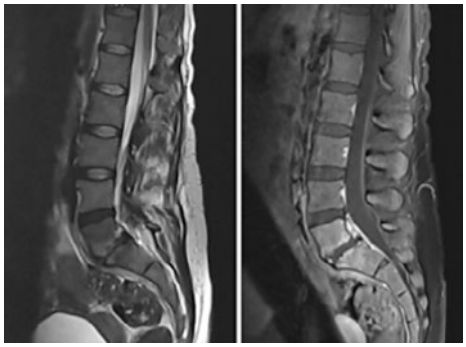

Figure 1: MRI of the lumbar spine (T2 left, T1 right).

However, our initial evaluation further revealed severe microcytic, hyporegenerative anemia (hemoglobin 64 g/l), biopsy-proven leucocytoclastic vasculitis of the lower legs, hepatosplenomegaly and a nephritic urinary sediment. Looking for a unifying diagnosis, bone marrow biopsy was unremarkable without signs for hemolysis or deficiency of substrates and kidney biopsy showed focal segmental glomerulonephritis. Hepatic work up ruled out infectious hepatitis or metabolic disease. Due to the persistent back pain and the patients conviction that "the problem is in my back", we performed a ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT), showing marked lumbar spinal inflammation being highly suspicious of spondylodiscitis at L5/S1.

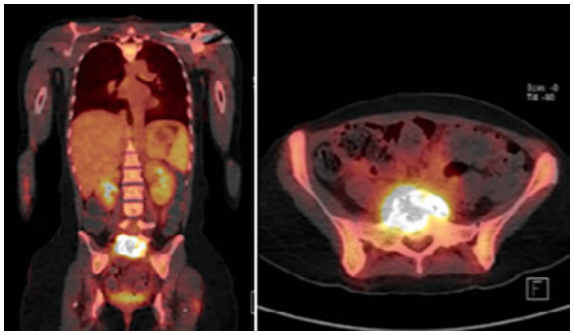

Figure 2: PET/CT with hypermetabolism in transition L5/S1.

The diagnosis could be confirmed by biopsy demonstrating *Candida albicans* related spondylodiscitis. A treatment with an echinocandin (caspofungin) was initiated given intravenously for two weeks followed

by oral fluconazole for a total of six months. CRP, haemoglobin, serum creatinine, proteinuria and vasculitic skin lesions resolved during the treatment. However, the L5/S1 intervertebral disc remained destroyed by the *Candida* infection requiring spinal surgery in the near future.
Conclusion: A frequent problem turned out to have a rare cause. Candida spondylodiscitis is a very uncommon cause of low back pain, especially in an immunocompetent patient without other risk factors for fungal infections. Despite the typical symptoms (fever, back pain), apparently normal MRI scans initially misguided our diagnostic work up. In specific situations, PET/CT may help to distinguish between inflammatory and degenerative disease.

P343

2-year results of a critical incident reporting system in a service of internal medicine

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Introduction: In 2015 a computer-based critical incident reporting system (CIRS), accessible to all staff members, was implemented in our hospital. In the service of internal medicine all events are addressed to a single CIRS coordinator who sorts them into two groups: those to be analysed within the service versus those necessitating external interlocutors. The latter are sent to the CIRS coordinators of the concerned departments and of other specific directorates. Internal events are submitted to different CIRS multi-professional specialists who may work alone or in groups (fig. 1).

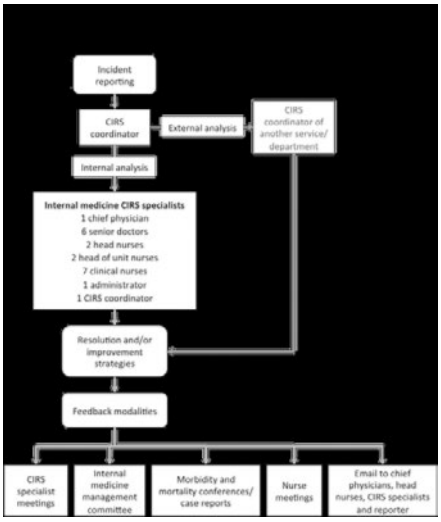

Figure 1

Here we report the first summary of this implementation.
Methods: We collected data about the total number of incidents and the profession of reporters. We categorised the incidents into 22 subtypes derived from the OMS classification and examined the feedback modalities used for these incidents' analysis.
Results: Between 2015 and 2016 we collected 1224 reports with a constant reporting rate of about 1 report/100 hospitalisation days, corresponding to about 1.7 reports a day. All events were analysed and categorised (fig. 2).
Nurses reported most incidents (89%), notably falls, medication administration errors and equipment problems. Doctors reported 9% of the declared events, mostly related to clinical situations. Clinical-related incidents increased from 5% in 2015 to 14% in 2016, in contrast to other subtypes whose incidence remained stable. There were 2 main feedback modalities. Recurring incidents such as falls or loss of personal items were analysed by the CIRS coordinator, supported by 1 or 2 staff members. Their analyses and potential solutions were directly discussed with the reporter and the involved staff. Incidents with higher impact and improvement potential were discussed at monthly management committees, CIRS specialist or nurse meetings, so as to identify improvement strategies. Selected clinical incidents were addressed using the London protocol at morbidity and mortality conferences (10 times/year) or published as clinical cases.

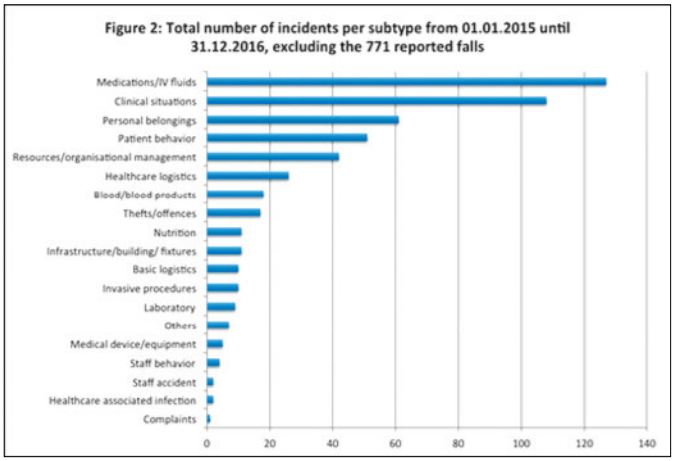

Figure 2

Conclusion: In our service CIRS participation (and satisfaction!) is excellent. While all incidents are analysed, the current challenge is to transform these analyses into daily improvements. Major limitations include the still complicated organisation, the need to prioritise, as well as the lack of personal and financial resources available to analyse the more complex incidents.

P344

Evaluation of a multicomponent childhood obesity counseling program in primary care using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework

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Background: Primary care providers can use behavioral lifestyle interventions to effectively treat overweight and obese children, but implementing these interventions is challenging. Most childhood obesity intervention evaluation studies focus on effectiveness. Few studies describe implementation. We evaluated critical components of a childhood obesity intervention, so stakeholders could implement it in other settings.
Methods: We evaluated a pilot implementation study of an existing structured lifestyle intervention in the Canton of Bern, Switzerland. The intervention was aimed at children 6-8 years old, whose BMI was over the 90th age-adjusted percentile. It was led by a primary care physician and consisted of 10 sessions, spread out over a year-long period. We used the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) evaluation framework to describe the pilot implementation study. We stratified description of RE-AIM components at the patient- and physician-level. For Reach, at the patient-level, we counted the number of children screened for BMI. At the physician-level, we counted the number of physicians invited to participate in the study. For Effectiveness, at the patient-level, we measured change in BMI z-score. We determined Adoption at the patient-level by the number of children included and, at the physician-level, by the number of participating physicians. For Implementation, we counted the number of consultations held per patient. For Maintenance, at the patient level, we counted at the number of children who discontinued the intervention; at physician-level, we counted the physicians who still used components of the intervention two years after the study ended.
Results: Reach: 864 children were screened; of these, 65 were overweight or obese. A total of 394 physicians were invited to participate in the study. Effectiveness: BMI z-score significantly decreased (–5.6%, p = 0.01). Adoption: 14 participating physicians treated 26 patients. Implementation: the mean number of consultations was 8. Maintenance: 9 (35%) children discontinued the intervention; 6 (50%) physicians we contacted continued to apply at least one component of the intervention.
Conclusions: The intervention effectively reduced BMI z-score. The RE-AIM framework helped us summarize critical components of the implementation study so others could more easily implement the program in other settings.

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Challenging fever – case report of a patient with fever of unknown origin

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Introduction: Fever of unknown origin (FUO) is still a diagnostic challenge. The list of disorders causing FUO is very long. We report the case of an 81 year old woman where after numerous investigations only splenectomy provided the diagnosis.
Case report: While the female patient presented to the hospital, she reported general weakness, fatigue and loss of weight during the last month. Past medical history was remarkable for monoclonal gammopathy of undetermined significance (MGUS) and chronic inflammatory demyelinating polyneuropathy (CIDP). For the latter she regularly received intravenous immunoglobulins. At admission no outstanding clinical features were registered. Important laboratory findings are specified in table 1. Chest radiograph was unremarkable. Blood cultures remained without bacterial growth. An abdominal ultrasound and CT scan showed no explanation for the clinical situation.

Table 1: Laboratory findings at admission.

Parameter	Result	Normal range
Haemoglobin	89	120–160 g/l
Leukocytes	6.2	4–12 G/l
Thrombocytes	327	150–300 G/l
C-reactive protein	261	<8 mg/l
Erythrocyte sedimentation rate	66	<12 mm/h
Free light chains lambda	23.5	5.7–26.3 mg/l
Free light chains kappa	17.3	3.3–19.4 mg/l
Kappa/lambda ratio	0.74	0.26–1.65
IgM	0.9	0.4–2.4 g/l

During the hospitalisation the temperature was repeatedly elevated up to 39 °C and the state of the patient declined gradually over the next weeks. An empirical trial of antibiotics and the probatory administration of steroids had no effect, considerably elevated markers of inflammation and fever persisted. Based on the patients history with MGUS of the type IgM a lymphoproliferative disorder was discussed. ^{18}F-FDG PET/CT showed a slightly increased uptake in the spleen and an enhancement in the ascending colon. But even with the biopsies of the colon the suspicion of a lymphoma could not be confirmed. Because of further deterioration of the patient and despite only slightly increased glucose uptake in the marginally enlarged spleen, splenectomy was performed with immediate disappearance of the fever. Histologically the diagnosis of a diffuse large B-cell lymphoma (DLBCL) was made and chemotherapeutic treatment was started. After twelve days fever recurred and the patient died because of a sepsis with staphylococcus aureus.
Conclusion: This case demonstrates the difficulties to find the underlying disease of fever of unknown origin. Beside thorough history-taking, repeated physical examinations, laboratory tests and basic imaging procedures, ^{18}F-FDG PET/CT scan can add important clues for further investigations of lymphoproliferative or infectious disease. In this case only splenectomy provided finally the diagnosis of the lymphoma. The diagnosis of primary splenic diffuse large B-cell lymphoma is often made by core-needle biopsy, but splenectomy seems to improve survival.

POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE IV / ALLGEMEINE INNERE MEDIZIN IV

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Smoke by any other name: heat-not-burn tobacco cigarettes

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10 Jahre informatikbasierte CIRS-Erfassung an einer mittelgrossen internistischen Klinik

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Einleitung: Die Erfassung von kritischen Ereignissen (critical incidents, CI) mit potentiellem Schaden für Patienten hat sich zur Reduktion von Systemfehlern im Qualitätsmanagement in Schweizer Spitälern zusehends etabliert. Wir berichten über unsere Erfahrungen seit der Umstellung von der Erfassung auf Papierformularen auf ein IT-Programm.
Methodik: In unserer 80-Betten-Klinik wechselten wir 2007 nach zwei Jahren Erfassung auf Papier auf eine spitalweit eingesetzte, anonyme Informatiklösung. Wir analysierten die Meldefrequenz, die CI und die daraus getroffenen Massnahmen. Semesterweise fanden klinikinterne Konferenzen (Pflege, Ärzte, geladene Gäste) mit Fokussierung auf Lösungsansätze statt. Freigeschaltete Meldungen können von MA gelesen werden.
Resultate: Im Jahr nach der Umstellung stieg die Melderate von ca 60/J. auf 152/J. an, in den Folgejahren war sie um 66–115/J. In den 10 Jahren wurden 944 CI erfasst. Ca. 65–70% der Meldungen stammen von der Pflege, ca. 25–30% von Ärzten und ca 5% von anderen Berufsgruppen. Mit 390 Meldungen standen falsche Medikamentendosierungen an der Spitze (Abb. 1). Die 115 Meldungen bez Gerinnungsmedikamente beinhalteten 86 Probleme bez Liquemin (davon 45 bez Liqueminperfusoren). 2016 war bei rund 90% der CI Unachtsamkeit mitbeteiligt. In den klinikinternen Konferenzen wurden in 82 Themenbereichen 99 Massnahmen erarbeitet und umgesetzt. 5 Themen wurden insg zwei und 2 Problemkreise drei Mal behandelt, zT wegen sich inzwischen veränderten Gegebenheiten, z.T. wegen Lösungsansätzen mit weiterem Verbesserungspotential.
Schlussfolgerung: 1) Ein konstruktiver und offener Umgang mit CI führte rasch zu einer breiten Akzeptanz mit erfreulichem Meldeverhalten. 2) Die Eingabemöglichkeit an jedem PC erhöht die Meldefrequenz im Vergleich zum Papierformular. 3) Aus den Meldungen und in klinikinternen Konferenzen werden geeignete, die Sicherheit erhöhende Massnahmen erarbeitet und umgesetzt. 4) Bekannte und potentiell als gefährlich eingestufte Fehler (Gerinnung) werden eher wahrgenommen/gemeldet. 5) Menschliche Unachtsamkeit ist eine häufige Fehlerquelle und gehört zu den schwierig beeinflussbaren Faktoren (Personalfluktuation, Aufgabe von Gewohnheiten), Mitarbeiter erkennen/ korrigieren Fehler aber auch. 6) Die Häufigkeit von Fehlern korreliert mit der Häufigkeit einer Tätigkeit. 7) CIRS hat sich als wertvolles Instrument zur kontinuierlichen Verbesserung der Qualität bewährt.

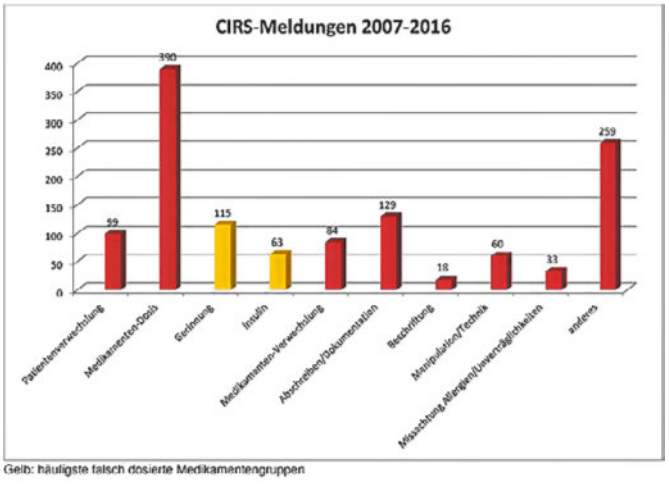

Abbildung 1: CIRS-Meldungen 2007–2016.

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Is performance-based functional impairment associated with readmission and death? Results of a prospective cohort study

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Introduction: Readmission and death are frequent after a hospitalization and difficult to predict. Risk factors are manifolds, and we could intuitively consider that patient's functional impairment may be one of those risk factors. However, only few studies assessed the association between functional impairment and readmission. Although those studies tend to report a significant association between functional impairment and readmission, they are often limited by a retrospective design, and by the use of subjective self-reported functional assessment, such as the Activities of Daily Life (ADL) or the Instrumental ADL (IADL). We assessed whether a performance-based functional impairment at discharge is associated with readmission and death after an acute medical hospitalization.
Methods: We prospectively included patients aged ≥50 years admitted to the Department of General Internal Medicine of Fribourg Cantonal Hospital. Functional status was assessed shortly before discharge using the Timed Up and Go test performed twice in a standard way by trained physiotherapists. Functional impairment was defined as a test duration ≥15 seconds. In a multivariable logistic regression adjusted for potential confounders, we assessed the association of functional impairment with unplanned readmission and death, within 6 months after discharge.
Results: Table 1 describes the baseline characteristics of the population.

Table 1: Baseline characteristics.

Variable	TUG test duration ≥15 seconds (n = 129)	TUG test duration <15 seconds (n = 209)
Age (years), median (IQR)	80 (72–86)	70 (61–79)
Men, n(%)	47 (36.4)	121 (57.9)
Charlson comorbidity index, median (IQR)	8 (6-10)	6 (4-8)
Multimorbidity, n(%)	125 (96.9)	177 (84.7)
At least one admission in the last 6 months, n(%)	49 (38.0)	46 (22.0)
Duration of TUG test (seconds), median (IQR)	23 (18–34)	10 (8–12)
Elective admission, n(%)	2 (1.6)	11 (5.3)
Length of stay (days), median (IQR)	9 (6–15)	5 (4–9)

Within 6 months after discharge, 107/338 (31.7%) patients had an unplanned readmission and 31/338 (9.2%) died. Functional impairment was associated with higher risk of death (adjusted OR 2.44, 95% CI 1.15–5.18), but not with unplanned readmission (adjusted OR 1.34, 95% CI 0.84–2.15). We also didn't find a significant association between functional impairment and the total number of unplanned readmission (adjusted OR 1.59, 95% CI 0.95–2.67). The most frequent causes of readmission were cardiovascular, oncological, and infectious diseases, and were similar regardless of functional status.

Table 2: Causes of 6-month unplanned readmissions.		
Diagnosis category	**TUG test duration ≥15 seconds (n = 46)**	**TUG test duration <15 seconds (n = 61)**
Cardiovascular disease, n (%)	10 (21.7)	12 (19.7)
Infection, n (%)	9 (19.6)	7 (11.5)
Oncological disease, n (%)	7 (15.2)	11 (18.0)
Respiratory disease, n (%)	6 (13.0)	7 (11.5)
Neuropsychiatric disease, n (%)	5 (10.9)	7 (11.5)
Gastro-intestinal disease, n (%)	3 (6.5)	6 (9.8)
Osteoarticular disease, n (%)	2 (4.4)	5 (8.2)
Endocrine or metabolic disease, n (%)	2 (4.4)	3 (4.9)
Other, n(%)	3 (6.6)	5 (8.2)

Conclusions: In this prospective cohort study, functional impairment at discharge of an acute medical hospitalization was associated with higher risk of death, but not with unplanned readmission within 6 months after discharge. Objective and simple performance-based assessment may represent a better prognostic measure for mortality than for readmission.

P349

Pushing patients back to the general practitioner after hospital: as easy as a rendezvous?

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Introduction: Transition from hospital to home is a frail period for discharged patients. Patients go back to their own general practitioner (GP) with various delays and sometime too long to prevent a potentially avoidable readmission. We aimed to assess the feasibility of systematic setting an appointment with the GP at discharge.
Methods: LEAR-HF study focused on the implementation of a transition plan for heart failure patients. Setting an appointment was part of the plan. We included all patients hospitalized with symptomatic heart failure and discharged to home. We excluded patients with hemodialysis or absence of written consent. As soon as the discharge day was known, a nurse visited the patient to set the appointment with the GP. If the appointment can't be set before discharge, she reminded and encouraged the patient during follow-up calls at days 3, 7, and 18. Self-reported outcomes were rate and time to book an appointment, and time to the first consultation within 30 days after discharge.
Results: We included 147 patients over 13 months, mean age 78.1 years old (SD 10.7). 30-days readmission rate was 21.4%. The nurse could set an appointment for 22% patients (33/147) and only 3% before discharge. If done, median time to book the appointment was 5.0 days after discharge (SD 5.9). 87% of patients reported having seen their own GP within 30 days after discharge (129/147). Median time to first consultation was 6.0 days (SD 5.4). No association was found between outcomes and readmission rate (fig.).

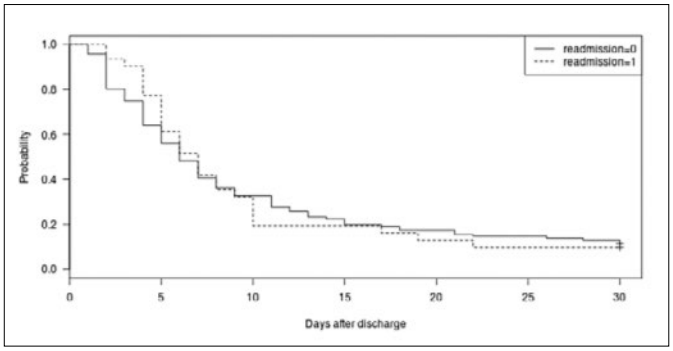

Figure: Kaplan-meier curve for time until first visit to the general practitioner. HF-patient discharged to home. There was no difference between hospitalizations followed by a readmission (dashed line) or not (solid line, p-value 0.978).

Conclusions: The majority of HF-patients go back to their GP in the 30 days following their discharge. Unexpectedly, many refused to book an appointment during their hospitalization. Reason remains unclear. Further studies should identify reasons of this delay and determine if some are modifiable. We also should assess whether a shorter delay reduce readmissions: current recommendations about appropriate time to follow-up are based on expert opinions and limited literature.

P350

Medical collaboration during ICU admission decisions: a qualitative study of internists' and ICU physicians' perceptions

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Background: Intensive care (ICU) admission decisions are complex particularly for seriously ill patients. They involve collaboration between the referring internists and ICU physicians. Good collaboration is associated with patient health-related outcomes and healthcare providers' satisfaction with the decision making. How physicians perceive each other roles can influence the quality of collaboration.
Aims: Explore internists' and ICU physicians' perceptions of their roles and how perceptions relate to experience of collaboration during admission decisions.
Methods: In-depth interviews with ICU physicians (n = 12) and internists (n = 12) working in a Swiss tertiary care hospital. Interviews were analyzed using an inductive thematic approach.
Results: Internists and ICU physicians had the same perception of their various respective roles. Both groups of physicians estimated that their colleagues usually performed their roles satisfactorily. Shortcomings were reported in complex situations involving seriously ill patients and gave rise to tensions. Sources of tension related to: 1. Imparting information about the patient: ICU physicians complained that internists did not provide the relevant information, thus making the decision more difficult. Internists complained that ICU physicians did not trust them and expected to be convinced of the appropriateness of intensive care. 2. Choosing comfort care: ICU physicians felt that internists did not take their responsibility and let them make a comfort care decision. 3. Misunderstanding about ICU physicians' expected role: Internists reported they sometimes only wanted ICU physicians' advice, whereas ICU physicians assumed the internists wanted the patient to be admitted to intensive care.
Conclusion: ICU admission decisions involving seriously ill patients can give rise to tensions between internists and ICU physicians. Further research should determine if physicians' dissatisfaction leads to inappropriate admission decisions.
Funding: Swiss National Science Foundation, NRP 67 "End-of-life"

P351

Medical residents working with vulnerable patients improve their psychosocial skills: a Swiss pilot study

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Background: Scientific literature has shown that patients at high risk of vulnerability are involved in more encounters perceived as difficult by physicians. Physicians involved in difficult encounters denoted worse psychosocial orientation practice and physicians who experience many of their patients as difficult are more likely to end in burnout. This study aims to take advantage of a specific setting, the Department of Ambulatory Care at the University of Lausanne, a university outpatient primary care clinic, in which medical residents frequently work with patients holding high levels of vulnerability. The main objective of this study was to assess the medical resident beliefs about psychosocial aspects of health care, both, before and after, working in a university setting dealing with patients at high socioeconomic risk.
Methods: This is a prospective pilot study with a 6 months follow-up. To assess medical resident beliefs about psychosocial aspects of health care we used the Physician's Belief Scale (PBS). We compared the PBS score of medical residents both before and after having worked 6 months in the outpatient clinic. A second wave of medical new residents (n = 16) is currently under study (final results are expected in march-april 2017), with which we will be able to extend the sample size to a total of 27 to perform a similar analysis.

Results: All the new medical residents were included (n = 11). Mean age 32.4 years (± 3.3 sd). 7 women and 4 men. Mean of years of training 5.3 years (± 1.1 sd). After 6 months, we observed a decrease on the global PBS score mean from 79.5 to 76.4 (p = 0.47 using a Wilcoxon rank sum test). If we analyse by gender group, we observe a PBS score decrease for women (from 75.8 to 69.8) and an increase for men (from 85.75 to 87.7). Indeed, after six months we observed that the differences between genders tended to be significant, which was not the case at enrolment (p = 0.10 vs. p = 0.44).
Conclusions: We observe an improvement of the medical residents PBS score after 6 months working with patients in socio-economical adversity. Even though the observed differences are not statistical significant, probably due to the small sample size, we could conclude that working with patients in socioeconomical adversity improve the medical residents' beliefs about psychosocial aspects of health care, and that there may be gender differences in this improvement.

P352

Geriatric palliative care: defining and delineating the concept, challenges and strategies

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Background: The increasing life expectancy and the associated changes in end-of-life morbidities forecast major challenges for public health. A coherent management strategy based on scientific evidence is widely lacking. The University Hospital Lausanne has therefore launched a unique Chair of Geriatric Palliative Care (GPC).
Objectives: To define the core concept of GPC and its ethical underpinnings, and to delineate its major challenges as well as strategies to tackle them.
Methods: We conducted a literature review and theoretical reflections, oriented by an ethics of care perspective, to conceptualize the field of GPC, identificate the challenges and propose strategies.
Results: GPC is a professional field at the intersection of two closely analogous specialties. Geriatric and palliative care are both highly multi-professional activities with distinctly patient- and family-centred activities aimed at improving quality of life, personal autonomy and social participation in the face of death. The synergies that result from joining these two specialties may serve as a role model for collaboration in the increasingly fragmented medicine of today. As the severely ill elderly constitute a highly vulnerable group, their wellbeing depends on a notion of care that is multidimensional, oriented toward relational autonomy and sustainable. The challenges that GPC faces include particularly the care and treatment decisions, both at the end-of-life and anticipating the end-of-life. Concrete tools such as advance care planning intervention have to be studied in methodologically impeccable trials across the different health care settings. A second challenge is the coordination of care, improved by the cybermedicine, in order to share any relevant information in emergency situation. A third approach has to be the sustainable enhancement of professional competencies, in particular with regard to communication and ethical skills.
Conclusion: The goal of GPC is to develop and offer evidence-based strategies of management for the elderly population with severe and life-limiting conditions. For this aim, the promotion of advance care planning is a major investment to improve decision process. Moreover, the coordination of care management will ensure a better access to the patient's central information by eliciting goals of care. Finally, it is central to develop practical wisdom to deliver care that is responsible to the patient and family needs.

P353

The role of hepcidin in iron homeostasis in inflammation – an exploratory pilot subgroup analysis in medical inpatients

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Introduction: Iron metabolism depends on hepcidin in terms of absorption, transmembrane transport in the small intestine and recycling of iron in macrophages including iron release and sequestration. Especially inflammatory states and diseases including infections decrease iron availabilty. The primary aim was to analyze the correlation between hepcidin and iron-dependent laboratory markers (neutrophil granulocytes, procalcitonin, erythropoietin, IL-6, TNF-α, IL-3, hemoglobin, serum transferrin receptor, transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH, MCV).
Methods: Study design: Prospective, cross-sectional, observational, exploratory pilot subgroup analysis. Primary endpoint: Correlation of hepcidin with neutrophil granulocytes, procalcitonin, erythropoietin, IL-6, TNF-α, IL-3, hemoglobin and serum transferrin receptor, transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH and MCV levels. Inclusion criteria: Age: ≥18, medical inpatient (hospitalization >24h), CRP >5 mg/l. Exclusion criteria: History of dialysis-dependent chronic kidney disease, use of erythropoiesis-stimulating agents, pregnancy, history of allogeneic stem cell transplantation. Two venous punctures: 1. after admission 2. >=5 days of hospitalization. Pearson product-moment correlations for hepcidin and the mentioned laboratory parameters (see primary aim) were calculated. The cut-off level was set at >/= +/-30% correlation due to multiple testing.
Results: Forty randomly selected medical in-patients with CRP >5 mg/l were analyzed. The mean age was 69.5 years (range 54–78), 50 percent were male. The Pearson correlation showed a positive correlation of hepcidin levels with TNF-α and procalcitonin levels whereas hemoglobin and GFR (CDK-EPI) showed an inverse correlation with hepcidin levels.
Conclusion: Procalcitonin and TNF-α showed a positive correlation with hepcidin levels, which could be well explained by inflammation and disease activity. GFR and hemoglobin were inversely correlated to hepcidin levels. Hepcidin is renally excreted, which could well explain higher hepcidin concentration in decreasing kidney function. Interestingly, several other well-known markers of inflammation including IL-6 showed a Pearson correlation below 30 percent. The correlation of hepcidin with inflammation and its mediators needs further study, especially taking into account that the first anti-hepcidin drugs are being tested in clinical trials.

Pearson correlation coefficients for hepcidin and different laboratory parameters

	Hepcidin vs. laboratory parameter	Pearson correlation coefficient
Positive correlation	Hepcidin vs. Procalcitonin	0.60
	Hepcidin vs. TNF-α	0.40
Negative correlation	Hepcidin vs. GFR	–0.82
	Hepcidin vs. Hemoglobin	–0.51
	Pearson correlation with hepcidin below +- 0.3: neutrophil granulocytes, erythropoietin, IL-6, TNF-α, IL-3, serum transferrin receptor (sTfR), transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH, MCV levels.	
	± 1.0 equals full correlation, 0 equals no correlation	

P354

Evolution of medication in heart failure patients hospitalized in a Swiss university hospital

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Background: Patients with heart failure (HF) patients are frequently on polypharmacy (5+ drugs), and subsequently at risk of potentially deleterious drug-drug interactions (DDI). Our objective is to study the trends and determinants in the number and classes of medicines prescribed and in the prevalence of polypharmacy among patients hospitalized for HF.
Methods: Retrospective analysis of discharge data in the department of Internal Medicine of the Lausanne university hospital between 2008 and 2015. DDIs were estimated according to the criteria of the Geneva university hospitals.
Results: Data from 3'666 hospitalizations (mean age 77.6 ± 12.4 years, 47.1% women) were analyzed. Almost all patients (3'527, 96.2%) were on polypharmacy at discharge, and 631 (17.2%) were discharged with 15+ drugs. The prevalence of polypharmacy remained stable at 96.5% in 2008 and 96.8% in 2015, but the prevalence of patients with 15+ drugs increased from 12.2% in 2008 to 21.2% in 2015 (p = 0.05) (table 1).

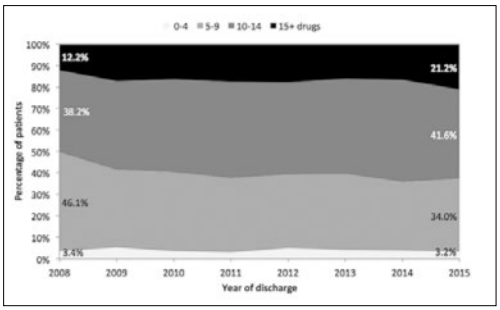

Table 1: Polypharmacy.

The most frequently prescribed medications were diuretics (79.0%), angiotensin-related drugs (angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors, 62.8%) and ß-blockers (58.7%). Increased comorbidities, HF as a comorbidity and compliance to ESC guidelines were positively associated while being discharged home or increasing age were negatively associated with polypharmacy. Almost two thirds (2'327, 63.5%) of patients had at least one potential DDI. The prevalence of potential DDIs increased from 19.4% in patients taking less than 5 drugs to 83.7% in patients taking 15+ drugs. Conversely, the prevalence of patients with at least one potential DDI remained stable throughout the study period (66.8% in 2008 and 59.1% in 2015, p = 0.180) (table 2).
Conclusion: Almost all patients with HF are on polypharmacy. The prevalence of patients taking 15+ drugs is increasing, but no concomitant increase in DDIs was found.

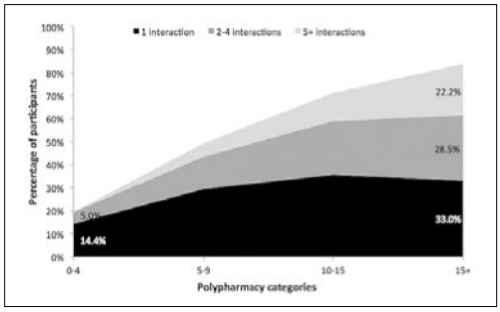

Table 2: DDI.

P355

Progress! Medication Reconciliation: a national programme to improve medication safety at transitions in care

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Introduction: Poor communication and information loss put patients at risk for medication discrepancies at hospital admission and discharge. Studies have shown that in up to half of patients the medication history at admission contains errors, potentially leading to unintended omissions, duplications or incorrect dosages of medications in hospital and post-discharge. Medication Reconciliation (MedRec) is an effective strategy for reducing such risks and is already a routine practice in many countries. The goal of the programme *progress! Medication Reconciliation* is to promote this practice in acute care hospitals in Switzerland.
Methods: The programme consisted of two main elements: a campaign to raise awareness and a pilot project conducted in eight hospitals. The pilot focused on a best possible medication history (BPMH) at admission as the basis for a safe prescribing process. Each hospital designed and tested its own BPMH process taking into account the quality standards for a BPMH as defined by the programme. For example, some hospitals conducted the BPMH solely with medicine interns, while others involved pharmacy staff such as pharmacists and pharmacy assistants. The evaluation focused on the practical experiences with these processes.
Results: The evaluation demonstrated that the participating hospitals laid the groundwork for further improving their medication process. Several challenges to sustainable implementation were identified, many of them revolving around the time needed to access and compare medication sources for the BPMH and to conduct the other steps such as systematically interviewing the patient and documenting the medication list. Important conditions of successful implementation are institutional support, electronic tools which are integrated into the workflow, ensuring continuous training and supervision of frontline staff and clearly defining roles and responsibilities while promoting a culture of interprofessional collaboration.
Conclusion: Medication Reconciliation is regarded as an important patient safety measure, however, at this time there are still many obstacles to widespread sustainable implementation. To further promote MedRec in Switzerland, tools developed by *progress!* will be made available to all Swiss hospitals and a position paper will be published. Researchers in Switzerland are encouraged to further investigate effective models for implementing MedRec, such as selection criteria for targeting high-risk patients.

POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE I / ALLGEMEINE INNERE MEDIZIN I

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Differences in the course of Italian- and German-speaking patients' outcome after interdisciplinary pain program

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Background: Management of chronic pain patients is a challenge in primary care. Available evidence shows that perception, coping, and treatment of pain varies among different populations and cultural regions. In particular, it is unknown how much immigrants in Western European countries profit from pain management programs. The aim of this study was to quantify state and changes of health state and quality of life of immigrant native Italian-speaking patients with fibromyalgia or chronic back pain before and after a 4-week, interdisciplinary inpatient pain program and to compare the results with German-speaking patients.
Methods: The prospective cohort study with 62 Italian-speaking and 63 German-speaking patients measured health-related quality of life, pain, fear and depression comparing at baseline, after 4 weeks of pain program and at 1 year follow-up. Differences between the two groups were tested on significance by generalized estimation equations (GEE). This method modeled changes of health by multivariate logistic

regression adjusting for sex, education, number of comorbidities and the baseline score over both follow-ups for each scale.
Results: Italian-speaking patients (n = 62) showed higher proportions of males, lower educated and less burdened by comorbidities than German-speaking patients (n = 63). At baseline, physical and psychosocial health, depression and fear of the Italian-speaking patients were worse than German-speaking patients, with the exception of less pain in the Italian-speaking patients on the SF-36. Changes of health showed more improvement in German- than in Italian-speaking patients on all scales and at both follow-ups. In GEE, the highest differences were observed in SF-36 physical functioning (p = 0.036), HADS anxiety (p = 0.031) and HADS depression (p = 0.017). On SF-36 bodily pain the difference was not significant (p = 0.142).
Conclusions: This study detected that short- and midterm outcome of Italian-speaking patients was worse than that of German-speaking patients, even after adjustment for baseline differences. The reasons for that are unclear and may have consequences for future management of Italian-speaking patients in interdisciplinary pain management programs. This supports the hypothesis that patients with migration background may have special needs in therapeutic management. A cultural sensitive approach in multidisciplinary and subsequent ambulatory management might enhance the positive outcome in the short- and mid-term.

P357

Life and death: a comparison of ICU physicians' and internists' survival predictions for patients assessed for intensive care

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Background: Expected improvement in survival is the main justification for admission to the intensive care unit (ICU). To make a decision, physicians must estimate the patient's prognosis whether he is cared for on the ward or in the ICU. Contradictory estimations may explain the occurrence of disagreements between the referring physicians and the ICU physicians about the appropriateness of ICU admission. Physicians' ability to accurately predict survival of a patient assessed for intensive care is not known.
Aims: Assess referring internists' and ICU physicians' accuracy in predicting patient survival on the ward and in the ICU, and determine whether the survival estimates correlate with the admission decision and with observed survival.
Methods: All consecutive requests for ICU admission made for patients hospitalized in the Division of General Internal Medicine of the Geneva University Hospitals were identified. The ward and the ICU physicians involved were contacted within 12 hours and asked to estimate patient survival using predefined categories of probabilities. The admission decision and the patient characteristics were collected. We used regression models for the analysis.
Results: 201 patients were included, of whom 140 (69.7%) were admitted into the ICU. Overall 58 patients (28.9%) died within 28 days. Physicians predicted a survival benefit from intensive care for most patients. Agreement between internists and ICU physicians was good (Spearman rho 0.5). Higher survival ratings by both groups of physicians were associated with higher proportions of admitted patients, but the admission decision was more strongly influenced by the ICU physicians' estimates. Observed patient survival was strongly associated with predicted survival by both physicians. The internists' prediction however was more accurate than the ICU physicians', whether the patient stayed on the ward (areas under the ROC curves 0.74 vs 0.69) or was admitted into the ICU (area under the ROC curve 0.76 vs 0.63).
Conclusion: Internists more accurately predict survival for patients assessed for admission to intensive care than ICU physicians. However, ICU physicians' estimates more strongly influence the admission decision.
Funding: Swiss National Science Foundation, NRP 67 "End-of-life"

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"The Mission Possible Project": successful reduction of overtime in residents through implementation of doctor's assistants and structural changes

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Introduction: Despite the limitation of resident working hours by federal law to 50 hours per week, many hospitals experience difficulties to establish these limitations. In a survey by the Swiss association of residents and seniors (VSAO), mean weekly working hours were 56 hour/week, resulting in an average of 135 extra hours per year and resident nationwide. Between 2011 and 2016, the Department of Internal Medicine of the KSB implemented a number of measures to reduce the work load and the extra hours of residents in training. We hypothesized that these measures would result in a reduction and eventually complete avoidance of overtime.
Methods: 5 time points over the 5 years of the implementation of measures were defined. 2011: baseline, 2013: +0.5 doctor's assistant/ward/26pts, 2015: +0.5 resident/ward, 2016: +1 resident as evening shift ("clean up doc" at the end of the shift). For each year, daily overtime in the same two months (February, March) was collected, in 2016 two additional months (September, October) with more experienced residents were analysed. Residents worked during the time period on regular wards, weekends and absences were not included. For subgroup analysis, residents were grouped according to in-house experience (0–5, 6–11 and >12 months experience at KSB).
Results: The average overtime per day was 2.08 ± 0.17h in 2011, 2.25 ± 0.22h in 2013, 1.33 ± 0.19h in 2015, 1.28 ± 0.14h in 2016 and 0.46 ± 0.70h in mid-2016 (fig. 1, p <0.05). Subgroup analysis revealed the largest reduction of overtime provided by the doctors assistant (2011–13) in the intermediate experienced group. The positive effect of the additional ward resident was found in all groups, the largest effect was in the inexperienced groups, while the evening shift (2015–16) was most profitable for experienced residents (fig. 2). By mid-2016, the average overtime for all residents was further reduced, with most being able to almost completely suppress their overtime.
Conclusions: a) 3 specific measures reduced the overtime of residents to 0–1h. b) Additional residents on the ward are helpful for inexperienced residents. c) At higher training levels, doctor's assistants and evening shift residents are more effective to reduce extra hours, underlining the acquired capacity of experienced residents to delegate tasks, an essential feature of efficient practice. d) After deduction of the costs of extra hours, the additional moderate net costs consisted of 2 doctors' assistants.

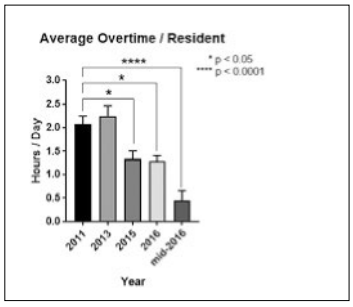

Figure 1: Mean daily overtime in hours per resident.

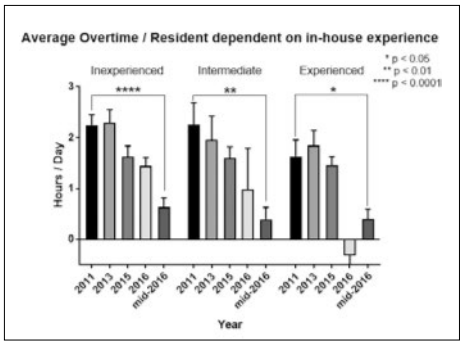

Figure 2: Overtime according to in-house experience.

P359

Practical experience of physicians after a structured communication training for the postmortem autopsy conversation with relatives: results of a representative survey

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Background: Autopsy rate has been declining for decades, in Switzerland as well as all over the world. This negative trend might create important problems because autopsies ensure valide causes of deaths. Moreover medical training of physicians and quality of patients' care rely in part on the possibility to perform autopsies. An important obstacle for getting permission to autopsy seems to be the poor communication skills of physicians.
Methods: After performing a communication training with physicians in the Department of Medicine (DM), the new communication strategy was applied for the postmortem autopsy conversation with relatives. Moreover, we developed a structured questionnaire to find out the practical experience of the participating doctors in regard to their conversation skills.
Results: In the period from November 2014 to October 2015 489 patients died in the DM. 353 questionaires could be evaluated. In 76% of all evaluated conversations, the new guide of the communication training was applied. In 86% of the cases, the conversation was felt as open and relaxed with the relatives. Seven % felt the conversation as oppressive and unpleasant and 7% did not answer the question. In 89% of all evaluated questionnaire the doctors could understand the decision of the relatives for performing an autopsy or not.
Conclusion: In summary, the majority of the physicians have accepted and used the new guide for optimized conversation skills. In most cases, the conversation was perceived as comfortable. We suggest, that the medical staff should receive regular training in communication skills for a confident and better conversation with patients and their relatives.

P360

Trends and determinants of polypharmacy and potential drug-drug interactions at discharge from hospital, 2009–2015

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Introduction: Polypharmacy is increasingly common and associated with risk of drug-drug interactions (DDIs). We aimed to measure the trends and determinants of polypharmacy and DDIs among patients discharged from the department of Internal Medicine of the Lausanne university hospital.
Methods: Retrospective study including 18'075 adult patients discharged between 2009 and 2012. Polypharmacy and excessive polypharmacy were defined as [5–9] and 10+ drugs, respectively. DDIs were defined according to the criteria of the Geneva University Hospital.

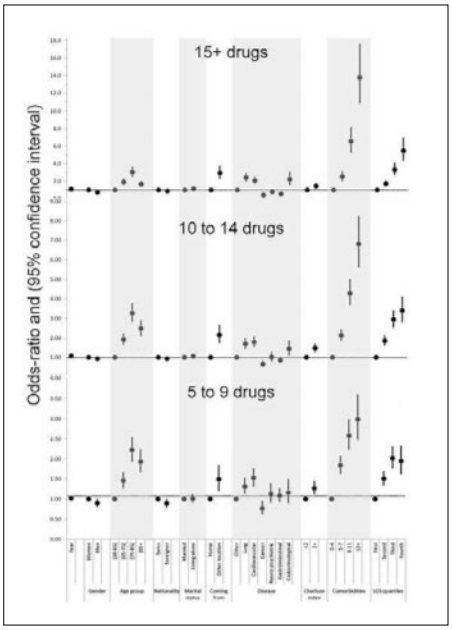

Figure 1: Polypharmacy.

Results: Polypharmacy decreased from 45% in 2009 to 41% in 2015, while excessive polypharmacy increased from 40% to 46%. In 2015, 13% of patients received 15+ drugs. age, coming from other health care settings, higher Charlson Index, number of comorbidities and quartiles of LOS to be significantly and independently associated with polypharmacy and excessive polypharmacy. The risk of having at least one DDI decreased from 66.9% (95% CI: 64.8–68.9) in 2009 to 59.3% (57.6-62.0) in 2015 (p <0.001). Multivariate analysis showed number of drugs [Odds ratio and 95% confidence interval: 3.69 (3.32–4.11); 9.39 (8.34–10.6) and 20.3 (17.1–24.0) for [5–9], [10–14] and 15+ drugs, respectively], gastrointestinal disease [3.16 (2.76–3.61)] and cancer [1.38 (1.19–1.59)] to be positively associated, and lung [0.82 (0.74–0.90] and endocrinological [0.63 (0.53–0.74)] diseases to be negatively associated with risk of DDI.
Conclusion: Excessive polypharmacy is increasing among hospital patients, and is associated with an increased risk of DDI. The decrease in the overall risk of DDI could be due to an improved management of multidrug therapy.
Keywords: polypharmacy; excessive polypharmacy; drug-drug interactions; epidemiology; hospital

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An almost fatal "Müsli" resulting in a superwarfarin intoxication

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Background: Vitamin K antagonists are essential in the management of coagulation disorders through inhibition of vitamin K 2,3-epoxide reductase (VKOR). Superwarfarins are long-acting, high affinity VKOR inhibitors and used as rodenticides.
Case report: A 50-year-old woman with a schizoaffective disorder presented with severe acute neck and abdominal pain. Clinical examination showed multiple subcutaneous hematomas at the site of insulin injection. Laboratory analyses revealed pathologic coagulation assays (INR >6) and severe anemia (Hgb: 5.8 g/dl). With a slightly elevated fibrinogen and normal factor V activity, acute liver failure was ruled out. A CT scan of the abdomen was performed detecting a hemorrhagic ovarian cyst without active bleeding sites. After the transfusion of one erythrocyte concentrate, the hemoglobin level increased adequately and remained stable. While the administration of 1000 IU 4-factor prothrombin concentrate and 30 mg Vit. K stabilized initial coagulopathy, a minimum of 30 mg Vit. K daily for another 50 days was required in order to keep the INR below 1.5 (fig. 1). Although repetitively denied by the patient, an intake of long acting warfarin was suspected. However, urine toxicological screening using a fast immunochromatographic assay and a wide range LC-MS screen for xenobiotics did not reveal any agent explaining the patient's symptoms. Furthermore, a subsequent serum LC-MS screen for anticoagulant agents was negative. Plasma mixing studies restored abnormal prothrombin time ruling out an acquired inhibitor problem. As clinical suspicion persisted, the patient's serum was specifically tested for the presence of superwarfarins. A specific LC-MS method identified the presence of difenacoum. After being confronted, the patient admitted rodenticide ingestion with suicidal intent. A bag with this substance ambigously labeled with "Müsli" (intended for mice – and not "Birchermüsli") was meanwhile found in the basement.

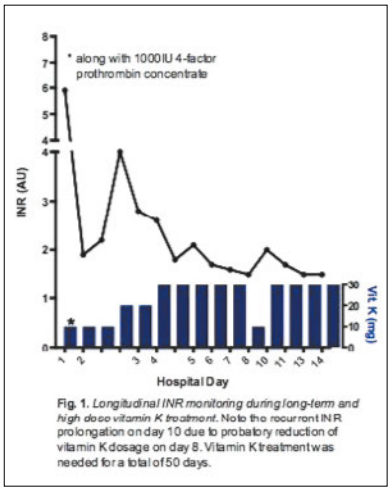

Figure 1

Conclusions: 1) This case illustrates the long-acting and high affinity anticoagulant effect of superwarfarins, widely available as rodenticides occasionally consumed with suicidal intent. 2) Due to the long-acting effect of superwarfarin (difenacoum $T_{1/2}$: 128d), long term and high dose vitamin K treatment is essential along with continuous prothrombin-time monitoring (fig. 1). 3) Our report emphasizes the importance of staying persistent when high clinical suspicion is present despite so-called negative test results.

P362

The minimal clinically important difference (MCID) raises the significance of outcome effects above the statistical level

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Background: In measurement of outcome effects, the patient's subjective perception to feel a change in health defines clinical effectiveness irrespective of statistical significance. The aim was to illustrate and discuss current and proposed new concepts of effect quantification and significance.
Methods: Different methods for determining minimal clinically important differences (MCIDs) are reviewed and further developed focusing on their characteristics and (dis)advantages.
Results: In controlled studies, empirical score differences between verum and placebo become statistically significant if sample sizes are sufficiently large. For example, a score difference of 5 points (scale 0–100) between the verum and the placebo effect becomes statistically significant, if the sample sizes are n ≥33 for each of both groups at a standard deviation = 10 of the score differences (baseline to follow-up). MCIDs by contrast, are defined by patients' perceptions, which led to "anchoring" of effects by the "transition" item, where patients rate their change of health between baseline and follow-up in an evaluation study. The MCID for improvement by the "mean change method" is the difference of the mean change experienced by the "slightly better" group minus that of the "almost equal" group. The MCID can be expressed as absolute or relative score, as effects size (ES), standardized response mean (SRM) and standardized mean difference (SMD) (bivariate). It can further be adjusted by multivariate regression modeling. In our example of knee osteoarthritis, the MCID for pain relief was 8.74 score points, 17.15% of the baseline score, ES = 0.407, SRM = 0.413, SMD = 0.469. This is consistent to the range of 0.30–0.50 for MCIDs reviewed in literature. After adjusting for potential confounders, the MCID was 7.09 score points or an increase of 2.9% per score point to feel better (logistic regression).
Conclusion: Absolute and relative MCIDs are easy to interpret and apply to data of investigative studies. MCIDs expressed as ES/SRM/SMD reduce bias, which mainly results from dependency on the baseline score. Multivariate linear and logistic regression modeling further reduces bias by adjustment for possible confounders and increase validity. Anchor-based methods use clinical/subjective perception to define MCIDs and should be clearly differentiated from distribution-based methods that provide statistical effect significance only.

Angst F et al. J Clin Epidemiol. 2016; epub 13.12.16.

P363

Specialized care can increase hospital's financial risk under DRG-based reimbursement

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Introduction: Specialized care is rewarded with higher reimbursement premiums under DRG based reimbursement. Hospitals, under increasing financial pressure, may strive to increase hospital revenues by increasing the proportion of specialized care. However, due to a higher level of medical risk and more heterogeneous patient characteristics, specialized care might also carry a higher financial risk and eventually decrease profitability.
Methods: We obtained the Fallkostenstatistik from the Swiss National Statistics Office from 2013. We grouped the cases with the software used for hospital planning provided by Canton of Zurich, version 2013.1. After cleaning the data, 798,975 cases remained. We performed multivariate regression analysis and Monte-Carlo simulations. Normcosts (total costs per case normalized per case weight) were used as a proxy for hospital profitability.
Results: Mean normcosts for specialized care cases were 10,773.6 CHF (SD 10,594.6 CHF) and 10,264.6 CHF (SD 8,052.3 CHF) for non-specialized care patients. The independent variable "Specialzed care" was a significant predictor of higher normcosts in multivariate regression analysis (p <0.01). Monte-Carlo simulations of excluding specialized care led to a substantial improvement in hospital profitability, with a modeled decrease in normcosts (i.e. increase in profitability) by 260 CHF per case. Within specialized care, large differences in profitability due to systematic imbalances in DRG-related reimbursement could be found, with models implying an increase in pneumology care from 1% to 2% of total cases increasing normcosts by 190 CHF per case and increases in oncology from 1% to 3% of cases decreasing normcosts by 73 CHF per case, as assessed with Monte-Carlo simulations.
Conclusions: Specialized care can increase hospital's financial risk. Arbitrage due to imbalances in the DRG system may lead to oversupply of some medical services and unmet medical needs on the other. DRG systems need to be designed as to incentivize the delivery of a mix of care which meets patients needs; supply should follow demand. Further, efficiency and quality of care should determine hospital profitability, not portfolio engineering.

P364

Current practice of testing for factor V Leiden and Prothrombin G20210A mutation in Lausanne University Hospital

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Introduction: The predictive value of factor V Leiden and the G20210A prothrombin mutation regarding recurrent venous thromboembolism (VTE) is limited and does not influence subsequent patient management. Hence, systematic testing for such genetic thrombophilia should be avoided, but to which extent such testing is practiced in Switzerland is currently unknown. We therefore aimed to examine the current practice of factor V Leiden and/or G20210A prothrombin mutation testing in a University Hospital.
Method: We included 2106 adults patients with an acute or prior VTE hospitalized in Lausanne university hospital between January 2013 and December 2015. We assessed the frequency of FV Leiden and/or prothrombin G20210A mutation testing, the determinants of FV Leiden and/or prothrombin G20210A mutation testing, and the association between testing and outcomes.
Results: Overall, FV Leiden and/or prothrombin G20210A mutation testing was performed in 67 (3.2%) patients with VTE. On average, during the study period, factor V Leiden and/or G20210A prothrombin mutation were tested in 22.3 patients with VTE per year. Younger patients with a private insurance had a higher likelihood of having such testing.

Table 1: Factors associated with thrombophilia testing.

Testing for FV Leiden and/or prothrombin G20210A mutation	No (N = 2039)	Yes (N = 67)	P-value	OR (95%CI)	P-value
Age, years	68.7 ± 17.2	55.1 ± 16.3	<0.001	NA	NA
Age ≥65 years (%)	1322 (64.8)	19 (28.4)	<0.001	0.19 (0.11–0.33)	<0.001
Female gender (%)	1026 (50.3)	36 (53.7)	0.583	1.26 (0.77–2.07)	0.362
Swiss national (%)	1589 (77.9)	53 (79.1)	0.820	1.50 (0.81–2.77)	0.201
Coming from home (%)	1750 (85.8)	50 (74.6)	0.010	0.48 (0.27–0.85)	0.011
Private Insurance (%)	197 (9.7)	10 (14.9)	0.154	2.00 (0.99–4.07)	0.054

NA: not assessable

Patients coming from home were less likely of having FV Leiden and/or prothrombin G20210A mutation testing. Patients with FV Leiden and/or prothrombin G20210A mutation testing had similar length of stay compared to VTE without such testing (median: 7.7 versus 9.9 days, p = 0.319); no statistically significant difference was found regarding in-hospital mortality.

Table 2: Outcome associated with thrombophilia testing.			
Testing for FV Leiden and/ or prothrombin G20210A mutation	No (N = 2039)	Yes (N = 67)	P-value
In hospital mortality (5)	142 (7.0)	1 (1.5)	0.085
Length of stay§	9.9 (3.3–19.9)	7.7 (4.1–14.4)	0.319
§ Median and [interquartile range], between group comparison using Kruskal-Wallis test			

Conclusion: FV Leiden and/or prothrombin G20210A mutation testing in hospitalized patients with a prior VTE was unfrequently performed. Hence, 22 FV Leiden and/or prothrombin G20210A mutation testing were performed per year, which represents roughly 1% of the patients with VTE admitted in Lausanne University hospital each year. In the majority of cases, the practice of thrombophilia testing for patients with VTE in Lausanne University hospital complies with guidelines.

P365

Adherence to recommendations for preventive care in primary care: a cross-sectional study in Switzerland and France

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Objective: As preventive activities are an effective way to reduce the burden of chronic diseases, our aim was to document preventive care practices of primary care physicians [f1] in Continental Europe (Switzerland [cantons of Geneva and Vaud] and France [Alsace, Pays de la Loire]).
Methods: This was a cross-sectional questionnaire survey conducted in 2015 in a randomly selected sample of 3400 community-based PCPs (1000 in Switzerland, 2400 in France). The doctors were asked how often they ped the following twelve preventive procedures: blood pressure, weight and height measurements, screening for dyslipidemia, alcohol screening and brief intervention, screening for smoking (and brief intervention), colon and prostate cancer screening, and influenza immunization). Response options on the five point Likert scale were never, rarely, sometimes, often, always. The PCPs were considered to be performing the preventive measure regularly if they declared performing it often or always.
Results: 764 participants returned the questionnaire. The proportion of PCPs who reported that they performed the preventive procedures regularly varied upon the procedure: blood pressure measurement (98%), height measurement (52%), screening for smoking and brief intervention (93%), annual influenza immunization for at-risk patients <65 years (38%), It was also dependent on the country, with 1) higher frequencies in Switzerland (vs France) for the following practices: height measurement, alcohol screening and refraining from screening for prostate cancer, and 2) lower frequencies for the following practices: smoking cessation advice or influenza immunization for at-risk patients <65 years.
Conclusions: Whereas some preventive measures now appear to be part of primary care routine, others are not applied by the majority of physicians. Further studies should explore whether these findings are related to miss-knowledge of common guidelines, or other implementation barriers in primary care.

POSTER TOUR 2: MÉDECINE INTERNE GÉNÉRALE / ALLGEMEINE INNERE MEDIZIN / MÉDECINE SPECIALISÉE / FACHMEDIZIN

P366

Polyglobulie bei Anabolikamissbrauch

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Einleitung: Unterschiedliche Anabolen Androgene Steroide (AAS) werden nicht nur im professionellen Bodybuilding sondern zunehmend bei ambitionierten Hobbybodybuildern oft in Kombination eingenommen.
Fallbeispiel: Wir präsentieren einen Fall von einem 55jährigem Mann, der wegen drei Wochen bestehender Kopfschmerzen, vermindertem Antrieb sowie wiederholten Schwächeanfällen ohne Bewusstseinsstörungen durch den Hausarzt zugewiesen wurde. Laborchemisch zeigte sich ein Hb von 210 g/l, Hk 0,59 sowie Kreatinin von 132 µmol/. Im Somatostatus war das überproportioniert muskulöse Erscheinungsbild bei einem BMI 33,3 kg/m^2 auffallend. Anamnestisch war zu erfahren, dass der Patient wiederholt die letzten Jahre verschiedene Anabolika zur Leistungssteigerung einsetzt hatte. Unter dreimaligem Aderlass mit je 450 ml war das Hb mit 192 mg/l rückläufig. Da der Patient hierunter bereist beschwerdefrei war, drängte er auf raschen Austritt.
Schlussfolgerungen: Polyglobulie ist eine dominante Nebenwirkung bei supraphysiologischen Testosteronbehandlungen und im Besonderen bei Missbrauch von Anabolika. Sie wird trotz anderer offensichtlicher Hinweise oft nicht entdeckt. In randomisierten Studien zur Testosteronersatztherapie bei Hypogonadismus konnte gezeigt werden, dass das Risiko der Polyglobulie mit steigender Dosierung signifikant zunimmt und dies mehrheitlich bei Männern ab dem 60. Lebensjahr. Dabei tritt initial eine signifikante, dosisspezifische Suppression von Hepcidin, einem Peptid in der Regulation der Eisenhomöostase, auf. Dies gilt aktuell als ein gesicherter pathophysiologischer Mechanismus beim Anstieg des Hämatokrits. Ein Problem stellt die Beratung und Behandlung der Betroffenen dar, da der Anabolikamissbrauch illegal sowie die Thematik tabuisiert und schambesetzt ist. Mit einer modifizierten Form des Motivational Interviewing (MI) besteht eine Möglichkeit den Missbrauch so zu thematisieren, dass die Gefahr eines Gesprächabbruchs durch den Patienten minimiert werden kann.

P367

Baseline characteristics of individuals using a new online-tool assessing cardiovascular risk factors (www.swissheartcoach.ch)

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Background: Controlling the epidemic of CVD requires a multifaceted strategy targeting modifiable cardiovascular risk factors. In 2012 the Swissheart Foundation – in cooperation with experts in the field – started to develop an online programme called **www.swissheart-coach.ch**. The project addresses the general population (primary prevention) as well as individuals with established CVD (secondary prevention). Computer-based education may be used as an effective strategy for transferring knowledge and skill development to patients. We undertook a survey to characterize the baseline data (e.g. cardiovascular risk profile) of the registered users during the first six month since launching, potentially indicating the attractiveness and use of tool.
Methods and results: The project was launched by advertisement in lay press in March 2016 and since then users' data have been systematically collected. From March to September 2016, a total of 1217 people registered their data on **www.swissheartcoach.ch**. Twenty-eight subjects (0.02%) were excluded from the analysis since only data of gender, age and BMI were available. The analysed sample's (n = 1189) mean age is 58.6 years (SD = 12.3) and 46.2%

were women. Overall, 7.2% reported to be smokers and only 4% to suffer from diabetes type 2. From those who know their blood pressure (BP) (83.7%), only 6 % have a BP ≥140/90 mm Hg.
Conclusion: Data analysis is ongoing and will be available in more details in May 2017. First results suggest that the registered users' cohort is a rather healthy population. Therefore, the potential of lifestyle changes in this population might have only a small effect on their cardiovascular risk profile as it already seems to be low. Still we believe that the implementation of an internet-based educational system for lay persons and health care professionals is an innovative strategy in Switzerland to foster motivation and know-how regarding cardiovascular risk factors and lifestyle changes.

P368

Daily business or not – two cases of rare complications following bone marrow biopsy

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Introduction: Bone marrow biopsy is a common procedure to diagnose several hematological disorders. Although an invasive procedure, it is a save intervention with a complication rate of 0.05%. Known complications are bleeding, local infection and nerve damage. Risk factors for adverse events include myeloproliferative disorder, treatment with aspirin (and other putative platelet dysfunction), warfarin, obesity or disseminated intravascular coagulation. We present 2 cases of serious complications following a bone marrow biopsy.
Case report: A 77-year old man was referred for further evaluation of a thrombocytosis. Blood tests excluded an iron deficiency in the presence of a hyperchrome and macrocytic anemia while treated with dual platelet aggregation inhibition in the context of a coronary heart disease with stent implantation 4 months ago. To decide the further management of the platelet aggregation inhibition therapy in the case of a possible myeloproliferative disease a bone marrow biopsy was performed. Shortly after the intervention the patient complained of pain in the gluteal area. The following computed tomography (fig. 1) with angiography showed a pseudoaneurysm of the left superior gluteal artery with active hemorrhage and intragluteal hematoma. Dual platelet aggregation inhibition was paused and 1 platelet concentrate was administred, the patient fully recovered without intervention. In the second case, a 40-year old woman on hemodialysis treatment due to a chronic glomerulonephritis was evaluated for BMP by reason of leukocytosis. As a result of a bleeding from the left internal iliac artery with retroperitoneal hematoma causing anemia she was transferred to our hospital. Interventional radiologic coiling and substitution of 4 erythrocyte concentrates was followed by a monitoring of 1 day in the intensive care unit. The patient was discharged after 6 days. Aspirin 300 mg was paused for 2 weeks. The computed tomography depicts the way of the biopsy needle (fig. 2).

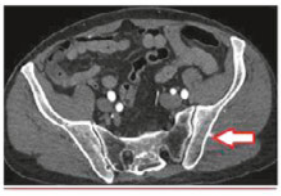

Figure 1: Active bleeding from pseudoaneurysm of the left superior gluteal artery with hematoma of the left gluteus medius muscle

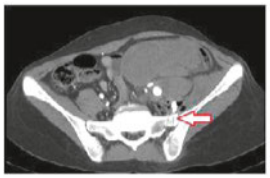

Figure 2: The computed tomography depicts the way of the biopsy needle (arrow) touching left internal iliac artery with consecutive retroperitoneal hematoma

Conclusion: In general bone marrow biopsy is a safe procedure, independent of the examinators experience. Nevertheless in every case the indication for this examination is to verify thoroughly and paying attention to a technically correct procedure is essential. Suspected complications require quick diagnostic steps including computed tomography and rapid therapy to avoid life threatening conditions after this standard diagnostic procedure to minimize morbidity and mortality.

P369

An unusual cause of severe recurrent gastroenteritis – a case report

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Introduction: An 82 years-old man known for ulcerative colitis and hypertension was hospitalized for the 5th time in 1 month with the same clinical characteristics: acute nausea, vomiting, diarrhea, low blood pressure, acute renal failure and leukocytosis. Following each episode he recovered quickly, but the day after returning home the symptoms reappeared, requiring another hospitalization. Various pathologies were considered instigating numerous investigations. At this 5th admission, a close look at the patient's record showed that his antihypertensive drug (olmesartan) had systematically been suspended at admission. At discharge, as blood pressure raised and renal function recovered, he was told to take his usual medication again. We did a challenge test with 40 mg olmesartan. After 1h, he suffered of nausea, vomiting and diarrhea. The symptoms disappeared within 4 hours. C4 complement and C1 esterase inhibitor function were normal as well as serum tryptase. We retained the diagnosis of visceral angioedema induced by olmesartan.
Method: We searched PubMed, UpToDate and Google Scholar with the keywords "angiotensin II receptor blocker" (ARB), "angioedema", "visceral" and "intestinal". As we retrieved very little literature, we extended our search with the key words "angiotensin converting enzyme inhibitor" (ACEI).
Results: We found sparse literature about ARB-induced intestinal angioedema, only case reports. ARBs and ACEIs are responsible for similar side effects, sometimes with cross-reactions. ACEI-induced visceral angioedema is better described (estimated frequency 0.1–0.2%). The diagnostic criteria are: timing with medication intake, abdominal pain/emesis/diarrhea, normal C1 esterase inhibitor and C4 levels, CT-scan showing segmental intestinal edema, and absence of alternative diagnosis. The pathophysiology is explained by bradykinin increase due to ACE inhibition with ACEIs and other less understood mechanisms with ARBs. Genetic predisposition, hormonal influence or inflammatory pathways may also be involved.
Conclusion: This case report of ARB-induced intestinal angioedema reminds us of this rare but potentially life-threatening side effect. Delayed diagnosis can lead to unnecessary investigations and mistaken treatments. More generally, it reminds us that unexplained symptoms may be due to medications. Careful anamnesis, sometimes with detailed retrospective medical record study, can be more helpful than repetitive blood sampling and extensive imagery.

P370

Pulmonary foreign body granulomatosis is an important differential diagnosis in patients with intravenous drug abuse and suspect radiological examination

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Introduction: Pharmaceutical tablets contain filler agents such as talc, microcrystalline cellulose or crospovidone. By intravenous injection of such pulverized tablets these filler agents accumulate in the pulmonary capillary bed and may cause foreign body granulomas. Granulomas can develop in the pulmonary arteries or in the interstitium of the lung. After repeated intravenous exposure this inflammatory process may lead to interstitial pulmonary fibrosis and emphysema.
Case report: A 32-year-old man with a long history of intravenous drug abuse (IVDA) was transferred by ambulance to our hospital in an overall bad condition, with fever (39 °C), chills and dyspnea. Clinical examination revealed crackles in the lower lung fields. Blood tests showed increased inflammatory values. The chest X-ray raised strong suspicion of miliary tuberculosis. Initially an empiric antibiotic therapy with ceftriaxone and clarithromycin was started to treat pneumonia. A computed tomography (CT) of the chest showed a micronodular pattern. For further diagnostics a flexible bronchoscopy was performed for a bronchoalveolar lavage. With the additional hypothesis of a foreign body granulomatosis a transbronchial biopsy was taken. This

showed multiple granulomas within the alveolar walls. All granulomas contained amorphous birefringent polarizable foreign material. There were no signs of malignancy; biopsy and culture were negative for tuberculosis. The reason for the elevated inflammatory values was an influenza A infection; therapy with oseltamivir was started. The patient left the hospital after four days against medical advice.

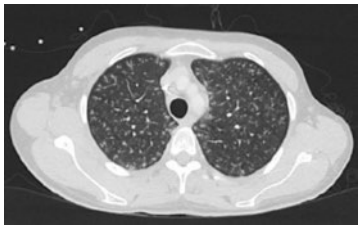

Figure 1: Chest CT scan: multiple pulmonary nodules.

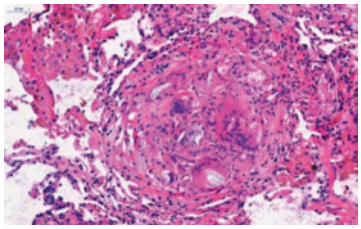

Figure 2: Granuloma with several foreign body giant cells]

Conclusion: This case emphasizes the importance of the differential diagnosis of pulmonary foreign body granulomatosis in patients with IVDA and a suspect chest X-ray. The history of IVDA is crucial and the diagnosis is proved with a lung biopsy: amorphous birefringent polarizable foreign material in granulomas is pathognomonic. The therapy is symptomatic and the cessation of IVDA is mandatory.

P371

Pacemaker implantation: not every erythema is a bacterial infection and needs an explantation

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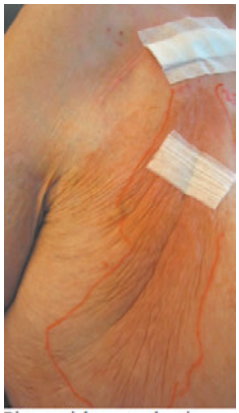
Case report: We report on a 63 year old obese patient with an assumed pacemaker pocket infection after pacemaker implantation two months ago, due to a sick sinus syndrome with symptomatic bradycardia. Locally there was a 20 cm long, very painful erythema with hyperthermia and swelling. Repeated echocardiography revealed no evidence for vegetation or indirect signs for endocarditis. Pacemaker function was correct. We started an empiric antibiotic therapy and explanted the pacemaker together with the electrodes. Because of negative microbiology (repeated blood cultures, also in an antibiotic window; negative serological testing for Coxiella burnetii, Bartonella spp., Aspergillus spp., M. pneumonia, Brucella spp., Legionella pneumophila, T. whipplei, and Candida spp., negative biopsy and negative pacemaker culture) and a nonspecific histology (only some neutrophile and eosinophile granulocytes) we supposed pacemaker dermatitis (Pacemaker contact dermatitis or postimplantations erythema).



Picture: right pectoral region

A trial with prednisone 60 mg daily resulted in an explicit improvement of the symptoms with decrease of redness, pain, swelling and induration. Since the pain increased again after dose reduction to 30 mg prednisone daily, we raised prednisone to 50 mg/d. After complete recovery a new pacemaker was implanted on the contralateral side without any complications. Two months later, prednisone dose could be tapered to 20 mg/d.
Conclusion: After exclusion of bacterial infection, pressure dermatitis or postimplantation erythema must be considered in patients with local signs of inflammation around the pacemaker pocket. Histological examination of the affected skin can contribute to the diagnosis. In case of suspected contact hypersensitivity to implant material, allergological exploration should be performed (patch testing, in selected cases lymphocyte transformation test). Depending on the cause, cutaneous reactions are occasionally self-limiting (postimplantation erythema) or the pacemaker can translocate subpectoral or subcostal (pressure dermatitis). Corticosteroid may reduce skin symptoms of contact dermatitis, but recurrence is common. In many cases, however, removal of the pacemaker is inevitable. Special gold-plated or entirely polytetrafluoroethylene coating pacemaker systems are available for reimplantation. In our case the early consideration of pacemaker dermatitis eventually could have prevented the explantation and reimplantation of the pacemaker.

P372

Swimming induced pulmonary edema (SIPE) or immersion pulmonary edema is a rare form of non-cardiogenic pulmonary edema

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Introduction: SIPE is a rare form of non-cardiogenic pulmonary edema. The frequency of SIPE is rising because of the increasing popularity of endurance sports competitions like triathlons.
Case report: We report on a 66 years old, sporty and healthy patient with acute dyspnea and chest pain while swimming in the Lake of Constance. Upon arrival of the emergency rescue service peripheral oxygen saturation was 85% (with an increase to 92% with 2 l oxygen), blood pressure 139/92 mm Hg with a pulse of 71/min. Clinical findings were normal except bibasilar crackles on pulmonary auscultation. ECG showed negative T waves in I, II, III, aVF and V6 and chest X-ray revealed alveolar pulmonary edema (fig. 1a). Echocardiography showed a normal left ventricular ejection fraction without underlying dyskinesia. Although the symptoms dissolved spontaneously and quickly ashore, we performed coronary angiography. We found only slight coronary sclerosis with no relevant stenosis. Heart rhythm monitoring revealed no rhythm disturbances. Since the alveolar pulmonary edema resolved spontaneously on the X-ray (fig. 1b) and causes for cardiogenic pulmonary edema were excluded, we diagnosed a SIPE.

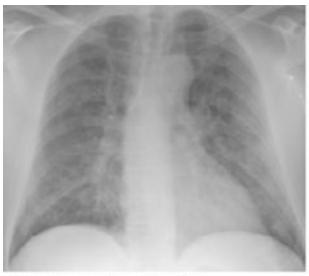

Fig 1a: chest radiograph at first

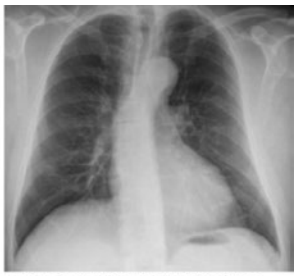

Fig 1b: chest radiograph two days later

Figure 1: X-ray.

Discussion: SIPE has first described in divers and swimmers 1989. Nearly 300 cases have since been published. Incidence and prevalence is rising in endurance swimming competitions with a reported prevalence of 1.4% in triathletes. Pathophysiology of SIPE is not fully understood. It's presumed to originate from exercise-induced elevation of pulmonary capillary pressure causing mechanical stress failure of the pulmonary capillaries. Other factors, which favour a SIPE are: immersion, elevation of the negative intrathoracic pressure and hypothermia. Also cold water, negative static lung load, exertion, fluid loading and low vital capacity are postulated risk factors for SIPE. In order to diagnose SIPE with typical acute symptoms (dyspnoea,

haemoptysis) appearing during swimming or shortly after, there must be an absence of other causes (laryngospasm, water aspiration) and complete disappearance of the alveolar pulmonary edema on the chest X-ray within 48h. First treatment measures include leaving water, stopping physical exercise and seeking medical care. Therapy is supportive with oxygen and possibly diuretics. Prognosis is good without any structural or functional lung damage. Patients suffered from SIPE are at increased risk of relapse in the same situation.

P373

Aortic valve reconstruction with autologous pericardium instead of prosthetic replacement: new technique and preliminary results of the first 3 cases in Western Switzerland

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Introduction: For more than 10 years, a new technique of aortic valve reconstruction (AVR, stenosis as well as insufficiency) has now been described in Japan with more than 400 cases reported with a mean follow-up of 2–3 years (known as the Ozaki technique, cf. references). We report the first 3 cases in Western Switzerland.
Method: Review of medical records and case report of operated patients with the Ozaki technique for aortic valve reconstruction between November and December 2016 in a Western Switzerland private clinic.
Results: 3 patients have had AVR by the Ozaki technique for: 1. ♂ 46 years old, indication: congenital unicuspid aortic valve, small aortic annulus with high risk of prosthesis-patient mismatch evaluated by effective orifice area in relation to body size; 2. ♂ 68 years old, indication: 6 weeks post-endocarditis due to Streptococcus mitis oralis aortic valvular insufficiency grade IV/IV; 3. ♀ 47 years old, indication: aortic valve fibro-elastoma with severe regurgitation of 50–60% and relative contra-indication to long-term anticoagulants due to co-medication interactions. The hospital follow-up was favorable for all three, apart from the second case which was complicated by a right sided hemothorax reoperated within 12 h but with uneventful recovery thereafter, with remarkable results on the early post-operative echocardiography follow-up for all 3 cases.
Conclusions: This new surgical technique needs to be known as it offers new perspectives and alternatives as to both classic surgical techniques (bioprothesis, mechanical valve) and the new transcatheter aortic valve implantation (TAVI). The main interest of this technique is that the implantation of foreign material is no longer needed and the prescription of lifelong anticoagulants or anti-platelets becomes unnecessary, with the hope that the use of autologous pericardium will prove a durable alternative to biological valves. The only restriction to keep in mind is that this technique has no more than a 10 year follow-up since the first reported cases and a mean 2 to 3 years follow-up on the large series reported in 2014.

References:
A total of 404 cases of aortic valve reconstruction with glutaraldehyde-treated autologous pericardium. Ozaki S, Kawase I, Yamashita H, et al. J Thorac Cardiovasc Surg. 2014;147(1):301–6.
Aortic Valve Reconstruction Using Autologous Pericardium for Aortic Stenosis. Ozaki S, Kawase I, Yamashita H, et al. Circ J. 2015;79(7):1504–10.

P374

Case report: intestinal granulomas in a 22-year old Ethiopian woman with abdominal pain

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Introduction: We present a rare case of gastrointestinal (GI) granulomatous disease in a patient originating from a region with high prevalence of tuberculosis (TB) and discuss the diagnostic approach.
Case presentation: A 22-year old Ethiopian-born female living in Switzerland for 5 years presented with a history of abdominal pain, bloating, weight loss, intermittent diarrhea and vomiting of two months. She reported one episode of pain in the right knee 4 months before hospitalisation, but was otherwise healthy and under no medication. Clinical examination showed a tender, meteoritic abdomen. Laboratory work-up displayed anemia (Hb 111 g/l) and elevated CRP (80 mg/l). Stool tests were negative for common parasitic and bacterial pathogens, while calprotectin was elevated (580 µg/g). Colonoscopy showed non-ulcerating pancolitis, and biopsy revealed chronic epitheloid, non-caseating granulomatous infiltration with low active inflammation, intact crypt architecture and no signs of ulceration. Gastroduodenoscopy also revealed diffuse epitheloid granulomatous infiltration, one granuloma appearing necrotic, while vascular involvement was absent.

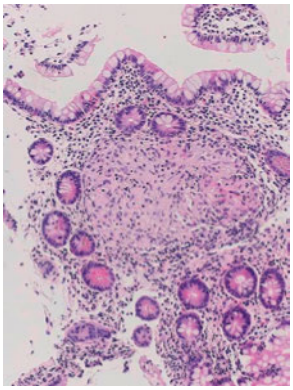

Figure 1: Biopsy of the colon showing epitheloid granuloma.

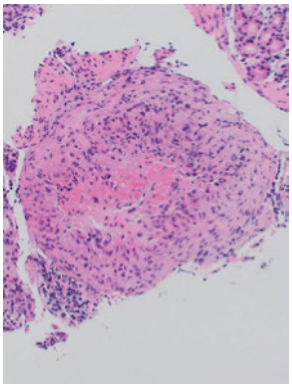

Figure 2: Necrotic epitheloid granuloma in duodenal biopsy.

Computer tomography showed thickened walls of the colon, small subpleural and peribronchial nodules of the lung with one enlarged hilar lymph node, interpreted as post-bronchitic and unspecific. Differential diagnosis included TB of the GI tract, autoimmune, and inflammatory bowel disease. Extensive tests for infectious diseases and interferon gamma stimulation test in blood were negative, as were TB cultures and PCR from biopsy. Rheuma factor, soluble interleukin-2 receptor and neopterin were elevated, serum angiotensin-converting enzyme level was within normal range. Corticosteroid treatment was started, under which inflammation markers normalized. Re-colonoscopy showed a reduction of granulomas, CT scan of the lung resolution of nodules. Finally, histology from transbronchial biopsy confirmed epitheloid granulomas, and the diagnosis of sarcoidosis of the GI tract and lungs was made. Azathioprin was added to the treatment regime, under which symptoms of the patient improved.
Conclusion: Differential diagnosis of granulomatous disease is challenging in patients at risk for tuberculosis. Sarcoidosis of the GI tract is very rare (5–10% of overall cases), and primarily manifests with unspecific symptoms. Before establishing immunosuppressive treatment, infectious diseases, in particular TB must be excluded.

P375

Vocal cord dysfunction: a forgotten differential diagnosis in acute dyspnea

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Introduction: Vocal cord dysfunction (VCD) is a clinical phenomenon describing an inappropriate episodic adduction of the true vocal folds. The prevalence for VCD is unclear but is estimated to be found in up to 5% of supposed asthmatic patients. Patients typically present themselves at the emergency department with acute upper airway obstruction. Concomitant psychiatric morbidity, gastroesophageal reflux disease and postnasal drip might observed as supplementary risk factors. Since internists are not familiar with VCD, diagnosis is often delayed and leads to unnecessary costs and treatment including intubation and tracheostomy.
Case report: A 61-year-old female patient with severe dyspnoe attacks for many years was considered to suffer from severe and therapy-resistant asthma culminating in admission to an intensive care unit few years ago. Patient history was further remarkable for multiple hospitalisations due to asthma attacks, suspicion of Morbus Widal, reflux, headache and depression. At presentation, the patient was suffering from an acute and severe dyspnoe attack, cough with white sputum and sore throat without fever. Arterial blood gas analysis (under 12 L supplementary oxygen) showed severe respiratory insufficiency (pH 7.44, pCO_2 5.37kPa, pO_2 6.04 kPa). Chest X-ray showed no pulmonary infiltrate. The patient was diagnosed with infectious exacerbation of asthmatic disease and antibiotic therapy (Ceftriaxon) was initiated. Further workup showed normal lung

function, discordant with uncontrolled asthma activity. Subsequent detailed history including the use of a VCD screening checklist suggested the presence of vocal cord dysfunction. Following logopedic intervention and start of proton pump inhibitor therapy the patient was dismissed without symptoms. Close follow-up is planned.
Conclusion: This case report highlights the importance of detailed history taking also in patients with longstanding and established diagnoses. In addition, awareness of VCD, recognizing patients at risk and including this differential diagnosis in patients with severe resistant asthma might reduce unnecessary treatments and hospitalisations.

POSTERTOUR 2: MÉDECINE SPÉCIALISÉE I / FACHMEDIZIN I

P376

Wandering through a rock-garden – case report of Tracheobronchopathia Osteochondroplastica

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Chronic cough is a very common symptom in general medicine. Sometimes CT and bronchoscopy may reveal an uncommon cause: Tracheobronchopathia Osteochondroplastica (TO). We present a case of this very rare disease. A 71 year old female patient presented with chronic cough for more than a year. She describes waking up from cough at night, especially having heavy attacks in the morning with some tough mucus. She also experiences being hoarse all day with foreign body sensation in the throat. Initial pneumological consultation showed bronchial hyperreactiveness, but inhalation therapy brought no relief. A trial with a proton pump inhibitor was also unsuccessful. A CT scan was performed demonstrating several small lesions adjacent to the tracheal wall amounting to the thyroid gland and beneath. Bronchoscopy then revealed impressive findings of TO. The entire tracheal wall showed multiple firm nodules with intact mucus membranes along the cartilaginous rings sparing the Pars Membranacea.

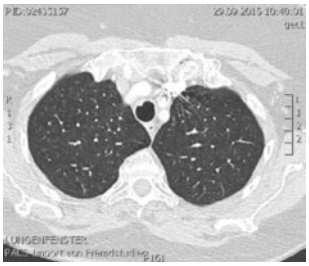

Figure 1: CT.

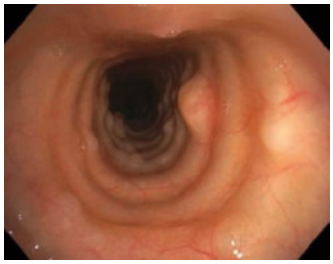

Figure 2: Bronchoscopy.

Since there is no causative therapy, aware of the benign course of the disease, we recommended using antitussive agents to control the patient's chronic cough. TO is a very rare airway disease of unknown etiology characterized by accumulation of cartilaginous and osseous nodules. It was first described during autopsy by Rokitansky in 1855. TO is mostly incidentally detected in CT Scans, during intubation or bronchoscopy. Symptoms of patients are usually chronic cough despite adequate treatment trials, exertional dyspnea, hoarseness, occasional hemoptysis and recurrent pulmonary infections. Diagnosis is established via radiology and bronchoscopy demonstrating characteristic small submucosal nodules in the trachea sparing the posterior wall. It can affect the entire trachea ranging as far as the main bronchi, in some cases causing atelectasis. Lesions may be so numerous that the bronchscopic aspect may appear as a "rock-garden". Histopathology shows calcification, chondrification or lamellar ossification, with possible foci of bone marrow and hematopoesis. The underlying etiology and pathology of TO are unclear. Differential diagnosis include tracheal neoplasms, calcificating tuberculosis, tracheobronchial calcinosis, Wegener granulomatosis and relapsing polychondritis. The course of TO is benign with only slow progression. Only few of the cases showed or developed more severe airway obstruction. Therapy focusses on symptom control using centrally acting antitussive agents.

P377

Myocarditis associated with campylobacter enteritis

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Introduction: Myocarditis in developed countries is very often associated with an infectious etiology, especially viral infections. An association with bacterial infections is much less frequent – especially the association with campylobacter enteritis is reported only in few cases.
Case report: A 24-year-old, healthy young man was admitted to our emergency department because of sudden chest pain, increasing with deep inspiration. Apart from transient fever and watery diarrhea for the last 3 days the clinical history as well as the actual vital signs were unremarkable, no cardiovascular risk factors were known, no drug intake. An ECG showed only non-specific findings. Initial blood tests showed elevated cardiac and inflammatory markers (Troponin-I 5297 ng/l (normal value <30 ng/l), C-reactive protein 201 mg/l (normal value <8 mg/l)). An echocardiography revealed only mildly reduced left-ventricular ejection fraction with an infero-lateral hypokinesia (fig. 1). While computed tomography coronary angiography could rule out coronary artery disease, cardiac magnetic resonance imaging showed extensive areas of late gadolinium enhancement in the basal segments of the inferolateral wall (fig. 2). Diarrhea as well as chest pain ceased during the next days without specific treatment. Stool culture revealed campylobacter jejuni (retrospectively due to tartare ingestion 5 days before symptom onset). So we were able to make the diagnosis of campylobacter-associated myocarditis.

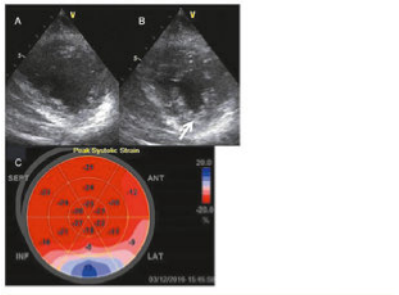

Figure 1: Initial transthoracic echocardiography; A – parasternal short axis still-frame, showing the left ventricle in enddiastole; B – parasternal short axis still-frame, showing the left ventricle in endsystole with hypokinesia inferolaterally (arrow); C – "Bulls' eye" showing the distribution of longitudinal peak systolic strain (very sensitive marker of systolic function) of the left ventricle; a reduced strain in the inferolaterobasal region can clearly be demonstrated (blue area)

Figure 1

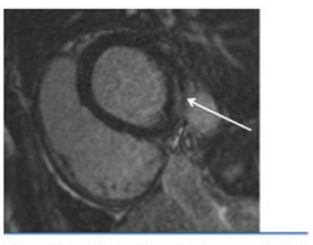

Figure 2: Cardiac magnetic resonance imaging (delayed enhancement imaging) showing hyperenhancement in the inferolateral basal wall (arrow)

Figure 2

In an outpatient control 4 weeks later the patient described an uneventful course. The echocardiographic findings as well as laboratory findings were normalized.
Conclusion: Campylobacter jejuni-enteritis is a rare cause of myocarditis; a special feature is the short time interval of one to five days between the onset of enteritis and the onset of myocarditis. To understand the relation between Campylobacter infection and myocarditis, and at least prevent co-accurance, it might be important to identify the pathomechanism, which is not known yet.

P378

Watch AF – Smartwatches for detection of atrial fibrillation

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Introduction: Detection of atrial fibrillation (AF) is of pivotal importance for stroke prevention. Recent studies confirmed the merits of long-term monitoring. Currently available diagnostic tools are burdened with disadvantages of inconvenience, costs or invasiveness. In a previous study we tested an app that employed photoplethysmographic (PPG) signals of a smartphone camera to distinguish between AF and sinus rhythm (SR) based on the newly developed Preventicus® Heartbeats algorithm. That retrospective study has been shown to achieve a sensitivity and specificity of 95%. In the WATCH AF study, this algorithm is tested for the first time with PPG signals from a smartwatch (Samsung) and a wristband (Wavelet health). Our study aims to determine the accuracy of these applications compared to an ambulatory ECG system.
Methods: In this prospective, blind, international, multicenter-study, 600 subjects are being recruited until March 2017. Subjects must be of legal age. SR group is age- and gender-matched with the AF group. Pulse wave curves will be recorded for five minutes simultaneously with a smartwatch on one and a wristband on the other arm (sides randomized). At the same time, an ambulatory ECG system will record a synchronous ECG as reference. The pulse wave curve data will be analysed in a blinded manner off-line with the Preventicus® Heartbeats algorithm and will then be labelled as either SR or AF. Additionally, information about cardiovascular risk factors, concomitant disease and medication, are collected. Primary target parameters are the app's sensitivity and specificity in correctly detecting AF compared to an automatically interpreted ECG. Secondary target parameters include the proportion of non-evaluable recordings in the overall study and differences between the two devices.
Results: The enrolment is expected to be complete in March 2017. Complete trial results are expected for in April 2017.
Conclusion: WATCH AF is the first study to validate PPG signals from the wrist to detect AF in a blinded, ECG controlled fashion.

P379

A fulminant Wilson's disease in a case of pretended glucose-6-phosphate dehydrogenase deficiency

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Wilson's disease is an autosomal recessive disorder of impaired biliary copper excretion that results in the accumulation of copper in various organs including liver, cornea and brain. Orthotopic liver transplantation is indicated in advanced cases with hepatic decompensation or in patients with fulminant Wilson's disease. We describe herein a Wilson's disease presenting with fulminant hepatic insufficiency and hemolytic anemia. A 19-years old female girl from Italian Origin, anamnestic known for a Glucose-6-phosphate dehydrogenase deficiency (G6PD) and thalassemia minor was admitted because of fever since 4 weeks, accompanied by bone pain and chills. At the admission, she is hemodinamically stable, icteric, with subfebrile temperature. At the physical examination, the Murphy's sign is positive and liver was slightly enlarged. Laboratory tests show a Coombs negative haemolytic hypocromic anaemia with hemoglobin 49 g/l, haptoglobine 0.10 g/l, lactate dehydrogenase (LDH) 816 U/l with unexpected elevation of the direct bilirubin 64.2 µmol/l with total bilirubin 78.2 µmol/l and slight elevation of liver enzymes (aspartate aminotransferase (ASAT) 143 U/l, normal alanin aminotrasnferase (ALAT) 40 U/l, normal alkaline phosphatase 45 U/l and elevated gamma-glutamyl transferase (γGT) 189 U/l. Inflammatory syndrome is noted with an elevated C-reactive protein (CRP) 26 mg/l and leukocytosis 20.9 g/l. An abdominal ultra-sound and a biliary-tract IRM confirmed cholecystitis and gallbladder sludge with liver and spleen slighlty enlarged with no other liver or biliary (intra or extra-hepatic) lesion. Acute liver failure is however suspected with hypoalbuminemia, coagulopathy (V and VII factors decreased), an international normalized ratio (INR) at 3.3 and a prothrombin time (TP) at 22%. After contact with gastro-enterologist, fulminant hepatitis in an undiagnosed Wilson's disease is suspected and patient is transferred for urgent liver biopsy. It is noteworthy that dosage of the G6PD activity was normal (16 IE/gHB with normal values between 12.14 IE/gHb). Serum copper was high (10.3 microM) and ceruloplasmin was low (0.05g/l). Wilson's disease was further confirmed by liver biopsy. Urgent liver transplantion was carried out successfully because of a dramatic progression of acute liver failure. Hepatic failure and hemolytic anemia should alert physian to look for Wilson's disease especially in young women.

P380

Long term relapse of Whipple's disease: a case report and literature review

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Whipple's disease is an infection caused by the bacteria Tropheryma whipplei. It leads to several systemic symptoms such as malabsorption, diarrhea, arthralgia, weight loss and fever. The usual primary treatment is an intravenous antibiotic (e.g. ceftriaxone) for 2 weeks followed by a one-year oral treatment with cotrimoxazole. Our patient was a 71-year-old woman who has been diagnosed with a long term relapse of Whipple's disease in 2016. She has been successfully treated for Whipple's disease in 1987. In 2016 she presented with diarrhea, significant weight loss, fever and newly diagnosed rheumatoid arthritis. Diagnosis was based on biopsy samples obtained from the stomach and the duodenum showing periodic acid-Schiff-positive macrophages. A quantitative real-time PCR assay was also performed to detect T. whipplei DNA in the biopsy samples. Due to ceftriaxone allergy treatment was initiated with meropenem for 2 weeks. Therapy is currently in progress with cotrimoxazole until May 2017. Under treatment gastroenterological and rheumatic symptoms decreased. As shown in several studies arthralgia vs. diarrhea and weight loss is equally frequent in patients suffering from Whipple's disease. Arthritis is often shown as a first symptom. Therefore, we hypothesize that T. whipplei infection causes rheumatic disease with gastroenterological symptoms. Although incidence of Whipple's disease is very low, studies show IgG against T. whipplei in 70% of a healthy population. The bacteria can be found in the lamina propria of the gastrointestinal tract in 2–4% of all asymptomatic patients. Several host factors, e.g. immunodeficiency seem to be responsible for disease onset.

P381

Acute Stroke following Amiodarone administration in a patient with atrial fibrillation

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Introduction: Guidelines recommend a limit of 48 hours after the onset of atrial fibrillation (AF) for cardioversion without anticoagulation. Amiodarone is often used for the treatment of AF and it is known to cause chemical cardioversion.
Case: In Mai 2016, a previously healthy 65-years-old woman presented to her GP with non-specific complaints including inappetence and an increasingly deteriorating general condition. The patient denied any form of chest pain. The imaging studies showed pleura effusions of moderate size on both sides and the patient was referred to our emergency department. He was in a stable condition, with a blood pressure of 135/102 mm Hg and an abnormal heart rhythm (irregular, 150/min). There were no signs of an infection, but clinical signs of cardiac congestion. The ECG showed AF with a frequency ranging from 150 to 180 bpm. The duration of the AF was unknown. The frequency remained above 170 bpm, despite rate-control with a beta blocker. After injecting Clexane 80 mg i.v, a single

dose of amiodarone (150 mg) was intravenously given. The AF was successfully converted into sinus rhythm. On the following day the patient suffered a wake-up stroke with a sudden right-sided motor weakness and dysarthria. A gadolinium-enhanced MRI confirmed multiple acute cerebellar infarctions in the territory supplied from the posterior inferior cerebellar artery, the cortical branches of the basilar artery and of the posterior cerebral artery left. Vascular investigations showed an acute occlusion of the P1 segment of the left posterior cerebral artery. No other intracranial arterial occlusions that could suggest an in situ atherothrombotic mechanism or an artery to artery embolism were documented. Because of the multiple infarctions in the posterior circulation and because of the clear association between the neurological deficit and the cardioversion a thromboembolic stroke following amiodarone was postulated. M-mode echocardiography revealed an enlarged left atrium, suggesting long-standing AF. Anticoagulation was started 4 days later. The patient showed a complete recovery and was discharged.
Conclusion: Thromboembolic events following electric cardioversion are a well described complication. However, thromboembolism by pharmacological cardioversion of AF may be underestimated and therefore the importance of anticoagulation prior to pharmacological cardioversion may not be underestimated.

P382

High-intensity interval training as treatment strategy for heart failure patients with preserved ejection fraction: a protocol proposal for a prospective single-blind randomized controlled trial

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Background: Chronic heart failure (HF) is a common symptom complex characterized by shortness of breath, fatigue, fluid retention and severe exercise intolerance. HF with preserved ejection fraction (HFpEF) occurs in about 50% of all HF patients. Remodeling and fibrosis stimulated by inflammation appear to be main factors for the progression of HFpEF. Furthermore, iron deficiency (ID) has been recognized to be a common comorbidity in HFpEF. The lack of prognostic treatment options in HFpEF urgently calls for new therapeutic approaches. While beneficial effects of exercise training and iron substitution have been demonstrated in HF with reduced ejection fraction, they have not yet been evaluated in HFpEF. Therefore, the aim of this study to be discussed is to investigate the effect of exercise training in HFpEF patients with optimally adjusted iron values. Exercise tolerance measured as peak oxygen uptake (VO_{2peak}) will be the primary outcome.
Method: The proposed study will be a prospective single-blind randomized controlled trial in a primary care setting including 98 patients with stable HFpEF. Patients will undergo 3 study visits including measurements of disease-specific biomarkers, cardiac and arterial vessel structure and function, exercise tolerance, habitual physical activity, body composition and quality of life (QoL). After the first visit, patients with ID will undergo iron substitution until sufficient iron levels are reached (over max. 12 weeks), in order to ensure comparable baseline conditions for the training intervention. The study measurements will be repeated after 12 weeks in both, initially iron deficient and non-iron deficient patients. Patients will then be randomized to the intervention or control group, stratified by initial iron-deficiency status. The intervention group (n = 49) will attend a supervised 12-week high-intensity interval training on a bicycle ergometer. The control group (n = 49) will be advised to continue usual care. After 12 weeks, the study measurements will be repeated in all patients to monitor the effects of the intervention. At 6 months, 1, 2, and 3 years after the last study visit, telephone interviews will be performed to assess medical outcomes (e.g. hospitalizations, cardiac events, death) and QoL.
Outlook: This study is expected to add important knowledge about the potential utility of a novel treatment strategy in HFpEF patients, which may help to improve both, QoL and functional status.

P383

Liver pain revealing Rendu Osler syndrome: in a case report

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Introduction: Rendu-Osler disease is an inherited multisystem angiodysplasia transmitted as an autosomal dominant, which can be complicated by vascular visceral malformations, including liver.
Methods: Patient, 36 years old, mother of 3 children without special background, consults for liver pain with sensation of heaviness in the right upper quadrant.
Results: The examination reveals a history of repeated spontaneous epistaxis, clinical examination purpose, mucocutaneous telangiectasia, hepatosplenomegaly. Abdominal ultrasound showed homogeneous hepatosplenomegaly, a trunk door permeable, and the existence of arteriovenous fistulas hepatic Doppler color and helical computed tomography. Upper gastrointestinal endoscopy esophageal varices objectified stage I-third lower esophageal without telangiectasia. The rendu osler disease is diagnosed in our patient by the criteria of Curacao, the staging revealed no other systemic involvement. The patient was put under medical treatment and clinical monitoring and strict paraclinical, with a family screening.
Conclusions: Hepatic vascular malformations should be sought routinely in all patients with the rendu osler syndrome, color Doppler ultrasound The test is best suited for the hepatic vascular changes during the initial assessment and monitoring of patients. Medical treatment is effective for some symptomatic forms, liver transplantation should be considered as currently the treatment of choice for severe and complicated forms.

P384

The Model for End-stage Liver Disease as a predictor of short-term mortality in *Staphylococcus aureus* bloodstream infection: a single-centre observational study

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Introduction: Laboratory-based prediction models may support clinical decisions in *Staphylococcus aureus* bloodstream infections (BSIs), which carry a particularly high mortality. Previous studies suggest that the laboratory-based Model for End-stage Liver Disease (MELD) score is a risk factor for mortality in critically ill patients with infections. For *S. aureus* BSIs, we therefore aimed to assess a potential association of the MELD score with mortality.
Methods: In this single-centre observational study, all consecutive patients with a first episode of methicillin-susceptible *S. aureus* BSI occurring between 2001 and 2013 were included. Relevant patient data were retrieved from our prospective in-house BSI surveillance. We assessed the association of the MELD score at day of BSI onset (range ± two days) with 30-day all-cause mortality using uni- and multivariable logistic regression analysis.
Results: 561 patients were included in the final analysis. The MELD score at BSI onset was associated with 30-day mortality in *S. aureus* BSIs (odds ratio per 1-point increase, 1.06; 95% confidence interval, 1.03–1.09; P <0.001). After adjustment for relevant patient and infection

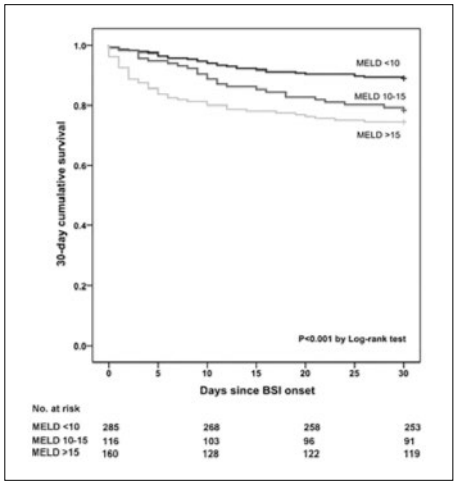

Figure 1

characteristics, an increased MELD score remained a strong predictor of 30-day mortality (adjusted odds ratio per 1-point increase, 1.05; 95% confidence interval, 1.01–1.08; P = 0.005). In time-dependent analysis, a MELD score at BSI onset of 10–15 points and >15 points (reference, <10 points) was significantly associated with death before day 30 (P <0.001; fig. 1).
Conclusions: In our study population, the MELD score at BSI onset was an independent predictor of mortality in *S. aureus* BSIs. The MELD score may be part of clinical decision support systems in patients with suspected or confirmed BSI.

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Anaphylactic shock to bilastine

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Introduction: Antihistamines are drugs that antagonize the activity of histamine receptors. H1-Antihistamines are firstline treatment for chronic urticaria and are used to treat allergic reactions. Anaphylactic reactions to antihistamines are very unusual.
Methods: We describe the case of a 53-year-old woman with history of chronic urticaria experiencing urticaria, angioedema and syncope to multiple H1-antihistamines (hydroxyzine, cetirizine and fexofenadine). In order to proof tolerance with an alternative H1-antihistamine a double-blind provocation test with bilastine versus placebo was performed.
Results: After a cumulative dose of 37 mg bilastine (90 minutes), the patient developed generalized urticaria. Prednisolone 100 mg per os was given immediately. After 360 minutes, the patient felt dizziness with drop of blood pressure (84/54 mm Hg) and tachycardia (107/min). The patient recovered after intramuscular injection of 0.3 mg adrenaline. One hour after the reaction, blood sample showed an elevated tryptase (36.7 µg/l) which normalized several days later, consistent with a mast cell-activation in IgE-mediated reaction. Finally, the urticaria was treated with monthly injection of 300 mg omalizumab with good tolerance without recurrence of urticaria (follow-up 5 months).
Discussion: Hypersensitivity reactions to H1-antihistamines are very rare and only twelve cases have been reported in literature. Above all, cetirizine has been implicated in these reactions. The exact mechanisms are speculative, but the piperazinine ring has been implicated in some cases of cetirizine hypersensitivity. However, this hypothesis remains controversial as prochlorperazine, an antiemetic drug containing a piperazinine ring, was well tolerated in another case after cetirizine anaphylaxis. Other groups suspected a hypersensitivity to side chains of cetirizine. Interestingly, an intolerance reaction to cetirizine has also been reported.
Conclusion: This is the first report of an anaphylactic reaction to bilastine. Patients may react to one single or multiple H1-antihistamines, which is challenging in the treatment of chronic urticaria. Prediction of crossreactivity is difficult because the epitope has not been identified. Careful assessment of the risk/benefit ratio is necessary to avoid potentially harmful provocation tests. Omalizumab should be considered as first choice treatment in patients with chronic urticaria and H1-antihistamines hypersensitivity.

POSTERTOUR 2: MÉDECINE SPÉCIALISÉE II / FACHMEDIZIN II

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Painless swelling of the forefoot and recurrent subcutaneous abscesses of the lower leg – two distinct presentations illustrating the spectrum of eumycetoma in a non-endemic country

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Introduction: Eumycetoma is a neglected tropical disease that is characterized by the triad of painless swelling, sinus formation and purulent discharge. This chronic disease causes significant disability if diagnosed late.
Methodology: We report two cases of eumycetoma presenting to our hospital, one early presentation with a painful swelling of the left forefoot in a 41-year-old man from the Indian subcontinent (Patient 1) and one late presentation with recurrent subcutaneous abscesses of the left leg extending into the ankle joint in a 21-year-old Eritrean migrant (Patient 2).

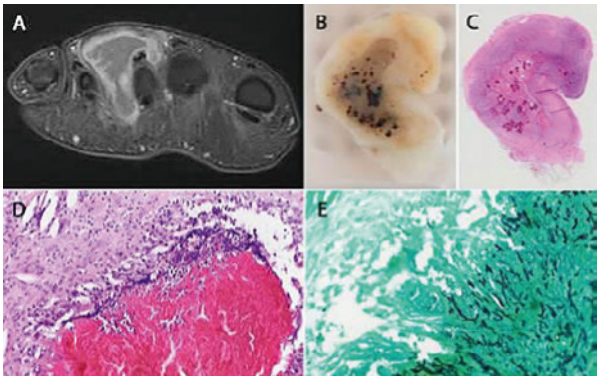

Figure 1

Results: Patient 1 had emigrated from India to Switzerland in 1996, and his last visit to the Indian subcontinent (Pakistan) was five years ago. He presented with a soft tissue mass on his left forefoot, which has been steadily growing over three months. Owing to the initial suspicion of a soft tissue tumor, the patient underwent complete surgical resection. Histopathology revealed fragments of black grains and a granulomatous necrotizing inflammatory reaction surrounding fungal hyphae (fig. 1).
Identification of *Madurella mycetomatis* as the causative organisms was established by panfungal polymerase chain reaction (PCR).
The patient was treated with itraconazole for six months with regular therapeutic drug monitoring without evidence of relapse 30 months after treatment cessation. Patient 2 had emigrated from Eritrea about four months before presentation to our hospital with progressive pain and swelling of his left ankle. On examination, a painful fluctuation was noted below his medial ankle consistent with a subcutaneous abscess (fig. 2), which was drained and sent for culture.

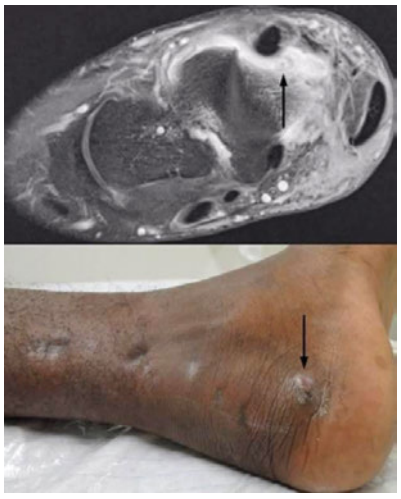

Figure 2

He reported recurrent local infections on his left foot since the age of 10. Abscess cultures revealed growth of a mold, which was identified as *Madurella mycetomatis* using panfungal PCR. Treatment with itraconazole 100mg twice daily was initiated, which resulted in marked reduction of pain after four weeks. Unfortunately, the patient was transferred to Italy and was lost to follow-up.
Conclusion: The present cases underscore the importance of considering epidemiological clues for eumycetoma in the differential diagnosis of painless soft tissue swellings or recurrent subcutaneous abscesses of the feet. Physicians in countries currently hosting refugees from East and Central Africa or the Indian subcontinent need a high index of suspicion for this neglected tropical infection.

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Fever after treatment with rituximab and bendamustin – don't forget the ticks!

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Case report: A 79 year-old patient suffering from follicular lymphoma stage IV was referred to our clinic for further evaluation of daily fever >39 °C, fatigue, arthralgias, imbalance and weight loss. A recent relapse of lymphoma had been treated with rituximab and bendamustin. Clinical examination showed cachexia and slightly enlarged and indurated cervical, supracalvicular (left) and axillary (right) lymph nodes. Laboratory analyses demonstrated anemia (Hemoglobin 9.2 g/dL; normal range: 14.4–17.5 g/dL), elevated C-reactive protein (CRP 86 mg/L; <5 mg/L) and ferritin (1600 mg/L; 22–275 mg/L) but normal lactate dehydrogenase (165 U/L; <220 U/L). Blood cultures and serologies for an infectious aetiology (Parvovirus B19, Brucella, Coxiella) were negative. PET-CT showed increased FDG-uptake in bone marrow and lymph nodes and needle biopsy of the latter was compatible with recurrent lymphoma. However, broad spectrum bacterial PCR (16s rRNA) from blood and lymph node was positive for *Candidatus Neoehrlichia mikurensis* establishing the diagnosis of neoehrlichiosis. Whithin a day after initiation of antibiotic therapy with doxycyclin fever ceased and the patient recovered quickly. He did not recall a tick bite.
Discussion: *Candidatus Neoehrlichia mikurensis* is a tick-transmitted, nonculturable intracellular bacterium recently identified to cause prolonged fever in immunocompromised patients particularly after rituximab. Additional symptoms include malaise, weight loss, myalgias, arthralgias as well as vascular and thromboembolic events. Up to 8% of swiss Ixodes ticks are infested with *Ca. N. micurensis*. Nevertheless, neoehrlichiosis remains a rarely identified disease suggesting only mild and transient symptoms in immunocompetent hosts. However, neoehrlichiosis should be actively searched for using molecular diagnostics in immunocompromised patients with fever and/or unexplained inflammation since exposure is easily possible in Switzerland and treatment with doxycyclin is simple and highly effective.

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Pulse corticosteroids-induced bradycardia

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Introduction: High dose intravenous (pulse) corticosteroid therapy is used to treat a vast array of diseases. Pulse corticosteroids-induced bradycardia is rare and has been seldom reported.
Methods: We describe the case of a patient with neutrophilic dermatosis who developed bradycardia after pulse methylprednisolone. We used the Naranjo adverse drug reaction probability scale to determining the likelihood of a causal relationship between bradycardia and steroid administration.
Results: A 36-year-old woman was admitted to our unit for myalgia and fever. Patient's medical, family, allergy and travel history was insignificant. She was taking no drugs or medications and denied contact with ill persons. A part from fever (38.8 °C), parameters (blood pressure, heart rate [HR], saturation) were normal. Physical examination revealed tenderness over the right deltoid and lumbar area, painful cervical lymphadenopathy and tender vesico-pustular lesions over the face, neck, arms, thighs and back; bipolar aphthosis was also present. Besides leucocytosis and an elevated CRP (233.5 mg/l), blood tests (kidney and liver function, common viral serologies and a complete immunological panel) were normal. ECG and chest X-ray were unremarkable. Biopsy of one skin lesion showed dermal neutrophilic infiltrate without vasculitis. We considered a diagnosis of acute neutrophilic dermatosis. Pulse methylprednisolone therapy (1 g/day for 3 days) was introduced. Improvement was dramatic with rapid disappearance of pain and fever, resolution of skin lesions and normalization of inflammatory parameters. 48 hours after the first pulse of methylprednisolone, the patient presented asymptomatic bradycardia (HR: 40 BPM) with an HR of 32-38 BPM in the 2 following days. ECG showed normal sinus rhythm without AV conduction abnormalities. We opted for watchful waiting. The patient was switched to oral prednisone (1 mg/kg per day) on day 4. 72 hours after the last pulse HR was normalised (>60 BPM). The patient was finally discharged at day 10. At 1-month follow-up the patient, still on oral steroids, is fine and HR is normal.
Conclusion: In the absence of other drugs or medical conditions that could affect HR, and with a Naranjo scale of 7 (probable relation), we believe that patient's bradycardia should be ascribed to pulse methylprednisolone. We suggest that HR should be routinely evaluated in patients receiving pulse corticosteroids and particularly in those with cardiac risk factors.

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Spinal tuberculosis – almost a forgotten differential diagnosis for back pain in the western world

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Extrapulmonary tuberculosis (TB) is rare. Bone TB accounts for about 10% of all extrapulmonary TB cases. The spine is the most frequently affected location. TB treatment becomes challenging because of the spread of multi-drug resistant (MDR) TB. A 28 yo patient was referred to our hospital for further diagnostic because of a radiological diagnosed pulmonary and spinal mass of unknown origin with suspected compressive myelopathy. She had been complaining for almost nine months of upper back pain during her pregnancy, and after giving birth. She was treated with painkillers and physiotherapy, later on; she developed ataxic gait and hyperreflexia. The patient immigrated from India 2 years ago. She had no known history of or exposure to TB. CT-Imaging on admission demonstrated Growth in the right upper pulmonary lobe with infiltration of the paravertebral tissue on thoracic level 4–6, infiltration of the thoracic vertebral bodies 4–7, compression fracture of thoracic vertebral body 5 with high grade that was narrowing of the spinal canal. M. tuberculosis was cultured from sputum and spinal biopsies. Testing by Genexpert showed a rifampicin resistance mutation. Due to the neurocompressive symptoms, we began an empiric antituberculosis treatment combination with amikacin, linezolid, moxifloxacin, ethambutol, pyrazinamid, cycloserin and clofazimine for assumed MDR-TB. 2 weeks later a spinal surgery with decompression and stabilisation was performed. The postoperative period showed nearly complete recovery of neurological symptoms. The final phenotypic resistance testing revealed rifampicin, streptomycin, ethambutol and isoniazid resistance, following the results we could reduce the TB treatment to 5 substances. The patient tolerated the treatment well; the laboratory monitoring showed no sign of toxicity. However the follow-up audiological testing disclosed impaired hearing in the high frequencies. Consequently, the dosis of amikacin was reduced. Finally, the patient has recovered well. In the follow-up exams, the patient had a normal gait and no signs of a peripheral polyneuropathy. Spinal TB is an uncommon condition, which is often overlooked and misdiagnosed because of the rarity in the western world. Considering TB as a diagnosis and considering risk factors can avoid delays in diagnosis and management and subsequently prevent significant neurological complications. additionally physicians should be aware of the increasing risk of MDR-TB.

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A rare cause of severe systemic inflammation and bilateral femoral head osteonecrosis

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Introduction: Femoral head osteonecrosis is a rare disease occurring not infrequently bilateral. Superinfections are rare and can be associated with risk factors for bacteremia (central lines, urinary tract infection, etc.).
Case report: A 63-year-old female patient with severe pain from bilateral femoral head osteonecrosis was admitted for bilateral hip joint replacement. Blood analyses are shown here:

Table: Blood analysis

	Result	Normal values
Hemoglobin	86 g/l	120–160 g/l
Leucocytes	13.5 G/l	4–10 G/l
Platelets	604 G/l	150–300 G/l
Albumin	18.9 g/l	34–48 g/l
C-reactive Protein	228 mg/l	<8 mg/l

Three months earlier the patient was hospitalized in another clinic because of an urosepsis with *Escherichia coli*. At that time, chronic hip pain exacerbated and advanced bilateral femoral head osteonecrosis was diagnosed radiologically. Two weeks after discharge the patient had fever, felt weak and increased inflammatory markers (CRP 168 mg/l) and a low hemoglobin of 66 g/l (which was 89 g/l at discharge) were measured. An upper and lower endoscopy, CT scan and a bone marrow aspirate were performed without further diagnostic clues. Finally, an ^{18}F-FDG PET/CT Scan showed FDG-uptake in both hips what was considered as a consequence of femoral head osteonecrosis.

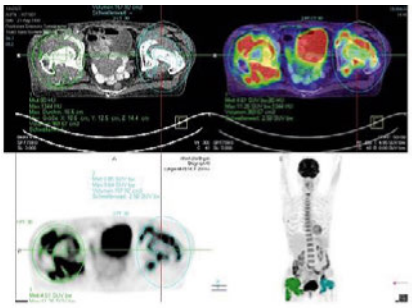

Figure 1: PET-CT Scan.

The implantation of a total hip prosthesis was performed first on the right side. As preoperatively planned the femoral head was taken for histological and microbiological examinations. Postoperative antimicrobial treatment with intravenous amoxicillin/clavulanate was started. Histology showed destruction of the femoral head and osteomyelitis. A pansensible *E. coli* was grown. Ten days later, a Girdlestone situation was created on the left side. *E. coli* osteomyelitis could also be diagnosed there. Amoxicillin/clavulanate was changed to ceftriaxone and after 4 weeks to ciprofloxacin per os. A rapid clinical improvement and a slow decrease of the inflammatory markers occurred. After 12 weeks, antimicrobial treatment was stopped and after an interval of 2 weeks and normal CRP, the implantation of the left hip joint was done. One year later, the patient was free of pain and had a good function of both prosthesis.
Conclusion: In patients with femoral head osteonecrosis and elevated inflammation markers, superinfection should be considered. It is very important to initiate a histological and microbiological examination of the femoral head. FDG uptake is unspecific and cannot differentiate between neoplasia and inflammation caused by necrosis or infection. Only few cases of documented bilateral superinfection of bilateral femoral head osteonecrosis were found in the literature.

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IgG4-related disease without IgG4. Don't forget the plasmablasts

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Introduction: IgG4-Related Disease (IgG4-RD) is a rare autoimmune disorder. Histologically, it is characterized by the infiltration of IgG4 plasmablasts in different organs and fibrosis. Different studies suggest that IgG4-RD predisposes to the development of certain tumours.
Methods: We describe the case of a patient with multiple fibrotic nodules in which IgG4-RD was suspected.
Results: A 60 years-old woman was referred to us for a with a 5-year history of recurrent pancreatitis without a definite cause despite multiple investigations, including biopsies. A thoraco-abdominal CT scan performed during the 4th year of follow-up showed multiple bilateral basal nodules; needle biopsy concluded to chronic pachypleuritis withoutof malignancy. PET/CT scan at 5-month interval showed progression of nodules. Transbronchial biopsy was non contributive. Another CT scan at 3-months interval showed augmentation of lung lesions and s micronodular infiltration of omentum. A few days later the patient developed jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) visualized stenosis of the common bile duct that was treated with stenting; endobiliary brush cytology and biopsies were negative for malignancy. The patient was referred to our department for further evauation. Patient's medical and family history was insignificant and physical examination unremarkable. Kidney and liver function, viral serologies and a complete immunological panel including protein electrophoresis and immunofixation were normal. Flow cytometry showed abundant circulating IgG4-positive plasmablasts suggesting an IgG4-RD. PET/CT was repeated and showed multiple hypercaptating lesions at pancreas and lung. Thoracoscopic wedge resection of two pulmonary nodules was performed. Histology was consistent with metastases of a moderately differentiated adenocarcinoma with mucinous differentiation; immunohistochemistry could not distinguish between lung or pancreatic origin. Analysis of the lymphocytic infiltrate showed an IgG4/IgG ratio of à 75% compatible with IgG4-RD. The patient, actually at the 5th FOLFIRINOX cycle, is asymptomatic without radiologic evolution.
Conclusion: When we encounter a fibrotic disease of unknown etiology, IgG4-RD is often evoked but rarely found. Normal serum IgG4 levels should not preclude diagnosis in a patient with a high clinical suspicion of IgG4-RD. Identification and measurement of IgG4 plasmablasts by flow cytometry can be a useful tool.

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Neurolisteriosis mimicking progressive multifocal leukoencephalopathy in an immunocompromised patient

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Introduction: A 78 year old man presented to our emergency department complaining of severe diarrhea for three days. The patient was taking methotrexate and prednisone 50 mg for a remitting seronegative, symmetrical synovitis for 14 months. On admission the patient was hemodynamically stable and afebrile. His CRP was elevated at 173 mg/l, leucocytes were 9200/ul with a lymphocyte count of 140 /ul. Fluid replacement was initiated and stool cultures were performed. On day 2 the patient developed a fever of 39 °C. Given a suspicion of infectious enteritis blood cultures were taken and empiric antibiotic therapy with piperacillin/tazobactam was initiated.
Methods: Given intermittent somnolence despite antibiotic therapy, although the patient had no headache, focal neurologic signs or signs of meningeal irritation, a MRI of the brain and a lumbar puncture were performed on day 7 respectively on day 9.
Results: The blood and stool cultures grew *Listeria monocytogenes* after 24 hours. Antibiotic therapy was deescalated to amoxicillin (2 g IV every four hours). The MRI of the brain showed in the right temporal lobe a lesion of the white matter that appeared hypointense in T1 and hyperintense in T2, typically seen in patients with progressive multifocal leukoenzephalopathy (PML).The CSF showed a minimally elevated cell count with 8 polymorphonuclear cells / mL. Protein and

glucose were normal. The CSF culture showed no growth, but the patient was on antibiotic therapy for eight days. The eubacterial PCR and the specific PCR for HSV I and II, CMV, EBV and JC were negative. Under treatment for listeriosis the patient improved, his altered neurological status normalized. A control MRI three weeks later showed a clear regression of the temporal lesion, which retrospectively was clearly interpreted in line with an encephalitis due to *Listeria monocytogenes*.
Conclusion: CNS-listeriosis is challenging to diagnose. As described here, the symptoms are often atypical, meningeal signs uncommon and the CSF findings non-specific. *Listeria monocytogenes* has a predilection for the brainstem and cerebellum; lesions in the temporal lobe as in our case have rarely been reported. The clinical course in our patient is highly suggestive of cerebral listeriosis which needed a prolonged antibiotic therapy of six weeks. Brain imaging and lumbar puncture should be considered early in immunosuppressed patients with listeria and any neurological symptoms.

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Involvement of the adaptive immune system in metamizole-induced agranulocytosis

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Introduction: Metamizole is an analgesic and antipyretic drug that represents an alternative when NSAID and acetaminophen are contraindicated. Nevertheless treatment with metamizole can lead to life-threatening agranulocytosis in rare cases. To date mechanisms underlying metamizole-induced agranulocytosis (MIA) remain unknown. A few cases of patients re-exposed to metamizole reacted with rapid onset and more severe symptoms are known. This suggests that the adaptive immune system could be a key player in the pathogenesis of MIA.
Methods: A clinical cohort has been created including MIA patients, metamizole tolerant patients and unexposed healthy donors. PBMC of these three groups are being cultured with metamizole and its metabolites *in vitro*. Cellular activation is analyzed by measurement of CD69 upregulation and proliferation with flow cytometry. Generation of metamizole-reacting T cells lines is performed as well.
Results: The reactivity of T cells from MIA patients towards metamizole or its metabolites has been investigated using capacity of T cells to proliferate, to secrete cytokines (TNFα) and to be cytotoxic (CD107a) after antigen encounter. So far a T cell response against metamizole could not be obviously shown. Indeed the proliferation seen in MIA patient was only moderate and did not reach statistical significance when compared with control groups. Furthermore, TCL generation was not easily achieved and TCL reactivity could not be kept *in vitro* over a long period. T cell response in MIA patients cannot be excluded either at this point.
Conclusion: These non-significant results may be due to several reasons: a low detection threshold, an inadequate stimulation, a still unknown metabolism or a maladjusted protocol to the drug used. Furthermore, the time period between the disease outbreak and the *in vitro* analysis was on average of 49.5 months. According to the practical experience acquired on delayed type hypersensitivity reaction to drugs, the optimal diagnostic window is between 6 weeks and 6 months after a complete and sustained acute symptoms resolution. It is known that the number of specific memory cells in the peripheral blood decreases over time. For this reason, 49.5 months appear to be too long to allow the detection of memory cells with conventional methods. Therefore we cannot conclude that metamizole did not induce a T cell response in MIA patients.

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Comparison of new and old definitions for diagnosis of sepsis in non-ICU patients

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Background: Definition of Sepsis used to be based on SIRS criteria. However, these criteria turned out to be too permissive and diagnosis of sepsis did not have impact in prognosis or treatment. The new definition (Sepsis 3.0.) is based on organ dysfunction and should more reliably select patients with critical infectious situations.
Methods: Inclusion criteria were hospitalized febrile patients, in whom an infectious disease consult was performed. ICU-patients were excluded. Sepsis diagnosis was made with both old and new definition. For the old definition, at least two of four SIRS criteria had to be present. For the new definition, quick SOFA score was done. If this was positive, sepsis was confirmed with an at least two point increase in SOFA Score.
Results: 176 patients were included. 29 patients had no sepsis in both definitions. While according to the old definition, 144 patients were diagnosed to have a sepsis, this was present in only 70 patients according to Sepsis 3.0. 67 patients were found to be septic in both the old and the new definition. Only three patients were "upgraded", having no sepsis according to the SIRS definition but fulfilled the criteria of Sespis 3.0.
Conclusion: In Non-ICU patients, only about half of the patients with Sepsis according to the old definition fulfil criteria of Sepsis 3.0. These could have implication for case-weights in the DRG-System.

Table 1

		New (Sepsis 3.0)		
		sepsis	no Sepsis	total
Old Definition	sepsis	67	77	144
	no Sepsis	3	29	32
	total	70	106	

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Treatment of Helicobacter pylori unmasking Whipple's disease

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Case: A 54-year old man presented with a 10 year long history of twice weekly intermittent fever, arthralgia, soft tissue swelling and systemic inflammation. Numerous medical evaluations at different institutions including innumerable tests for malignant, infectious or autoimmune diseases, including PET/CT scans and bone marrow biopsy yielded no conclusive results. Histology of a duodenal biopsy had shown no evidence for Tropheryma whippelii (TW) in 2009. The only short period the patient reported lack of symptoms was following a treatment with amoxicillin, metronidazol and pantoprazol for a helicobacter pylori (HP) infection. Triggered by the history of response of the symptoms to antibiotics during HP eradication therapy, a new search for Whipple's Disease (WD) was initiated. Again no histological signs for TW were found in a duodenal mucosal biopsy. However, PCR for TW was positive in duodenal mucosa and in stool. Treatment with cotrimoxazol had to be changed to ceftriaxone due to a severe DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), followed by doxycycline and hydroxychloroquine for an ongoing 12 months. The medical condition improved dramatically within days of starting ceftriaxone treatment: Systemic inflammation and symptoms disappeared and physical performance improved rapidly. The patient has been free of any symptoms since August 2016.
Discussion: Whipple's Disease is a rare, systemic infection caused by the intracellular bacterium Tropheryma whippelii (TW). Clinical presentation may vary greatly and can mimic multiple clinical conditions. All organs can be affected. In classical gastrointestinal WD, the clinical condition and PAS-positive foamy macrophages in the lamina propria of duodenal mucosa lead to the diagnosis. In extraintestinal disease, the histological or PCR finding of TW in specimens are proof of infection. TW can be a commensal of the upper GI-tract, therefore a PCR result in both duodenal mucosa and stool leaves a 10% likelihood of false positivity. The diagnosis of a TW-associated condition must then be assumed by the clinical response to antibiotic therapy. In our patient, careful history taking led to a clinical suspicion, the response of a year-long clinical illness to antibiotics on two occasions makes us confident to classify our patient as having probable, albeit not completely proven TW associated systemic infection.

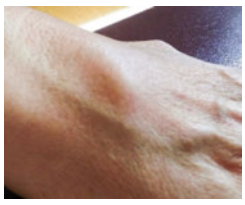

Figure 1: Intermittent soft tissue swelling.

POSTERTOUR 2: MIG AMBULATOIRE / AMBULANTE AIM / MÉDECINE DE FAMILLE I / HAUSARZTMEDIZIN I

P396

Written interprofessional communication in the follow-up of homebound patients

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Introduction: In the follow-up of homebound, polymorbid patients, health professionals in Geneva often use a point-of-care notebook to share information with each other ("*carnet de liaison*"). The aim of the study was to analyse how and for what health professionals used such notebooks and to explore their perceptions regarding the strengths and weaknesses of such written notes for interprofessional collaboration.
Methods: We conducted a mixed-method study among health professionals caring for homebound patients in the canton of Geneva, Switzerland. A sample of notebooks of homebound elderly patients in Geneva was first analysed descriptively. Then 6 focus groups interviews were conducted with different groups of health professionals (doctors, nurses and nursing aides). Focus groups were transcribed verbatim and analysed thematically.
Results: The analysis of 11 notebooks revealed that most of the time, the intended recipient of written information was unspecified; content focused mainly on somatic health and medication; explicit interprofessional communication was rare and patients never wrote down any information. There were no explicit care plan goals.
Thirty-one health professionals participated to the focus groups. Several themes emerged. Participants felt that the notebook embodied the primary care network and was a milestone in the follow-up of homebound polymorbid patient. However, in the absence of a shared electronic health record, most of them complained about having to write the information down at least twice. The fact that the notebook was accessible to anyone and was considered the patient's property influenced how and what professionals wrote in the notebook. Lack of patient contributions to the notebook was a source of concern.
Conclusions: Our results show that fulfilment of notebook's primary function (*i.e.* share information and communicate among health professionals) is suboptimal. In order to enhance patient-centered, written interprofessional communication, more attention should be paid to defining and implementing care plan goals.

P397

Regional variation in primary care in Switzerland? Work Force Study 2015

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Introduction: The issue of shortage of General Practitioners (GPs) is an important matter of debate. With the Work-Force-Study 2015 the current work situation of GPs was assessed. The aim of this study was to evaluate whether in primary care regional variation exist in terms of working hours, workload, and job satisfaction in Switzerland.
Methods: In 2015 a 7-page survey assessing the work conditions was sent to 3554 Swiss GPs. In total, 1299 surveys (response rate of 36.6%) were available for analysis. The questionnaire was available in German (n = 964), French (n = 273) and Italian (n = 62). The study population consisted of 26% female GPs and the average age was 55 years. The data was analysed for potential differences between cities, agglomeration, and countryside. For the classifications of these categories a definition of the Federal Statistical Office was applied. Additionally the data was investigated for potential differences between the three linguistic regions in Switzerland.
Results: GPs on the countryside have more patient contact per week compared to their colleagues in the city (36.7 hours vs. 33.3 hours, p = 0.002). Rural doctors provide essentially (p <0.001) more emergency services (38.1 days per year) than in the city (10.1 days per year). Country doctors are as satisfied with their workload (p = 0.35) and work situation in general (p = 0.415) as their colleagues in the other regions. The proportion of GPs who perceive a lack of GPs lies between 55.7% and 65.3% without reference to rurality (p = 0.053). In the German-speaking part GPs have weekly contact with their patients during 33.8 hours whereas in Romandy they have 35.6 hours and in Italian-speaking part 35.0 hours (p = 0.045). German-speaking GPs see 104.4 patients, French-speaking 83.1 patients and Italian-speaking 91.1 patients in one week (p <0.001). The proportion of GPs being available by phone after working hours for their own patients is highest in the Italian-speaking part (89.1%), in the other regions this proportion lies by 49.2% (p <0.001).
Conclusion: Despite higher workload on the countryside, the job satisfaction does not essentially differ between city and countryside. In the city as well as in rural areas shortage of GPs is considered a serious issue. We found significant differences between the linguistic regions in Switzerland that should be considered when implementing political measures.

P398

Use of new oral anticoagulants in an academic primary care medicine facility: where are we now?

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Direct oral anticoagulants (NOAC) have become the first alternative to vitamin K antagonists (VKA) showing a reduced hemorrhage risk, short half-life, lack of food interaction, need for monitoring and minimal drug interactions. The only drawback is the limited availability of an antidote. Few studies have looked at the adoption of these drugs by primary care physicians.
Objectives: To evaluate the proportion of patients currently receiving VKA eligible for NOAC and to facilitate interns uptake of the new recommendations.
Method: The study was conducted within the Division of Primary Care Medicine. All patients receiving VKA and followed-up between April 2015 and May 2016 were included. Based on the HUG recommendations on NOAC, we designed a study file exploring: sociodemographic data, indications for anticoagulation, duration of follow-up, number of venous and capillary INR checks, proportion of therapeutic values, therapeutic adhesion, and the presence or absence of contraindications to NOAC. After a pilot test, interns were asked to analyze a set of electronic medical records (EMR).
Results: Each intern spent 2 hours conducting in-depth analysis of 5-7 EMR. Fifty-seven patients on VKA were identified (men: 71.9%; mean age: 63.6, standard deviation: 14.6 years). Indications for anticoagulation were: treatment or prevention of thromboembolic events (n = 13, 23%), prevention of stroke by non-valvular atrial fibrillation (AF) (n = 19, 32.7%), prevention of stroke by valvular AF or mechanical valve (n = 17, 30.7%), others (n = 8, 13.6%). In the 35 (61.4%) patients eligible to NOAC therapy, the average duration of VKA treatment was 5.4 (SD: 4.7) years. The previous year's mean number of venous and capillary INR measurements was 9.4 (SD: 10.6) and 9.7 (SD 9.5). The percentage of patients with INR within the therapeutic range in more than 50% of tests was 38.2%. Therapeutic adhesion was evaluated as good in 50%. Only 21.2% had medical contraindications and 8.8% pharmacological contraindications. After considering all factors, 22 (63%) patients could benefit from a change in oral anticoagulation in favor of NOAC. However, only 11% had been switched to NOAC during the one-year study period.
Conclusion: A minority of patients had safe and effective anticoagulant therapy. Nearly two-thirds on VKA could theoretically be switched to a NOAC while the actual rate of change was low. Next step will imply measuring the impact of training on the guidelines adoption.

P399

Syrian crisis: an innovative sanitary response in the canton of Vaud

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Introduction: The Swiss government started a resettlement program, in collaboration with the United Nation High Commission on Refugees (UNHCR) to facilitate the arrival of particularly vulnerable refugees from Syria. As those refugee families don't follow the usual procedure for asylum seekers, a dedicated healthcare program is needed. Around 1800 persons are expected to arrive in Switzerland between 2016 and 2017 from the resettlement program. The objectives of the present project are: 1) To provide the necessary healthcare for this particularly vulnerable population in the canton of Vaud. 2) To gather information about this population, in terms of medical conditions, but also from a more holistic view of the families, as we know they are selected on vulnerability criteria. This can be used as a feedback to the health authorities about the specific needs of this population.
Method: An interdisciplinary family consultation was set up for those families, staffed with a pediatrician, a general practitioner, an interpreter, as well as a nurse practitioner. At the 1st consultation, a health assessment is provided to the family at the same time.

Vaccinations are proposed and screening for tuberculosis is planned for children systematically. Patients can then be oriented toward different medical specialties as needed. A second consultation is planned two months later for a clinical follow-up, to pursue the vaccination plan, and to discuss the results if tests were performed. A shared meeting with the medical team concludes the assessment. After this 2nd consultation, a follow-up with a private general practitioner and/or pediatrician is organized.
Results: Between July and December 2016, 60 persons have been seen for a first medical evaluation, including 32 adults and 28 children. The adults had on average complaints concerning 3.1 chapters of the ICPC-2 classification (classification of symptoms and medical conditions for primary care), and children 1.3. With the use of a validated vulnerability scale published by Bodenmann & al: 2 adults were identified with 4 axes of vulnerability and 3 with 3 axes. One child was identified with 3 axes.
Conclusion: The interprofessional model of a consultation for Syrian migrant families is feasible. It could be implemented in other cantons receiving Syrian refugees and could be extended to different refugee populations. Medical information about this population can be useful to the health authorities.

P400

Monitoring of patients with chronic diseases in primary care using electronic medical record

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Purpose: Non-communicable diseases account for about 80% of health costs in Switzerland. Long term care for patients with chronic diseases poses a huge challenge. Deficits exist regarding monitoring and structured follow up. Our goal was to develop an evidence based and practical tool to help monitor patients with chronic diseases by means of an electronic health record (EHR).
Methodology: Five highly prevalent chronic diseases were chosen to develop the monitoring tool: Diabetes mellitus type 2, arterial hypertension, asthma, osteoarthritis and chronic heart failure. A best practice review among international guidelines was performed searching for indicators how to monitor each disease. In order to find further relevant indicators, this search was complemented by a systematic review of primary literature on the subject "monitoring". The resulting two data sets were then combined and evaluated by selected experts of each speciality by means of a Delphi procedure (fig. 1).

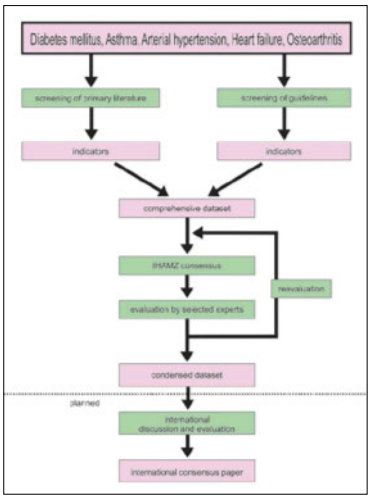

Figure 1: Study flow.

Results: This multi-step procedure resulted in a condensed set of indicators, divided into sublayers to maximise ergonomics. A cockpit serves as an overview of fixed goals and set procedures to facilitate disease management. An additional tab contains information on non-disease specific indicators, as for example allergies and vital signs (fig. 2).
Conclusion: To our knowledge this study represents the first scientifically founded recommendation for the standardised long term monitoring of chronically ill patients in general practice. The ergonomic layout of the monitoring tool enhances user friendliness and facilitates chronic care by means of an EHR. In the near future, the Delphi procedure will be extended to an international level aiming at a European consensus paper on monitoring of chronic diseases by means of EHR.

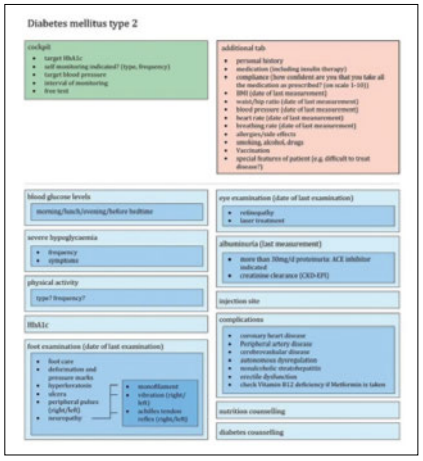

Figure 2: Monitoring tool for Type 2 Diabetes mellitus.

IHAMZ: Institut für Hausarztmedizin Zürich (Institute of Primary Care, University of Zurich)

P401

Involvement of a group of simulated patients in a patient advisory group to conduct iterative cycles of evaluation and adaptation of communication material to the public. Results from a pilot project

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IIntroduction: Guidelines recommend a participatory approach with target populations when developing decision aids and communication materials (CM). While focus groups enable patients to comment on CM, they are often conducted with final versions of CM, limiting opportunities for significant changes. Iterative cycles of evaluation and adaptation allow users to shape CM at early stages of development and to verify whether changes improve the CM. We aimed to test the feasibility and yield of involving a group of simulated patients in a patient advisory group to improve CM developed within a statewide colorectal cancer (CRC) screening program.
Methods: We invited simulated patients aged 50–69 years involved in the teaching of medical students from the University of Lausanne to participate in a patient advisory group. Exclusion criteria were personal history of CRC. We planned 2h meetings every 3 months and used a cyclic approach: we submitted the CM beforehand, collected the comments during group discussions, identified specific adaptations to be made, adapted the CM, and re-submitted the modified CM to the group for further adaptations. Participants received a CHF 50.– voucher per meeting for their participation.
Results: Out of the 20 eligible simulated patients invited, 5 (25%) accepted the invitation. They came to 4 meetings every 3 months over a 12-month period. Their comments helped to identify discrepancies between the intended and perceived tone of messages in CM, test the proposed solutions and readapt based on repeated evaluation. In particular, they commented on the overall presentation, the vocabulary, formulations, and the character of the message. In addition, they suggested developing new CM for people with special needs. All participants said they would recommend others to participate in these groups and approved the process of implicating patients in the development of CM.
Conclusion: The participative approach of having CM be reviewed by a patient advisory group improved the CM and helped identify critical elements and avoid discrepancies in the CM. The cyclic approach was useful to clarify our understanding of the comments of the participants. This pilot project highlighted the willingness of participants to be implicated in the process of evaluation of medical CM. The method should now be rigorously tested in particular with populations with special needs.

P402

4-year-long-term follow-up in diabetes patients after implementation of the Chronic Care Model in primary care

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Introduction: Implementing the Chronic Care Model (CCM) via involvement of specially trained practice nurses improves cardiovascular risk profile as well as perception of care among type 2 diabetes patients in small primary care practices (PCP) on the short term. Little is known on the long term effects of this intervention.
Methods: Cross-sectional survey among the participants of the cluster randomized controlled CARAT trial (30 PCPs, 303 diabetes patients) three years after its completion.
Outcomes: proportion of patients still treated according to CCM, possible reasons for discontinuation, glycosylated hemoglobin (HbA1c), blood pressure (BP), LDL-cholesterol, and accordance to CCM (assessed by PACIC (Patient Assessment of Chronic Illness Care)).
Results: 40.9% of practices (40.7% of patients) continued using the CCM. PCPs originally randomized to the intervention arm were significantly more likely to still using the CCM (p <0.001). Main reasons for discontinuation were organizational (40.9%) and financial aspects (18.1%) and the general practitioner refusing to hand over treatment responsibility (18.1%). Development of HbA1c, BP, LDL-cholesterol and PACIC showed some significant positive effects in favor of practices originally randomized to the intervention group and practices continuing to treat patients according to the CCM.
Conclusions: Diabetes care according to the CCM including the involvement of practice nurses is a reasonable tool to improve care also in the long-term. CCM-training of the whole team is essential to overcome organizational challenges. Continuous team education, technical decision support, as well as recognition of the importance of these new structures by health care policy might improve the long term clinical effect of the team approach.
TRIAL REGISTRATION: The study protocol was published in Cardiovascular Diabetology in 2010, registration number: ISRCTN05947538.

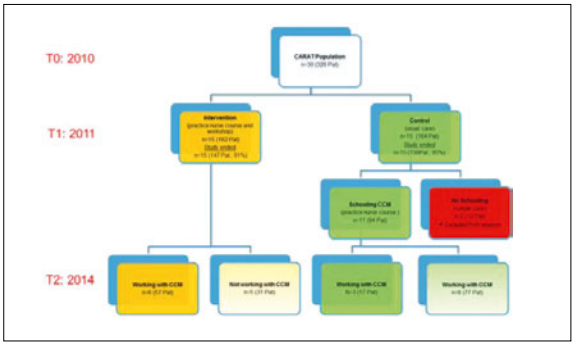

Figure 1: Implementation of the Chronic Care Models over 4 years.
CARAT = Chronic CARe for diabetes trial, n = number of primary care practices, Pat = patients, CCM = Chronic Care Model

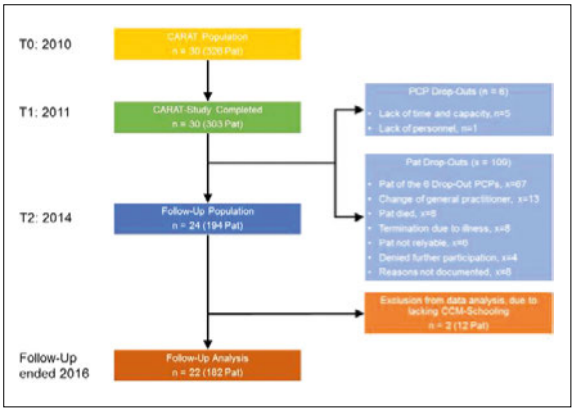

Figure 2: Study Population and Drop-Outs.
CARAT = Chronic CARe for diabetes trial, n = number of primary care practices, x = number of patients, Pat = patients, CCM = Chronic Care Model, PCP = primary care practice

P403

Vulnerable patients in an academic community health centre in Geneva: health needs, services utilization and impact of nurses front-line consultation

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Introduction: The community health centre (CAMSCO) of the Geneva University Hospital (HUG) is a unique academic structure in Switzerland, serving as a walk-in clinic for patients with socioeconomic vulnerability and as a port of entry into the public healthcare system. Nurses conduct first-line comprehensive assessment and do triage and orientation. We aimed at characterizing patients health needs, health services utilization and the impact of front-line nurses consultation.
Methods: We included all patients consulting in August 2016 and extracted data from their health records.
Results: The 483 patients were mostly female (60.9%), aged 40.1 (SD: 11.9) years old. Only 1.5% were insured in Switzerland and 8.1% were homeless. They originated from Europe (17.4%), Asia (23.2%), Latin America (39.5%) and Africa (19.9%). It was the first contact ever with HUG in 26.7%, whereas 47.3% had consulted CAMSCO in the previous year. The mean number of HUG consultation in the previous year was 2.8 (SD: 5.4). Patients entailed 553 consultations and had an average of 1.5 (SD: 0.7, range: 1-6) health complains. Women chief complains were sexual or reproductive (38.5%) and osteoarticular (9.1%) whereas men had mainly dental (14.6%) and skin (11.4%) complains. Mental health problems were frequent secondary complains. Access to prescription medicines was the main reason for consulting in 10.5% of the whole cohort. Seventeen (3.1%) consultations were triaged as urgent and required referral to the emergency room and 22.6% necessitated a complementary consultation by the intern on site. Nurses could manage 21.5% cases alone. Main referral destinations were division of primary care medicine (22.6%), gynecology and obstetrics (16.6%) and dentists (8.5%). On a 5-point Likert scale assessing subjective case complexity, average score was 2.2 (SD: 1) points. On average, consultations lasted 21 (SD: 14) minutes.
Conclusion: CAMSCO acts as an advanced primary care health post in the community with a high patients turnover. Its activity highlights hidden healthcare needs of very diverse populations in urban context in Switzerland. Front-line nurses solve a consequent share of cases and patients showed overall limited health services utilization. Yet, given the variety of health problems severity and nature, effective referral processes with secondary structures is required. Access to dental healthcare and to medicines represents major challenges in this vulnerable group of population.

POSTERTOUR 2: MÉDECINE INTERNE GÉNÉRALE V / ALLGEMEINE INNERE MEDIZIN V

P404

Mst1 expression in serum is an independent prognostic marker in breast cancer patients

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Backgroud: Mammalian sterile20-like kinase 1 (Mst1) is a major inhibitor of cell proliferation, involved in apoptosis, oncogenesis, and organ growth via its ubiquitously encoded serine threonine kinase. Mst1 has tumor-suppressor function in human breast cancer. Mst1 deletion or mutation is associated with tumorigenesis, whereas Mst1 overexpression leads to tumor cell apoptosis and decreases tumoriproliferation. Breast cancer is the most common cancer in women worldwide and second most common cancer overall. Still, there is a limited choice of prognostic factors and individualized treatment strategies.
Methods: We measured Mst1 levels in patients' plasma in order to elucidate their correlation with the overall and disease free survival (OS, DFS). ELISA was used as an efficient and effective method to quantify Mst1-concentration in the serum of breast cancer patients. Blood samples were prospectively collected for 12 months at the Department of Breast Surgery, Yangpu Hospital. 98 women were included and completed the follow up of 98 months. Blood samples were taken prior to any surgical or antitumor treatment. Distribution of tumor grades and receptor status were representative. The majority of the patients presented with carcinoma of a ductal type with luminal subtype, grade 2.
Results: Average Mst1-level was 1.8 µg/mL and was used to discriminate Mst1-positive vs. Mst1-negative breast cancers. Patients with positive expression of Mst1 had a significantly better overall and disease free survival (P <0.0001) (fig. 1A, B). Univariate Cox analysis indicated that Mst1 positivity had a significant difference in overall survival in breast cancer patients (P = 0.010). In multivariate Cox analysis, Mst1 positivity maintained significance as an independent prognostic factor in breast cancer (*P* = 0.002).

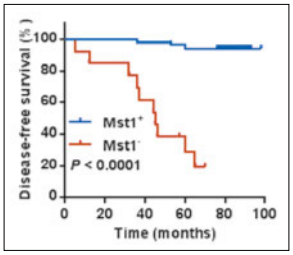

Figure 1A

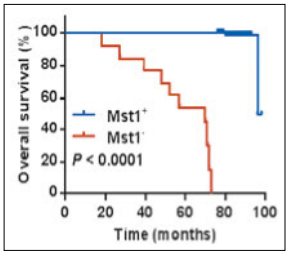

Figure 1B

Conclusion: We were able to demonstrate that Mst1-positive patients had a significantly better overall and disease free survival and that Mst1 is an independent prognostic factor in breast cancer. Our methodological concept facilitates a direct translation into clinic, as it is easy, feasible, exact and much less biased than immunohistological estimations. Also, the sampling (plasma) is incomparably more attractive for daily routine and patients' comfort. We suggest a novel way to assess Mst1-levels in breast cancer patients, which can be used to predict prognosis and therapy response, and may present potential opportunities in breast cancer therapy.

P405

Large pericardial effusion and pulmonary involvement in a patient with eosinophilia – two severe symptoms of a rare disease

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Introduction: Blood eosinophilia and tissue eosinophilia can be caused by numerous diseases that include infectious, allergic, neoplastic, primary hematologic disorders and other reasons like medications. To identify the cause is a challenging problem. The identification of organ involvement by eosinophils is important to prevent severe and life-threatening complications.

Case report: A 52-year old woman with marked persistent eosinophilia, cough and fever episodes every two to three weeks was admitted to our hospital for further evaluation. The chest x-ray showed an enlarged heart. Blood tests showed a severely elevated blood eosinophilia of 75% (absolute 11 G/l) (fig. 2). Abdominal ultrasound, gastroscopy and colonoscopy showed no organ manifestation. Results for HIV, parasites and a rheumatological screening were all negative. The transthoracic echocardiography and CT scan of chest (fig. 1) showed a large pericardial effusion. After puncture (700 ml) just three days later the pericardial effusion filled up again. The cytological examination showed no malignant cells but also lots of eosinophils, as did the investigations of the lung (broncho-alveolar lavage and biopsy). A bone marrow punction showed a slight hypercellularic blood forming bone marrow with overcome of eosinophils as can be seen in an early phase of an eosinophilic leukaemia or an idiopathic hypereosinophilic syndrome. The genetic results showed no positive results for associated myeloproliferative neoplasms. The idiopathic hypereosinophilic syndrome is an exclusion diagnosis and we assume in our case, because we found no other reason, that´s the most likely diagnosis. Because of the large pericardial effusion and marked persistent eosinophilia and pulmonary involvement we started with an immunosuppressive medication (prednisolone). Just ten days after the eosinophilic blood count normalized (fig. 2) and under the therapy echocardiographically no pericardial effusion was seen anymore.
Conclusion: Marked persistent eosinophilia is a diagnostic dilemma and identifying the cause is a challenging problem. A systematical approach can help to detect organ involvement and thus prevent of ongoing severe organ damage.

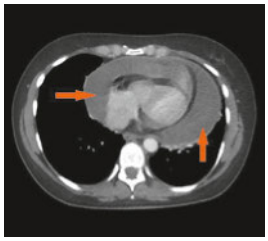

Figure 1: Large pericardial effusion in CT scan.

Figure 2: Count of Eosinophils in peripheral blood.

P406

Early readmissions after medical rehabilitation

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Introduction: Early readmissions (occuring within 30 days after discharge), are frequent and costly events. They have been investigated in several settings, but data after medical rehabilitation are scarce. Levels of comorbidity and functional impairment have been suggested to be associated with early readmissions. Since 2014 rehabilitation structures in Switzerland are requested to collect both comorbidity measured by the Cumulative Illness Rating Scale (CIRS) that assesses on a 4 level scale the severity of the diseases affecting 14 organic systems; and functional impairment measured by Functional Independence Measure (FIM scale) for the building of a national tariff structure. We took this opportunity to examine whether these validated scales are, actually, related with early readmissions.
Methods: Data concerning patients admitted in two medical rehabilitation services were extracted from the information system of the Geneva University Hospitals. Only patients discharged towards

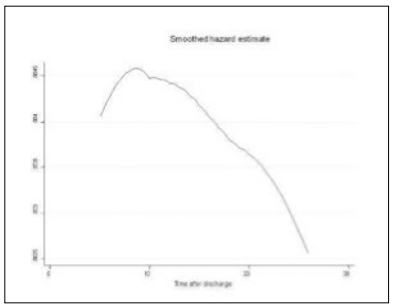

Figure 1: Early readmissions dynamics.

their own home were included. Any new hospital admission occurring within 30 days in any of the structures of the Geneva University Hospitals after discharge was considered as an event. If patients were hospitalized several times during the observation period, only the first stay was considered. Survival analysis methods were used for describing readmission dynamics and assessing which variables were associated with the failure events.
Results: During the years 2014 and 2015, 3374 patients were included in the analysis. Among them 424 (11.2%) were readmitted within 30 days, of which half of them being readmitted within 13 days. The risk of readmission was at its peak 9 days after discharge of the index stay, decreasing steadily after.

Table: Variables associated with early readmissions.

Variable	Hazard Ratio	95% CI
Age (per additional year)	0.99	0.98–1.01
Sex (M vs. W)	1.08	0.76–1.54
CIRS scale at admission of index stay (per additional point)	1.03	1.01–1.06
FIM scale evolution during index stay (per additional point)	0.99	0.99–1.01

Comorbidity was the only variable significantly associated with an increased risk of early readmission.
Discussion: The dynamics of early readmissions in medical rehabilitation was not different from the one observed in general internal medicine. In this study, we did not make a distinction between planned and unplanned readmissions. However, people returning home after medical rehabilitation are rarely planned for additional investigations or procedures. Comorbidity was the only dimension associated with early readmissions. The distinction between avoidable and unavoidable readmissions should be further investigated as the former may be related with quality of care.

P407

Interprofessionnal training in "Breaking bad news" with simulated patients: participants' satisfaction

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Background: Breaking bad news is a stressful situation for patients, their family and also caregivers. This difficult task needs many skills such as communication and interprofessionalism. These two skills are increasingly taught in Swiss University. However, only a few practical courses exist for physicians and nurses during postgraduate and practice years. A program has been tested for five years at Lausanne University Hospital. It gives caregivers the opportunity to practice breaking bad news in pair, namely physician and nurse, with simulated patients. We aimed to assess the satisfaction of the participants.
Methods: From 2011 to 2016, 35 practical courses were given to 3–11 participants each. Physicians (including students in practical years) and nurses participated after achieving a 1.5 hour theoretical course. Each four hours practical course contains two to three 15 minutes long scenarios, with simulated patients. These are replayed up to twice and feedback is given. All participants received a questionnaire with 14 items and the possibility to add comments. Three items of applicability/ transferability, personal achievement and tailored/personalised teaching were evaluated . We regrouped the free comments into four main themes.

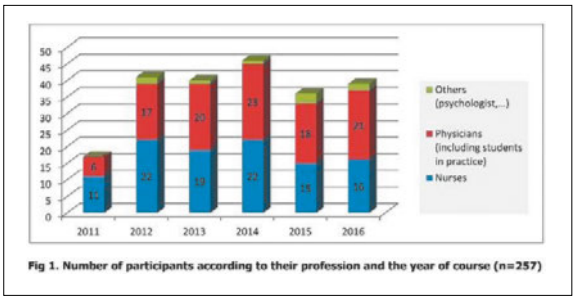

Fig 1. Number of participants according to their profession and the year of course (n=257)

Figure 1

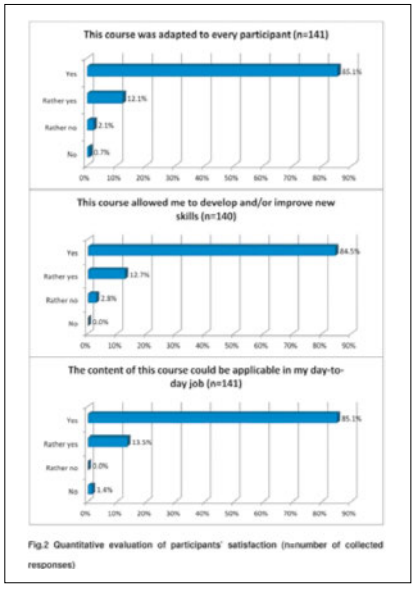

Fig.2 Quantitative evaluation of participants' satisfaction (n=number of collected responses)

Figure 2

Results: Of 257 participants, 136 were nurses (52.9%), 112 physicians (43.6%) and 9 were from other fields such as psychologists (3.5%) (fig. 1). 142 assessments (55%) were obtained, anonymised and analysed. Of the three items evaluated all were highly accepted (fig. 2). The evaluations' qualitative analysis permitted the extraction of the following main four themes: 1/ the course could be longer and might be offered periodically as continuous training (refresh courses); 2/ the high quality/fidelity of the simulated patients: 3/ the particularly adapted scenarios (timeframe and contents) which were transferable to the participants day-to-day reality and 4/ the development of interprofessionnalism as a strong new skill.
Conclusions: Interprofessional training in "breaking bad news" with simulated patients gives high satisfaction to pairs of physicians and nurses. However, few have the opportunity to attend, depending on the number of sessions. Larger resources could improve attendance rates. Further research is needed to measure the efficacy of this training on participants' skills improvement and patient's satisfaction.

P408

Hypercalcemia – an uncommon summation of causes

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Introduction: Hypervitaminosis D and milk alkali Syndrome both are rare causes of hypercalcemia. We present a case with severe hypercalcemia due to these two causes in combination.
Case report: A 52 year old mental coach presented with a right-sided paroxysmal headache since 3 days, global muscle weakness, great thirst and polyuria. He denied taking any medication. Blood tests showed severe hypercalcemia with suppressed parathyroid hormone, very high 25-OH and elevated 1,25-OH-vitamin D3 levels and acute kidney injury. Computed tomography of the chest and abdominal sonography were unremarkable, free light chains in serum were normal. No evidence was found for a parathyroid-independent extrarenal calcitriol production like a granulomatous disease or malignancy. Intravenous saline hydration was started. After two days we added Torasemid 5 mg/d for 5 days. Because of the slow regression of calcium we applied intravenous Pamidronate (Aredia) 60 mg once. Interrogated again the patient specified the substances he took with a view to purification and encouraging health. He took every day four capsules of WLS Vitamin D3 containing 50.000 units of vitamin D3 for at least two weeks. For the same duration he consumed 2 teaspoons/day of alkaline supplements (Basenpulver Herbamed) against overacidification. Although he denied eating large amounts of milk products we witnessed him consuming up to 4–6 yoghurts a day during hospitalisation. Following hospitalization, serum calcium and renal function normalized slowly but hypervitaminosis D persisted very long. More than 3 months later 25-OH vitamin D3 level was still above 418 nmol/l.
Conclusion: Hypercalcemia with consecutive kidney injury due to vitamin D intoxication is rare because very high doses are necessary. Consumption of large doses of vitamin D (50,000 IU/d) for 8 weeks in

young men did not change their calcium levels significantly. Therefore, we assume that the ingestion of Basenpulver and milk products (resulting in a milk alkali syndrome) enhanced the hypercalcemia. It is alarming that over the counter vitamin products which are supposed to benefit health are sold with no recommendation of exact daily or maximum dosage and no warning for intoxication symptoms. Patients do not consider vitamins or food supplements as medication. Therefore they often do not specify them when asked and do not fear side effects. Thus, it is very important to ask patients specifically for vitamins or food supplements.

P409

Drug rechallenging and an unlucky acute generalized exanthematous pustulosis manifestation

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Drugs sides effects especially antibiotics side effects are often misdiagnosed and classified as allergy. Drug allergy is reported in 20–40% of patients in the USA but close to 95% is not a real allergy. The most recent guidelines stress about reintroduction of antibiotics in patients with possible but not confirmed past drug reaction. Penicillin allergy histories are more likely to be rechallenged with the same or similar medication in the future, especially if Penicillin is the preferred therapy. Antibiotic reintroduction challenging is crucial even if adverse events may happen. Acute Generalized Exenthematous Pustulosis (AGEP) is a rare severe T-cell mediated drug reaction with an incidence of 1–5 par million/year. AGEP is characterized by acute formation of sterile pustules on erythematous background, fever and neutrophilia. We reported a case of a 68 years old male patient hospitalized for a dermohypodermatitis with a reported unspecific cutaneous rash after Amoxicillin administration in 1980. Amoxicillin+clavulanic acid was the preferred antibiotic to treat the recent infection. Forty-eight hours after first dose administration, the patient quickly developed a diffuse erythema with several follicular pustules suspected for AGEP with diagnostic score at 8 (EuroSCAR) (Image 1 and 2). Causative drug was immediately removed and antibiotic change was provided. None of systemic omplications of AGEP had been observed. Cutaneous test had been done 6 weeks later and confirmed Amoxicillin allergy. Our unlucky experience must not discourage antibiotics rechallenging. Penicillin allergy encompass different hypersensitivity reactions. Past history with antibiotics should be interpreted carefully in order to give opportunity to rechallenge patients with antibiotics.

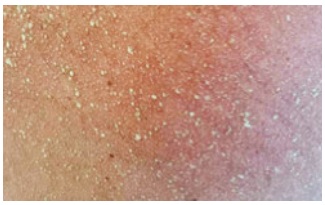

Figure 1

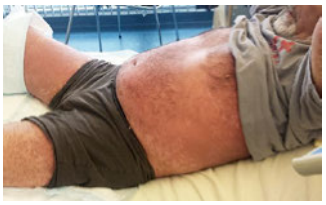

Figure 2

P410

Protocol of the Swiss Longitudinal Cohort Study (SWICOS) in rural Switzerland

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Introduction: Increased longevity and consequent major changes in demographics and population lifestyles necessitate new approaches to reduce the burden of aging-related diseases (including CVD) and maintain an optimal quality of life. This study aims to examine and longitudinally follow health status and disease risk factors in a Swiss rural cohort, evaluating all health related research and practice disciplines to assure development of new implementable and successful preventive strategies for healthy aging.
Methods: Small villages of rural regions in Switzerland with low migration rates have been selected for this longitudinal prospective study. All residents (age ≥6 years, no upper age limit) are eligible. Target enrolment number per village is 300. Examinations and measurements encompass medical history, anthropometry, cardiac and vascular health, pulmonary function, physical performance, nutritional, mental and emotional status, biochemical and molecular analyses. Follow-up examinations (identical to baseline) will be performed after 5 and 10 years, and in 10-year intervals thereafter.
Results: In the first participating village, more than 300 participants have been enrolled so far. Enrollment will start in a second participating village in 2017.
Conclusions: This study will allow to: (1) identify "hidden" (asymptomatic and/or unrecognized) health problems which enhance risk for chronic diseases; (2) identify barriers to accessing health care and adapting health behaviours; (3) evaluate efficacy of present preventive strategies and recommendations; (4) evaluate knowledge and attitude towards ongoing health programs and public health recommendations; (5) monitor change and progress towards the national health objectives; (6) formulate new preventive strategies and recommendations based on the findings and knowledge base of the last 10 years; (7) formulate models for successful prevention of chronic diseases and for healthy aging.

P411

Summertime swimming in the lake of Zurich suddenly turning into shortness of breath and hemoptysis

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Case report: A 66 year old male presented with acute onset of shortness of breath NYHA IV, coughing and hemoptysis. Spending a summer afternoon together with his wife and grandchildren at the lake of Zurich, the symptoms began after having swum about 200 meters. Ambient and water temperatures were around 20.0 °C. He had no relevant past medical or allergic history. He denied submersion injury or aspiration. His initial oxygen saturation was 89% with normal blood pressure. A respiratory examination showed bilateral crackles. Laboratory findings included a normal arterial blood gas analysis and electrolytes, a pro-NT-BNP within normal limits and a slightly elevated troponin1 of 84 ng/l (<57 ng/l). Resting ECG did not show any signs of acute ischemia and echocardiography showed normal ejection fraction with normal wall motility. A thoracic computed tomography scan showed bilateral ground glass opacities in the peripheral lungs. We initiated treatment with furosemide intravenously. Symptoms of pulmonary edema resolved within 24 hours. We diagnosed swimming induced pulmonary edema (SIPE) because of typical clinical manifestation and complete remission of symptoms after very short duration. Slightly elevated troponin was interpreted secondary to possible elevated pulmonary arterial resistance during SIPE with normal ECG and returned to baseline within two days.
Discussion: The etiology of acute pulmonary edema is interpreted as fluid movement into the alveoli secondary to alteration in one or more of Starling's forces. The exact mechanisms of SIPE, however, remain unclear. It has been hypothesized that immersion elevates cardiac output for a given oxygen consumption and increases preload and thus leads to capillary leakage.
Conclusion: In the setting of acute onset of dyspnea and coughing after swimming exercise and without notable co-morbidities, SIPE is an important differential diagnosis. Risk factors for developing SIPE have been identified as exposure to cold water, arterial hypertension, overhydrating, female gender and previous episodes of SIPE. SIPE is frequently a self-limiting condition, prognosis is good with supportive treatment only.

P412

Effectiveness of lipid-lowering therapy in a hematopoietic stem cell transplant cohort

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Introduction: Hyperlipidemia is frequently observed in patients after hematopoietic stem cell transplantation (HSCT), but is often undertreated. With a growing appreciation of the elevated incidence

of cardiovascular complications in these patients, the use and effectiveness of lipid-lowering therapy is of great interest.
Methods: A retrospective, single center cohort study with a total of 1196 patients (>16 years) who underwent a first autologous or allogeneic HSCT at the University Hospital Basel from 1973 to 2013 and survived >100 days after was performed. Patients were grouped according to the type of their first HSCT (autologous or allogeneic) and follow up was censored if a subsequent HSCT of the other type was performed. For the examination of the effectiveness of the therapy, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglyceride (TG) values before and a minimum of 30 days after start of treatment were analyzed. The frequencies of prescriptions of different drugs were further examined.
Results: A total of 223 patients (18.7 %) received any kind of lipid lowering therapy at any time point during the follow-up time, 33 of which (14.8 %) were already treated at baseline. 53 patients (23.8%) underwent at least one autologous, 170 (76.2%) at least one allogeneic HSCT (11 and 16 of them more than one, respectively).

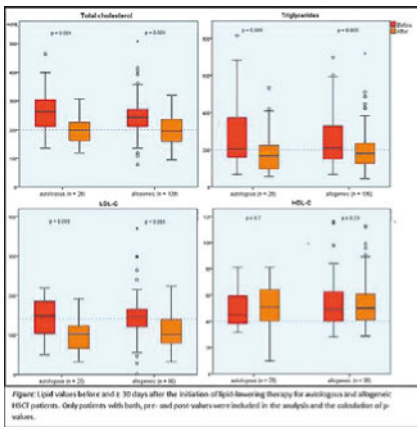

Figure 1: Lipid values before and after therapy.

Median age at first transplantation was 60 (IQR 48.8–64.3) and 47 (IQR 36.7–56.1) years for autologous and allogeneic patients, 66 and 64% were males respectively. Median follow-up time was 6.3 in the autologous and 9.8 years in the allogeneic group with a maximum follow-up time of 26.1 and 35.0 years and median time to initiation of lipid-lowering treatment was 1.2 years in the autologous and 4.1 years in the allogeneic group (p <0.001) with a maximum delay of 16.5 and 32.4 years, respectively. A highly significant reduction of TC, LDL-C and TG-levels was observed, while no change in HDL-C-levels occurred (fig.). No difference in terms of the amount of reduction was found when autologous and allogeneic HSCTs were compared. Statins accounted for the great majority of drugs used (85.2 %) with atorvastatin being the most commonly prescribed (Table).
Conclusion: Lipid-lowering therapy leads to a significant reduction of TC, LDL-C and TG levels irrespective of the type of transplantation. Therapy was started significantly later among patients who received an allogenic transplantation.

	Prescriptions[1]	%
Atorvastatin	147	50.5
Fluvastatin	3	1
Melovastatin	1	0.3
Pravastatin	30	10.3
Rosuvastatin	34	11.7
Simvastatin	31	10.7
Unknown statin	2	0.7
Bezafibrate	1	0.3
Fenofibrate	30	10.3
Ezetimibe	9	3.1
Orlistat	1	0.3
Herbal drug	1	0.3
Unknown	1	0.3
	291	

Table: Lipid-lowering drugs used in the cohort. Combinations of drugs were possible.
[1]Dose-changes were not considered as a new prescription, whereas a new start of the same medication with a pause > 1 month was counted again.

Table: Drug Prescriptions.

POSTERTOUR 3: MÉDECINE SPECIALISÉE IV / FACHMEDIZIN IV

P413

The relation of bloodpressure and target organ damage in the Swiss hypertension cohort study

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Introduction: Arterial hypertension is widely spread. Previous studies have shown an association between elevated blood pressure and target organ damage (TOD). The aim was to analyze differences between TOD groups regarding systolic and diastolic office blood pressure (SOBP, DOBP) across follow up. Further, patients who developed symptomatic TOD during study period were compared with patients not developing TOD focusing on blood parameters at baseline (BL).
Methods: The Swiss Hypertension Cohort Study was a prospective observational study recruiting patients in primary care between 2006 and 2013. Patients eligible had to be ≥18 years old. TOD was defined as myocardial infarction, coronary artery disease, revascularization, stroke/TIA, heart failure, arterial obstructive disease, stenosis of the carotid arteries, a glomerular filtration rate ≤30 ml/min and retinopathy. Asymptomatic TOD was defined as left ventricular hypertrophy in the ECG or echocardiographic, chronic kidney disease with GFR 30–60 ml/min, microalbuminuria (30–300 mg/24h), an elevated fasting blood glucose level (>6.9 mmol/l) or postprandial blood glucose >11 mmol/l or HbA1c>7% or carotid stenosis.

Results: The mean age of the cohort at BL (n = 1004) was 64 years (SD = 13.22), 55.6% were male. At baseline 49% (n = 489) had no TOD, 30% (n = 300) had asymptomatic TOD and 21% (n = 214) had symptomatic TOD. During study period, 32 patients developed a new symptomatic TOD. We found that DOBP significantly differed across hypertensive TOD groups at various time points indicating lower DOBP with increasing TOD (see fig. 1).

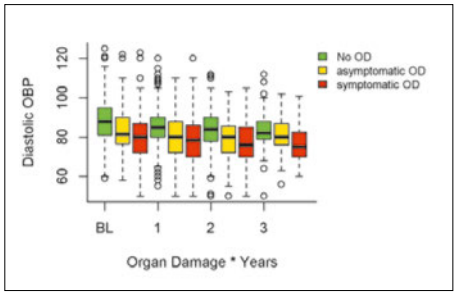

Figure 1: DOBP over follow up and TOD categories.

This effect was less pronounced in SOBP where lower SOBP was only observed in the group of symptomatic TOD at BL (see fig. 2). Further, patients who developed a symptomatic TOD during study period had lower HDL cholesterol (median = 1.2 vs 1.36 mmol/l, p =

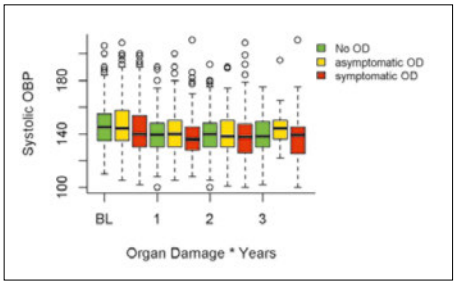

Figure 2: SOBP over follow up and TOD categories.

0.012), higher creatinine (median = 82.0 vs 77.75 p = 0.049), higher uric acid (median 434 vs 338 umol/l, p = 0.005) and lower DOBP (median 78 vs 86 mm Hg, p <0.001) at BL compared to patients without or asymptomatic TOD.
Conclusions: Results indicate that a low DOBP is a predictor of TOD. This could be the case because of decreased coronary perfusion during diastole. Further analyses are needed to disentangle the effect of confounding parameters such as age and pharmacological blood pressure therapy. Several studies suggest that a too low DBP is associated with elevated morbidity and higher rates of TOD.

P414

A rare cause of acute kidney failure after abdominal surgery

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A 48-year-old woman was admitted with acute right sided, colicky type of flank- and abdominal pain and acute oliguric renal failure 6 days after uneventful, laparoscopic Hyster- and Salpingectomy including peritoneal resection of endometriosis. Upon admission she was afebrile with a normal blood pressure of 143/89 mm Hg and a heart rate of 109/min. Blood and urine tests showed an elevated creatinine of 381 µmol/l, a CRP of 35 mg/l, a hematuria of non- glomerular origin, unselective glomerular proteinuria and significant leucocyturia. A complete blood count and electrolytes were within normal limits. Due to her past medical history of symptomatic kidney stones, imaging studies were performed (Ultrasound, CT), showing no sign for urinary tract obstruction including nephrolithiasis or urolithiasis. A pre-renal cause of acute renal failure seemed unlikely as volume status and blood pressure were normal and fractional excretion of sodium was >1%. She had taken Ibuprofen as a postoperative analgesic but stopped 3 days prior to admission. Due to suspected urinary tract infection treatment with ceftriaxone was initiated but stopped after urine cultures came back negative. As creatinine further increased and the patient became anuric a renal biopsy was performed which showed normal kidney tissue. Shortly before initiating hemodialysis on day 4 normal urine production resumed and creatinine values dropped to a normal value of 67µmol/l within the next 4 days. In the context of this patient's abdominal surgery, the above mentioned normal investigations and the spontaneous recovery of renal function we postulated that reflex anuria (RA) was the most likely cause of this patient's acute renal failure. RA is a rare phenomenon of an acute functional but not structural renal impairment from both kidneys as a reaction to irritation or trauma to one kidney, its ureter or severely painful stimuli to other organs. The pathogenesis is not entirely understood. Various different reflex mechanisms are described in the literature leading to an intrarenal arteriole or ureteral spasm causing colicky type of flank pain which was also present in our patient. The therapy of RA is to eliminate painful stimuli which we also successfully implemented in our patient. In conclusion in patients with unexplained anuric renal failure, particularly after urogenital or gynaecological surgery, RA should be kept as a differential diagnosis.

P415

Characteristics and outcome of migrant patients without a stable resident status starting hemodialysis in a Swiss university hospital center

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Background: Migrants without permanent resident status is a vulnerable population in regards of medical care. They frequently present with chronic medical conditions, including Chronic Kidney Disease (CKD). In this work, we analyzed the characteristics and the outcome of migrant patients starting chronic hemodialysis in our center.
Methods: Migrant patients without a stable resident status in Switzerland were retrospectively identified among patients who started hemodialysis between 2000 and 2014 in the hemodialysis center of the University Hospital of Geneva. Demographic and medical data were recorded by reviewing their medical records.
Results: Among 594 patients starting hemodialysis, we identified 29 migrant patients (4.9%, 1.93 patients per year) of whom 15 came from Africa, 2 from South America, and the 12 others from Eurasia. Eighteen were asylum seekers, 3 had a tourist visa, and 8 were undocumented. Compared to the local Swiss resident, migrant patient were younger (mean age 44 vs. 52 years), more of femal gender (55% vs. 45%) and had less cardiovascular comorbidities. Two thirds of the patients had vascular and diabetic causes for End Stage Renal Disease and 34% were smokers. Seven patients were already hemodialyzed before arriving in Switzerland. Seventeen obtained a permanent resident status, 5 are still waiting for regularization, 4 left Switzerland and 2 were lost to follow-up. Among the 22 patients who stayed in Switzerland, 2 died while on hemodialysis, 11 were transplanted of whom one died accidentally after being transplanted and 9 were still on hemodialysis. Mean time from first dialysis in our country to transplantation was 268 ± 126 weeks.
Conclusions: In our center, nearly 2 migrant patients per year start hemodialysis without a permanent resident status in Switzerland. They are significantly younger and more often women, and had less cardiovascular comorbidities than our permanent Swiss resident patients. Sixty-six percent obtained a permanent resident status and 38% received a renal transplant.

P416

Anti-GBM antibody (Goodpasture's) disease

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Introduction: Anti-glomerular basement membrane (GBM) antibody disease is rare, with an estimated incidence of 0.5 to 0.9 cases per million per year in Caucasian populations. The disease is caused by autoimmunity to the NC1 domain of the α-3-chain of type IV collagen and leads to rapidly progressive (crescentic) glomerulonephritis and pulmonary haemorrhage. The prognosis of untreated anti-GBM antibody disease is extremely poor.
Case report: A 55-year-old male smoker was admitted with pulmonary haemorrhage since 6 weeks. X-ray showed diffuse pulmonary infiltrates, CT scan demonstrated multiple nodules as well as ground glass opacities, and the performed bronchoscopy verified alveolar haemorrhage. Renal workup showed a moderate insufficiency and glomerular haematuria. Together with demonstration of anti-GMB-antibodies the diagnosis of anti-GBM antibody (Goodpasture's) disease was made. The patient was transferred to a tertiary care hospital. The patient was treated with steroids, cyclophosphamide, and plasma exchange. Pulmonary haemorrhage improved rapidly and glomerular filtration rate (GFR) returned to normal. Due to thrombocytopenia kidney biopsy was refused.
Discussion: Pulmonary haemorrhage and rapidly progressive (crescentic) glomerulonephritis are clinical hallmarks of anti-GBM disease. Anti-GBM antibodies are almost present and the antibodies level correlates with the severity of nephritis. Although X-ray and CT-scan can demonstrate pulmonary involvement, an increased uptake of inhaled carbon monoxide (D_LCO) is the most sensitive indicator of recent pulmonary haemorrhage. Patients with lung pulmonary haemorrhage are often current smokers. Kidney biopsy,

unless contraindicated, shows linear deposition of IgG along the GBM. Plasmapheresis removes circulating anti-GBM antibodies and is accompanied by corticosteroids as well as cyclophosphamide. The risk of recurrence is low.
Conclusion: Anti-GBM antibody (Goodpasture's) disease is a rare and life-threatening disease. Concurrent treatment with plasmapheresis and immunosuppression is recommended.

P417

Limited knowledge about limitations of a laboratory parameter: physicians and HbA1c

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Background: Since discovery of HbA1c in the late 60ies and its implementation into clinical practice in the 70ies and 80ies of the last century, this parameter has become a hallmark of diabetes care. However, this test has limitations, and we conducted a questionnaire with key questions about laboratory test.
Methods: A survey using a questionnaire with five open questions was conducted: 1. HbA1c shows mean glucose values of what time period? 2. What exactly is measured by the test? 3. What is a normal value for HbA1c (diabetics)? 4. What circumstances may lead to false low HbA1c values? 5. What circumstances may lead to false elevated HbA1c values?
Results: 53 physicians participated (28 residents, 4 students and 20 senior physicians), all working in a department of internal medicine in hospitals of Switzerland. For question one, two and three, correct answers where given in 85, 85 and 55 % respectively. However, for question four and five concerning limitations of the parameters, correct answers where given only in 11 and 19 % respectively. With exception of question 1 (HbA1c shows mean glucose values of what time period?), no differences between junior and senior physicians were present.
Conclusion: Our survey shows a considerable lack of knowledge about limitations of a widely used laboratory test. This might reflect our general inadequate high confidence in laboratory tests.

P418

Denosumab disguises the true cause of severe and sustained hypophosphatemia in a patient with advanced prostate cancer

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Introduction: Concurrent hypophosphatemia and hypocalcemia are well known adverse events in treatment with denosumab, which is widely used in metastatic bone disease. Fibroblast growth factor 23 (FGF23) mediated tumor induced osteomalacia (TIO) is a rare paraneoplastic syndrome, leading to severe hypophosphatemia. Here, we present a patient with advanced prostate cancer, who developed hypocalcemia and severe, sustained hypophosphatemia after initiation of denosumab therapy, primarily masking the cause of phosphate (Ph) wasting, which in particular was due to FGF23 induced TIO.
Case report: A 79-year old man with bone and lymph node metastases from castration-resistant prostate cancer (mCRPC) presented with severe hypophosphatemia (0.2 mmol/L, normal range 0.8–1.5 mmol/L) and hypocalcemia (1.5 mmol/L, normal range 2.2–2.6 mmol/L). Treatment with abiraterone/prednisone and denosumab had been initiated three weeks earlier. Renal function was normal, parathyroid hormone (PTH) levels were elevated and levels of 25-OH and 1,25-(OH)2 vitamin D3 were normal with oral calcium (Ca) and vitamin D3 supplementation. Inadequately high renal Ph excretion without additional urinary electrolyte wasting was detected (Ph excretion fraction 24%). Treatment with high parenteral doses of Ca, Ph, oral 25-OH and 1,25-(OH)2 vitamin D3 normalized serum Ca- and PTH levels within one month. However, severe hypophosphatemia due to urinary Ph loss persisted despite high doses of Ph supplementation (6.9 g/d). Additional work-up revealed an elevated serum level of FGF23 (4 times above upper limit of normal). Ph and calcitriol supplementation was continued until the patient died from progressive prostate cancer 13 months later.
Conclusion: Denosumab induced hypophosphatemia was initially suspected in this patient with mCRPC. FGF23 induced hypophosphatemia is an uncommon but potentially life-threatening paraneoplastic syndrome most commonly found in mesenchymal tumors. Tumor induced osteomalacia in mCRPC is rare but may be underdiagnosed and should be considered in severe and sustained hypophosphatemia. Although clinical studies are lacking, several lines of evidence suggest that TIO may be associated with aggressive mCRPC behavior. FGF23 excess and severe hypophosphatemia may both contribute to a poor prognosis in affected patients. FGF23 receptor inhibitor treatment is under preclinical/clinical development and may be an approach to control TIO and the underlying malignant disease in the future.

P419

You eat with your eyes first: a case report

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Introduction: Nowadays bariatric surgery is an established treatment of morbid obesity. Since 2006 the number of interventions in Switzerland quintupled to more than 5000 operations in 2015. Long-term follow-up of these patients is critical and includes continuous assessment of nutritional status.
Case report: A 48-year-old women presented with progressive loss of vision and hemeralopia for 6 months. Her past medical history was remarkable for Roux-en-Y-gastric bypass (RYGB) 19 years ago and adjustable gastric banding 8 years ago. Due to psychiatric comorbidity, follow-up after surgery remained difficult and adherence to vitamin supplementation was insufficient. Ophthalmological examination revealed a clearly reduced visual acuity (OD 0.25, OS 0.16), bilateral papilledema (OD Frisén grade 3, OS grade 4), complete loss of color vision and severe xerophthalmia. Headaches and symptoms/signs of elevated intracranial pressure were absent, other differential diagnoses of papilledema (e.g. inflammatory, circulatory or neoplastic) were excluded by MR-imaging and lumbar puncture. However, laboratory analyses demonstrated severe deficiency of vitamin A (<0.07 µmol/L [reference range 1.05–2.45]), 25-OH vitamin D (36 nmol/L [75–220]), vitamin E (4.1 µmol/L [11.6–46.4]) and zinc (7.2 µmol/L [9.0–26.0]). Oral substitution with vitamin A 25'000 IU, vitamin E 400 IU, and vitamin D 800 U per day was initiated together with multivitamin and trace element supplementation. 8 weeks later ophthalmological follow up showed remarkable improvement of vision (OD 1.0, OS 0.64), hemeralopia, xerophthalmia, color vision and partial improvement of papilledema.
Comment and conclusions: Vitamin A is an important co-factor for corneal and conjunctival development, retinal phototransduction, prevention of xerophthalmia and function of the central nervous system. Commonly, hypervitaminosis A is associated with pseudotumor cerebri-like syndromes with papilledema, but hypovitaminosis A as a contributing factor has been also described. Intestinal resorption of lipophilic retinol is regulated by several factors: Exocrine pancreatic function, bile salt secretion, intestinal postabsorptive mechanisms and retinol-binding protein whose synthesis is zinc-dependent. Bypassing the proximal small intestine in RYGB leads to malabsorption syndromes which can be severe and develop insidiously as shown in our Patient.

P420

Epidemiological and diagnostic profile of diabetic retinopathy in an internal medicine department

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Introduction: Diabetic retinopathy is a serious and frequent degenerative complication of diabetes responsible for blindness and low vision throughout the world, which is why screening should be systematic and early. Our study aims to specify the frequency of diabetic retinopathy (RD) And its epidemiological and clinical profile in diabetic patients followed in an Internal Medicine department.
Methods: This is a retrospective study involving 200 diabetics, followed by the internal medicine department E.P.S.P.Ghoualem (Oran). All patients underwent complete ophthalmologic examination.
Results: Diabetic retinopathy was objectified in 30% of cases. There were 10 men and 50 women. The mean age was 57.5 years and the mean duration of diabetes was 9.15 years. The mean HbA1c is 10.8%. Retinopathy was classified as minimal in 14%, moderate in 10%, severe in 2%, and proliferating in 4% of cases. 10 patients have nephropathy among whom 4 patients have RD. Dyslipidemia is present in 60% of cases. Our patients with retinopathy were under oral antidiabetics (ADO) in 30% of cases, insulin in 60% and 10% in ADO + insulin therapy. Diabetes was type 2 in 81.4%, type 1 in 9.5%. Diabetic retinopathy was asymptomatic in 82% of cases, visual

blurring occurred in 17.6% (8) and visual acuity decreased in 0.4%. The treatment was based on hygiene-dietetic rules, the intensification of antidiabetic treatment and optimization of insulin therapy aiming at a glycemic balance with glycemic objectives adapted to each case. 20 patients required laser photocoagulation.
Conclusion: Diabetic retinopathy increases with the duration and poor setting of diabetes. Optimal glycemic control and regular ophthalmologic examination are important therapeutic weapons in reducing the incidence of diabetic retinopathy.

P421

GLP-1 Analogs for the treatment of postprandial hyperinsulinemic hypoglycemia after gastrectomy – a novel therapeutic option?

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Introduction: Severe postprandial hypoglycemia is a well-known if rare phenomenon in patients after gastrectomy for any indication. Since bariatric surgery is the most effective available treatment to achieve sustained weight loss in obese patients the number of procedures is increasing and more patients suffer from adverse effects including postprandial hypoglycemia. Pathogenesis is not fully understood; presently treatment is based on dietary advice and a variety of compounds. In 2013 Abrahamsson published case reports of patients suffering from significant postprandial hypoglycemia treated with liraglutide, a GLP-1 agonist. We present two cases responding to once-weekly GLP-1 agonists exenatide slow release and dulaglutide.
Methods and results: Case 1: A 51-year-old patient suffers from gastrointestinal stroma tumor (GIST) first diagnosed 12 years ago. In two steps she underwent gastrectomy and esophagojejunostomy. The GIST is controlled with Imatinib. For the past 9 years she suffered from daily hypoglycemic events including several instances of unconsciousness and seizures. Treatment with dulaglutide led to cessation of symptoms. We used continuous glucose measurement (CGMS, images 1 and 2) before and after the intervention to demonstrate the effect of the drug. **Case 2:** A 42-year-old, man with obesity stage III (BMI 41.6 kg/m^2) had Roux-en-Y gastric bypass surgery six years earlier. Ever since he suffered from multiple neuroglycopenic episodes including several times hypoglycemia induced seizures. Dietary education and a trial with hydrochlorothiazide did not improve his situation. We started him on exenatide slow release. There was no further event while on the drug. CGMS to document hypoglycemia off the drug could not be written, the patient did not want to discontinue the treatment for this purpose.
Discussion: Bariatric interventions lead to increasing numbers of patients with the uncommon but potentially debilitating complication of severe postprandial hypoglycemia. Excessive incretin answer to glucose stimuli is thought to be partially responsible. Treatment with GLP-1 is therefore counterintuitive. Published case reports and our own limited experience seem to indicate that there is a place for GLP-agonists in this situation. Further studies will be necessary to elucidate the mode of action and to determine the validity of the approach in clinical practice.

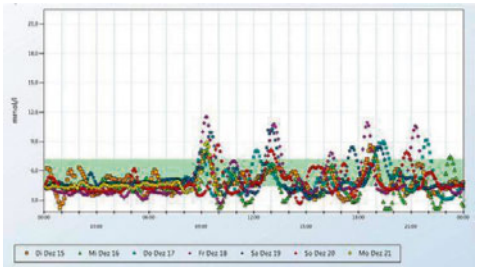

Figure 1

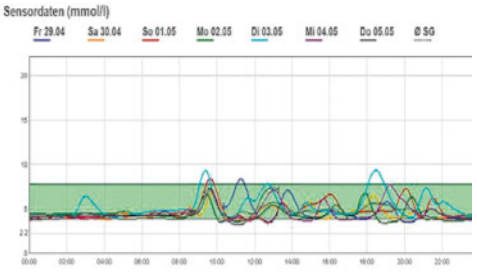

Figure 2

P422

Prolactinoma, an often missed cause of hypogonadism in man

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Introduction: Prolactinomas are the most frequent type of pituitary adenomas. Hyperprolactinaemia in man induces central hypogonadism, but decreased libido as initial symptom is often dismissed and diagnosis delayed until symptoms as headache, visual impairment or hypopituitarysm appear. The occurrence of sudden headache, diplopia, visual field defects, nausea and vomiting should suggest pituitary apoplexy as a result of an unrecognized pituitary adenomas.
Case report: A 43-year-old male suffering from recurring vomiting, nausea and diplopia when looking upwards since several days presented in our emergency service. He reported long-standing loss of appetite paradoxically accompanied by weight gain, diffuse symmetrical face and neck swelling and episodic headaches for several months with currently increasing frequency. He referred testosterone deficiency since 2006 treated with Nebido (Testosterone) every 4 weeks. In the physical examination he had ptosis, incomplete oculomotor palsy on the right, bitemporal hemianopsy and slight edematous swelling of the skin. Laboratory testing revealed severe hypoosmolar hyponatremia (119 mmol/l) due to hypocortisolism (<40 nmol/L; 101–536 nmol/l), central hypothyroidism (fT4 <5.2 pmol/L; 9.0–19.1 pmol/L) and hyperprolactinemia (4807 mU/L; 45–230 mU/L). MRI showed subacute bleeding in a cystic intra- and suprasellar pituitary adenoma (2.3×1,9×1.4 cm) with infiltration of the cavernous sinus, elevation of the chiasm and optic nerve and affection of the oculomotor nerve on the right consistent with hemorrhagic apoplexy of a macroprolactinoma. We initiated substitution with Hydrocortison and Levothyroxin and started dopaminagonist therapy with Cabergolin. Furthermore, sellary pressure was released by transphenoidal surgery. Sodium concentration increased rapidly, Prolactin dropped and four weeks later, ptosis and incomplete oculomotor palsy completely resolved. Testosterone withdrawel failed, therefore it was reintroduced by transdermal application.
Conclusion: Particulary in men with unexplained gonadal dysfunction, prolactin should be measured. In patients suffering from sudden headache, vomiting and diplopia pituitary apoplexy should be considered. In case of a hypoosmolar hyponatraemia, which simulates SIADH (syndrome of inappropriate antidiuresis) cortisol determination should be carried out.

POSTERTOUR 3: MÉDECINE SPECIALISÉE V / FACHMEDIZIN V

P423

Patients with diabetes and chronic kidney disease: an interdisciplinary program to support medication adherence (PANDIA IRIS STUDY)

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Introduction: Despite effective treatments, 30% of diabetic patients (type 2) develop kidney disease over time. A diabetes-kidney **interdisciplinary program** was set up by the Lausanne University Hospital (CHUV) and the PMU (*Policlinique Médicale Universitaire*). A novel medication adherence program is part of this approach. The purpose of the study is to assess the impact of the medication adherence program on the long term medication adherence and clinical outcomes of patients with diabetes and chronic kidney disease.
Design: One-center, prospective, randomized study (6- vs. 12- month intervention).
Intervention: usual medical consultations (every 2–3 months) will be preceded by a 20 minutes interview with a pharmacist. The interview is semi-structured with a motivational feedback based on the adherence data. Adherence will be measured using electronic pillbox (gold standard). A report of the interview will be sent to the physician(s) and the nurse(s). Group A (n = 35) will benefit from this program during 12 months and group B (n = 35) during 6 months. At the end of the intervention, the interviews will be interrupted but the medication adherence will continue to be monitored electronically (tot. = 24 months).
Inclusion criteria: Patients of either gender aged ≥18 years; type 2 diabetes; chronic kidney disease (estimated MDRD-eGFR ≤60 ml/min/1.73 m^2 or albumin/creatinin >30 mg/mmol); complete exams performed within the previous 6 months.
Outcomes: Electronic medication adherence (longitudinal data) during 24 months; ADVANCE score (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and UKPDS score (United Kingdom Prospective Diabetes Study) at baseline, 6 months and 12 months post-intervention; patients' satisfaction.
Results: The inclusions started in April 2016. Currently, 13 patients are included in the program; 10 refused to participate. The reasons for refusal are: the use of the pillbox, perceived as too complicated (n = 5); too many appointments (n = 2); complex social and economic situation & difficult to change pharmacy (n = 1); not interested unless paid (n = 1); no time (n = 1); refuses any study (n = 1).
Conclusion: Pilot phase shows that the study is feasible; Pharmacists, physicians and nurses involved in the program are showing interest and are pro-active in the inclusion process.
The abstract was presented at the Forum Managed Care (Bern, 15.06.2016)

P424

Emergency departement activity and summer temperature: on overwiev of the last decade

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Background: In 2015, during the most hot period of the heat wave, we have observed an increased trend in the number of consultation by the emergency department of Public Hospitals of Southern Switzerland, compared to previous years (2013 e 2014) [1]. However this hypothesis has been verified based on a short period of time (12 days). We therefore decided to study the phenomen on several months and over a period of more than 10 years excluding the two hospital sites where the activity could be influenced by the flow of a large number of tourists.
Aim: The aim of the study was to verify a correlation between the measured temperatures and the number of registered accesses by the emergency department, over a long period of observation.
Methods: We prospectively collected the number of emergency department visits and mean daytime atmospheric temperature for the summer months (July to August) from 2004 to 2015 in Bellinzona Regional Hospital and from 2000 to 2015 in Mendrisio Regional Hospital, both in Switzerland.
Results: In Bellinzona 1710 ± 168 (mean ± SD) monthly visits with a mean temperature of 31.6° ± 1.3 °C were observed. No association between temperature and number of visits per month was identified (r = 0.31; p = 0.07). In Mendrisio mean number of monthly visits was 1409 ± 196 with a temperature of 31.9° ± 1.8 °C. No association between temperature and number of visits was found (r = 0.21; p = 0.15).
Conclusions: The study conducted over a long period it seems not to confirm our initial remarks which they showed a match between the peaks of maximum temperature registered and the activity by the emergency department . Increase of the number of consultations seems associated P74 only with short periods of exceptionally high temperatures as was july 2015.

1 Lepori M, et al. Swiss Medical Forum 2015 suppl 3 P74.

P425

Vascular amyloid deposition and necrotizing myopathy – an uncommon clinical presentation in immunoglobulin light chain amyloidosis

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Introduction: Typical clinical manifestations of Immunoglobulin light chain (AL) amyloidosis include nephrotic-range proteinuria, restrictive cardiomyopathy and hepatomegaly. We present a rare manifestation with vascular amyloid deposition and necrotizing myopathy and suggest a link between these histopathological alterations.
Case report: A 72-year-old man is admitted to the department of general internal medicine with an eight months history of proximal muscle weakness, progressive dysphagia, and weight loss of 10 kg in absence of night sweat or fever. Monoclonal gammopathy of undetermined significance was diagnosed 15 years ago; follow-ups were stopped after 4 years. On physical examination macroglossia and proximal tetraparesis (M4) are noted. Laboratory evaluation reveals elevated liver enzymes, creatinine, creatine kinase (CK), and a nephrotic-range proteinuria. An M-gradient IgG lambda is demonstrated by electrophoresis/immunofixation (21 g/l), together with elevated free light chains (FLC) lambda (512 mg/l) and normal FLC kappa (17.10 mg/l, ratio 0.03). Bone marrow biopsy demonstrates 20–30% infiltration with clonal plasma cells. Cardiac magnetic resonance imaging (MRI) reveals global left ventricular late gadolinium enhancement. Brain natriuretic peptide and highly sensitive troponin I are moderately elevated (481 ng/l and 91 ng/l (ref. <30 ng/l)). Electroneuromyography of the deltoid muscle and MRI of the thighs are suggestive of myopathy. Endoscopic swallowing evaluation reveals severe oropharyngeal dysphagia. All remaining CRAB-criteria are negative. No amyloid is detectable in the periumbilical subcutaneous fat. A vastus medialis muscle biopsy confirms vascular AL amyloidosis and necrotizing myopathy. Other common causes for necrotizing myopathy such as anti-SRP syndrome, preceding infectious disease or statins are absent. A nerve biopsy shows no amyloidosis. Weekly dose-reduced bortezomib, cyclophosphamide, and low dose dexamethasone are started to prevent further organ damage.
Conclusion: We hypothesize that in analogy to nervous system and kidney, vascular amyloid deposition might facilitate myopathy through blood supply impairment. Two negative biopsies highlight the focal nature of the disease. A negative biopsy must never exclude amyloidosis. Amyloidosis should be suspected in patients with a monoclonal plasma cell disorder presenting with proximal muscle weakness, macroglossia, dysphagia, and elevated CK.

P426

Small molecule screen for inhibitors of adipogenesis as a strategy to accelerate hematopoietic recovery

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Background: Worldwide, more than 50.000 Hematopoietic Stem Cell Transplantations (HSCT) are performed annually, although the mortality rate still is close to 50% after allogeneic transplantation. Forty percent of these fatalities relate to the patients being severely immune compromised during the post-ablation period, before the graft has fully reconstituted the hematopoietic system. Reducing the time of engraftment is therefore critical to increasing the chance of survival in these patients. Preventing bone marrow (BM) adipocyte formation in the post-transplant period has been demonstrated to accelerate hematopoietic stem cell (HSC) engraftment and subsequent hematopoietic recovery in mice.
Methods: In order to uncover novel modifiers of BM adipocyte differentiation, we performed a high-throughput label-free *in vitro* screening on the BM-derived mesenchymal stromal cell (MSC) line, OP9. This cell line was demonstrated to be both a useful model to efficiently differentiate into adipocytes as well as to support hematopoiesis *in vitro*. Using Digital Holographic Microscopy (DHM), we screened the Prestwick library of FDA-approved drugs, the Swiss Chemical and the Natural Product collections for inhibitors of adipocytic differentiation based on real-time lipid accumulation. We have validated this novel method with existing adipogenesis quantification techniques, simultaneously quantifying cell confluency and toxicity thanks to a an in-house developed Cell Profiler plugin. Hits have been validated via dose-response curves and counterscreens including hematotoxic assays and functional *in vitro* and *in vivo* assays.
Results: From the initial more than 4000 compounds around 1% rendered as validated hits that inhibited OP9 adipocytic differentiation. These compounds were also non-toxic to the stroma, did not affect cell number and had a strong potency (EC50 <1 uM). From these compounds, 15 were permissive for primary murine hematopoietic stem and progenitor cell (HSPC) expansion and are currently being tested in primary HSPC/MSC co-cultures and in murine HSC transplantation. Of note, MarrowQuant and whole mount confocal microscopy techniques have been developed to measure in vivo BM adipogenesis in this context.
Conclusion: All current clinical approaches to enhance hematopoiesis target the HSC itself. Here we propose targeting BM adipogenesis as an alternative pharmacological strategy to improving hematopoietic recovery beyond current G-CSF standard.

P427

Paraneoplastic dermatomyositis revealing non-Hodgkin lymphoma

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Introduction: Dermatopolymyositis is an inflammatory disorder of unknown origin. Twenty to thirty percent cases of this disease is associated with a cancer. The most involved organs are the ovary, the breast, digestive tract and the nasopharynx. The association to hematologic malignancies is rare. We report the case of a dermatomyositis revealing non Hodgkin lymphoma.
Case report: A 55 year-old woman without pathologic history presented a typical dermatomyositis diagnosed with the presence of eyelid heliotrope erythema, gottron's papules in the right hand, periungueal erythema and muscular weakness in the pelvic and scapular belt. The muscular dysfunction was confirmed by electromyography and biopsy. On the first examination, no evidence of malignancy was seen. Otorhinolaryngeal examination, CT scan, colposcopy, fibroscopy and mammography were normal. A treatment by corticosteroids was started relayed by methotrexate due to severity of the dermatomyositis. Secondary, the patient received intravenous immune globulines because of corticoid resistance. The outcome was favorable. Six months later, appeared a febrile pancytopenia. The CT scan showed disseminated hepatic nodules associated with intraperitoneal effusion leading to an exploratory laparotomy. The hepatic biopsy revealed a large B cell lymphoma CD20+ on immunochemistry. The patient presented a septic shock two days after laparotomy leading to death.
Conclusion: The diagnosis of dermatomyositis must lead to systematic and repeated screening for an associated cancer or hematologic malignancy to initiate an adapted chemotherapy.

P428

Modern first-line treatment of metastatic germ-cell cancer

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Introduction: The treatment of metastatic germ-cell cancer (GCC) is based on the prognostic classification of the international group "IGCCCG" that was published in 1997 based on treatments delivered between 1975 and 1990. Many diagnostic and therapeutic advances have occurred since then.
Methods: We retrospectively reviewed charts of 1163 patients with GCC who were treated at the University Hospital Zurich between 1991 and 2016 for whom electronic files were available. Overall 204 patients who received cisplatin plus etoposide based first-line combination chemotherapy were identified and analyzed.
Results: Median follow-up time was 4.7 years (range 0.3 to 22.4 years). Patients belonged to the good risk (n = 127), intermediate risk (n = 39) or poor risk (n = 38) groups according to the IGCCCG classification. The progression-free survival (PFS) probability was 71% and the overall survival (OS) probability was 88% at 5 years for the entire patient cohort. PFS at 5 years differed in the three prognostic groups according to the IGCCCG score: 83% (good risk), 69% (intermediate risk) and 30% (poor risk), p <0.001. However, OS at 5 years was not different among good risk and intermediate risk patients (94% vs 91%, p = 0.62), but differed to poor risk patients (65%, p <0.001). OS, but not PFS seems better than predicted by the published IGCCCG score, particularly in the intermediate and poor risk groups, which may be explained by better salvage treatment.
Conclusions: The overall survival of patients with GCC has improved. An update of the IGCCCG score that is currently used for prognostic classification is urgently needed.

P429

Chronic diarrhea at advanced age – a rare case of chronic myelomonocytic leukaemia manifested as colitis

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Introduction: Chronic myelomonocytic leukemia (CMML) is a rare malign disorder in stem cells which can be diagnosed by a monocytosis in peripheral blood and by dysplasia in bone marrow overlapped with myeloproliferative neoplasms. Most patients are in the seventies and show extramedullary manifestations in lymphoreticular organs, but also in brain, testes and ovaries. In only 5.7–13% is the gastrointestinal tract involved [1]. The here described patient presents a even more rare case of CMML which started as chronic diarrhea and ended up in being a leukemic colitis.
Case report: A 83 year old male was presented with a 1-month-history of chronic diarrhea, no fever but an abnormal weight loss of 14 kg. With stool and blood cultures infections could be excluded as root causes for diarrhea. The colonoscopy (fig. 1) showed an ulcerous colitis with inflamed tissue; medical treatment with NSAIDs as potential explanation could be excluded and CT scan did not show any signs for ischemia.

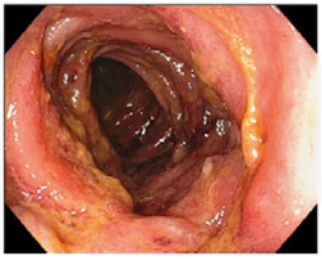

Figure 1: Sigmoid colon, inflammation and ulcera.

A first therapy approach with steroids and mesalazin against inflammatory bowel disease brought no improvement. A full blood exam stated leukocytosis, monocytosis, thrombocytopenia and anemia which lead to a bone-marrow puncture. All signs were pointing to CMML and genetic analyses were performed to complete the diagnosis along the WHO definition. However, the patient didn't show any typical CMML-symptoms. Progressive symptoms with hemorrhagic

stool, abdominal pains and free air in abdomen made a subtotal colectomy necessary. The histopathological report confirmed the CMML diagnosis by infiltration of immature mono- and leukocytes in connective tissue of mucosa [fig. 2].

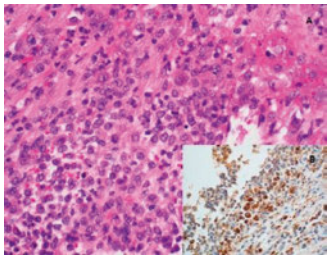

Figure 2: Mucosa, infiltration by immature monocytes.

Results: CMML is a rare form of leukemia and manifests usually with symptoms like fatigue, weight loss, fever and night sweats. Chronic diarrhea as primary manifestation is untypical and very rarely described in literature [2]. Nevertheless, leukemic infiltration should be considered as part of differential diagnosis, when all other common causes have been ruled out.
Conclusion: Complex cases with atypical symptoms demand a close collaboration of medical disciplines to identify non obvious causes for seldom diseases.

1 McCullough KB, Kristen B. Chronic Myelomonocytic Leukemia: a Genetic and Clinical Update. Curr Hematol Malig Rep. 2015;10(3):292–302.
2 LoSavio AD, Bunnag AP, Rubin DT. Colonic infiltration with chronic myelomonocytic leukemia. Nat Clin Pract Gastroenterol Hepatol. 2007;4(4):229–33.

P430

Digital clubbing, painful joint swelling and periostitis in a patient with lung cancer – a paraneoplastic syndrome known as hypertrophic pulmonary osteoarthropathy or Pierre Marie Bamberger syndrome. A case report

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Introduction: Hypertrophic pulmonary osteoarthropathy (HPO), also known as the Pierre Marie Bamberger syndrome, is defined by painful swollen joints, digital clubbing and periostitis. It is a paraneoplastic syndrome with an incidence ranging from 0.64 to 17% in patients with lung cancer. But it can also be associated with extrapulmonary malignancies and various other diseases. The primary form of hypertrophic pulmonary osteoarthropathy is less common. We present the case of a lung cancer patient with disabling pain of the right lower leg caused by a soft tissue metastasis and a HPO.
Case description: A 58-year-old woman with an adenocarcinoma of the lung, AJCC stage IV, presented with enduring pain in the right lower leg for two months. The therapeutic regimen had just been switched to Nivolumab because of tumor progression on first-line chemotherapy. The clinical examination revealed digital clubbing of hands and feet, discrete swelling of the right ankle and severe tenderness on palpation of the right ankle and the right proximal fibula.

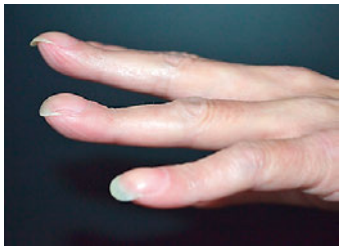

Figure 1: Digital Clubbing.

The X-ray of the right lower leg was unsuspicious. The Magnetic Resonance Imaging of the region showed a tumor in the lateral origin of the soleus muscle as well as a periostitis of the distal lower leg. Based on the patient's history, the clinical presentation and the radiologic findings we diagnosed a soft tissue metastasis of the lung cancer in the proximal soleus muscle and a hypertrophic pulmonary osteoarthropathy. We administered cortisone and morphine

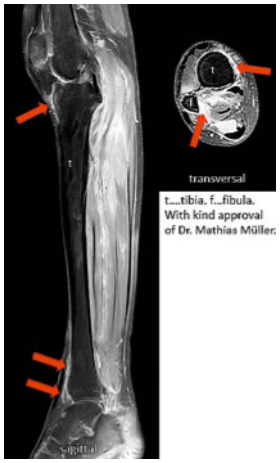

Figure 2: MRI Periostitis.

derivatives, only resulting in a slight improvement of the pain. Finally the patient was referred for a local radiation which brought relief. The matter of pathogenesis and therapy of HPO is not completely resolved. A symptomatic therapeutic attempt with NSAID failed in this case. The most efficacious therapeutic option for HPO is the treatment of the cancer disease, so the immunotherapy with Nivolumab was continued after radiation of the metastasis.
Conclusion: Lung cancer patients present with hypertrophic pulmonary osteoarthropathy in up to 17%. It may occur either in patients with advanced disease or in early stages, sometimes even before the tumor is diagnosed. It is crucial to be aware of the combination of digital clubbing, painful joints and periostitis as a potential paraneoplastic syndrome.

P431

Sclerosing mesenteritis – a rare disease mimicking malignancy

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In March 2016, a 74-year-old woman presented herself at our emergency department with coughing, abdominal pain, emesis and bloody diarrhea for several days. She reported weight loss of 20kg during the last 8 months. Her body mass index was 12.2 kg/m^2. She complained of recurring abdominal pain and diarrhea for a longer time. However, several gastrointestinal endoscopic examinations did not explain her complaints. The patient has been treated for a large cell lung cancer several years ago and was since then in complete remission. Furthermore, she had a history of alcohol- and benzodiazepine abuse and she continued smoking. She was known to have an alcoholic liver cirrhosis with a stage Child A. At admission, the patient was in a reduced general condition, hypotensive, the oxygen saturation was not measurable and her mental status was seriously altered. A CT-scan of the lung and abdomen was performed, showing bilateral infiltrates suggestive for pneumonia and massive non-specific intraabdominal calcifications. A bronchoscopy demonstrated a purulent bronchitis and S. aureus was isolated. Appropriate antibiotic therapy was initiated and infection parameters decreased, but the general condition remained poor. Unexpectedly, the patient died after 13 days. At autopsy a purulent pneumonia was found and interpreted as the most probable cause of death. In addition, the mesenterium showed extensive calcifications, fibrosis and chronic inflammation. After exclusion of a neoplasia and a IgG4-associated disease as well as in correlation with the clinical patient history a Sclerosing Mesenteritis was diagnosed. Sclerosing Mesenteritis is an idiopathic primary inflammatory and fibrotic process that affects the mesentery. Its etiology remains unclear, although several mechanisms have been suggested such as previous abdominal surgery or trauma, autoimmunity, paraneoplastic syndrome, ischemic injury, and infection. Furthermore, there seems to be a strong association with nicotine abuse. Patients affected often present with anorexia, nausea, diarrhea, weight loss and fever. A standard therapy is not established, mostly prednisone is used, but experience is limited.
Conclusion: Sclerosing Mesenteritis may mimic malignancy or infection. It should be considered in the differential diagnosis of abdominal tumors.

P432

The intimate relationship between Foley catheters, urinary incontinence, and death after a new-onset stroke

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Introduction: Urinary incontinence (UI) increases mortality after new-onset stroke. However, this association might be confounded by frequent indwelling urinary catheters (IUC) in this population. The aim of the present study was to explore the relationship between IUC, UI and death in the post-stroke period. We also explore the best time to assess UI (at the time of maximal neurological defect, or one week after the stroke) to predict one-year mortality.
Methods: We included all patients with a first-onset stroke recorded between 1995 and 2011 in the prospective South London Stroke Register. The patients were followed for one year. The unadjusted impact of UI and IUC on time to death was analysed using Kaplan-Meier survival analysis and unweighted two-sided logrank test to compare groups. A multivariate Cox model was used to adjust for age, Glasgow coma scale, pre-stroke and post-stroke Barthel indices, sex, impaired swallow test, motor deficit, diabetes, and inclusion year. The predictive values of UI assessed at maximal deficit or seven days after stroke were compared using receiver-operating curves.
Results: 4477 patients were followed for one year after their first stroke. UI and IUC were present in 43.9% and 31.2% of patients. UI and IUC were both associated with one-year mortality in unadjusted (HR 6.84; 95%CI: 5.98–7.83 and HR 5.30; 95%CI: 4.70–5.98) and adjusted analysis (aHR 1.78; 95%CI: 1.46–2.19 and aHR 1.84; 95%CI: 1.54–2.19). Stroke patients with UI and IUC had twice the mortality rate compared to patients with only UI (HR 10.24; 95%CI: 8.72–12.03 versus HR 4.70; 95%CI: 3.88–5.70, p <0.001). UI assessed after one week performed slightly better for predicting one year mortality than UI assessed at maximal neurologic deficit. Limitations of this study include the lack of a standardized definition of UI and the lack of information regarding the indication for urinary catheterization.
Conclusion: IUC in the post-stroke period is associated with death, especially among UI patients.

POSTERTOUR 3: MIG AMBULATOIRE II / MÉDECINE DE FAMILLE II / AMBULANTE AIM II / HAUSARZTMEDIZIN II

P433

Spontaneous intracranial hypotension

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Introduction: We describe a case of spontaneous intracranial hypotension with a fluctuating disease course over several weeks. Definitive diagnosis could only be made with repeated magnetic resonance imaging (MRI).
Case report: A 25-year old woman presented with acute headache that had begun after strenuous exercising but without notable trauma. She reported the pain to vanish in a horizontal position and to reoccur within seconds when being upright. She also reported repeated vomiting. Neurological examination and cranial computed tomography (CT) were normal. Brain MRI showed no clear signs of intracranial hypotension which was suspected due to the orthostatic nature of the headache (fig. 1). MRI of the cervical spine showed T1 isointensity in the epidural space from C2-C4 which was interpreted as an epidural hematoma. The patient was referred to the neurosurgical department at the University Hospital in Zurich. Repeated spinal MRI showed no focal cerebrospinal fluid leak (CSF). The patient improved spontaneously and was discharged with the presumptive diagnosis of spontaneous intracranial hypotension. Three days later she represented with severe headache, neck stiffness and right sided peripheral facial palsy. Repeated brain MRI showed diffuse pachymeningeal contrast enhancement as a typical sign of intracranial hypotension (fig. 2). CT myelography showed a CSF leak at L5/S1. Application of an epidural blood patch resulted in prompt resolution of the headache and the facial palsy.
Discussion and conclusion: Spontaneous intracranial hypotension refers to the occurrence of a CSF leak leading to CSF hypovolemia and hypotension without a preceding causative event. Orthostatic headache is the prototypical manifestation. Diagnosis is made by MRI [1]. The acronym SEEPS (for **S**ubdural fluid collections, **E**nhancement of the pachymeninges, **E**ngorgement of the venous structures, **P**ituitary enlargement, and **S**agging of the brain) recalls the typical findings [2]. It is frequently misdiagnosed because the neurological examination is usually normal. Our case is notable because initial brain MRI was negative. It stresses the importance of the history of present illness as the most important diagnostic tool. Confronting a specific and persisting symptom clinicians must refrain from excluding a diagnosis prematurely and consider repeated testing.

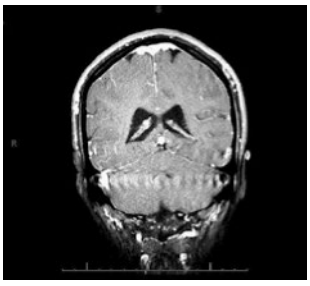

Figure 1

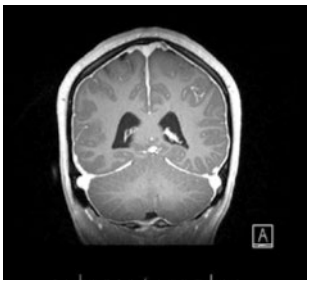

Figure 2

References:
1 Mokri B. Neurol Clin. 2014;32(2):397–422.
2 Schievink WI. JAMA. 2006;295(19):2286–96.

P434

Complementary and alternative medicine use by forced migrants living in the canton of Vaud: a pilot survey

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Introduction: Complementary and alternative medicine (CAM) is used by about a third of the population in different countries. In Switzerland nearly half of the population used CAM at least once during their life, and the most frequently types of CAM used were homeopathy, osteopathy and acupuncture. Among migrants, studies in the US and in Asia showed the same prevalence of CAM use as the native population of a country. However the type of CAM used varied according to ethnicity. Some studies showed an association between self-perceived discrimination and CAM use. The objective of this pilot study was to search for the prevalence and type of CAM used by forced migrants in the canton of Vaud and to evaluate their self-perceived discrimination.
Methods: A cross-sectional study with questionnaires was performed among a convenience sample of forced migrants in the canton of Vaud, Switzerland. The questionnaire was filled in between August and December 2015 using face-to-face interviews, in French, English, Arabic and Tigrinya languages.
Results: In this first study in Switzerland about CAM use and self-perceived discrimination among forced migrants, a total of 61 of them participated in the study. The mean age of the sample was 27.8 (IQR: 18–48) and 78.7% were male. Eritrea (55.7%), Kosovo (4.9%) and Afghanistan (4.9%) were the most often encountered nationalities. The majority (91.7%) declared they trust their physician about their healthcare advices. Lifetime prevalence of CAM use was 45.9%. A third (31%) of the CAM used was herbal medicine. CAM use during the last twelve months was reported by 27.9% of them. Herbal medicine use was much more with self-use (70%) than with the recommendation of a health professional. Among forced migrants who were using CAM, 54.2% informed their physician about their use.

Self-perceived discrimination was reported by 36.7% of forced migrants, with 70% of them reporting discrimination because of their national origins. CAM users reported significantly more discrimination than non-users (44.4% versus 30.3%, p = 0.027).
Conclusion: Forced migrants used complementary and alternative medicine for a half of them during their life and for a third during the last twelve months, especially herbal medicine. A half informed their physician about their CAM use. Self-perceived discrimination was reported by a third of forced migrants and it was associated with CAM use.

P435

Cold and pale – rare and unusual: a case report of hypothenar-hammer syndrome

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Introduction: Hypothenar-Hammer-Syndrome (HHS) is a rare disease, primarily affecting young men, presenting with painful, cold and pale digiti IV and V. Repetitive, blunt trauma to Guyon's canal leads to thrombus formation, subsequent occlusion of hand arteries and ischemic necrosis. Local anatomy of the ulnar artery (superficial palmar arc) makes it susceptible to injury. Angiography is the diagnostic gold standard. Management of choice is intra-arterial lysis; operative approach is rarely required.
Case report: A 30-year-old male presented in our ER with sharp pain, pallor, numbness and temperature loss in left fingers IV and V, which began 5 hours prior, after using his hand as a hammer whilst tiling floors. Patient's medical and family history was unremarkable, especially no Raynauds-, cardiac, rheumatic, vascular or coagulation disorders were known. He regularly consumed alcohol, tobacco and cannabis. Clinical examination showed skin marbling, hypothermia and dysaesthesia of the hypothenar, digits IV and V, with prolonged capillary refill and pathological Allen-test. Segmental pulse oscillography showed a pathological flow volume diagram of digits III–V. Primary Raynaud's seemed unlikely due to isolated occurrence in digits IV and V, as were secondary Raynaud's aetiologies e.g. arteriosclerosis, diabetes or lupus. Normal differential blood count spoke against myleproliferative neoplasia. Cardiac arterial emboli, cryoglobulinaemia, thoracic-outlet-syndrome, CREST and paradoxical embolism were ruled out. CT-angiography revealed distal thrombotic occlusion with no aneurysm of the ulnar artery at the pisiform bone, and no stenosis further proximally. HHS was diagnosed. We commenced pulse-spray arterial lysis and systemic anticoagulation with i.v. heparin. Control angiography at 24h showed regular perfusion of the ulnar interdigital arteries, with persistent partial thrombosis of the distal ulnar artery up to the superficial palmar arc. Anticoagulation was converted to phenprocoumon and combined with an antiplatelet agent (aspirin). Clinical and radiological examination at week 12 revealed normal results.
Summary: HHS is an important differential diagnosis in patients presenting with unspecific Raynaud's-signs, ischemic pain and hypothermia of the ulnar palm and fingers. Significant delay of diagnosis and therapy are associated with high morbidity. It thus remains imperative to draw physicians' attention to the disease's presentation and treatment options.

P436

Prevalence of multimorbidity in Swiss family practices: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

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Introduction: Multimorbidity, commonly defined as two or three or more chronic conditions within one person, is a growing challenge in view of the aging of the population. Management of multimorbidity is frequently the responsibility of the family practitioner, increasing the complexity of health care. Estimation of its prevalence differs significantly between studies according to different methodologies and definitions of multimorbidity. We estimated prevalence of multimorbidity in a national and representative sample of patients from family medicine practices using the Sentinella network.
Methods: We used data from 2904 patients of all ages, attending 118 family practitioners from the Sentinella network from September to November 2015. Recorded data included date of birth, gender and a list of 75 chronic conditions derived from International Classification for Primary Care version 2 (ICPC-2). Prevalence of multimorbidity, defined first as two or more chronic conditions, and secondly as three or more chronic conditions, was estimated and stratified by gender and age group. We also examined which group of chronic conditions participated most to this multimorbidity.
Results: Prevalence of two or more chronic conditions, and three or more chronic conditions was respectively estimated to 52% and 35%, without significant gender difference. Prevalence of two chronic conditions by age group was 6.2% for patients below the age of 20, 19% for those between 21 and 40, 44.8% in the age group between 41 and 60, 71.8% for those between 61-80 and 85.8% in the above 80-age group. The most prevalent conditions were cardiovascular (42.5%), psychological (28%) and metabolic or endocrine (24%).
Conclusion: Our study highlighted the high prevalence of multimorbidity in a representative sample of patients of all ages in family practices in Switzerland. High prevalence of cardiovascular, psychological and metabolic conditions was underlined. These new elements could help to guide resource allocations and post-graduate training.

P437

Outpatient withdrawal from high-dose benzodiazepine dependence – novel approach with interprofessional collaboration and electronic monitoring of polypharmacy

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Introduction: There is no well-established protocol for the management of high-dose benzodiazepine (BZD) withdrawal. Discontinuation of high-dose BZD in dependent patients occurs by dose tapering and psychosocial support, and is generally unsuccessful. Interventions that increase patients' autonomy and motivation along with individually driven tapering regimens might be promising. At the Psychiatric Hospital Basel, agonist substitution - usually with the long-acting BZD clonazepam – is initiated during hospitalization. We present a novel concept for tapering BZD using the case of a 35-year-old unemployed male patient with depression and co-dependence on cannabis and lorazepam (20–25 mg/d, Internet purchase). Outpatient withdrawal started February 18, 2015.
Methods: Commercially available multidose punch cards (7×4 cavities) were equipped with a film containing loops of conductive wires. A microchip records date and time when a loop is broken i.e., when a cavity is emptied. After discharge, our patient consented to get his medication in weekly e-punch cards which he picked up from the community pharmacy, immediately after his weekly visit with the psychotherapist. Withdrawal was centred on the BZD tablets the patient would and could intentionally left-over. BZD tablets were repacked in portions of daily doses and spread over all cavities. Tapering was obtained by reducing the mg-content of the cavities by the amount equivalent to leftovers, which determined the rate of dose reduction. Physician, psychotherapist and pharmacist exchanged weekly figures of past week intake which were discussed with the patient during the following psychosocial session in order to determine dosage changes for the next punch card.
Results: Over the 28-week monitoring period, **dispense** of daily clonazepam was reduced from 8 mg to 2 mg, and of daily lorazepam from 7.5 mg to 5 mg. Amount **taken** was always less and ended at daily clonazepam 1.5 mg (80% reduction). No withdrawal symptoms occurred. Cannabis abstinence was reached at week 16. For physician and pharmacist, extra-time consumption was within usual practice. Satisfaction was given for all participants.
Conclusion: Successful withdrawal from high-dose BZD resulted from collaboration between different healthcare professionals, use of electronic monitoring with graphical feedback, and empowerment of the patient who dictated the speed of tapering.

P438

Inappropriate use of arthroscopic meniscal surgery in degenerative knee disease: an observational study from Switzerland

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Background: Current evidence suggests that arthroscopic knee surgery has no added benefit compared to non-surgical management in degenerative meniscal disease. Yet in many countries arthroscopic partial meniscectomy (APM) remains among the most frequently performed surgeries. We quantify and characterize the current use of

knee arthroscopies in Switzerland, assessing a distinctively non-traumatic patient group.
Methods and results: We assessed claims of a non-accident insurance plan of a major Swiss health insurance company (Helsana group) for surgery rates of APM, arthroscopic debridement and lavage in patients over the age of 40, comparing years 2012 and 2015. Claims were analyzed for prevalence of osteoarthritis, associated interventions and insurance status. Surgery rates for Switzerland were calculated using weighted projections. In all, 648,708 and 647,808 patients were examined in 2012 and 2015 respectively. The incidence of APM, debridement and lavage was 2,520 in 2012 and 2,282 in 2015 in non-traumatic patients aged over 40, consisting mostly of APM (95.6%). Osteoarthritis was diagnosed in 24.6% of inpatients. In all of Switzerland, APM was performed an estimated 9,958 and 10,203 times in middle-aged (40–64) and 5,854 and 4,815 times in elderly (≥65), non-traumatic patients in 2012 and 2015, respectively. This translates into a surgery rate of 209 per 10^5 person-years for all ages. Supplementary private hospital insurance and chronic diseases were associated with a higher risk for surgery. High deductible class and use of pain medication were associated with a reduced risk for surgery.
Interpretation: APM is widely-used in non-traumatic patients in Switzerland, although it provides no significant benefit according to current evidence. Surgery rates did not change in non-traumatic middle-aged patients between 2012 and 2015. Accordingly, the potential of inappropriate use of APM in non-traumatic patients in Switzerland is high and current practice needs to be changed.

P439

Performances of a brief assessment tool for the early diagnosis of geriatric syndromes in family medicine

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Introduction: Although early detection of geriatric syndromes has been shown to limit functional decline, it is rarely implemented in family medicine because of lack of training and lack of time for a full geriatric assessment. The AGE project (active geriatric evaluation) aimed at developing and validating a brief assessment tool (BAT) for family physicians (FP) to detect geriatric syndromes. This study aimed to estimate diagnostic performance of the BAT compared to a comprehensive geriatric assessment.
Methods: Prospective diagnostic study conducted inone university primary care clinic and three private practices, canton of Vaud, Switzerland. Eligible patients were aged at least 70 years old, routinely followed in one of the recruitment sites, able to provide informed consent and without previous geriatric assessment. FPs performed the BAT, followed by a comprehensive (2 hours) geriatric evaluation performed within the next two months. Both the BAT and the full geriatric assessment targeted the following eight syndromes: cognitive impairment, mood disorder, urinary incontinence, visual impairment, hearing loss, undernutrition, osteoporosis, gait and balance impairment.
Results: Out of 85 patients, 53 (62.4%) were included at the university clinic and 32 (37.7%) in private practices. Mean age was 78 years (SD 6) and 46/85 (54.1%) were females. Prevalence of each syndrome ranged between 30.0% (malnutrition and cognitive impairment) and 71.0% (visual impairment). Patients suffered from a median number of 3 syndromes (IQR 2 to 4). Negative predictive values (NPV) ranged between 73.5% (95%CI 61.4% – 83.5%) and 84.1% (95%CI 69.9% – 93.4%), apart from visual impairment with a NPV of 50.0%. Median time to perform the BAT was 20 min (range 5–60).
Conclusions: The BAT performed well to screen elderly patients for geriatric syndromes when compared to a full geriatric assessment, and was feasible in routine practice.

P440

Interior renovation of a primary care office leads to a biased patient experience for about 1 year

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Introduction: Measuring patient experience is key to assess quality of care. But in a previous study we found patient experience can be biased: a renovation of the interior design of a general practitioner (GP) office lead to a better patient experience also in domains not affected by renovation known as perceptual bias. The aim for this study was to assess 1) how long a perceptual bias lasts and 2) if this bias can be reproduced in a second renovation.
Methods: We conducted this study in a GP office with 2 GPs in Switzerland that was renovated twice within 3 years (fig. 1: left before, right after).

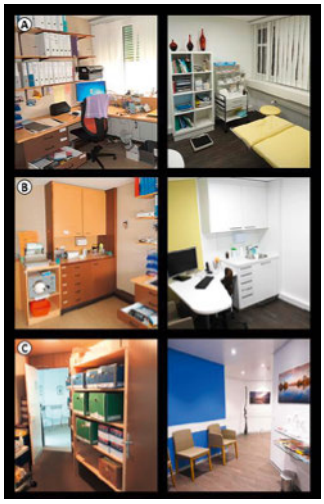

Figure 1

We assessed patient experience at baseline (before the first renovation) and after 2 months (follow-up 1, FUP1) in a previous study and extended FUP for this study to 14 months (FUP2) after the first and 3 months (FUP3) after a second renovation. Each time, we invited a consecutive sample of 180 patients presenting for a routine consultation to participate anonymously in a paper survey. Patients graded patient experience in 4 domains on a 6-point Likert-scale: appearance of the office; qualities of medical assistants and GPs; and general satisfaction. We compared crude mean scores of each domain from baseline until FUP3. In a multivariate regression model, we adjusted for patient's age, gender and for how long patients had been their GP.
Results: The response rate for all consecutive samples of patients was 84–94%. At baseline, patients aged 60.9 (17.7) years, 52% females, and 67% were with their GP for >5 years.

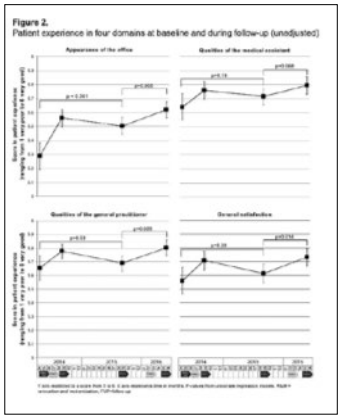

Figure 2

Figure 2 shows crude mean scores per domain of patient experience. After a first renovation, we found a regression to the baseline level of patient experience at FUP2 except for appearance of the office ($p < 0.001$). After a second renovation (FUP3), patient experience improved in appearance of the office ($p = 0.008$), qualities of the GP ($p = 0.008$), and general satisfaction ($p = 0.014$). Qualities of the medical assistant showed a trend of improvement ($p = 0.068$).
The multivariate model did not change results.
Conclusions: Interior renovation of a GP practice causes a perceptual bias for >1 year that positively influences patient experience also in domains that are not affected by a renovation.
We could reproduce this bias in a second renovation strengthening evidence for causality. This implies, to restrict measurement of patient experience to at least one year after interior renovation in primary care and therefore avoid biased estimates when measuring patient experience.

P441

The life threatening side of otitis media – a case report of pneumococcal meningitis

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Introduction: Acute otitis media (AOM) is a common infection, mainly affecting children, typically presenting with unilateral otalgia and decreased hearing. Otoscopic examination is the diagnostic standard. Streptococcus pneumonia is the most frequent bacterial cause. Complications such as mastoiditis, facial paralysis, labyrinthitis and meningitis develop in less than 0.5% cases in adults. Therapy of choice is amoxicillin.
Case report: A 55-year-old female was referred to our ER after having been found in her home with an altered, confused mental status. Recently, she had been complaining of ear pain. At admission, she was restless, septic, with a GCS of 6, requiring intubation. Orientating cranial CT showed opacification of the left mastoid air cells, as well as intracranial air entrapment and cerebral edema. During the CT, the patient suffered a seizure, which was successfully terminated with midazolam. With a high clinical suspicion of otogenous bacterial meningitis, empirical antibiotic therapy with tazobactam was commenced. In left ear otoscopy otitis media was diagnosed. Lumbar puncture revealed a high intracranial pressure (>50 mm Hg), liquor was positive for pneumococcal antigen. The antigen was also detected in the urine, confirming the diagnosis of pneumococcal meningitis. Antibiotic therapy was converted to empirically ceftriaxon and vancomycin, then ceftriaxone only (as per antibiogram). A surgical exploration of the mastoid was performed, revealing purulent secretion. A tympanostomy tube was temporarily inserted. In the control CT scan signs of high intracranial pressure were persistent. Neurovascular ultrasound showed an increased blood flow in the medial cerebral artery, which we interpreted as indirect signs of vasospasms. A therapy with nimodipine was installed. Within 12 days a vast clinical improvement was observed. The patient suffered no neurologic deficits, was spatially and temporally orientated and independently mobile so that discharge to a neurorehabilitation was feasible.
Summary: Despite AOM being generalised as a trivial infection, delay in diagnosis and therapy can be lethal. Pneumococcal meningitis is a rare, life threatening complication, occurring in only 4% of invasive pneumococcal infections, with a case-fatality rate of up to 25%.

P442

Interprofessional collaboration between physicians and community pharmacists – where are barriers and facilitators?

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Introduction: Today, one profession can no longer hold all knowledge and skills that is needed for safe and quality care. Although the Federal Office of Public Health published in 2013 concrete examples of interprofessional collaboration, many mistake it for interdisciplinary work. Because different professionals can hardly work together if they do not learn together, Swiss research programs will be launched in 2017 for projects in interprofessional teaching in medicine curriculum. Simultaneously, a political proposal (so called Postulat Humbel) requested in 2012 to demonstrate which new role community pharmacies could play to guarantee access to high quality care. In this context, we aimed at searching literature for barriers and facilitators to physician-pharmacist collaboration in primary care.
Methods: A pragmatic literature search was performed in PubMed and google scholar on Jan 1st 2017 with variations of the terms: interprofession* OR collaborati* AND physician* AND pharmac* AND "primary care" AND barrier* and the restriction "-education". We present the key messages of the 156 retrieved articles which may be pertinent for Switzerland.
Results: Individual, contextual and exchange factors influence interprofessional relationship. Some issues seem predisposed such as medication review, medication dose adjustment, repeat dispensing, therapeutic substitution and medication adherence. Management of patients with abuse potential could be expanded. Physician-pharmacist collaboration in primary care is highly facilitated by reciprocal trust in capabilities and knowing each other, co-location or geographical proximity, and regular face-to-face contact. Beside lack of motivation and willingness, lack of time and remuneration are often cited as barriers to the implementation of interprofessional collaboration. Technical difficulties may hinder information sharing, and confidentiality remains a topic of concern. The current main barrier seems the poor acceptance of the new pharmacists' role and their provision of additional services. Adding diagnosis to prescriptions could represent a first step in shared decision making. Prescribing by pharmacists represents a clear hurdle.
Conclusion: The literature contains many articles on physician-pharmacist collaboration, but implementation is still in its early stages. However, the Swiss Federal Council is evaluating how community pharmacists could play a more important role in primary care in future.

POSTERTOUR 3: MIG AMBULATOIRE III / MÉDECINE DE FAMILLE III / AMBULANTE AIM III / HAUSARZTMEDIZIN III

P443

Concordance in the perception of complaints between general practitioners and their multimorbid patients: a cross-sectional study in Swiss primary care

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Background: Multiple chronic health conditions (multimorbidity) is inevitably leading to multiple treatment procedures, unless health conditions are prioritized along patients' needs and preferences. Thus, for improving healthcare, it is crucial for GPs to know what condition the patient is suffering most. The aim of our study was to investigate to what degree GPs perceive the subjectively most important complaint (MIC) of their multimorbid patients, and therefore to assess the GP-patient concordance in regard to MIC's.
Methods: Cross-sectional analysis based on a cluster-RCT among 46 GPs and 334 multimorbid patients (≥60 years taking ≥5 drugs for at least 6 months) in Northern Switzerland recruited between March 2015 and July 2016. Intervention group GPs (n = 20) were asked to list the four MIC of the patient, and patients (n = 128) were asked to list their MIC. MIC's were classified using the ICPC-2 coding system on chapter and component level. We defined as concordance if the ICPC-2 code of patient's MIC was identical with one of the MIC codes on GP's list. We classified concordance into full, moderate and low, depending on the patient's MIC code ranked first, second or third/fourth on GP's list. We defined as discordance if the patient's MIC code was not listed on GP's list. Complaints frequencies were measured in the whole study sample (n = 334). Statistics included descriptive measures using the statistical software R, version 3.2.
Results: Mean age of patients was 76.9 (SD 8.1) years, 38% male, taking 7.9 (SD 2.6) drugs on long-term. The most frequent complaints were pain, weakness / tiredness, shortness of breath and dizziness (fig. 1). Patient-GP concordance of the MIC was given in 101/128

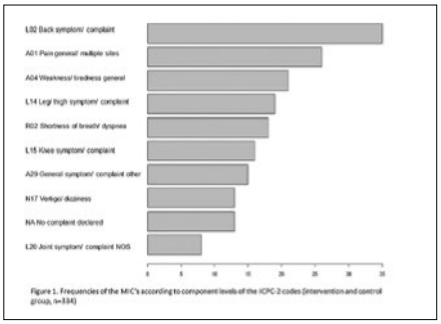

Figure 1. Frequencies of the MIC's according to component levels of the ICPC-2 codes (intervention and control group, n=334)

Figure 1

(78.9%) on the ICPC-2 chapter level, while 86/128 (67.2%) were full, 8/128 (6.3%) moderate and 7/128 (5.5%) low concordance. If the MIC's were classified on ICPC-2 component levels, concordance was given in 83/128 (64.8%), whereby 72/128 (56.3%) were full, 6/128 (4.7%) moderate and 5/128 (3.9%) low concordance (fig. 2). In 27/128 (21.1%) there was discordance (chapter level).

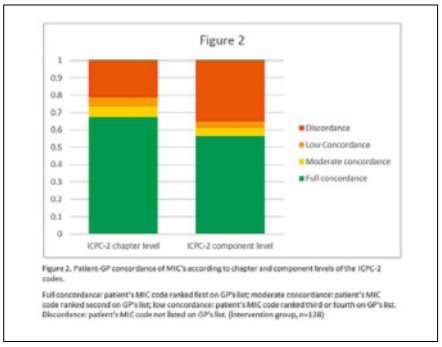

Figure 2

Conclusion: A majority of GPs perceives the MIC of the multimorbid patient correctly, but there is room for improvement: 21% of family physicians do not list the MIC of the patient at all in a four-part list. Thus, directly addressing patient's complaint as part of the encounter might help for better coping with multimorbidity and improving the quality of care for multimorbid patients.

P444

Diversity in the clinic: analysis of transcultural consultations requested by primary care physicians

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Introduction: Because of current geopolitical contexts and migratory fluxes, primary care physicians (PCP) encounter an increasing amount of culturally diverse patients in their practice. This cultural diversity impacts the consultation and requires additional expertise. At the Geneva University Hospitals, a transcultural consultation is available for all health care professionals, providing cultural evaluation of referred patients, and issuing clinical recommendations. The aim of this research was to understand the type of clinical difficulties encountered by PCP caring for culturally diverse patients and their relevance for cultural competence training of PCP.
Methods: We conducted a retrospective analysis of all transcultural consultations requested by PCP between 2006 and 2015. We included situations for which a cultural evaluation was completed and excluded those for which only telephone advice was given. We analyzed consultation request intake forms and consultation reports issued to the PCP. We analyzed patient and provider characteristics, motives of consultation requests, issues identified by the cultural evaluation and recommendations made to PCP.
Results: 32 consultations were included in the analysis. The main reasons for consultation were clarification of patient's socio-cultural context and exploration of patient's explanatory model of illness. The main issues identified by the cultural evaluation were the high level of socioeconomic vulnerability interfering with health care management, divergent explanatory models between patient and PCP, necessity to refer to mental health care, and linguistic barriers to optimal communication. Recommendations included integration of additional professionals and modifications of clinical management.
Conclusion: PCP confronted with culturally diverse patient population need additional knowledge and skills. Useful competencies include understanding the impact of socio-economic vulnerability on illness self-management, tools to explore patient models of illness and the impact of culture on the expression of distress.

P445

Autoimmune limbic encephalitis with anti-LGI1 antibodies, a treatable cause of behavior and memory disorder: a case report

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Introduction: A 79 year-old healthy man was hospitalized with progressive memory impairment, confusion and abnormal perioral movements. Brain magnetic resonance imaging (MRI) revealed left amygdalo-hippocampal swelling with contrast enhancement. Electroencephalography (EEG) revealed paroxystic electrical activity without clinical correlate. Antiepileptic treatment did not alter the symptoms. A repeated MRI showed a second similar lesion located in the right hippocampus. Cerebrospinal fluid (CSF) was clear with one leukocyte pro microliter and normal proteinorachia. Antibodies with anti-LGI1 specificity were positive in the blood and CSF. A diagnosis of autoimmune limbic encephalitis with anti-LGI1 antibodies was made, and treatment consisting of high dose methylprednisolone bolus followed by 0.6 mg/kg of prednisone orally and 2 g /kg of immunoglobulins intravenously was administered, with dramatic improvement of symptoms. A thorough investigation for the presence of neoplasia was negative.

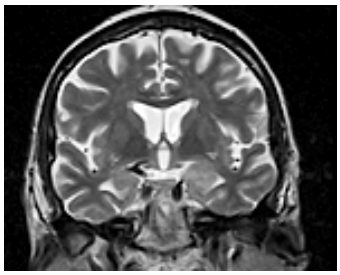

Figure 1: T2.

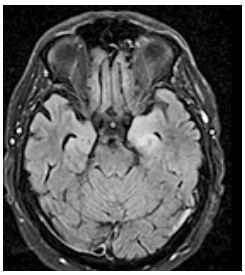

Figure 2: T2*FLAIR.

Methods: We searched PubMed° for relevant articles using the keywords "limbic encephalitis", "LGI1 antibody", and "faciobrachial dystonic seizure"
Results: Limbic encephalitis is a subacute disease, with progressive memory impairment and confusion, with or without faciobrachial dyskinesia. Men in the 7th decade are mostly affected. The EEG is pathological in more than 50% of patients. MRI shows hypocampic hypersignal in T2 or T2 FLAIR. The diagnosis is confirmed by isolation of anti-VGKC antibodies above 400 pmol/L, with anti-LGI1 specificity, in the CSF and serum. A neoplasia is associated in 10 to 20% of cases. Administration of corticosteroids for 4 to 6 months, along with immunoglobulins or plasmapheresis, leads to rapid clinical improvement. Relapses are rare and generally respond to Rituximab administration. Atrophy or sclerosis of the hippocampus can occur in case of delayed treatment.
Conclusion: Autoimmune limbic encephalitis with anti Lgi1 antibodies should be evoked in patients with subacute memory and behavioral troubles, in particular when associated with faciobrachial dyskinesia. Though the etiology is rarely paraneoplastic, assessment for the presence of cancer is warranted. Timely treatment with corticosteroids and immunoglobulins leads generally to remission of the symptoms. For these reasons, awareness of its semiology and early diagnosis are important in order to start specific treatment as soon as possible.

P446

Securing an adequate follow-up in patients with discrepancies between the preliminary and final radiology report in the emergency department

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Introduction: In the setting of an emergency department (ED), preliminary radiological findings are often reported via telephone. The final report can be different, especially after being reviewed by a senior radiologist. If those additional findings aren't adequately communicated, they are prone to be lost to follow-up with possibly detrimental results e.g. in the case of suspect pulmonary lesions. In larger departments, validating hundreds of reports per day can be strenuous, therefore an automated process is desirable.
Methods: Diagnoses and radiology reports are usually recorded in an unstructured manner. We used natural language processing (NLP) and

named entity recognition (NER) to find expressions denoting ICD-10 entities. In order not to miss possible pathological findings we also searched for keywords, such as "tumor", "nodule", "infiltrate" in the radiology report. A suspected mismatch would then prompt a manual comparison of clinical diagnoses and the final report. To validate this approach we used a random sample of cases.
Results: The validation of the algorithm itself to match ICD-10 codes to free text fields was done using a set of diagnoses which were manually encoded by two independent observers. The matching-results were found to be sufficient on a 3-digit code level (ICD-10 main diagnosis group). It was noted, however that the variability in phrasing, spelling, naming and abbreviating entities was rather large. Also a difference in jargon was found between clinical diagnoses and radiological reports. It was therefore necessary to define a thesaurus, a list of abbreviations and additional text parsing rules to improve entity recognition. We are currently adapting the methodology as to reduce the number of false positive mismatch warnings.
Conclusions: Text mining and named entity recognition are challenging for a number of reasons, including multiple names and abbreviations for a given diagnosis as well as simple typos. Using the methods described we were successful in automating the process to avoid overlooking findings which are contained in the final written radiology report only and to secure an adequate follow-up. It has to be stated that we could only identify a small number in which those discrepancies had a clinical impact. Nevertheless we plan to improve the algorithm to allow for deployment in the near future.

P447

Abdominal pain and very high alkaline phosphatase level – is there a coherence?

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Introduction: Little is known about a coherence of intestinal angioedema, very high alkaline phosphatase and asymptomatic factor V Leiden Mutation.
Case report: A 22-years old professional endurance sportswoman was presenting several time with sudden abdominal pain, nausea and vomitus over a period of almost 2 years. An asymptomatic factor V Leiden Mutation was known and the only daily taken drug was an oral anticonception (Desogestrel). In the physical examination we founded an epigastrical pain on pressure without peritonism. The blood results showed a very high level of alkaline phosphatase (3500 U/l) with normal inflammation parameters and gamma-GT. In a computer-tomography we documented edematous thickened ileum terminals and colon ascendens. A stenosis of the terminal Ileum, with a normal mucosa was found in the colonoscopy. In a MRI which was performed a day after, the stenosis and the edematous tissue was disappeared. Therefore an intestinal angioedema was proven. We did not find any infection (EBV, CMV, Leishmania, Yersinia) or porphyria. The C1-Esterase and tryptase levels were normal. We stopped Desogestrel and the patient was asymptomatical and two months later alkaline phosphatase was 135 U/l.
Discussion: The clinical signs can be explained with an intestinal angioedema. High levels of alkaline phosphatase are known as transient benign hyperphosphatasemia in children but not in adults and especially not in coherence with angioedema. As we know there is no coherence known with angioedema, transient benign hyperphosphatasemia factor V-Leiden Mutation and desogestrel. We consider that there is a coherence and the patient therefore was without any symptoms after stopping the intake of daily desogestrel.
Conclusion: This case shows that a very high alkaline phosphatase without signs of a liver disease or osteomalacia also in adults should be considered as transient benign hyperphosphatasemia. Also there might be coherence with intestinal angioedema, factor V-Leiden Mutation and desogestrel. Further research is needed.

P448

Sleep disturbance related to nocturnal leg cramps in Geneva: a prospective observational study with a feasibility perspective

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Introduction: Cramps are involuntary painful muscle contractions. They affect almost one in two people over 60 in primary care. In declarative retrospective study, cramps were shown to cause severe pain and sleep disturbance. Studies are needed to assess therapeutic options, but before considering a randomized controlled trial, we wanted to confirm the burden related to cramps in a primary care setting as well as the feasibility of such a study.
Objective: The objective of this study was to prospectively explore the cramps' frequency, duration, severity and related sleep disturbance.
Methods: We planned to enroll 600 patients in 30 practices, between march 2014 and September 2015. Questionnaires and daily log were distributed to patient to prospectively obtain information about demographics, cramp frequency, severity, sleep disturbance, and treatment. A research assistant realized 3 telephone interview during the the study.
Results: We included only 102 people in 14 practices, among them, 86 (86%), reported cramps during the 2 weeks of the study. Overall cramp frequency was 2,26/week, overall duration was 5 minutes. Overall severity was 4,17 on analog numerical scale from 0 to 10, overall sleep disturbance was quoted 5,28 on analog numerical scale from 0 to 10. Overall Pittsburgh sleep quality index was 7, while 28 patients reported a score >8 and 46 reported a score >5.
Conclusions: These results confirmed the severe pain and sleep disturbance already showed in previous studies but questioned the feasibility of a randomized controlled trial in our setting.

P449

Exploration of social and psychological difficulties related to acne by the general practitioner: a systematic review

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Introduction: Acne vulgaris is a chronic inflammatory disease of the skin affecting a very large proportion of the general population. It can have a considerable negative impact on patients' mental health and quality of life and has been associated with high rates of depression, anxiety and suicide. Acne patients must be screened for psychosocial distress in primary care. The aim of this systematic review was to study how general practitioners explore the psychological, psychosocial and psychiatric distress caused by or linked to acne vulgaris in their ambulatory practice.
Methods: We searched Pubmed, Medline, Cochrane, Embase, Psycinfo and Cinahl from inception until February 3rd 2016. We included literature reviews, observational studies, interventional studies and review articles. All non-pediatric acne patients with no treatment susceptible of causing psychological distress, including isoretinoin, and suffering from psychosocial distress due to acne were considered. Data extraction included study, population, context and intervention characteristics, and relevant subjective and objective outcomes. A narrative synthesis was performed.
Results: Our search resulted in five relevant articles. Many quality of life and mental health assessment tools were described, but no information was given on their use in general practice. One Australian study specifically explored psychological intervention in primary care. Overall, our results suggested that psychological aspects are neglected in the therapy of acne patients, without any supportive quantitative data.
Conclusion: Very little data is available on the exploration of psychosocial suffering in acne patients in primary care. No adequate acne-specific tool has been validated for psychosocial screening in general practice. Research should be undertaken to assess how general practitioners explore psychosocial suffering caused by acne. We suggest maximising awareness on this issue amongst general practitioners, validating a straightforward and ergonomic tool to do so and assessing its clinical use in primary care.

P450

Access to electronic records of general practitioners and specialists in rural central Switzerland for spatial analyses

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Background: For many countries, the geographic distribution of general practitioners (GPs) and specialists remains insistently unequal despite the notable increases in overall supply. How physicians are distributed and how their patient populations differ in healthcare utilization dependent on geographical and demographic factors are aspects requiring great consideration during healthcare planning. Therefore, we asked, is there a maldistribution of physicians in Central

Switzerland and if so, does it influence healthcare accessibility in rural areas?
Methods: Data was provided from the Physicians Association's and MedKey, a patient data trust center. Physicians were asked prior to analysis for access to their patient's electronic health records. They were given 3 options to choose from, (1) full access to anonymized electronic records for all research going further, (2) only allow access to records for this research project, and (3) no access to records. For this analysis responses one and two were treated as a yes and option three as no. Using the Eurostat's degree of urbanization, physicians were designated into regions (urban, suburban, rural) dependent on population density. The physicians' locations will be geocoded, at the street level, and paired with their patient population, at the zip code level. Analyses will be performed to estimate travel time and distance between physicians and their patients, and to examine the associations between physician's distributions by the degree of urbanization and patient characteristics.
Results: From the data provided, 938 letters for consent to utilize electronic records were sent to practicing physicians working in Central Switzerland. 183/342 (54%) urban physicians responded, 141 (41%) of them give access to the records. 236/433 (55%) suburban physicians responded, 173 (40%) of them give access. 95/163 (58%) rural physicians replied, 87 (53%) of them give access. Of the respondents 345 (67%) were GPs and 169 (33%) were specialists. Yes responses by Cantons, 222 were from Lucerne, 65 Zug, 52 Schwyz, 24 Nidwalden, 18 Obwalden, and 17 from Uri.
Conclusions: From the gathered data, a spatial analysis will investigate the distribution, provision and utilization of primary care and specialty care in Central Switzerland. Generalizability will be limited due to varying response, however, rural physicians were more willing to give access to their data than urban or suburban physicians.

P451

Which factors influence the use of Electronic Health Record (EHR) during the first ten minutes of the clinical encounter?

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Introduction: The Electronic Health Record (EHR) is used in about 12–55% of clinical encounters, especially at the beginning. Several factors related to physician, patient, consultation or spatial characteristics may influence the use of the EHR. However no studies have specifically assessed the relative importance of each of these factors for EHR use during clinical encounters. The aim of the study was to identify the physician, patient and consultation characteristics that influenced EHR use by primary care physicians during the first ten minutes of the consultation.
Methods: A cross-sectional study was conducted at the Division of Primary Care at the Geneva University Hospitals. Seventeen residents at the end of their training as general internists provided 6–8 self-videotaped clinical encounters. Use of the EHR was defined by use of the keyboard and/or the screen during the first 10 minutes of the clinical encounter. The influence on EHR use of patients' characteristics (sex and age and language spoken), physicians' characteristics (sex, age, self-perceptions regarding EHR use) and consultation characteristics (new-follow-up, content of consultation, language used) were evaluated using multivariate analyses.
Results: A total of 142 videotaped consultations were included. Both addressing biomedical content ($p = .0178$) and having little clinical experience ($p = .0213$) increased the use of the EHR. There was also weak evidence that being a male MD ($p = .1010$) or conducting a new consultation rather than a follow-up ($p = .0967$) could also increase the amount of EHR use. There was no evidence that physicians' self-perceptions regarding the use of computer, or patients' characteristics influenced their EHR use.
Conclusion: The results suggest that only a few elements regarding the physicians or the consultation characteristics were associated with EHR use during consultations. Because lack of clinical experience seemed linked to increased use of the EHR, training on how to use the EHR in a patient-centered manner should take place early in medical training in order to minimize the negative impact of EHR use on the physician-patient relationship.

POSTERTOUR 3: MÉDECINE SPÉCIALISÉE III / FACHMEDIZIN III

P452

Cryptoccocal infection as a sign of severe underlying immunodeficiency

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Introduction: Cryptococcosis is an AIDS-defining opportunistic infection and a sign of severe immunosuppression. With wide access to antiretroviral therapy Cryptococcosis has become a rare disease in high-income countries like Switzerland. But incidence is still high in countries with high prevalence of HIV/AIDS.
Case: A 33-year old Kenyan man was admitted to our hospital because of episodes of recurrent vomiting and syncope. He reported reduced appetite, unintentional weight loss, night sweats, malaise and intermitting fever. During the past 10 days, he suffered from position-dependent headache. At the emergency department the patient had two epileptic seizures. On clinical examination the patient was skinny, vital signs were normal. The laboratory diagnostics showed a microcytic, hypochromic anaemia (Hb 116 g/l) and leucopenia (3.8 G/l, lymphopenia 0.3 G/l). The cranial computed tomography was unremarkable and the cerebrospinal fluid (CSF) showed a total cell count of only 2 cells/µl with a slightly increased protein (0.49 g/l). The patient was admitted to the intensive care unit and an anticonvulsive therapy with Levetiracetam was started. The subsequent magnetic resonance imaging scan of the neurocranium was unremarkable with no signs of increased intracranial pressure. Surprisingly, the cytopathological examination of the CSF showed Cryptoccocus neoformans, cryptoccal antigen was positive in the CSF and all blood cultures grew Cryptoccocus neoformans. An antifungal therapy with Amphotericin B and Flucytosin was started. In the meanwhile the HIV screening test was positive. The patient was transferred to a neurological intensive care unit. Due to repeatedly elevated cerebrospinal pressure >25 cmH2O, a continuous ventricle drainage was placed. Despite highest intensive care, the patient developed a fulminant cerebral oedema with compression of the CSF spaces and transtentorial herniation as well as a herniation through the foramen magnum. Nine days after the admission the patient died.
Conclusions: This case shows a fatal central nervous system infection due to Cryptoccocus neoformans in a patient with unknown HIV. Cryptococcosis is often fatal, even if treated, and early recognition is mandatory.

P453

When your dog suddenly barks silently

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Case description: A 59-year-old patient was admitted due to acute onset of dizziness, vomiting and bilateral hearing loss. A week earlier, his illness started with influenza-like symptoms, followed by severe nausea, protracted emesis, progressive dizziness, vertigo and unstable gait. Almost complete bilateral hearing loss occurred the day before admission. The patient lived alone with numerous small animals (goats, cats, dogs), he consumed alcohol excessively. On examination, he had a temperature of 38.2 °C, looked ill with signs of severe vestibulo-cochlear failure (unsteady gait with drift to left, Weber and Rinne-testing was not heard, bilateral positive head impulse test and spontaneous left-beating nystagmus) but no neck stiffness. Blood tests showed leucocytosis of 20.7 G/l with marked left shift, thrombocytopenia of 43 G/l, and C-reactive protein of 85 mg/l. Cerebrospinal fluid (CSF) analysis revealed a polynuclear pleocytosis of 493/µl, with a lactate of 3.3 mmol/l (N <2.0). Treatment with ceftriaxone, amoxicillin and aciclovir was started. A cerebral MRI disclosed multiple small subacute supratentorial ischemic lesions. The echocardiography demonstrated an apical akinesia as sequela of a myocardial infarction and a thrombus within the apex. Coronary angiography was normal without coronary stenosis. Cultures of blood and CSF were negative. However, broad-spectrum PCR of the CSF was positive for *Capnocytophaga canimorsus*. The patient was treated with i.v. Ceftriaxone for 10 d, recovered slowly of his neurologic deficits over 6 months but at the end needed a cochlear implant for persisting deafness.
Discussion: *Capnocytophaga canimorsus*, a slow growing gram negative rod, is part of the commensal oral flora of dogs and cats. It can cause severe septic infection, especially in immunocompromised patients (i.e. asplenia, liver cirrhosis, excessive alcohol consumption). *C. canimorsus* infection activates the blood coagulation cascade; thromboembolic myocardial infarction has been described in patients with *C. canimorsus* sepsis and normal coronary arteries. Meningitis due to *C. canimorsus* goes along with a high rate of sensorineuronal hearing loss. Our patient with typical risk factors of dog and cat exposure, combined with excessive alcohol consumption, sufferred from two classical complications of systemic *C. canimorsus* infection, notably meningitis with bilateral hearing loss and thromboembolic cardiac involvement despite normal coronary arteries.

P454

Ivermectin-associated athralgias. Blame it on the mite?

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Introduction: Ivermectin is used to treat a variety of parasitoses. Post-treatment side effects, or Mazzotti reaction (i.e. fever, headache, chills, arthralgia, rash, eosinophilia, anorexia) may occur due to antigen release from dying parasites. Common in onchocerciasis, Mazzotti reaction in scabies has been described only once in a patient with crusted form. (Ito T., 2013).
Methods: We describe the case of a patient who developed polyarthralgias after oral ivermectin for scabies.
Results: A 46-year-old woman developed a pustular rash after swimming in a lake 4 months before hospitalisation. The rash appeared on her buttocks and progressively extended to the trunk, arms, and legs. The initial differential diagnosis included cercarial dermatitis, toxidermia, and autoimmune disease. Skin biopsy showed features of parasitosis but no parasites were seen. Oral and topical steroids and antihistamines were tried without success. One month before hospitalisation, empiric ivermectin treatment (2 doses of 200 ug/kg at 2-week interval) was administrated with slight clinical improvement. Two days after the second dose, the patient developed serious polyarthralgias requiring hospitalisation. Pain relief was obtained with paracetamol and opioids. Patient's past medical, family, allergy and travel history was insignificant. Parameters were normal. Physical examination revealed painful and tender elbow, wrists, knees and ankles. Itchy erythematous, papular and vesicular lesions on the trunk, buttocks, thighs and wrists were present. Besides an elevated CRP, blood tests comprising common viral serologies and a complete immunological panel were normal. Dermoscopy allowed identification of *Sarcoptes scabiei* and a diagnosis of scabies was made. Because of incomplete response to previous treatment, an additional cycle of ivermectin (2 doses 10 days apart) was prescribed. Arthralgias briefly worsened with the first of these 2 doses. The patient was discharged at day 7. At 1-month follow-up skin lesions had totally regressed and arthralgias disappeared.
Conclusion: In the absence of other drugs or medical conditions that could explain patient's symptoms, arthralgias were ascribed to a post-ivermectin Mazzotti-like reaction. Although hardly reported in scabies, it is likely that such reaction developed because of high parasitic load from long mistreated scabies. Clinicians should be aware of this potential complication particularly when treating crusted or long-standing scabies.

P455

A rare form of granulocytic meningitis

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Introduction: Granulocytic meningitis is a rare form of central nervous system (CNS) inflammation of various infectious, autoimmune and other causes. Exclusion of opportunistic infections, especially in patients with autoimmune diseases treated with immunosuppressive agents, can be a challenge. Brain biopsy is often needed for definite diagnosis.
Case report: A 60-year-old woman was referred for evaluation of weight loss (10 kg in 3y), increasing confusion and anemia. A seronegative, anerosive rheumatoid arthritis (RA) had been diagnosed a year earlier and was treated with leflunomide. The occurrence of memory loss and dysarthria had been ascribed to an atypical cerebral hemorrhage due to amyloid angiopathy a few months earlier. The patient's cognitive functions deteriorated rapidly and she started having fluctuating motoric neurological deficits. The cerebrospinal fluid (CSF) was slightly xanthochromic, showed a lymphocytic pleocytosis (37 Ly /39 cells/µl) and an elevated protein (1087 mg/l). The MRI (fig. 1) revealed leptomeningeal thickening with contrast enhancement as well as progredient subarachnoidal and parenchymatous micro-hemorrhages. Biopsies of meninges and brain confirmed the diagnosis of a granulomatous inflammation and amyloid angiopathy (fig. 2). Search for infectious causes by culture and PCR was negative. Therapy with leflunomide was stopped, intravenous pulse corticosteroid therapy was given for 5 days followed by oral prednisolone tappered over several months. Additionally, two doses of 1000 mg each of Rituximab were applied. Over 6 months, the ESR fell to normal, the anemia resolved and the cognitive impairment improved slowly albeit incompletely.
Discussion: Rheumatoid leptomeningitis (RLM) is a rare neurological complication of rheumatoid arthritis (RA). It usually occurs in patients with longstanding RA but can also be found early in disease or even as the presenting manifestation. Symptoms may include behavioral

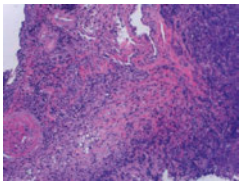

Figure 1: Histo-1_ LeptomeningitisCR.

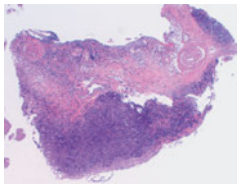

Figure 2: Histo-2_ LeptomeningitisCR.

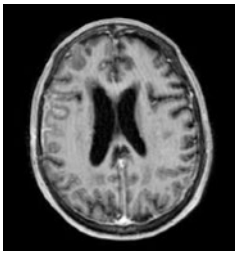

Figure 3: MRI_ LeptomeningitisCR.

changes, changes of consciousness, focal neurologic signs and seizures, headache, weakness and weight loss. Since RLM can develop regardless of systemic disease activity, it should be considered in any patient with RA and unexplained neurologic symptoms. Brain and meningeal biopsy are needed for diagnosis, allowing also to exclude opportunistic infections. Therapy consists of corticosteroids followed by immunsuppressive agents. Recent case reports show that the historically poor prognosis of RLM can thus be improved.

P456

Adult-onset Still's disease

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Introduction: Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease that occurs in less than 1 in every 100.000 people per year. Its classic symptoms consist of a triad of high spiking fever, joint-pain and a salmon-colored bumpy rash. It is a diagnosis of exclusion and symptoms may be unspecific and lead to a challenging search for a diagnosis.
Case: A 51-year-old male patient was admitted to our unit due to fever of unknown origin since three months, following a cold with a sore throat. He reported having episodes of exceptionally high fever spikes, predominantly at night. Patient history showed that he had been suffering from joint pain in his distal and proximal phalanges in both hands for over 1.5 years and his right hip for approximately 4 years. Joint pain was manageable with the use of mefenamic acid. He had not travelled outside of Switzerland or Austria for the past 9 years and worked in the recycling industry, as well as the fire department and denied contact with toxic substances. On admission blood work-up showed signs of inflammation, procalcitonin was negative, increased GOT, GPT, GGT, AP and markedly increased ferritin. Compared to a blood sample 4 months ago, we saw a substantial decrease in renal function, mixed proteinuria and an elevated erythrocyte sedimentation rate. Abdominal ultrasound and CT-scan only showed splenomegaly. Infectious diseases, hematological malignancies and immunological disorders were ruled out. AOSD was diagnosed with Yamaguchi's diagnostic criteria, of which the patient fulfilled three major (fever spikes, joint pain, leukocytosis) and four minor criteria (sore throat, elevated liver enzymes, negative tests for rheumatoid factor and antinuclear antibody, splenomegaly). Kidney biopsy showed acute interstitial nephritis, most likely drug-related (mefenamic acid) and no signs of vasculitis. The patient was started on 1000 mg methylprednisolone i.v. daily for three days and subsequently 50 mg prednisolone orally per day. Symptoms improved shortly after therapy was started.
Conclusion: AOSD is a rare disorder that should be considered in patients with fever of unknown origin. The distinctive salmon-colored bumpy rash might be a give-away symptom, but as seen in this case, is not obligatory. Infectious, hematological and immunological causes need to be ruled out beforehand and the diagnosis can be made with Yamaguchi's criteria, which are 96.2% sensitive and 92.1% specific for AOSD.

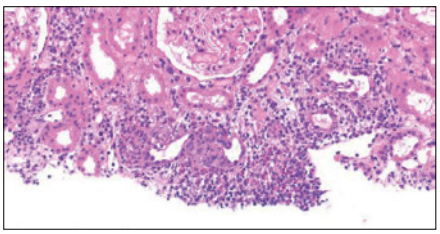

Figure 1: Renal histology 1.

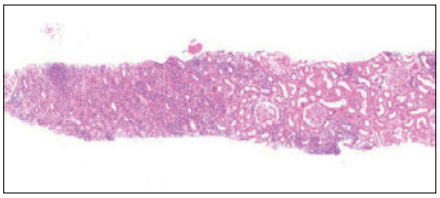

Figure 2: Renal histology 2.

P457

Atypical presentation of pneumocystis pneumonia in a tofacitinib treated patient with rheumatoid arthritis

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Introduction: Pneumocystis pneumonia (PCP) is a potentially life-threatening opportunistic infection in immunocompromised individuals. HIV-negative PCP patients, particularly those with inflammatory rheumatologic diseases, rapidly develop fulminate pneumonia with severe respiratory failure. As a diagnostic pitfall, in the early stages of PCP in these patients, respiratory symptoms are nonspecific and nonsevere. We report the case of a patient with rheumatoid arthritis (RA) treated with tofacitinib, who developed severe PCP with atypical clinical presentation.
Case report: A 78-year old male patient with RA treated with tofacitinib, an oral JAK inihibitor (a non-biologic targeted synthetic DMARD), methotrexate (MTX) and low dose corticosteroids (Prednisolon 5 mg daily) was admitted with arthralgia, nausea and confusion. Laboratory findings revealed hypercalcemia 3.12 mmol/l albumin-corrected with normal PTH and elevated 1,25-dihydroxyvitamin D3 (162 ng/l). Therapy of hypercalcemia was initiated at admission with intravenous sodium chloride solution (0.9%). For further investigation of hypercalcemia we performed a CT scan, that showed bilateral interstitial pneumonic infiltrates.

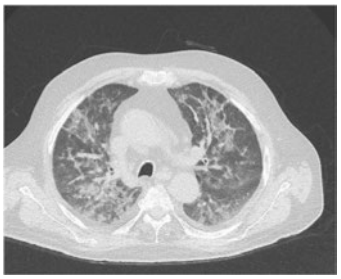

Figure 1: CT scan: bilateral pneumonic infiltrates.

We started an antibiotic therapy with ceftriaxone and clarithromycin. The patient developed respiratory failure with need for non-invasive ventilation/ high flow oxygen therapy on ICU. Bronchoalveloar lavage revealed a positive pneumocystis jiroveci PCR and adequate therapy with trimethoprim/sulfamethoxazole (TMP/SMX) and prednisone was initiated. After seven days intensive care, the patient was referred to the normal ward. Treatment with TPM/SMX had to be stopped because of severe hyponatremia and acute status of confusion. As second line therapy we initiated clindamycin and primaquine. Four days later we stopped the therapy due to thrombozytopenia. The patient recovered respiratorilly after 17 days of antibiotic therapy. Hypercalcemia resolved under adequate therapy of PCP and was – after exclusion of other possible causes – probably fungal associated.
Conclusion: PCP should be considered in RA patients on Tofacitinib treatment. The diagnosis can be challenging because of atypical clinical presentation. Hypercalcemia in conjunction with a pulmonary infection should raise the clinical suspicion of PCP. Considering the potentially fatal courses of PCP and with the rise of new biological and non-biological DMARDs it is important to evaluate carefully the need for PCP prophylaxis.

P458

A rare reason for genito-oral ulcerations

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Introduction: Behcet disease (BD) is an inflammatory multisystem disease of unknown origin. The clinical presentation is heterogenous, leading to delayed diagnosis. However, the main characteristic sign is a bipolar aphthosis. The prevalence is high in countries along the silk road (from Japan over the middle east to the Mediterranean countries). BD is rare in western Europe. However, an increase of case reports in our geographic region during the last years indicates the importance of knowing and recognizing the clinical symptoms of BD. Because of the lack of universally accepted diagnostic criteria, the mainstay of diagnosis is the clinical presentation and the exclusion of differential diagnosis.
Case description: We describe the case of a 20 years old male Swiss. He presented with oral and genital aphthosis. Because of oral

pain, intake of food and fluids was limited and the patient dehydrated. Two weeks before, the patient had already consulted several other physicians and was prescribed several symptomatic treatments without improvement of symptoms. The former medical history was unremarkable. Infectious causes and Crohn's disease were excluded by serologies and endoscopic and histologic investigations. Therefore, the suspicion of a first episode of BD was raised. After starting a therapy with prednison and colchicin, the patient recovered quickly. After hospitalization, the patient was seen in the rheumatological outpatient clinic. To underpin the diagnosis, HLA B51 was tested to be positive.
Conclusion: Our case is a classical example that the diagnosis of BD is difficult and needs a high clinical suspicion. The diagnosis of BD is difficult, hard to prove and can often be confirmed only at the long run after excluding many other possible diagnosis. Our patient was of western European origin, an ethnology that typically is rarely affected by BD. Our case report shows, that BD may occur as well in patients of western European origin. BD in our western population is probably more frequently then assumed. Therefor thinking of BD is those symptoms is not an orphan diagnosis.

P459

Amebic liver abscess in a man with liver hemangioma

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Entamoeba histolytica is a protozoan parasite that colonizes the large intestine of humans causing amoebiasis. It remains a significant cause of morbidity and mortality in developing countries and is responsible for up to 100,000 deaths worldwide each year. The clinical outcome of an E. histolytica exposure varies greatly and can present as diarrhea, dysentery or invasive amoebiasis. Amoebic liver abscess is the most common manifestation of extra-intestinal amoebiasis. We report the case of a man known for hemangioma, with superimposed amebic liver abscess. A 51-year-old male patient with a history of 3 weeks abdominal discomfort with epigastric heaviness, abdominal bloating, weight lost and the last 2 days fever up to 39 °C. He spent one week in India 4 months before. Clinical examinations show normal blood pressure (108/66 mm Hg), low-grade fever (37.3 °C) while the abdominal exam is insignificant. Laboratory tests show increased C-reactive protein (221 mg/l) and leukocytosis (15.0 G/l) without eosinophilia. Liver and pancreatic enzyme levels are normal. Urinary, stool and blood cultures are negatives. Antibody tests for Campylobacter Yersinia and Salmonella are negative. Abdominal ultrasound shows several hemangioma (V, VI and VII segments) and a new lesion at hepatic dome entering in differential diagnosis between abscess and hemangioma. An abdominal MRI confirms the presence of several hemangioma and shows an abscess of 4.5 cm in diameter, hard to drain, because of the diaphragmatic proximity (fig. 1). Two different antibody tests (ELISA at 1.43, IFAT at 320) confirm the diagnosis of amoebiasis. Under the treatment of 14 days of Metronidazole, followed by a week of paromomycine the patient fully recovers. A control MRI 6 months later shows a complete regression of the liver abscess, confirming ALA (fig. 2). Amoebic liver abscess (ALA) is an uncommon but potentially life-threatening complication of infection with the protozoan parasite E. histolytica. Complications involve rupture of the abscess causing spreading into the peritoneum, pleural space or pericardium. Recognition of variable presentation of ALA is vital, considering the curable nature of this disease and potentially fatal outcome of untreated abscess. In our patient, the presence of liver hemangioma was tricky, potentially leading to erroneous diagnosis. Travel history represents a key moment in the diagnostic process.

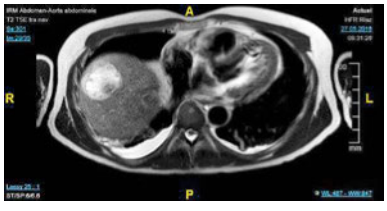

Figure 1

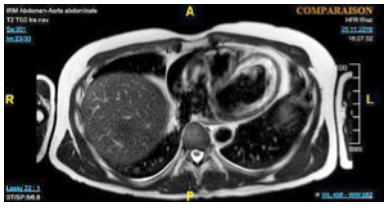

Figure 2

P460

From acute otitis media to acute kidney injury – a clinical case

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Introduction: Granulomatosis with polyangiitis (GPA; Wegener's) is a rare and potentially lethal systemic necrotizing granulomatous vasculitis of the small- and medium-sized arteries and veins, classically involving the upper and lower respiratory tracts with frequent involvement of the kidneys. Prevalence of otologic manifestations at beginning of disease varies from 19 to 61%; most frequent findings there are chronic otitis media, followed by serous otitis media and sensorineural hearing loss.
Case report: A 53-years old woman was evaluated in hospital for abdominal pain after returning from a journey to India, and a 4 weeks previously diagnosed and treated right sided acute otitis media with perforation and affection of the inner ear with persistent otalgia, otorrhoea, hearing loss and tinnitus. Clinical and sonographic abdominal examinations were inconclusive. Laboratory findings showed elevated inflammatory parameters. After an observation period of 4 days with spontaneous regression of abdominal pain, patient newly presented fever additionally to aggravation of otitis symptoms, slight dyspnoea and biltateral conjunctivitis. Unenhanced CT-scan showed acute mastoiditis and affection of inner ear on the right side as well as bilateral pulmonary nodules. Furthermore development of a rapid progressive renal failure with active urine sediment was noticed. Evidence of proteinase 3 antineutrophilic cytoplasmatic antibodies (PR3-ANCA), in combination with histological findings of focal segmental extracapillary proliferative glomerulonephritis in kidney biopsy, finally led to diagnosis of a granulomatosis with polyangiitis. Under immunosuppressive therapy with high-dose corticosteroids and cyclophosphamide patient showed a rapid improvement of symptoms and sings, induced to renal, pulmonal, abdominal, conjunctival and ear affections of vasculitis.
Conclusion: Occasionally otologic manifestations presents as the first signs of GPA, which makes diagnosis more difficult and delayed. Therefore, in cases of atypical inflammatory states of the ear or treatment failures GPA should be considered as a differential diagnosis. Histologic diagnosis from the middle ear is usually difficult (small specimens, lack of typical histologic findings), so that determination of ANCAs are helpful in making diagnosis, especially in ear limited disease. Early diagnosis and appropriate treatment is important to prevent progression of disease to an irreversible state.

P461

Septic encephalopathy or bacterial meningo-encephalitis in a patient with Parkinson's disease?

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A 85 year old caucasian woman known for Parkinson's disease and atrial fibrillation treated with rivaroxaban was admitted to our hospital with nausea, vomiting and elevated blood pressure since one day. Her blood pressure was 151/99 mm Hg, the heart rate 104 beats/min., the temperature 39 °C and the oxyganation 96% with 2l O_2/min. She was oriented, had no neck stiffness and her long standing symptoms of Parkinson's disease, e.g. tremor, rigor and orofacial dyskinesia had considerably worsened.Laboratory analyses showed thrombocytopenia and inflammation (Leucocytes 12.8×10^9/l, CRP 11 mg/L). However, chest X-ray and urine analysis did not identify an infectious focus. Empiric antibiotic therapy with amoxicillin/clavulanic acid was initiated and the patient satisfyingly recovered. After blood cultures were positive for Listeria monocytogenes treatment was adapted to amoxicillin and gentamicin. Due to anticoagulation lumbar puncture for CSF-analysis was not performed. On day 11 of hospitalisation the patient developed severe abdominal pain. CT-scan showed no abdominal pathology but pleural effusions. Two days later, the patient developed progressive dyspnea and somnolence and died one day later. The autopsy showed pneumonia and fresh pulmonary embolism. Morover subacute to chronic meningo-encephalitis was seen by the pathologist. Listeria monocytogenes (Lm) is an ubiquitous

gram positive rod capable of replication at a broad range of temperatures including refrigerated food (at 4 °C). It can be found on fruits, vegetables, meet, fish and cheese and may cause febrile foodborne enteritis. Immunodeficiency, pregnancy, alcoholism and advanced age are risk factors for invasive listeriosis like. The present case showed a meningo-encephalitis, only postmortem. The clinical presentation is often different to pneumococcal or meningococcal meningitis with a more gradual onset, less nuchal rigidity and more prominent movement disorders. Invasive Lm-infection is an important but rare disease with an incidence of 0.5–1 case/100'000 inhabitants and year (50–100 cases / year in Switzerland). Lm is inherently resistant to cephalosporins. Therefore, amoxicillin should be added to the empiric treatment regimen of suspected bacterial meningitis in patients with risk factors.

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POSTER SFGG / POSTERS SPSG

P462

Anticoagulant therapy in the elderly: how to be safe?

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Background: The management of anticoagulant treatment requires great caution in the elderly because of their frequent polypathology and polypharmacy. The aim of our study was to investigate the particularities of the use of anticoagulants in the elderly.
Methods: Retrospective study included 100 patients aged at least 65 years old and hospitalized for initiation of anticoagulation, was performed in an Internal Medicine Department between 2000 and 2015.
Results: They were 55 women and 45 men (sex ratio: 0.81), with a mean age of 75.7 ± 6.9 years. The indications for anticoagulant treatment were venous thromboembolism (VTE) (92%) and atrial fibrillation (AF) (8%). The VTE were divided into deep venous thromboembolism (DVT) of the inferior members (85%), superficial venous thromboembolism (SVT) (9%) and pulmonary embolism (PE) (6%). Eight patients had simultaneously two reasons for anticoagulation. Low molecular weight heparin (LMWH) was prescribed in 80% of patients and unfractionated heparin (UFH) in 20% of patients. The indication of UFH in our patients was a renal failure (creatinine clearance <30 ml/min). Overdose with heparin without bleeding was observed in 4 patients (30,7%) exclusively on heparin sodium. Heparin-induced thrombocytopenia was observed under LMWH in 2 patients (2.5%) and UFH in 4 patients (20%). The average length of overlap Sintrom®/heparin was 10.83 days ± 5.8. The average duration of treatment with Sintrom® was 17.22 days ± 7.9. The dose of Sintrom® initiation was 1 mg in 85% of patients and 2 mg in 15%. INR <2 was observed in 15% of patients. INR in the target area was obtained in 47% of patients with a mean dose of 2.33 mg of Sintrom®. An overdose under Sintrom® was noted in 38% of patients: average INR at 4.7. Seven patients had bleeding events. An overdose was noted in 4 among them. Fever, infection, inflammatory syndrome, hypoalbuminemia, hypoprotidemia and malnutrition were associated with a greater risk of overdose in our patients. Gastroduodenal ulcer disease, past medical history of gastrointestinal bleeding and renal failure <60 ml/mn were risk factors of bleeding in our patients.
Conclusion: The use of anticoagulants in the elderly requires a comprehensive assessment including comorbidities, geriatric settings and social environment.

P463

Risk factors of falls in the elderly: about 40 Tunisian patients

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Service de Médecine Interne B, Hôpital Charles Nicolle, Tunis, Tunisia

Background: Falls are common health problem in the elderly. Its origin is often multifactorial. The aim of our work was to identify risk factors of falls in elderly people, to study the contribution of clinical functional test to discriminate between fallers and no fallers, in order to establish preventive measures.
Methods: Retrospective study was conducted between September 2014 and January 2016 including 80 patients (65 years and over), followed at an Internal Medicine Department. Based on the presence or absence of a notion of falling in the previous year according to data from the anamnesis, we divided patients into 2 groups: case group (40 fallers) and control group (40 non-fallers). Risk factors of falls were screened by anamnesis and clinical examination. Timed up and go test, stop walking when talking and the unipodal stance test were realized in all patients after falls. Frailty was determined by SEGA score (Short Emergency Geriatric Assessment) after falls.
Results: The average age of faller's patients was 75.7 years old with a clear female predominance (30 W/ 10 M). The average number of contributing factors of falls was significantly more common among fallers (4) compared to non-fallers (2.8) ($p < 0.05$). Risk factors of falls identified in our study were: flat feet, knee osteoarthritis, osteoporosis, glaucoma, walking and balance disorders, nocturia and frailty. Otherwise, because of the low number of patients in our study, fallers and non-fallers were comparable in terms of average age, life style, polypathology of polypharmacy, urinary incontinence and loss of autonomy. Some clinical functional test allowed discriminating between fallers and non-fallers: Timed up and go test, stop walking when talking and the unipodal stance test.
Conclusion: A global care in the elderly, systematic screening for fall risk factors by all practitioners and establishing a "consultation falls" would prevent bad consequences of falls and improves the quality of life.

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POSTER PRESENTATIONS

P464

Impact of T-cell depletion on outcome of patients undergoing allogeneic hematopoietic cell transplantation (HSCT) for myelodysplastic syndrome (MDS)

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Introduction: MDS is a clonal haematological disorder and HSCT is the only curative option. In the transplant unit of Geneva University Hospital, we use partially T-cell depleted graft (TDEP) to reduce graft-versus host disease (GvHD). Here, we compared 3-years overall survival (OS), progression free survival (PFS), GvHD-free/relapse-free survival (GRFS), relapse incidence (RI) and transplantation-related mortality (TRM) between TDEP patients and non TDEP ones allografted for MDS. We also evaluated the impact of TDEP on acute and chronic GvHD.
Patients and methods: We analyzed 62 consecutive patients (44% were female, median age of 48 (range: 18–70) allografted for MDS (median EBMT risk score of 3, median disease risk index of intermediate risk) over a 19-year period (1998 to 2016) with MAC conditioning for 66% and RIC for 34%. Median time from diagnosis to HSCT was 7.5 months (range: 3–86). PBSC (90%) or BM (10%) grafts were from identical siblings (45%), MUD (42%) or MMUD (13%). T-cell depletion was performed for 52% of patients. Median follow-up was

4.6 years (range: 0–15). There was no significant difference between TDEP and non-TDEP for patient characteristics. OS, PFS were estimated using the Kaplan-Meier method. Cumulative incidence estimates of TRM and GvHD were calculated with RI defined as competitive events by the Fine and Gray method.
Results: 3-years OS for all patients was 42 ± 14%, PFS 40 ± 14%, GRFS 26 ± 12%, RI 37 ± 13% and TRM 25 ± 12%. 3-years OS for TDEP patients and for non TDEP ones was not different (48 ± 18% and 34 ± 21% respectively, p-value 0.317) (Graph). Similarly, there was not difference between TDEP and non TDEP patients for 3-years PFS (48 ± 18% and 28 ± 20%, p-value 0.321), 3-years GFRS (32 ± 17 vs 19 ± 17, p-value 0.111) (Graph), 3-years RI (36 ± 18% and 37 ± 20%, p-value 0.622) and 3-years TRM (26 ± 16% and 23 ± 18%, p-value 0.933). Finally, TDEP had no significant impact on 3-years grade 2-4 aGVHD when compared to the non TDEP (26 ± 18% and 31 ± 16%, p-value 0.656). It had not either on 3-years cGVHD (26 ± 18% and 28 ± 34%, p-value 0.637).
Conclusions: Our study shows that TDEP is feasible on patients undergoing HSCT for MDS and does not make the outcomes worse compared to non TDEP (OS, PFS, RI and TRM). Unexpectedly, TDEP does not significantly reduce the incidence of acute or chronic GVHD. However, the number of patients is small and the period span is long. These finding should be confirmed prospectively in larger cohort.

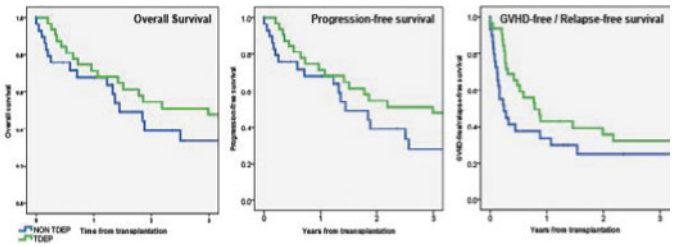

Figure 2

P465

Pretransplant lung function and performance status as mortality predictors after allogeneic hematopoetic stem cell transplantation: a single-center cohort study

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Introduction: Allogeneic hematopoetic stem cell transplantation (HSCT) remains associated with a high morbidity and mortality in spite of advances in HSCT management. Specifically, pulmonary complications account for a substantial proportion of deaths within the first 100 days after HSCT. Given the inconsistent association of pretransplant lung function parameters on mortality after HSCT and the significant changes in HSCT care over the last decades, the aim of our study was to estimate the effect of pulmonary function and comorbid conditions on mortality in patients undergoing HSCT.
Material and methods: We retrieved relevant clinical data of all consecutive patients at the Hematology division of the Basel University Hospital with a transplant for hematological disorders between 2008 and 2015. We examined the lung function at baseline and 3, 6 and 12 months after HSCT – including the 1-second forced expiratory volume (FEV1 % of predicted), FEV1/VCmax and diffusing capacity for carbon monoxide. Additionally, we assessed pretransplant conditions such as age, sex, Karnofsky Performance Status (KPS), donor type, and various risk scores in HSCT (HCT-CI, European Society for Blood and Marrow Transplantation [EBMT], revised Pretransplant Assessment of Mortality Score [PAM]). Using uni- and multivariate survival analysis, we evaluated potential patient- and transplant-related risk factors for all-cause mortality by including the following candidate variables: FEV1, KPS, age, conditioning intensity and donor type.
Results: Within the study period, 429 patients with predominantly acute leukemia (64%) or lymphoproliferative disorders (28%) underwent myeloablative (n = 330) and non-myeloablative (n = 99) HSCT at a median age of 54 years (interquartile range [IQR] 43–61 years). The analysis of the HCT-CI, KPS, EBMT and PAM score revealed median values of 2 (IQR 0–3), 90% (IQR 90–100%), 4 (IQR 3–5) and 15 (IQR 11–20), respectively. In univariate and multivariate analyses with a median follow-up of 12 months (IQR 3–36), a FEV1 of 50-79% vs. particular lower FEV1 of <50% and an impaired KPS <90% was significantly associated with a higher risk for all-cause death – independent of age, conditioning regimes and donor type
Conclusions: Taken into account the changes in practices, supportive care and management of comorbidities, in our cohort, a reduced pretransplant lung function and impaired performance status remain independent predictors of mortality in HSCT.

Table 1. Uni- and multivariate Cox proportional-hazards regression analysis of patient-and transplant related risk factors.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**p-values**	**HR (95% CI)**	**p-values**
FEV1 (% of predicted)				
≥80	reference	-	reference	-
50-79	1.7 (1.2-2.5)	0.006	1.6 (1.1-2.4)	0.011
<50	2.8 (1.4-5.8)	0.004	2.5 (1.2-5.1)	0.014
KPS (%)				
≥90	reference	-	-	-
<90	1.8 (1.3-2.5)	0.001	1.7 (1.2-2.4)	0.002
Donor type				
matched-related	reference	-		
mismatched-related	1.7 (0.7-4.1)	0.274	-	-
matched-unrelated	1.4 (1.0-2.0)	0.052		
mismatched-unrelated	1.2 (0.8-1.9)	0.371		
Age (years)				
<54	reference	-	-	-
≥54	1.3 (0.9-1.7)	0.108		
Conditioning intensity				
non-myeloablative	reference	-	-	-
myeloablative	0.8 (0.6-1.2)	0.844		

P466

Haploidentical hematopoietic bone marrow transplantation with consecutive living kidney transplantion from the same donor in a sickle cell disease patient with end-stage renal failure

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Introduction: Homozygous Sickle cell disease (SCD) patients suffering from end-stage renal disease (ESRD) show a variable outcome after kidney transplantation. We present a case of a 27-year old patient with severe SCD and ESRD who underwent haploidentical bone marrow transplantation (BMT) with consecutive living kidney transplantion (LKT).
Methods: The patient suffered from multiple complications of SCD including stroke with secondary hemorrhage, symptomatic epilepsy, ESRD and uncontrolled hypertension. The rationale for BMT was uncontrollable iron overload. A reduced intensity conditioning regimen was used with (fludarabine, cyclophosphamide and 2Gy of TBI, dose-adjusted to ESRD). Graft-versus-host disease (GvHD) prophylaxis consisted of post-transplant high-dose cyclophosphamide, cyclosporine A (CyA) and mycophenolate mofetil (MMF). The donor was her 56-year old mother with HbS trait, the stem cell source was bone marrow, the cell dose 4.74×10^8 nucleated cells/kg. During conditioning daily hemodialysis was performed to keep drug levels stable. Neutrophil engraftment occurred on day +26, chimerism at day +19 was 98%. HbS increased from 1.3% pre-HSCT to 40.0% 6 months after HSCT. Hemoglobin values increased from 70 g/L pre-HSCT to 110 g/L post-HSCT and reticulocytes from 16 G/L to 124 G/L. Erythropoietin levels increased from 2.3 IU/L pre-HSCT to 178 IU/L 6 months after HSCT. During the follow-up, the patient did not show any sign of acute GvHD or vaso-occlusive crisis, hemolysis or sickling. Relevant complications were disease-related (therapy resistant hypertension and epileptic seizure due to former brain damage). On day +151 a LKT from the same donor was performed. The initial immunosuppressive treatment with MMF was continued, CyA was switched to tacrolimus and steroids were added for 3 months. The post-transplant period was uneventful. Currently, 12 months after haploidentical BMT and 6 months after LKT there are no signs of GvHD, the blood chimerism is 100%, the kidney allograft function is very good (GFR 73 ml/min/1.73 m^2) and immunosuppression is withdrawn. Iron overload is being corrected by regular phlebotomies. The patient no longer requires antihypertensive medication and there is evidence of vascular remodeling.
Conclusions: This is the first report of a successful haploidentical BMT followed by kidney transplantation from the same donor in a patient with SCD.

P467

Promising success rate of hematopoietic stem cell remobilization with vinorelbine and filgrastim in acute myeloid leukemia with primary mobilization failure

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Introduction: Autologous stem cell transplantation (ASCT) is used to consolidate a first remission in good- and intermediate-risk acute myeloid leukemia (AML) patients, and peripheral blood stem cells (PBSC) are the predominant graft source. Few data exist on the failure rate to mobilize a sufficient number of PBSC in AML patients after documented achievement of a first complete remission. In addition, the efficacy of subsequent PBSC remobilization and the outcome after ASCT using remobilized PBSC are unknown in AML patients with primary mobilization failure.
Methods: In this single-center retrospective analysis, we evaluated our strategy using a single dose of 35 mg/m^2 vinorelbine and filgrastim as a rescue procedure to remobilize PBSC of AML patients in first complete remission (CR1) following primary mobilization failure after two cycles of induction chemotherapy. We aimed to determine the survival rates of AML patients successfully remobilized with vinorelbine compared to conventionally mobilized patients.
Results: Between 05/2005 and 01/2015, 69/85 (81%) AML patients in CR1 underwent successful collection of PBSC after two cycles of induction treatment whereas 16/85 (19%) patients had primary mobilization failure. With 37.5% (6/16 patients), the rate of mobilization failure was highest in *NPM1*mut-*FLT3*wt patients as compared to the other genomic subgroups. In 9 of the 16 (56%) patients with primary mobilization failure, subsequent treatment with vinorelbine and filgrastim mobilized sufficient PBSC to enable these patients to proceed to ASCT consolidation whereas the seven patients with failure after vinorelbine mobilization ultimately underwent conventional chemotherapy consolidation. Finally, we observed that progression free and overall survival rates were not different between primary and secondary mobilizers nor were hematologic recovery or transplant-related mortality.
Conclusion: Our data suggest that vinorelbine remobilization is an effective rescue option for AML patients in first remission with primary PBSC mobilization failure, thereby enabling such patients to proceed to subsequent ASCT consolidation.

P468

Efficacy of granulocyte colony stimulating factor in combination with erythropoiesis stimulating agents in the treatment of anemia in patients with lower-risk myelodysplastic syndromes: a systematic review

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Introduction: The myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic stem cell disorders characterized by dysplasia and peripheral cytopenias with a propensity to evolve towards acute myeloid leukemia (AML). The treatment of patients with lower-risk MDS (IPSS: low or intermediate-1) includes the application of hematopoietic growth factors like erythropoiesis stimulating agents (ESA) eventually in combination with granulocyte colony stimulating factor (G-CSF). However, the evidence on the additional effect of G-CSF on erythropoiesis remains unclear. The goal of this systematic review is to identify the level of evidence for treatment of anemia by EPO + G-CSF in lower-risk MDS patients.
Methods: We performed a systematic literature research by examining the Cochrane Library, Embase and PubMed databases. We additionally checked ongoing trials and conference abstracts of the American Society of Hematology and the European Hematology Association. We focused on interventional studies investigating the effect of G-CSF combined with ESA in patients with lower-risk MDS. Therefore, only randomized controlled trials (RCTs) investigating ESA + G-CSF vs. ESA were considered. Endpoints of interest were the

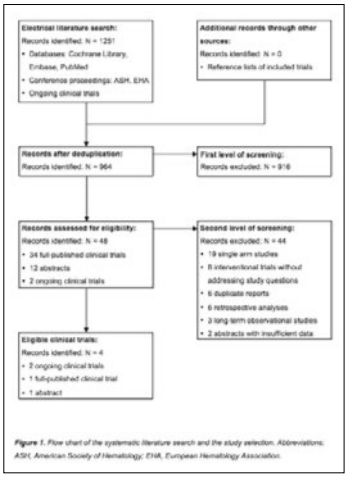

Figure 1

erythroid response according to IWG 2000/2006, reduction in red blood cell transfusion and transfusion-independency.
Results: We could identify only two small RCTs. In 2006, Balleari et al. performed a small RCT investigating the effect of recombinant human EPO (rhEPO) 10'000 IU s.c. 3×/week vs. rhEPO + G-CSF 300 µg s.c. 2×/week for at least 8 weeks in 30 patients. Erythroid response was 73% (11/15) in patients receiving rhEPO + G-CSF compared to 40% (6/15) receiving rhEPO only after 8 weeks. Nair et al. submitted an abstract to the Blood Journal in 2006 of a RCT investigating the effect of rhEPO 10'000 IU + G-CSF 150 µg 1x/week vs. rhEPO alone for 12 weeks in 68 patients. Erythroid response was 65% in the arm with rhEPO + G-CSF compared to 33% with rhEPO alone. Furthermore, we identified two relevant trials (NCT00234143, NCT01196715), which were terminated early without publishing relevant data.

Table 1. Treatment characteristics and erythroid responses of interventional trials mentioned in our systematic review. Abbreviations: G-CSF, Granulocyte Colony Stimulating Factor; rhEPO, Recombinant Human Erythropoietin.

	Balleari et al., 2006		Nair et al., 2006	
	Arm A	Arm B	Arm A	Arm B
Patients N (%)	15/30 (50%)	15/30 (50%)	55/68 (81%)	13/68 (19%)
Treatment	- rhEPO 10'000 IU 3x/week - G-CSF 300 µg 2x/week	- rhEPO 10'000 IU 3x/week	- rhEPO 10'000 IU 1x/week - G-CSF 150 µg 1x/week	- rhEPO 10'000 IU 1x/week
Erythroid response	11/15 (73.3%)	6/15 (40%)	N/A (65%)	N/A (33%)

Table 1

Discussion: G-CSF in combination with **low-dose** ESA seems to have a positive effect on the erythroid response in patients with low-risk MDS. However, the numbers of RCTs are low and the sizes of study populations are small. Moreover, RCTs on EPO-refractory MDS patients receiving **full-dose** (60'000–80'000 IU) are lacking and strongly needed in the future.

P469

Consolidation of second remission with autologous stem cell transplant is associated with improved survival in myeloma patients

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Introduction: Despite remarkable progress in the treatment of myeloma, the majority of patients consolidated with ASCT in first remission will relapse within a few years. Whereas numerous options have become available for relapse treatment, the role of ASCT to consolidate a second remission (ASCT2) remains less clear. In particular, randomized studies in relapsing myeloma patients are lacking comparing the strategy of prolonged administration with one of the current doublet or triplet combinations versus the concept involving a limited number of such cycles followed by ASCT2.
Methods: In this retrospective single-center study, we compared these two therapeutic options in consecutive myeloma patients with a first

relapse after ASCT1 between 2002 and 2015. We assessed the survival rates of myeloma patients consolidated with ASCT in second remission (ASCT2), and we compared them to myeloma patients receiving prolonged reinduction treatment without ASCT2.
Results: The cohort comprised 108 myeloma patients relapsing after melphalan-based high-dose chemotherapy (HDCT) with ASCT1. The second remission was consolidated in 68 patients with ASCT2, whereas 40 patients were treated without ASCT2. ASCT2 was more likely to be performed in myeloma patients with longer remission duration after ASCT1 (28.7 vs. 20.7 months) and with better response after ASCT1 (CR1 achieved in 66% versus 28%), whereas other parameters did not differ. There was no treatment-related mortality associated with ASCT2. ASCT2 was associated with longer progression-free survival as compared to a strategy omitting ASCT2 (PFS2: 30.2 months versus 13.4 months; $P = .019$). Despite a longer median follow-up of patients with ASCT2 (39.6 months versus 16.3 months; $P = .012$), fewer patients (57%; 39/68 patients) relapsed so far after ASCT2 compared to patients (70%; 28/40 patients) relapsing after second-line treatment without ASCT2 ($P = .045$). Overall survival (OS) was better for patients with ASCT2, with the median value not yet reached, compared with 25.9 months in patients without ASCT2 ($P < .0001$). We observed fewer patients (25%; 17 patients) dying of myeloma progression in the group with ASCT2 compared with 58% (23 patients) in the cohort without ASCT2 ($P = .001$).
Conclusion: Our results suggest that consolidating a second remission with melphalan-based HDCT with ASCT2 is associated with better survival rates in myeloma patients relapsing after first-line treatment including HDCT and ASCT1.

P470

Trends of incidence and mortality of chronic myeloid leukemia in Switzerland between 1995–2013

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Background: Chronic myeloid leukemia (CML) is a clonal haematopoietic stem cell disorder characterized and diagnosed by the presence of the oncogenic BCR-ABL fusion gene. CML is treated with specific tyrosine kinase inhibitors (TKIs), a standard therapy since the early 2000. This targeted treatment option has completely changed the prognosis for CML patients (pts). Based on population data from the cancer registry in Switzerland, we aimed to describe epidemiological data over different time periods between 1995–2013.
Methods: A retrospective observational analysis (age, incidence rate, mortality rate) was performed on data from pts with CML (ICD-O-3 code) reported to the Cantonal Cancer Registries between 1995 and 2013 and aggregated by the National Institute for Epidemiology and Cancer Registration. The Swiss Federal Statistical Office provided mid-year Population Estimates and the Cause of Death Statistics from all persons in Switzerland. Three time periods were defined, 1995–2000 (pre-TKI era), 2001–2006 (imatinib era) and 2007–2013 (first and second generation TKI era).
Results: 1'122 new CML cases were registered, corresponding to an extrapolated number of 1'843 new CML cases in the Swiss population during 1995-2013. This represents an median annual case number of 55 males (range 36 to 67) and 42 females (range 27–56) in entire Switzerland. Age-adjusted incidence rates of males were around 40–70% higher compared to females, however, remained stable for males and females during the observation period. Age-adjusted mortality rates decreased in males and females over the three time periods by 50–80% (fig. 1).

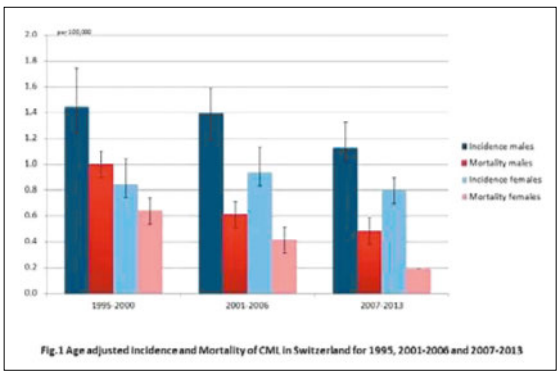

Fig.1 Age adjusted Incidence and Mortality of CML in Switzerland for 1995, 2001-2006 and 2007-2013

Figure 1

Conclusions: The results are the first population-based epidemiological data analysis from CML patients in Switzerland. We found a stable incidence of CML over the years observed and importantly, a significant decrease in the mortality rates reflecting the high efficacy of TKI treatment. Further survival analyses are planned to examine this decline in more detail. Moreover, longitudinal data on treatment, side-effects and outcomes is warranted.

P471

Revisiting G-CSF support for hematologic recovery after autologous transplantation in AML patients

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Introduction: In acute myeloid leukemia (AML), the use of granulocyte colony-stimulating factor (G-CSF) to support hematologic recovery in induction and consolidation treatment reduces the number of febrile episodes as well as the duration of neutropenia and of hospitalization. Despite these facts, it is not routinely used partly because of concerns of G-CSF possibly promoting the growth of residual leukemic cells. However, a number of prospective studies in AML patients have failed to demonstrate negative effects on survival rates when G-CSF is used to enhance hematologic recovery. In contrast, studies in AML patients undergoing autologous stem cell transplantation (ASCT) have not been reported so far. Therefore, it is largely unknown whether administration of myeloid growth factors after ASCT is safe in AML patients.
Methods: At our center, it was our policy to administer G-CSF after ASCT in all AML patients. In June 2015, however, increasing economic pressure prompted us to omit G-CSF after ASCT thereby saving the costs of G-CSF. In this retrospective study, we assessed the effects of changing our strategy from applying G-CSF for hematologic recovery after ASCT (in 103 AML patients) to omitting G-CSF (12 patients).
Results: We found that administering G-CSF shortened the median duration until neutrophil recovery was >0.5 G/l and >1.0 G/L after ASCT by four days ($P = .0001$) and five days, respectively($P = .0020$), whereas no differences were observed for platelet recovery and transfusion needs. At least one febrile episode during neutropenia after ASCT occurred in patients with (87.7%) and without (100%) G-CSF support ($P = .1932$), but patients with G-CSF tended to have fewer bacteremias (38.3% versus 66.6%; $P = .0654$). The median duration of hospitalization was two days longer in patients without G-CSF support (25 days versus 23 days; $P = .0603$). According to the current version of the diagnosis-related index of the Swiss in-patient reimbursement system, the shorter hospitalization of +G-CSF patients resulted in decreased total costs per patient of 3305 CHF (48 Mio U of G-CSF), and 3367 CHF (30 Mio U). No differences were observed in disease free ($P = .0938$) and overall survival ($P=.7999$) rates between +G-CSF versus -G-CSF patients.
Conclusions: Our data suggest that G-CSF support after ASCT is safe and associated with shorter time until neutrophil recovery, fewer bacteremia episodes, shorter hospitalization, and lower costs.

P472

Impact of different T-cell depletion techniques on the incidence of infectious complications after allogeneic hematopoietic stem cell transplantation

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Introduction: T-cell depletion (TCD), obtained by either *in vivo* anti-thymocyte globulin (ATG) administration or *ex vivo* depletion, is a strategy for Graft-versus-Host-Disease (GvHD) prevention after allogeneic hematopoietic stem cell transplantation (HSCT) [1–4]. The prolonged lymphopenia can result in increased incidence of disease relapse[1] and infections.
Patients and methods: We retrospectively evaluated the incidence of infectious complications in 236 consecutive patients who underwent allogeneic HSCT at our center from September 2010 to December

2015. 100 patients received TCD grafts by *in vivo* ATG administration (ATG group). 17 patients received partially TCD grafts obtained through incubation with alemtuzumab *in vitro* followed on day +1 by an add-back of donor T CD3+ cells[5] (pTCD group). 60 patients received grafts TCD by both methods. 59 patients did not receive any form of TCD (No-TCD group). Cumulative incidence estimates of infectious complications were calculated and compared using the Gray test. GvHD or death from other causes were defined as competitive events in the analysis.
Results: We didn't observe any significant difference in the 1-year cumulative incidence of bacterial infections in patients receiving TCD by ATG [45% (95%CI 35%-54.5%)] pTCD [58.8% (95%CI 31.2–78.5%)] or both [55% (95%CI 41.4–66.7%)] compared with patients receiving No TCD [52.5% (95%CI 38.9–64.5%)]. Similarly, the 1-year cumulative incidence of viral infections or reactivations was comparable in patients receiving No-TCD grafts [80.3% (95%CI 66.8–88.8%)] compared with patients receiving TCD grafts [ATG: 82.2% (95%CI 72.9–88.6%); pTCD: 76.5% (95%CI 45.7–91.2%); ATG+pTCD: 81.7% (95%CI 68.9–89.6%)]. Finally, no significant impact of TCD was observed on 1-year cumulative incidence of fungal [No-TCD: 6.8% (95%CI 2.2–15.2%); ATG: 18.1% (95%CI 11.2–26.3%); pTCD: 11.8% (95%CI 1.8–31.9%); ATG+pTCD: 18.3% (95%CI 9.7–29.1%)] and parasitic [No-TCD: 1.7% (95%CI 0.1–8%); ATG: 1% (95%CI 0.1%-4.9%); pTCD: 5.9% (95%CI 0.3%-24.2%); ATG+pTCD: 1.7% (0.1–8.3%)] infections.
Conclusion: The results indicate that the cumulative incidence of infections are similar in patients receiving TCD grafts compared to those receiving No-TCD graft, suggesting a favorable toxicity profile of different TCD strategy in respect of infections. These results should be confirmed by similar analysis in large scale, prospective clinical trials.

P473

Systemic inflammatory and autoimmune manifestations in the *Bernese Myelodysplastic syndromes cohort* and their influence on outcomes

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Introduction: Myelodysplastic syndromes (MDS) are heterogeneous clonal hematologic disorders affecting the hematopoietic stem cells, leading to ineffective hematopoiesis with a propensity to evolve towards acute myeloid leukemia. An increased prevalence of systemic inflammatory and autoimmune manifestations (SIAMs) has been described anecdotally in myeloid malignancies. Here we present an interim analysis of a study investigating the differences of disease- and patient-based factors as well as outcomes in MDS patients with/without SIAMs.
Methods: We performed a retrospective study of a patient cohort at our institution with newly diagnosed MDS between 01.01.08 and 31.09.16. Medical records of MDS patients were reviewed. We investigated differences between patient- and disease-based factors as well as overall-survival (OS), progression-free survival (PFS) and leukaemia-free survival (LFS) in MDS patients with and without SIAMs. SIAMs were classified according to Kastner, Davidson and Diamond. Autoimmune metabolic disorders, e.g. Diabetes mellitus, were excluded.
Results: 95 patients were diagnosed with MDS and 30 patients were identified with SIAMs (35%). SIAMs comprised affections of musculoskeletal system (33.3%), vascular system (26.7%), fever of unknown origin (23.3%), skin (16.7%), inflammatory bowel diseases (13.3%) and others (20%). SIAMs were treated with glucocorticoids (40%), Methotrexate (16.7%), biologicals (13.3%) and Cyclosporine (3.3%). For patient-based factors, we found a significant difference of cardiovascular comorbidities in MDS patients with SIAMs comparted to those without SIAMs. Age, gender and other comorbidities as well as exposure to chemotherapy were equally distributed. For disease-based factors, no difference in IPSS/IPSS-R was seen. CMML and RAEB-1 were more frequent in SIAM patients, in contrast RCMD was more often seen in MDS patients without SIAMs. Finally, the OS, PFS and LFS were equal for both groups.
Conclusion: The heterogeneity of MDS and SIAMs challenged our investigation. We found an increase of cardiovascular comorbidities in MDS patients with SIAMs. However, due to limited patient numbers our study allowed us to detect only trends. We are, therefore, interested in extending our investigational questions in a broader MDS cohort such as the *Swiss MDS Registry/Biobank* platform. Therefore, we aim to include additional MDS patients from this national and potentially international collaborators (Düsseldorf MDS Registry).

Table1: Organ involvements of SIAMs in MDS patients

Organ involvement	SIAM patients N = 30
Musculoskeletal	10 (33.3%)
Polyarthritis/Arthritis	6
Polymyalgia rheumatic	4
Vasculitis	8 (26.7%)
Vasculitis not further classified	5
Arteritis temporalis	3
Autoinflammation*	7 (23.3%)
Skin lesions	5 (16.7%)
Atopic dermatitis	2
Erythema nodosum	1
Pyoderma gangrenous	1
Parapsoriasis	1
Inflammatory bowel disease	4 (13.3%)
M. Crohn	2
Inflammatory colitis	1
Atrophic gastritis with parietal cell antibodies	1
Others*	6 (20%)
Enoral ulcera	2
Autoimmune uveitis	1
BOOP	1
SLE	1
Hashimoto thyroiditis	1
Autoimmune haemolysis	1
TOTAL	41

*fever of unknown origin, humoral activity
* Autoimmune uveitis/enoral ulcera/BOOP/SLE/Hashimoto/autoimmune haemolysis

Table 1

Table 2: Patient- and disease-based factors

		MDS without SIAM N = 65	MDS with SIAM N = 30	significance[2]
Patient-based factors				
Sex	Female	28 (43.1%)	10 (33.3%)	0.50
	Male	37 (56.9%)	20 (66.7%)	0.50
Comorbidities	Cardiovascular	41 (63.1%)	27 (90%)	0.0071
	Renal insufficiency	22 (33.8%)	12 (40%)	0.65
	Tumor	13 (20%)	5 (16.7%)	0.79
	Diabetes mellitus	13 (20%)	9 (30%)	0.30
Exposure to chemo- and/or radiotherapy before MDS		5 (7.7%)	2 (6.7%)	1.00
Disease-based factors				
MDS subtype	RARS	5 (7.7%)	1 (3.3%)	0.66
	RCMD	25 (38.5%)	6 (20%)	0.10
	RAEB-1	7 (10.8%)	7 (23.3%)	0.13
	RAEB-2	11 (16.9%)	6 (20%)	0.79
	CMML1/2	9 (13.8%)	8 (26.7%)	0.15
	Others*	8 (12.3%)	2 (6.7%)	

*suspected MDS, MDS not further classified
[2] Fisher test

Table 2

P474

Paraproteinemia after allogeneic hematopoietic stem cell transplantation: a transient phenomenon of underexplored significance

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Introduction: The clinical and biological relevance of paraprotein that newly arises after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in non-myeloma patients is unknown. In healthy subjects, the incidence of monoclonal gammopathy of undetermined significance (MGUS) ranges from 3–9% and significantly increases with age. In these individuals, the absolute risk of progression to plasma cell myeloma at 20 years is 5–58%, depending on the MGUS subtype. The aim of this study was to investigate the incidence, the course and the clinical relevance of paraproteins found after allo-HSCT.
Methods: We retrospectively analyzed a cohort of 403 non-myeloma patients (median age: 48y, range: 18–69y, 57% men, 43% women) who underwent allo-HSCT at the Division of Hematology of the University Hospital Zurich between January 2004 and December 2014. Patients with a MGUS before allo-HSCT were excluded from the study. The immunoglobulin subtype and the light chain restriction of paraproteins were determined by immunofixation.
Results: The incidence of paraproteinemia after allo-HSCT (56/403 patients, 14%) was higher than the reported incidence of MGUS in age-matched healthy subjects and in contrast to MGUS did not correlate with age. The majority of patients carried an IgG paraprotein (80%), while IgM paraproteins were detected in 12.5% of patients. Rarely, two types of paraproteins were identified simultaneously. In most patients (44/56, 79%), the paraprotein appeared transiently

within the first year after allo-HSCT with a median duration of 5.8 months (range 2.5–43.9 months). Post-allo-HSCT paraproteinemia was significantly associated with chronic GvHD, but no association was found with other clinical and laboratory parameters. Importantly, development of plasma cell myeloma or lymphoma was not observed in patients with paraproteinemia arising after allo-HSCT.
Conclusions: Our study reveals a high incidence of transient paraproteins after allo-HSCT that unlike MGUS are not related to age and follow the expected immunoglobulin subtype distribution. Patients with post-allo-HSCT paraproteinemia are not at increased risk of developing plasma cell myeloma as observed for MGUS inferring a distinct pathogenic mechanism. Skewing of lymphocyte subpopulations and alterations in cytokine levels in chronic GvHD may explain the expansion of a specific plasma cell subset.

P475

Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukaemia

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Introduction: Hypothyroidism may complicate of allogeneic hematopoietic stem cell transplantation (allo-HSCT); risk factors are analysed. Methods**:** We studied 229 patients with AML who underwent an allo-HSCT between 2003 and 2013 with different conditioning regimens (myeloablative, reduced-intensity, chemotherapy-based, total body irradiation-based). Thyroid stimulating hormone (TSH) and free thyroxin levels (FT4) were available in 104 patients before and after allo-HSCT.
Results: Median age at transplantation (n = 104) was 47 years [IQR 40–59], 37 (35.6%) were female and overall mortality was 34.6% (n = 36). After a median follow-up period of 47 [IQR 25–84] months, overt hypothyroidism (basal TSH >4.49 mIU/l, FT4 <11.6 pmol/l) was observed in 4 patients (3.8%) and subclinical hypothyroidism (basal TSH >4.49 mIU/l, normal fT4) was observed in 20 patients (19.2%). Positive thyreoperoxidase (TPO) antibodies were found in 5 (4.8%) patients. A total of 13 patients (12.5%) were treated with thyroid hormone replacement. Acute graft versus host disease of any grade (aGvHD) occurred in 55 (52.9%) and chronic GvHD of any stage (cGvHD) in 74 (71.2%) of the patients. The risk of developing hypothyroidism was higher in patients with repeated allo-HSCTs (p = 0.024) and with positive TPO antibodies (p = 0.045). Furthermore the development of overt hypothyroidism was inversely proportional to age (p = 0.043). No correlation was found with GvHD, HLA-mismatch and gender.
Conclusions: After allo-HSCT a significant number of patients experience thyroid dysfunction including subclinical and overt hypothyroidism. Long-term and continuous follow-up for thyroid function after HSCT is important to provide timely and appropriate treatment.

Table 1: Baseline characteristics.

	All patients (n = 104)	Patients with hypothyroidism (n = 24)	Patients without hypothyroidism (n = 80)
Age at diagnosis (years), median (IQR)	46 (39–58)	45 (39–57)	47 (39–58)
Follow-up period (months), median (IQR)	47 (25–84)	71.5 (39–87)	42 (24–76)
Donor			
Identical sibling n (%)	54 (51.9)	13 (54.2)	41 (51.3)
Unrelated n (%)	45 (43.3)	8 (33.3)	37 (46.3)
Mismatched related n (%)	3 (2.9)	2 (8.3)	1 (1.3)
TBI conditioning			
No TBI n (%)	56 (53.8)	10 (41.7)	46 (57.5)
TBI n (%)	48 (46.2)	14 (58.3)	34 (42.5)

Table 2: Hypothyroidism.

Hypothyroidism			
TSH before HSCT UI/ml, median (IQR)	1.83 (1.19–2.58)	2.42 (1.85–3.34)	1.56 (1.15–2.29)
fT4 before HSCT mmol/L, median (IQR)	14.6 (13.35–16.75)	14.15 (12.83–16.18)	15.1 (13.4–16.8)
Overt hypothyroisdism n (%)	4 (3.85)	4 (16.7)	0
Subclinical hypothyroidsm n (%)	20 (19.2)	20 (83.3)	0
TSH max. after HSCT U/ml, median (IQR)	2.87 (1.88–4.4)	5.58 (4.94–6.97)	2.57 (1.68–3.1)
fT4 after HSCT mmol/L, median (IQR)	14.9 (12.7–16.55)	14 (12.55–14.95)	15.75 (14.25–16.85)
Positive TPO Antibodies n (%)	5 (4.8)	3 (12.5)	2 (2.5)
Therapy with fT4 after HSCT n (%)	13 (12.5)	13 (54.2)	0

P476

Necrotic lymph-node infection with sporopachydermia cereana in a patient with acute myeloid leukemia: a case report

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Introduction: Sporopachydermia cereana is a rare yeast found in necrotic cactus tissue, predominantly in the Americas. Infection in humans has only been reported in 4 neutropenic patients with fatal course. Here we present a patient with acute myeloid leukemia (AML) and S. cereana infection.
Methods and results: We present the case of a 50 year old female patient who was diagnosed with normal karyotype AML in December 2015. She achieved complete remission after induction chemotherapy. During the 2nd induction cycle the patient developed persistent fever in neutropenia. Blood cultures showed growth of Sporopachydermia cereana, shown to be sensitive to azoles as well as amphotericin B, but resistant to caspofungin. Treatment was changed first to liposomal amphotericin B, and with the availability of MIC results to voriconazole. After a continuous fungemia, Blood cultures turned negative with the introduction of amphotericin B. A CT scan of the chest and abdomen prior to allo-HSCT after six weeks of treatment with voriconazole revealed new multiple necrotic mesenteric lymph nodes. An ultrasound-guided biopsy of a node revealed no growth on fungal cultures (Saboraud Agar), a Grocott stain revealed no hyphae or spores. A panfungal PCR of an ITS (Internal transcribed spacer) fragment revealed fungal DNA, which could be confirmed as S. cereana. Subsequent CT scans 4 and 6 weeks later revealed a regression of the affected abdominal lymph nodes. In the further course non-myeolablative conditioning with fludarabine and busulfan prior to allo-HSCT using PBSC from her HLA-matched brother was performed. The allo-HSCT was performed under voriconazole treatment with no further complications and the patient engrafted at day 20. Based on the susceptibility pattern, the treatment was changed to fluconazole 400 mg daily before discharge. Due to the complete radiological regression of the infection in follow-up scans and excellent general condition of the patient 5 months after HSCT, fluconazole was discontinued. The patient remains in morphological complete remission 6 months after HSCT and has a 100% donor chimerism.
Conclusions: The first published case of survival of infection with S. cereana exemplifies the continual progress made in treating infections in the severely immunocompromised patient. Diagnosis via ITS sequence-analysis seems reliable but a high index of suspicion is required for neutropenic patients who do not respond well to standard antimycotic therapy.

P477

Thalassemia intermedia with a rare mutation and unusual management: a case report

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We present the case of a 32 year old man from Sicily with β-thalassemia (Th). His parents and sister had a β-Th trait. At the age of 2 he showed hemoglobin (Hb) of 9 g/dL with HbA1 94.9% and HbA2 5.1%, Th minor was diagnosed. At 4 he got EBV-infection with symptomatic anemia (Hb 6.4 g/dL) and received first red blood cell concentrates (RBCc). HbA2 was 3.9%/ HbF 65% and diagnosis was changed to Th intermedia. Later his Hb remained at a level of 9 g/dL without transfusions. At 5 transfusions 2–3 RBCc every 3 weeks were started with concomitant chelation therapy to prevent from growth failure. His ferritin persisted beneath 1000 µg/l and clinically showed normal development without endocrine dysfunction, HIV or hepatitis, bone disease or pulmonary hypertension. Liver and heart MRI T2* / SQUID showed a severe iron accumulation in the liver but none in the heart. On 10/ 2014 he moved to Switzerland for work, hematologic controls were started in our policlinic. The patient showed good clinical condition with jaundice and slightly enlarged spleen. The Hb was 9.7 g/dL (2 days after RBCc), nucleated red blood cells (NRBC) 2/100 WBC, Platelets120 G/l, Bilirubin 114 µmol/l, Ferritin 886 µg/l, HbA2 3.1% and HbF 22.2%. A molecular analysis showed two heterozygotic mutations in HBB:c 93-21G>A (IVS-I-110) and HBB:c,-137C>G (-87C>G). We rated the aggressive transfusion regime as unnecessary and proposed its gradual reduction.
Methods: We aimed to identify the right transfusion regime and the need of additional therapy for this patient. RBCc were administered when anemia symptoms occurred or NRBC rose. A therapy with hydroxyurea was started on 02/2015, likewise antiplatelet therapy.
Results: Transfusion of RBCc could be reduced to 2 RBCc every 6–7 weeks with even improving quality of life. Hb below 7 g/dL and/or rising NRBC triggered transfusion although the patient generally had no symptoms of anemia. Last ferritin values varied between 300 to 500 µg/l, chelation could be consequently reduced. The HbF rose to 43%.
Conclusion: This compound heterozygocity of two known mutations is an unusual combination not previously reported in the literature. Both mutations found in mediterranean countries, usually lead to β+Th severe/intermedia. This patient was interpreted and managed during 25 years like a Th major. Therapy changes, prioritizing health status were well tolerated without clinical complications avoiding therefore unnecessary transfusions.

P478

Effect of baseline body mass index and body mass composition determined by bioelectric impedance in adults undergoing allogeneic hematopoietic transplantation

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Introduction: Body mass composition (BMC) might have an impact in outcomes of patients undergoing bone marrow transplantation. The aim of this study was to analyse the relationship between BMC before allogeneic hematopoietic stem cell transplantation (HSCT) and transplant outcomes in a cohort of patients transplanted between 2012 and 2014. Another objective was to determine if fat free mass index (FFMI) and fat mass index (FMI) have the potential of being more accurate indicators than Body Mass Index (BMI) to measure the relationship between nutritional status and overall survival (OS) and progression free survival (PFS) after HSCT.
Patients and methods: We realized a retrospective analysis in a cohort of 141 patients, aged over 18 years who received a first allogenic HSCT between 2012 and 2014. Bioelectrical impedance measurements were realized before HSCT to determine FFMI and FMI. We looked at the impact of these two indicators and BMI on OS and PFS. For FFMI and FMI we divided patients into: >90th percentile, between 90th and 10th percentile, and <10th percentile. For BMI we did a first analysis dividing patients with WHO BMI classifications <18, 18–24, and >24 but finding no relationship, we divided patients into: BMI <20, BMI between 20 and 30, and BMI >30. For all three indicators, we used Kaplan-Meier estimates to see OS and PFS. Cumulative incidence estimates of transplant related mortality (TRM) were calculated with the Fine and Gray method. Differences between curves were determined using Log-rank Mantel-Cox test.

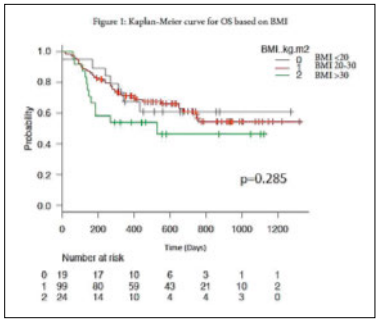

Figure 1: Kaplan-Meier curve for OS based on BMI.

Results: We found no statistically significant relationships between nutrition status and survival rates in any of the indicators considered. We did observe a relationship in which patients with the highest BMI had the lowest OS (fig. 1), but it was not statistically significant. Table 1 shows the impact of BMI, FMI and FFMI on OS and PFS.

Table 1: Results.

	BMI			FFMI			FMI		
	<20	20–30	>30	<p10	p10-p90	>p90	<p10	p10-p90	>p90
n	19	99	24	39	76	27	32	66	44
OS analysis (p)	0.285			0.79			0.72		
OS(%)	60	54	46	60	49	57	51	53	56
CI95%	(0.34–0.79)	(0.42–0.65)	(0.24–0.66)	(0.43–0.74)	(0.34–0.61)	(0.34–0.75)	(0.31–0.68)	(0.38–0.67)	(0.39–0.70)
PFS analysis (p)	0.78			0.68			0.133		
PFS(%)	45	47	33	43	50	39	38	53	38
CI95%	(0.21–0.66)	(0.35–0.57)	(0.08–0.61)	(0.27–0.58)	(0.38–0.61)	(0.17–0.60)	(0.21–0.53)	(0.38–0.65)	(0.21–0.54)

Conclusions: Inconsistent results may show that bioimpedance indexes are not ideal for measuring survival in HSCT patients. While some larger studies show more conclusive results (1), others are inconclusive (2). Retrospective analysis and small population were limitations of our study. A prospective analysis should be done in a larger population to establish if BMI is a prognostic marker in HSCT. Efforts to assist patients in achieving healthy nutritional status before HSCT could be beneficial in survival rates and studies measuring the results of these efforts may provide more clarity

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Donor specific antibodies in haploidentical allogeneic stem cell transplantation: a case report

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Introduction: Haploidentical stem cell transplantation (haplo-SCT) is increasingly performed if a HLA-matched donor is lacking. Data show an association of donor specific HLA-antibodies (DSA) with graft failure in this setting. DSA occur in up to 14% of recipients, and are oft a reason for rejecting the donor, but can be reduced with plasmapheresis and immunosuppression. Patients with myelodysplastic syndrome (MDS) oft develop alloantibodies because of transfusions and underlying immunologic dysregulation. We report on a patient with MDS and rapidly developing DSA, who successfully underwent haplo-SCT.
Case report: A 67 year-old man with transfusion dependent anaemia and severe thrombocytopenia was diagnosed with MDS RAEB I in August 2015. Azacytidin treatment had no effect on transfusion requirements. A decision for allo-SCT with BM as preferred stem cell source was met, but only his two sons (SM*1982 and GM*1989) were identified as possible donors. In July 2016, an antibody screening revealed broad HLA-alloimmunisation and anti-c and -E alloantibodies, showing incompatibility to SM*1982 (DSA B*50:01, MFI 4600; anti-c-and E alloantibodies). RBC incompatibility but no DSA was also

present against GM, who was selected for peripheral blood stem cell donation instead of BM. An antibody screening for HLA-antibodies 3 weeks before SCT revealed 49 new specificities and DSA also against GM*1989 (B55*01, MFI 12'400). Because of progressive disease, SCT was nevertheless carried on. DSA reduction was made with a single dose rituximab on day -12 and plasma exchanges from day –9 until day –1. On day 0, the B55*01 DSA was negative (MFI 199), with anti-c and anti-E alloantibodies still present. A reduced intensity conditioning (fludarabine, cyclophosphamide, TBI 200 cGy), post-SCT high dose cyclophosphamide, and cyclosporine and mycophenolate as GVHD prophylaxis were given. Neutrophils engrafted on day 17. At day 30, platelets were >50 x10^9/l, the absolute reticulocyte count was >30 x10^9/l and chimerism was 100% donor type. At day 180, he had hyporegenerative anaemia supported with erythropoietin and sustained engraftment of neutrophils and platelets. Alloantibodies against c, E and HLA- antigens were detected, but the B55*01 DSA was negative.
Discussion: In haplo-SCT, the presence of DSA can be challenging. A careful evaluation of donor-recipient compatibility, including HLA- and RBC-antibody assessment, is of great relevance, especially in HLA mismatched and haplo-SCT.

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Last minute salvage of a severe hypereosinophilic syndrome of unsuspected origin

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We report the case of a 52-year-old man, referred for an extreme hypereosinophilia. He presented fatigue, quick loss of 14 kg and night sweats. He was in poor clinical condition. Laboratory data showed the following: hemoglobin 105 g/l, leucocytes 114 G/l, platelets 55G/l – rapidly evolving to <10 G/l, neutrophils 27 G/l, lymphocytes 3.4 G/l, monocytes 2.2 G/l, eosinophils 81 G/l, no basophiles. Peripheral blood smear showed dysplastic eosinophils, neutrophils with toxic granulations, few dacryocytes. Liver and renal tests were normal, LDH 310U/l (N 135–225). Troponins were 224 ng/l (N <14) and NT-proBNP 2056 ng/l (N <172). Bone marrow was hypercellular with marked dysplastic eosinophilia, without excess blast or lymphoma and MF-1 fibrosis. CT-scan disclosed mediastinal and abdominal adenopathies, splenomegaly and a renal Bosniak IV lesion highly suspect for carcinoma. Hypereosinophilia-related organ damage assessment revealed extended cardiac ischemia on MRI study, and multiple ischemic brain lesion. High dose methylprednisolone was immediately started with modest effect on eosinophil count (decreased to 30 G/l). Imatinib and mepolizumab were attempted without success. Extensive workup for eosinophilia was negative: inguinal adenopathy showed normal lymphoid tissue, peripheral flow cytometry were negative for lymphoproliferative disease, JAK-2, BCR-ABL, FIP1L1- PDGFR-alpha, PDGRF-beta, FGFR, C-KIT and CALR mutation were absent. Total IgE was 4954 kU/l (N 5–50). Tryptase and anti-neutrophil cytoplasmic antibodies were negative, like the parasite workup. A paraneoplastic origin was suspected, but a surgical resection of the kidney lesion was impossible due to the severe thrombocytopenia and bad condition of the patient at this time. A PET-CT showed moderate activity of the adenopathies (SUVbw max 6.1 g/mL) with hypermetabolic liver infiltration (SUVbw max 9.2 g/mL). The kidney lesion was slightly hypermetabolic. Eventually, liver biopsy revealed classical Hodgkin's lymphoma. Modified ABVD-regimen chemotherapy was started and eosinophilia resumed within two days. Complete response was obtained and the patient fully recovered without cardiac or neurologic sequelae. Second lecture of the kidney imagery supported benign kystic lesion. Bosniak classification is an unperfect diagnostic tool, practitioner-dependant. This case reports a diagnostic challenge of unusual Hodgkin's lymphoma presentation with severe hypereosinophilia and dramatic response to chemotherapy.

P481

The Swiss MDS Registry/Biobank: sharing first experiences of the pilot phase of a cooperative research platform for personalized medicine in haemato-oncology

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Introduction: Myelodysplastic syndromes (MDS) are malignant hematological disorders with an increasing incidence in the elderly. Sequential accumulation of genetic lesions in hematopoietic stem cells and clonal selection are responsible for initiation and progression to secondary acute myeloid leukemia (sAML). Motivated by increasing insights in the heterogeneity of these disorders, the emerging impact on healthcare resources, the limitation of available data and the utility of longitudinally collected data/samples for translational studies, we set out to implement a cooperative research platform.
Methods: The *Swiss MDS Study Group* was founded in 2015. It is the first collaborative research consortium of hemato-oncologists from academic and non-academic hospitals in Switzerland. The group aims to improve MDS patient management and foster research based on the *Swiss MDS Registry/Biobank* (SMRB) platform. This platform enables to collect systematically and standardized data and samples from patients treated at different centres in every-day clinical practices. All adult patients with MDS, MDS/MPN and sAML diagnosed after 2008 can be enrolled. Patient-, disease- and management-related data is recorded with an *electronic Case Report Form*. Samples from peripheral blood and bone marrow are collected at diagnosis as well as before/after treatment.
Results: The platform was approved by the lead *Cantonal Ethics Committee* in Bern as a multicenter cohort study and the pilot phase started at the Inselspital Bern in 10/2015. The first MDS patient was enrolled in 01/2016 and data recording started in 06/2016. As for 01/2017 61 patients have been included of which 35 are in the prospective follow-up, the others died and were included retrospectively. Five centers signed the agreement and are ready to start enrollment in 2017; at least ten additional centers have expressed their interest in participating. Six sub-studies are currently running on this platform investigating clinical, translational, basic as well as health services research aspects in MDS patients.
Conclusions: Increasing insights in the heterogeneity of disease-, patient- and management-based factors are revolutionizing the way of treating MDS patients and designing studies. The SMRB provides a first cooperative research platform in Switzerland that allows to perform a variety of research projects dedicated to improve and personalize care of MDS patients treated in every-day clinical practices.

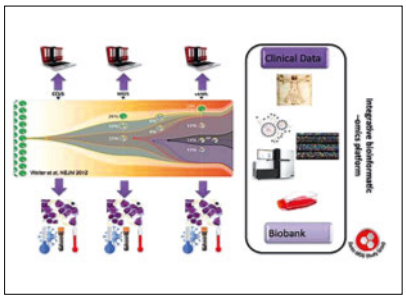

Figure 1: Platform for personalized medicine in MDS.

Figure 2: Swiss MDS Registry and Biobank platform.

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Injectable iron: fast, effective and well tolerated

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Introduction: Injectable iron is very useful for the treatment of iron deficiency anemia in cases of oral iron intolerance, malabsorption or in cases requiring rapid correction of iron stores. However, its use was not appreciated for several decades because of the history of adverse effects formerly reported. The currently available forms of injectable iron appear to be well tolerated. The aim of our work is to determine the indications, efficacy and tolerance of this treatment during iron deficiency anemia in a group of Tunisian patients.
Patients and methods: A retrospective study was conducted in a department of internal medicine. We have collected 9 cases of intravenous iron intake for iron deficiency anemia in the form of ferric saccharose complex (Venofer®) over an 18-month period from September 2011 to February 2013. The dose recommended was calculated according to the Ganzoni formula.
Results: There were 4 men and 5 women (sex ratio: 0.8). The median age was 47.55 years with extremes of 27 to 81 years. Initial hemoglobin was 5.7 g / dl with extremes of 3.9 to 7.6 g/dl. The mean globular volume was 66.22 fl (59.5–72.5). Ferritin levels were less than 7 ng/ml in all patients. The indications for treatment with injectable iron were malabsorption in 4 cases (celiac disease: 1 case, malabsorption post-gastrectomy: 2 cases and esophageal atresia: 1 case). In the other five cases, injectable iron was administered in the presence of a history of oral intolerance and non-response to iron. One of these patients also had anxiety attacks during transfusions. The mean dose received of intravenous iron was 310 mg distributed over 4 injections (2–7). The mean difference in hemoglobin after one week, after the second to third injectable iron cure, was 1.38 g / dl (0.45–2.8). Ferritinemia was corrected in all cases. The injectable iron treatment in this series had good tolerance in 8 cases: no allergic manifestations, no tachycardia, and normal systolic and diastolic blood pressure before and after the infusion. Only one case of tachycardia, agitation, tremor, and chills was noted in the same patient with transfusion intolerance.
Conclusion: Treatment with injectable iron has proved its effectiveness in our series as well as in the literature in the treatment of iron deficiency. No serious adverse effects were noted and the cures were very well tolerated with a correction of the martial reserves. It is, however, a series of small numbers.

P483

Integrative bioinformatic characterization of oncogenic pathways by phosphoproteinomics in myeloid cell lines: developping a novel diagnostic pipeline for personalized treatment

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Introduction: The myelodysplastic syndromes (MDS) are heterogeneous, clonal haematopoietic stem cell disorders caused by sequential accumulation of genetic lesions with a propensity to evolve towards secondary acute myeloid leukemia (sAML). The aim of our project is to build an integrative bioinformatics pipeline to analyze proteomic, transcriptomic and genomic data in order to characterize involved oncogenic pathways that drive and maintain the neoplastic phenotype. Here we show preliminary data on the ongoing phosphoproteome characterization in myeloid cell lines.
Methods: We performed a phosphoproteome (PPs) analysis of the myeloid cell lines NB4 (promyelocytic), K562 (erythroid) and THP1 (monocytic) that are characterized by established oncogenic drivers *PML-RARalpha*, *BCR-ABL1* and *MLL-MLLT3*, respectively (table 1). Cytogenetic analysis was performed by conventional cytogenetics and resequencing of myeloid driver genes by panel sequencing using *IonTorrent*®. PPs were enriched by the TiO_2 method and samples analyzed in triplicates by high-performance liquid chromatography combined with double mass-spectrometry (HPLC-MS^2). The raw data was analyzed using *MaxQuant*® and *R* was employed for further processing. Functional classification of PPs was performed with the web-based *PANTHER* analysis tool.

Cell line	Karyotype	Translocations	Deleterious mutations	Unclassified mutations
K562	human hypotriploid karyotype without sharp mode - 61 68XX, -X, -3, +7, -13, -18, +3mar, del(9)(p11?13), der(14)t(14;?)(p11;?), der(17)t(17;?)(p11?13;?), der(?18)t(15;?18)(q21;?q12), del(X)(p22)	BCR-ABL1		TP53, ASXL1
NB4	human hypertriploid karyotype with 3% polyploidy - 78(71-81)<3n>XX, -X, +2, +6, +7, +7, +11, +12, +13, +14, +17, -19, +20, +4mar, der(9)t(9;?)(q34;?), der(11)t(11;?)(?->::11p15->11q22.1::11q13->22.1:), der(12)t(12;?)(p11;?), 14p+, i(15;17)(q22;q11-12.1), der(19)t(10;19)(q21.3;p13.3)x2	PML-RARalpha	TP53	KRAS
THP1	human near-tetraploid karyotype - 94(88-96)<4n>XY,XXY, Y, +1, +3, +6, +6, -8, -13, -19, -22, -22, +2mar, add(1)(p31), del(1)(q42.2), i(2q), del(6)(p21)x2-4, i(7p), der(9)t(9;11)(p22;q23)(9)(p10)x2, der(11)t(9;11)(p22;q23)x2, add(12)(q24)x1-2, der(13)t(8;13)(p11;p12), add(?18)(q21) - carries t(9;11) associated with AML M5	MLL-MLLT3	CSDE1, NRAS	

Table 1: The 3 myeloid cell lines, their karyotypes, translocations and mutations detected in targeted panel sequencing. Note that the karyotypes have been imported from the DSMZ German Collection of Microorganisms and Cell Cultures.

Table 1

Results: We identified 12'374, 19'726 and 28'235 phosphopeptides corresponding to 5'012, 4'927 and 5'524 PPs, respectively. As shown in the Venn diagram in figure 1, 827, 333 and 382 unique PPs were identified in K562, NB4 and THP1, respectively. These unique PPs were further functionally annotated with *PANTHER*. Binding and catalytic activity were the most frequent functions of PPs shared across all cell-lines. Channel regulation and antioxidant activities were unique for THP1, whereas PPs with translational activity were found in NB4 and K562. More mature data will be shown at the meeting.
Conclusions: We were able to detect characteristic PPs of three pheno- and genotypically distinct myeloid cell lines. The further use of heavy labeled cell lines (SILAC = stable isotop labeling with amino acids in cell culture) will give us a more rigid background for quantitative comparison. This will allow us to step ahead to functionally characterize involved oncogenic pathways and perform network analysis. Our post-genomic, diagnostic approach will enable future personalized medicine in patients with myeloid neoplasms that are refractory to standard treatment.

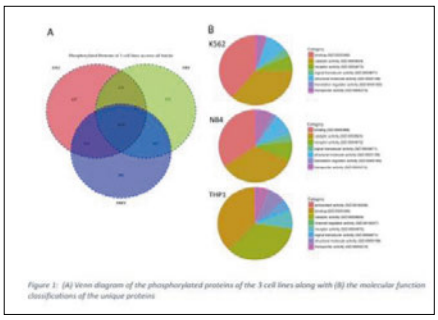

Figure 1: (A) Venn diagram of the phosphorylated proteins of the 3 cell lines along with (B) the molecular function classifications of the unique proteins.

Figure 1

P484

Phenotypic assays using zebrafish models for elucidation of hematopoietic toxicity

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Hematologic findings are one of the most common side effects encountered in preclinical safety testing of new drug candidates. The consequences of direct or indirect damage to blood cells and their precursors can be potentially life-threatening, and hence, hematotoxicity can lead to the termination of a promising drug candidate. Current hematotoxicity testing employs in vitro models with a cell viability read-out. However, this approach only allows a limited read-out and, for example, does not capture effects on later maturation stages of blood cell progenitors. Here, we propose the zebrafish as an alternative animal model that captures the full range of hematopoietic lineages and maturation stages in an in vivo setting. Therefore, we use different transgenic zebrafish lines that specifically mark subsets of different hematopoietic lineages, flow cytometry, high content live-imaging and automated drug administration and image analysis.

We have recently established an in vivo model that allows analysis of the potential impact of chemical compounds on the erythroid lineage (Lenard et al, 2016). Here, we use Phenylhydrazine to generate a haemolytic anemia model and assay the effect of concurrent drug treatment on modulation of erythroid regenerative capacity. Now, we are applying this procedure to a large size compound library of FDA-approved chemicals and optimize the procedure for automated drug administration, data acquisition and analysis. We are now one step closer in introducing this novel multiplex in vivo model to predictive and mechanistic preclinical safety testing, which eventually will complement existing in vitro hematopoietic approaches.

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Dissecting mechanisms of proliferative aging in hematopoietic stem cells

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Hematopoietic stem cells (HSC) sustain lifelong blood production. However, at any given time in steady-state, more than 90% of HSCs are dormant. Upon need of massive hematopoiesis, for instance upon bleeding, inflammation and infection, HSCs can be activated and rapidly cycle in order to spin off progenitors for blood production. Tight regulation of HSC turnover is crucial, as both over-production (leading to myeloproliferative neoplasms and leukemia) and under-production (in the worst case aplasia) would endanger survival. To study HSC cell cycle kinetics in vivo, our group established an in vivo HSC divisional tracking based on CFSE staining and steady-state transplantation. Results showed that the HSC pool consists of cells with distinct kinetics that can reversibly switch between dormancy and cycling. Importantly, HSCs with extensive proliferative history, e.g. during inflammation or aging, tend to switch to dormancy. We aim to understand how divisional history drives HSC towards quiescence in physiological and pathological events. We hypothesize that fast-cycling or enhanced turnover with aging might activate an intrinsic program that drives HSC toward quiescence. In this scenario, an intrinsic cell memory effect to prevent HSC exhaustion might be counterbalanced by an extrinsic drive for proliferation. Dysregulation of these pathways might cause bone marrow suppression, which in turn impairs recovery from infections, or alternatively lead to accumulation of genetic alterations and blood malignancies, especially in aged HSCs. To study HSC divisional behavior and quiescence in depth, we have recently coupled the CFSE tracking assay with Ki-67 intracellular staining. Analysis of young and aged mice in steady state and injections of cell-cycle activating compounds (e.g. Tpo and PolyI:C) shows that aged HSC delay their entry into cell cycle, if compared to their young homologues. In addition, time-course experiments suggest that, after each cycle, a proportion of cells slows down or enters quiescence, arguing in favor of a model where HSC are able to enter quiescence to avoid replicative stress and exhaustion. To understand the divisional behavior of the HSC compartment might allow to developing means for therapeutic intervention in HSC aging and pre-malignant HSC alterations. Also, it will be interesting to evaluate if basic findings on HSCs might hold true for other somatic stem cells systems.

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Treatment of AML with immunotherapies

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Introduction: Immunotherapies such as Bispecific T-cell engaging (BiTEs) antibodies and Chimeric Antigen Receptor (CAR) T cells have had a major clinical impact in the treatment of B cell neoplacias in recent years. BiTe antibodies consist of two antibody fragments (scFvs) linked together where one scFv always targets CD3. Binding of a BiTe to T cells and target cells results in the formation of an immunological synapse, T cell activation and killing of target cells. CAR T cells consist of a scFv linked to the signaling machinery of the T-cell receptor and costimulatory molecules. CAR T cells bind directly to their target cells. Acute Myeloid Leukemia is a clonal disorder of the hematopoietic stem/progenitor cells (HSPCs) and contains a subpopulation of leukemia-initiating cells (LIC) that can self-renew and give rise to a hierarchy of maturing blasts. While the proliferating mature blast pool is highly sensitive to chemotherapy, the quiescent LICs are relatively resistant and can be a source of relapse. We postulate that the only way to lasting success in poor-risk disease is to radically eliminate LICs and accept collateral damage to HSCs that, subsequently, can be replaced by transplantation. We aim to create a platform for the generation of immunotherapies directed against leukemic and HSC antigens, the first of which will be c-Kit (CD117). **Methods:** We will use mouse AML models as well as humanized models carrying human AML cell lines and primary human leukemia to evaluate safety and efficacy of BiTE antibodies, CAR T-cells and monoclonal depleting antibodies. The capacity to eliminate LICs as well as bystander effects on healthy hematopoiesis will be assessed. **Results:** We have established mouse leukemia cell line engraftment in wild type mice C57BL/6 as well as a human AML cell line (Kasumi-1) in NSG immunodeficient mice. We used a human phage display library and recombinant soluble mouse cKit protein to identify a novel anti-mouse cKit scFv. This scFv was expressed as an IgG and BiTE antibody as well as expressed on murine CAR T cells. *In vitro* and *in vivo* experiments are underway to determine the leukemia cell killing potential of the IgG and BiTE antibodies as well as the CAR T cells. **Conclusion:** Our goal is to use these immunotherapies to radically eliminate both AML-LICs and HSCs by targeting non-tumor-selective HSC antigens and to subsequently deal with the life-threatening HSC depletion by allogeneic HSC transplantation.

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A standardized quantification tool for bone marrow cellularity in histological sections

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The bone marrow (BM) is the seedbed of our blood, existing as hematopoietic/red or adipocytic/yellow marrow heterogeneously distributed with skeletal location, age, and physiological condition. Patients who undergo chemotherapy or suffer acute BM failure have a rapid adipocytic conversion of the marrow (red-to-yellow transition). After hematopoietic recovery such as upon hematopoietic stem cell transplantation (HSCT) following intensive chemotherapy, functional hematopoiesis is restored (yellow-to-red transition). Pathologist assessment of *BM cellularity* in H&E sections constitutes the Gold Standard to quantify hematopoietic function. BM failure or aplasia is usually defined as BM cellularity <10%. This expertise is not accessible to all laboratories, and multi-site standardization of BM cellularity quantification is often critical in the clinical and fundamental research setting. In our effort to systematically quantify BM components in histological sections in an unbiased manner, we developed and optimized a semi-automated image analysis tool for ImageJ, *MarrowQuant*. Area of hematopoietic cells, red blood cells, bone, and adipocyte ghosts are identified based on color and texture variation of H&E stained histological sections. We find that BM cellularity quantification correlates directly with scoring by four independent clinical pathologists from different countries, while quantification of bone and adipocytes compare with microCT volumetric measurement. The C57BL6 mouse has become the standard model of mammalian hematopoiesis. We have established a consistent map of cellularity in BM sections of homeostatic C57BL6 mice, and observe highly predictable red-to-yellow marrow transitions in the caudal tail and tibia. With age, regions of BM adiposity increase in the tibia and appear in the femur. Following HSCT, adipogenesis inversely correlates with kinetics of hematopoietic recovery. BM adipocytes reach maximum expansion 17 days post-transplant and hematopoiesis recovers after 25 days consistent with the exit of severe neutropenia and recovery of pre-transplant blood counts. We have observed that *MarrowQuant* can offer greater discrimination than pathologist evaluation on extreme cellularities (eg. 0–20% and 80–100%), which could become useful in certain settings. Validation on human trephine biopsies is currently ongoing, opening avenues for its application in experimental or clinical contexts requiring standardized measurements of various BM components.

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Correlation study between osteoporosis and hematopoiesis in the context of adjuvant chemotherapy for breast cancer

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Introduction: It was established that adipocytes in the bone marrow have an inhibitory activity on hematopoietic proliferation (Naveiras et al., Nature 2009). In osteoporosis, the osteoblastic/adipocytic differentiation equilibrium of the bone marrow stroma cells is altered, resulting an adipocytic infiltration of the bone marrow. This work attempts to establish if there is a correlation between osteoporosis and hematopoiesis before and after an adjuvant chemotherapy in the context of breast cancer. Osteoporosis is used as an indirect marker of the bone marrow adiposity.
Method: The clinical data of patients from the "breast cancer" cohort of the CHUV with a bone density exam (± 3 years from the diagnosis) were included in this project and classified according to their osteoporosis status. The evolution of the blood count was studied before and following the first cycle of adjuvant chemotherapy for breast cancer in correlation with the presence or absence of osteoporosis adjusted for age, toxicity of the chemotherapy and G-CSF treatment.
Results: Blood counts before chemotherapy: Our results, consistent with published data, indicate a negative association between t-score and neutrophil as well as thrombocyte counts prior to chemotherapy. Recovery after 1st cycle of chemotherapy: The evolution of the blood counts during the first cycle of chemotherapy was analyzed. The average day of leucocyte nadir is 9.9 ± 4.2 days. An increase of one point in TBS correlates with a decreased of 0.43 days on the time for leucocyte nadir with a p value of 0.0004. Our data thus suggests that the healthier the bone, the faster the decrease in total leucocyte after the onset of chemotherapy. Data points were insufficient to address the rate of recovery. From our analysis, the other significant response variable was infection with an odd ratio of 2.08 and a p value of 0.000989. The analysis suggests that a healthier bone is associated with a higher risk of infection. Probable selection and sampling bias will be discussed.
Conclusion: Our data confirmed the association between osteoporosis and lower blood count, already shown, in postmenopausal healthy cohorts, within a younger breast cancer cohort. The result of the blood count following chemotherapy suggests that the healthier the bone, the earlier the lowest blood count value. Further studies are needed to analyze the recovery after the lowest blood count and understand the dynamic behind it.

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Aspirin sensitizes leukemic/lymphoma cells to APO866, a NAD lowering agent

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Leukemic cells are highly prone to become resistant to treatment. Polychimiotherapies, by attacking leukemic cells through various pathways are aimed at preventing cell resistance development and also at maximizing killing effects. For these reasons, the development of new cell targeting therapies, i.e. those modifying metabolic pathways are most warranted. To this end, we evaluated the effect of aspirin (ASA) on enhancing the antitumor activity of APO866, a novel NAD lowering drug on a panel of various hematopoietic malignant cells. Hematological malignant cells were treated with or without ASA/APO866 alone or in combination for 96 hours, then cell viability and change in oxidative status were monitored using flow cytometry. We found that ASA synergistically increases APO866-induced death in various leukemia/lymphoma cell lines. ASA displays a potent cytostatic effect whilst APO contributes to increase the cytotoxicity. Mechanisms include enhancement of activation of caspase 3, exacerbation of mitochondrial depolarization, and increase of reactive oxygen species (ROS) production, when compared with those induced by each drug alone. In vivo preliminary results, combined administration of APO866 with ASA in a laboratory model of human aggressive lymphoma significantly decreased tumor burden and prolonged survival over single-agent treatment. Our results thus provide a rationale for potential combination of APO866 with ASA to assess the effect on hematological malignancies.

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Influence of blast CD56 expression on bone marrow adhesion

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Introduction: Acute myeloid leukemia (AML) is characterised by morphological, genetical and immunophenotypical heterogenity with substantial therapeutic and prognostic impact. Immunophenotypically aberrant CD56 expression on AML blasts is found in 13–29% of cases. CD56 (NCAM-1, neural cellular adhesion molecule 1) functions as an adhesion molecule, which is expressed physiologically on neuronal cells and natural killer (NK) cells. We postulate that CD56 leads to enhanced blast adhesion in bone marrow and hence complicates bone marrow aspiration. This might result in false low blast frequencies in aspiration cytology compared to histology, which bears substantial clinical impact, as blast frequencies are decisive for AML diagnosis (>20% blasts) and therapy monitoring. The aim of this study was to elucidate the effect of blast CD56 expression strength on observed discrepancies in blast frequencies between histology and aspiration cytology.
Methods: Retrospective analysis of 32 patients with CD56 positive and 34 patients with CD56 negative AML at diagnosis or relapse analysed in our center. CD56 positive AML were subcategorised according to expression strength in CD56 dim (15 cases) and CD56 bright (17 cases), by re-analysis of flow cytometric data. Selection criteria included: definite diagnosis according to WHO 2008 criteria; representative material in both aspirate cytology and bone marrow histology; complete datasets with information on cytology, histology and flow cytometry.
Results: Blast frequencies in the CD56 bright group were significantly lower in aspirate cytology (44%) compared to bone marrow histology (64%; p = 0.003, fig. 1). No significant differences were observed for the CD56 dim and CD56 neg groups.
Conclusion: AML cases with CD56 bright expressing blasts showed lower blast frequencies in bone marrow aspirate compared to histology. CD56 expression strength seems to be causative for that discrepancy, as CD56 dim expressing cases showed no significant difference compared to histology. If confirmed by others, the potential underestimation of blast frequencies for CD56 positive cases by aspirate cytology should be taken into account in AML protocols in the future. Furthermore larger prospective trials, as well as experimental data are required to elucidate if enhanced blast adhesion is the pathological cause for the reported inferior outcome of CD56 positive AML and subsequently might be targeted by novel specific agents.

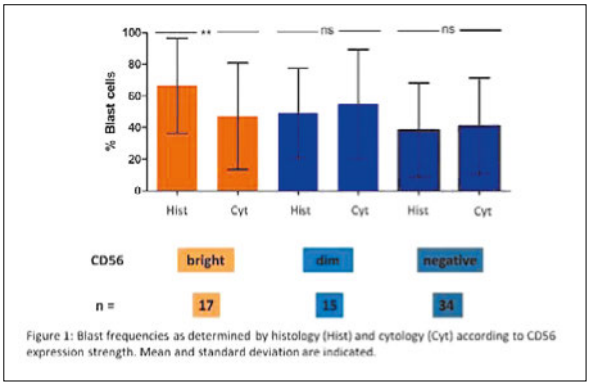

Figure 1: Blast frequencies as determined by histology (Hist) and cytology (Cyt) according to CD56 expression strength. Mean and standard deviation are indicated.

Figure 1

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Evaluation of the hemostatic profile in mouse models of advanced chronic liver disease

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Introduction: Advanced chronic liver disease (ACLD), a condition including cirrhosis and fibrosis, is characterized by changes in the coagulation system that embrace both hypo- and hypercoagulability. In this rebalanced situation, hypercoagulability can contribute, like genetic predisposition or environmental factors, to fibrosis progression and cirrhosis complications. Common routine hemostasis tests fail to reflect bleeding and thrombotic tendencies in ACLD patients. Therefore, a better understanding of underlying mechanisms is mandatory for setting-up new assays and treatments. Here, we assessed the hemostatic changes in 2 different models of ACLD in mice.
Methods: 9–15 adult male mice received i.p. 200 mg/kg of thioacetamide (TAA) 3×/week for 12 weeks or 1 ml/kg carbon tetrachloride (CCl_4) and phenobarbital (0.3 g/L in drinking water) twice per week for 11 weeks. At the end of the treatment mice were sacrificed; blood and organs were harvested for investigation.
Results: We observed a slight increase in body weight in both CCL_4/Phenobarbital (28.0 ± 2.7 vs 24.5 ± 3.9g, P <0.0001)and TAA (23.9 ± 3.6 vs 21.5 ± 3.9g, P = 0.0025) treated mice compatible with ascites development while mortality rate was higher in the CCL_4/Phenobarbital than in the TAA group (32% vs 13%). In control mice, liver histology revealed normal parenchymal architecture without fibrosis. In CCL_4/Phenobarbital treated mice, livers displayed extensive fibrosis with both portal-to-portal and portal-to-central bridging. Albeit present, fibrosis in the TAA treated group was less extensive. Interestingly, occlusive centrilobular vein thrombosis was more prominent in the TAA than in the CCL_4/Phenobarbital group, where we observed also partial periportal thrombosis. Coagulation investigation showed a slight decrease of fibrinogen in both CCL_4/Phenobarbital and TAA groups compared to the controls (1.4 ± 0.1 vs 1.7 ± 0.1 g/L, P = 0.04 and 1.3 ± 0.1 vs 1.7 ± 0.1 g/L, P = 0.01) and prolonged prothrombin time in both CCL_4/Phenobarbital and TAA groups compared to the controls (9.3 ± 0.1 vs 8.9 ± 0.03sec, P = 0.01 and 9.8 ± 0.2 vs 8.9 ± 0.03 sec, P = 0.007). Factor VIII was highly increased in the CCL_4/Phenobarbital group compared to the controls (350.4 ± 17.3 vs 194.3 ± 34.8%, P = 0.002) but not in the TAA group(282.8 ± 32 vs 194.3 ± 34.8%, P = ns).
Conclusion: These data provide the first evaluation of hemostatic profile in mice with ACLD. Additional data are needed to further characterize the bleeding and thrombotic tendency linked to murine ACLD.

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Comparison of two laboratory methods for thrombin generation in pregnancy with high risk for thrombosis

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Aims: Pregnancy and delivery are high-risk conditions for thrombotic complications. Women with heritable thrombophilia with or without thromboembolism in their medical history are at additional higher risk to develop thrombosis and are normally followed-up during pregnancy for evaluation of the prothrombotic state. Follow-up is done by clinical evaluation and sometimes it includes biological markers of activation of coagulation. A disproportional increase would theoretically predict high risk for thrombotic events but usefulness of these markers has not been validated in an evidence-based setting. Aims of this study were: a) to describe changes of biological markers of coagulation activation and thrombin generation in each trimester of pregnancy, b) to compare two different methods for assessment of thrombin generation, c) to check whether heparin prophylaxis in the third trimester affects thrombin generation.
Methods: Data on file of 102 consecutive pregnancies with hereditary thrombophilia or thrombosis were retrospectively analyzed. Pregnant women were routinely followed every 4-6 weeks for thrombotic complications during pregnancy. Any thrombotic event or preeclampsia or premature delivery were recorded. Thrombin-Antithrombin-Complex (TAT), D-Dimers (DD) and endogenous thrombin potential (ETP) by a functional chromogenic assay (CAT, calibrated automated thrombogram) were assayed routinely once in the middle of each trimester using standard methods.
Results: TAT (4.3 + 2.9, 6.4 + 5.2, 7.7 + 4.3 microg/L) and DD (0.9 + 1.5, 1.6 + 2.1, 2.0 + 2.3 microg/ml) were increased slightly but continuously and statistically significantly from each trimester to the other. Women receiving heparin prophylaxis showed the same pattern and did not differ from the whole cohort. CAT did not show any differences between trimesters. Women in third trimester with or without heparin prophylaxis did not differ with respect to DD (2.0 + 2.6 vs. 2.0 + 1.7 microg/ml), TAT (7.5 + 2.9 vs. 8.2 + 5.9 microg/L), CAT-ETP (1696 + 962 vs. 1715+804 AU).
Conclusions: TAT and DD were elevated as pregnancy progressed, as expected. CAT-ETP in addition to TAT does not add any value of information. TAT and DD do not add any safe value of information with respect to the effect of heparin prophylaxis and they might not be needed as isolated observation tools.

GASTGESELLSCHAFT SGKPT / SOCIÉTÉ CONVIÉE SSPTC

POSTER

P510

Acute health problems due to recreational drug use in patients presenting to an urban emergency department in Switzerland

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Objective: We described the frequency and the acute medical problems due to recreational drug use in patients presenting to an emergency department in Switzerland during 11 months. The results were compared with data from previous years.
Methods: The retrospective study was conducted at the University Hospital of Basel, Switzerland, between October 2015 and August 2016 and within the Euro-DEN project. All cases presenting with symptoms/signs consistent with acute toxicity of recreational drug use were included. Isolated ethanol intoxications were excluded. Drug tests were performed using immunoassays and liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results: During the study period there were 47'769 emergency department attendances of which 211 were directly related to acute toxicity of substances used recreationally. The mean patient age was 32 years, 71% were male. Alcohol co-use was reported in 46% of the cases, use of more than one recreational drug in 27% of the cases. Most presentations were related to cocaine (38%), cannabis (37%), and amphetamines/methamphetamines excluding MDMA (12%). A drug screening was available in 108 cases (51%). The most commonly analytically detected substances were cannabis (23%), cocaine (22%), and benzodiazepines (19%). There was one intoxication with a novel substance, presenting with hallucinations, chest pain, dyspnea, and palpitations after self-reported use of MDMA; using LC-MS/MS 2C-B could later be identified. The majority of patients (40%) had impaired consciousness (GCS <15) at presentation and/or pre-hospital, 11% were unconscious (GCS <8). Other frequent symptoms were tachycardia (35%), nausea/vomiting (29%), anxiety (27%), and agitation (24%). Most intoxications (55%) were of minor severity and there were no fatalities. Severe complications included 4 acute myocardial infarctions (cocaine involved in 3 of them), 1 case with multiple organ failure (cocaine monointoxication), psychosis (18 cases), and seizures (14 cases). Most patients (72%) were discharged

home, 10% took their own discharge, 9% were admitted to intensive care, 7% to psychiatric care.
Conclusion: Similar to the previous years, most medical problems related to illicit drugs concerned cocaine and cannabis. Symptoms mainly included CNS depression, nausea/vomiting, and/or sympathomimetic toxicity. Novel psychoactive substances seem to either be rarely used or rarely lead to emergency department consultations.

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Mechanisms of cytotoxicity in metamizole-associated neutropenia

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Objective: Metamizole, a non-opioid analgesic prodrug, rarely causes potentially life-threatening neutropenia and agranulocytosis. Currently, the mechanisms underlying metamizole-induced neutropenia (MIN) are only poorly understood. While immunological mechanisms are discussed, certain features are compatible with direct metabolic toxicity on granulocyte precursors in the bone marrow. Therefore, our objective was to investigate possible mechanisms toxicity by the main metamizole metabolites 4-methylaminoantipyrine (MAA), 4-formylaminoantipyrine (FAA), 4-aminoantipyrine (AA), and 4-acetylaminoantipyrine (AAA) in granulocytes and granulocyte precursors.
Methods: We treated HL60 cells (a promyelocytic cell line) and isolated human neutrophil granulocytes with different concentrations of metamizole metabolites (1 µM to 200 µM) with or without components of an oxidative system composed of horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2). We assessed the adenylate kinase release as a marker of cytotoxicity and the cellular ATP content as a marker of energy metabolism.
Results: MAA, FAA, AA, and AAA (up to 200 µM) alone were not cytotoxic and did not decrease the ATP content in HL60 cells or granulocytes. In the presence of HRP, MAA was not toxic for HL60 cells. H_2O_2 (100 µM) depleted the ATP content of HL60 cells by >95% and showed a minor cytotoxicity. This cytotoxicity was concentration-dependently increased by MAA and AA, whereas FAA and AAA were not cytotoxic under these conditions. In the presence of HRP and H_2O_2, ATP depletion by H_2O_2 (»90%) and increased cytotoxicity by MAA and AA were detectable, but attenuated compared to H_2O_2 alone. In the presence of oligomycin, which depleted the cellular ATP by approximately 60%, MMA was not cytotoxic. Determination of the time course revealed that ATP depletion was completed between 3 h and 12 h and that cytotoxicity started at 12 h. In granulocytes, H_2O_2 depleted the cellular ATP content by approximately 80% and MAA was not cytotoxic.
Conclusion: MAA and AA are cytotoxic only in the presence of H_2O_2, whereas FAA and AAA are not cytotoxic. Cytotoxicity of MAA and AA seems to be related to the H_2O_2-induced cellular ATP depletion, which may render cells more sensitive. The ATP depletion must be >90% before cytotoxicity is initiated. Granulocyte precursors appear to be more sensitive than granulocytes, which corresponds well with the clinical observations.

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Is there room for a closed-loop control to improve automated propofol delivery during anesthesia?

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Introduction: Propofol is generally administered by open-loop Target Controlled Infusion (TCI) devices for anesthesia induction and maintenance. The current algorithms driving TCI pumps are based on published pharmacokinetic models developed on small groups of healthy volunteers. Propofol infusion rates are adjusted aiming to a defined target, based on model-predicted plasma or brain concentrations. However, there is currently no monitoring of actual propofol level, which, if significantly different from the predicted one, could lead to important over or under drug exposures with clinical consequences for the patients. The aim of this analysis is to evaluate whether there is room for a closed-loop control in anesthesia delivery to optimize drugs dosages.
Methods: Propofol infusion rates required to achieve changing target brain concentration (6 à 4 à 5 mg/L) throughout a 15 min operation for a virtual male patient (70 kg, 170 cm, 36 y) were obtained with the model of Schnider *et al.* [1] as implemented in the BasePrimea pump (Fresenius Kabi, Germany). This subject was then simulated 10000 times under the estimated TCI dosage scheme, using the comprehensive population model with between-subject variability developed by Eleveld *et al.* [2] to describe plasma propofol concentrations in 660 patients. Median concentration with 90% prediction interval ($PI_{90\%}$) were calculated and compared to the target brain concentrations at equilibrium according to the TCI prediction. The percentage of virtual patients reaching propofol levels above 15 mg/L (maximum allowed in TCI) was also estimated.
Results: The figure shows median with $PI_{90\%}$ of the Eleveld model and TCI predicted concentrations along with the aimed target levels. Median ($PI_{90\%}$) concentrations of 5.6 (3.7–8.1), 3.7 (2.6–5.3) and

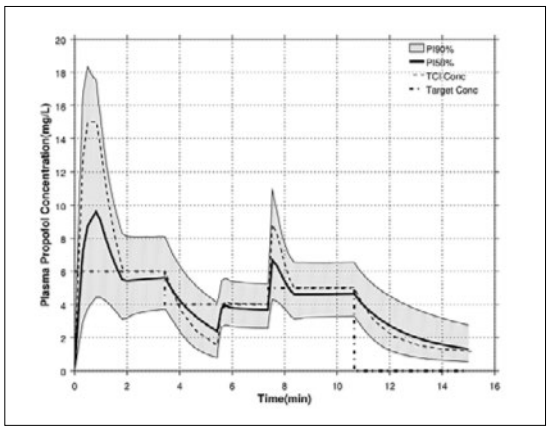

Figure 1
Plasma Propofol concentration vs. Time.

4.6 (3.3–6.5) mg/L were calculated when the target levels of 6, 4 and 5 mg/L, respectively, were achieved according to TCI predictions. Furthermore, 12% of the virtual patients were found with concentrations exceeding 15 mg/L within the first minute of propofol infusion.
Conclusions: These results show the potential for a closed-loop control of blood concentration to improve automated anesthesia delivery. A proportional-integral-derivative (PID) controller based on real-time propofol measurement to optimize infusion rate is currently under development.

References
1 Schnider TW, et al. Anesthesiol. 1998;**88**:1170–82.
2 Eleveld DJ, et al. Anesth Analg. 2014;**118**:1221–37.

P513

Direct oral anticoagulants: are they safer than vitamin K antagonists?

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Introduction: A significant fraction of the Swiss population is treated with anticoagulants. Bleeding complications are frequent, counting for about 10% of adverse drug reaction-related hospitalizations. After decades of exclusive use of vitamin K antagonists (VKA), direct oral anticoagulants (DOACs) are now available and their use is increasing. According to the published randomized controlled trials, DOACs are at least as effective as VKA, but might be safer.
Objectives: This study aimed to evaluate whether DOACs are safer than VKA by comparing their respective consumption with the number of hospitalizations for bleeding complications in an emergency department over the past years.
Methods: We retrospectively collected data from all patients treated with DOACs or VKA who were admitted to the Emergencies of CHUV for bleeding with externalization (any site) between 2011 and 2015. The severity of these hemorrhages was graded. Patient characteristics were recorded. The consumption data of DOACs and VKA were obtained from Interpharma and The Cooperative of the Swiss

Pharmacists for the years 2011 to 2015. Spontaneous reporting of bleeding events under DOACs and VKA to Swissmedic was extracted from the Vigilyze database.
Results: A total of 779 admissions for bleeding events were recorded, among which 250 in patients treated with DOACs or VKA. Only 15 cases were associated with DOACs and were compared with a sub-sample of 50 among the 235 cases of the VKA group. Patients in the VKA group were slightly older (79.3 vs 76.4 years; NS), with higher comorbidity Charlson scores (2.16 vs 1.46; NS), and lower renal function (44 vs 57 ml/min/1.73 m^2 GFR; p = 0.006). They had more often drug interactions (pharmacokinetic: p = 0.008; pharmacodynamic p = 0.004). The bleeding events did not differ significantly in their location, severity and management. The DOACs market share is growing with a number of DOACs units sold outpacing the VKA in 2015. The number of spontaneous reporting of DOACs-associated bleeding events to Swissmedic is higher than that of VKA since 2013.
Conclusion: The results tend to confirm a better safety of DOACs compared to VKA. However, VKA are prescribed to patients in less good condition and thus more at risk of bleeding, which may accentuate the difference in incidence of bleeding events. The over-representation of DOACs in the Swissmedic database might be due to reporting biases.

P514

Prevalence of polypharmacy in the Swiss HIV Cohort Study (SHCS)

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Introduction: Highly active antiretroviral drugs (ARVs) have transformed HIV infection from a deadly disease into a manageable chronic condition. As a consequence, HIV-infected individuals live longer and become older, affected by age-related comorbities leading consequently to polypharmacy and a higher risk of drug-drug interactions (DDIs) [1]. There is currently a lack of real-life clinical data on the extent of polypharmacy and DDIs. Moreover, the information on drug-gene interaction and pharmacogenetics (PGx) are scarce. In that context, we aim to describe the prevalence of polypharmacy and PGx-labeled drug prescription in the Swiss HIV Cohort Study (SHCS).
Methods: We have initiated a large-scale prospective observational study within SHCS at the occasion of patient's biannual cohort visits that implies the systematic documentation of all co-medications, along with plasma levels measurements of antiviral drugs and co-medications at risk of problematic DDIs. Patients are contacted by post one week before their SHCS visits and invited to report all their current medications in a record form. Drugs with PGx recommendations are identified according to the American and European authorities together with the evidence-based expert opinions aggregated by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [2].
Results: Data available at present from TDM routine service have shown that the most prescribed therapeutic classes are central nervous system and cardiovascular drugs representing 32% and 20% of the prescription, respectively. The proportion of patients receiving at least one non-HIV co-medication is of clinical importance, with a high prevalence of lipid-lowering agents (7%). On 10'030 prescriptions, 7.1% and 14.3% had a CPIC label grade A or B, respectively, affecting several therapeutic classes. Few drugs (1.2%) are recommended or required to be associated with a PGx test according to FDA as well. These results are in accordance with previous studies [3, 4].
Conclusion: In the growing healthcare challenge of personalized medicine and treatment optimization, research efforts must be pursued to improve the quality of ARVs prescriptions, especially with regards to potential DDIs.

References
1 Marzolini C, et al. J Antimicrob Chemother. 2011;66:2107.
2 CPIC: https://cpicpgx.org/genes-drugs.
3 Relling MV, Evans WE. Nature. 2015;526:343.
4 Frueh FW, et al. Pharmacotherapy. 2008;28:992.

P515

Falsely reduced glycated hemoglobin in a diabetic patient with HCV infection treated with ribavirin

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Ribavirin impairs the stability of red blood cells according to both in vitro experiments and clinical investigations. In a clinical trial, mean life expectancy of erythrocytes in hepatitis C patients treated with ribavirin was almost three times shorter than in hepatitis C patients without ribavirin treatment (46 vs. 112 days) [1]. In diabetes patients, dramatic reduction of red blood cells' life expectancy under ribavirin translates into a significant decline of the level of glycated hemoglobin (HbA1c), independently from any glycaemia changes. Dissociation between glycaemia and HbA1c levels, already reported in the literature [2], understandably complicates management of diabetes patients with hepatitis C. However, the issue of diabetes follow-up under ribavirin has not yet been assessed in a clinical study. A male patient, 64 years old, had insulin-dependent type 2 diabetes with a poor therapeutic adherence; as a result, his glycaemia and HbA1c levels were repeatedly above the targets (glycaemias 10 to 13 mmol/l, HbA1c 9.3%). He also had chronic viral hepatitis C with Child-Pugh A grade cirrhosis. In september 2016, he started antiviral treatment with sofosbuvir, daclatasvir and ribavirin. In november 2016, reduction of HbA1c to 6.4% (target levels 6.5 to 7.5% in diabetes patients) was witnessed, while glycaemic control was still poor (higher than 10 mmol/l). A new-onset anemia (hemoglobin 98 g/l) was also diagnosed. In december 2016, HbA1c went even further below the target values (HbA1c 4.7%); at the same time, glycaemias continuously measured during 7 days consistently remained above 10 mmol/l. In light of a known impact of ribavirin on the turnover of red blood cells, the new-onset anemia as well as a published case report [2], low HbA1c levels were deemed to result from a side effect of ribavirin treatment, rather than from any improvement in glycaemic control. A falsely lowered HbA1c can induce the physician to unnecessarily adapt the diabetes treatment with subsequent worsening of the glycaemic control, leading to potentially serious complications (hyperosmolar hyperglycemic state or ketoacidosis, depending on the type of diabetes). This observation prompted a retrospective survey to better characterize correlation between ribavirin treatment and glycaemic markers in patients suffering from both diabetes and hepatitis C infection (underway).

References:
1 Virtue MA, et al. Am J Hematol. 2004;76(2):107–13.
2 Robertson M. BMJ. 2008 1;336(7642):505.

P516

Systematic review of case reports on drug pharmacokinetic assessment in patients under hemodialysis

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Introduction: Besides tailored clinical trials in pediatric and adult patients on intermittent hemodialysis (HD), individual case reports on pharmacokinetic (PK) assessments provide an important source of information about drug dialysability and dose adjustments required in this vulnerable population. As there is no systematic guidance available for such PK studies, we aimed to provide a review of current clinician-initiated PK assessment and reporting practices.
Methods: We performed a systematic review of case reports on individual drug PK in HD patients published between 2000 and 2016. We evaluated them for their completeness regarding essential information on patient, drug and HD therapy related factors that may influence PK. We also reviewed the use of PK calculations of relevance in HD patients, in particular dialysis clearance CL_D, off-dialysis clearance CL_{off}, and amount of drug removed by HD, as suggested by available regulatory and methodological recommendations for PK assessment in this population.
Results: A total of 88 papers were retained in this review. The majority of case reports concerned non-renally eliminated drugs with Q_0 >0.7 (60%), and 85% of studied drugs were anticancer and anti-infective agents. Thirty-one case reports (35%) reported at least 50% of

relevant components in HD patients. CL_D was calculated in 33% of case reports, of which only 10% used the recovery gold-standard method. CL_{off} was calculated in 31% and the amount of drug removed by HD, which is important to calculate appropriate dose adjustments, was assessed in only 20%. Nineteen percent of studies simply reported a reduction ratio of drug concentrations before and after HD session.
Conclusions: Clinician-initiated PK assessments in HD patients are of definite usefulness for the community, but frequently lack important information to allow interpretation and translation of results to other patients. Additionally, calculations methods to estimate drug dialysability are rarely used to characterize PK information of relevance in HD patients. Limited PK data collected in a single patient could be further leveraged by taking into account published PK information in combination with PK modeling. Checklist and guidance for easy-to-implement PK calculations and pharmacometric modeling can be useful to further enhance publication of individualized dosing evaluations in pediatric and adult HD patients.

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Determination of transepithelial transport of ticagrelor in human intestine using in vitro Caco-2 cell monolayer assay

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Introduction: Ticagrelor is the first drug of a new non-thienopyridine oral antiplatelet agents category. Determination of drugs' affinity for P-glycoprotein (P-gp) efflux transporter is essential for estimation of drugs oral bioavailability and potential drug-drug interactions.
Method: In the current study, the intestinal permeability of ticagrelor as well as its potential P-gp mediated active transport was assessed. To this end, bidirectional transport of ticagrelor was performed using in vitro Caco-2 (human epithelial colorectal adenocarcinoma) monolayer model in presence and absence of the potent P-gp inhibitor valspodar.
Results: Ticagrelor presented high influx permeability with an apical-basolateral apparent permeability coefficient (P_{app}) of 6.0×10^{-6} cm/s. On the other hand, mean efflux ratio (ER) of 2.71 was observed for ticagrelor describing a higher efflux permeability compared to the influx component. Valspodar showed a significant inhibitory effect on the efflux of ticagrelor suggesting involvement of P-gp in its oral disposition. Co-incubation of the P-gp inhibitor decreased the efflux P_{app} of ticagrelor from 1.60×10^{-5} cm/s to 1.13×10^{-5} cm/s and decreased its ER by 70%. Results are presented in following table:

Ticagrelor concentration (µM)	Efflux P_{app} ($cm/s \times 10^{-5}$)	Influx P_{app} ($cm/s \times 10^{-5}$)	Efflux ratio
1	1.15 ± 0.13	0.81 ± 0.34	1.42
+ *Inh*	*0.92 ± 0.08*	*1.01 ± 0.21*	*0.90*
5	2.49 ± 0.24	0.59 ± 0.12	4.18
+ *Inh*	*1.72 ± 0.02*	*0.81 ± 0.10*	*2.12*
10	2.00 ± 0.12	0.56 ± 0.12	3.58
+ *Inh*	*1.31 ± 0.13*	*0.57 ± 0.08*	*2.29*
50	0.74 ± 0.06	0.47 ± 0.04	1.66
+ *Inh*	*0.57 ± 0.05*	*0.55 ± 0.07*	*1.03*
Mean	1.60 ± 0.79	0.60 ± 0.15	2.71
+ *Inh*	*1.13 ± 0.50*	*0.74 ± 0.22*	*1.59*

Values are expressed as mean ± standard deviation; P_{app}: Apparent permeability in Caco-2 cells; Inh: Co-incubated with P-gp Inhibitor valspodar 4 µM

Table

Conclusion: These results suggest a high permeability and a moderate active transport of ticagrelor by P-gp across the Caco-2 cell monolayer. However, in case of co-administration of ticagrelor with an inhibitor of P-gp, a striking impact on pharmacokinetics of ticagrelor appears unlikely in clinical conditions and does not seem to cause bleeding events in patients.

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Conceptual evaluation of urea rebound in pediatric hemodialysis patients by a physiology-based pharmacokinetic simulation study

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Introduction: Pediatric hemodialysis (HD) dosing and monitoring strategies are mainly derived from adult studies utilizing pre- and post-HD urea plasma concentration measurements. Accuracy of such HD evaluation approach depends on extent and duration of post-HD urea rebound, which occurs due to redistribution of urea from slowly perfused (peripheral) to quickly perfused (central) body compartments. The goal of this urea kinetic simulation study was to evaluate the expected urea rebound in pediatric HD patients.
Methods: Realistic pediatric HD prescription parameters and demographics were calculated over body weight (BW)-bands of 5 kg from a large registry database (DaVita) with ≥20 patients and >130 HD sessions per BW-band. Typical urea concentration-time profiles during and after HD sessions were simulated applying published urea kinetic data [1, 2] and implementing expected physiologically-based kinetic changes in pediatrics (age-, body weight, and gender-dependency of total body water [3, 4], cardiac output [5], and fraction of skeletal muscle mass [6] as indicator of slowly equilibrating somatic tissue mass). Time to regaining equilibrium (TTE) after HD sessions between central and peripheral urea concentration was calculated (i.e.at least 97% of complete equilibrium).
Results: In children up to 25 kg (10 years) predicted TTE was ≤5 min, in adolescents up to 35 kg (17 years) ≤10 min. In young adults (19–21 years, 40–120 kg) TTE was up to 25 min (longest in boys weighing >80 kg), while almost 90% of complete equilibrium was predicted to be achieved 5 min post-HD.
Conclusion: Results from urea kinetic simulations that take HD prescription parameters and physiologic changes in pediatric patients into account indicate that time to equilibrium is shorter in pediatric than in adult HD patients, with urea rebound occurring mainly within 5-10 min after HD sessions. This finding can be utilized to design optimal sampling time points in urea kinetic studies in pediatric HD patients.

References:
1 Pfister, et al. Hemodial. Int. 2008.
2 Odeh, et al. Clin. Pharmacol. Ther. 1993.
3 Watson, et al. Am. J. Clin. Nutr. 1980.
4 Cheek, et al. Am. J. Dis. Child 1966.
5 de Simone, et al. Circulation 1997.
6 McCarthy, et al. Pediatr. Obes. 2014.

P519

Potential drug-drug interactions at hospital admission: comparative performance of two drug interaction screening programs and clinical relevance

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Introduction: Drug-drug interactions (DDIs), which can lead to drug toxicity or diminished therapeutic effect, can be prevented by the use of DDI screening programs. The aim of our study was to evaluate the frequency of DDI at hospital admission by using two DDI screening programs, and to assess their clinical relevance.
Methods: Patients admitted to an internal medicine and infectious diseases ward at Geneva University Hospitals between March and end of May 2016 were interviewed by a pharmacist/clinical pharmacologist for medication reconciliation. This was part of the national pilot program "Progress: medication safety at transitions in care". The medication list was systematically screened by Lexi-Interact® and by the program from the Compendium Suisse des medicaments to detect potential DDI. All cases were independently reviewed by three pharmacists/clinical pharmacologists to evaluate the clinical relevance of detected DDI.

Results: A total of 64 patients were interviewed, 58% were men. The mean age was 65 years old. A mean of 7.6 drugs per patient per day were taken (range: 0 to 19), including "as needed" medication. The most frequently used drugs were paracetamol, acetylsalicylic acid (cardiologic indication) and esomeprazole. A total of 132 potential DDI were detected by the Compendium software, and 314 potential DDI were detected by Lexi-Interact® (no severity filter added). The mean number of DDI detected by each software was 2.2 and 5.0 respectively (range: 0–17 and 0–33 respectively). The majority were pharmacodynamic DDI (89.4 and 70.7% respectively). The three independent pharmacists/clinical pharmacologists judged a total of 87 DDI as being clinically relevant, representing approximately one third of all detected DDI by Lexi-Interact®.
Conclusion: Admitted patients are potentially subject to DDI as detected by DDI screening programs but not all of them are clinically relevant, and the different screening programs show variability in their performances.

P520

Association between sulfolane levels and the incidence of hemorrhagic cystitis in pediatric patients receiving busulfan-cyclophosphamide conditioning regimen: lack of modulation of cytochromes P450 by sulfolane in HepaRG cells

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Introduction: Hemorrhagic cystitis (HC) is one of the common complications of busulfan-cyclophosphamide conditioning regimen during allogeneic hematopoietic stem cell transplantation in children. In a retrospective analysis, a higher incidence of HC was observed in pediatric patients with higher sulfolane levels. We therefore hypothesized that sulfolane might increase the activity or expression of cytochromes P450 (CYP), which are involved in the first step of the metabolism of CY into its urotoxic metabolite acrolein.
Method: Different concentrations of sulfolane ranging from 0.5 to 5 µM were incubated with differentiated HepaRG (passage 19) cells seeded on 24-well plates at a density of 2×10^5 cells/cm^2 in a medium composed of phenol-free Williams medium E supplemented with 2 mM GlutamaxTM, 50 µM hydrocortisone hemisuccinate, 5 µg/ml insulin, 100 UI/ml penicillin and 100 µg/ml streptomycin at 37 °C, 5% CO2. Negative and positive controls with rifampicin (10 and 50 µM), omeprazole (50 and 100 µM) and phenobarbital (500 and 1000 µM) were used. Final concentration of DMSO during the time of induction was 0.1% in all conditions. After 72 hours of incubation with medium changes every 24 hours CYP activity was assessed by incubating a phenotyping cocktail composed of midazolam 5 µM (CYP3A4), S-mephenytoin 50 µM (CYP2C19), bupropion 50 µM (CYP2B6), flurbiprofen 10 µM (CYP2C9) and phenacetin 10 µM (CYP1A2) in phenol red-free Williams medium E. Reactions lasted 3 hours, after which incubation media and plated cells were collected for metabolite quantification by LC-MS/MS and gene expression analyses by RT-qPCR.
Results: HepaRG exposed to different levels of Su showed significant differences neither in CYP activity compared to controls, as measured by the velocity of metabolite production normalized to the total protein content, nor at the level of gene expression. For CYP2B6, induction by 2 fold was observed only at the mRNA level but did not exhibit increased activity while phenotyping with the probe drug. Known inducers of CYPs like phenobarbital, rifampicin, and omeprazole exhibited induction. Data from these experiments indicate no significant impact of sulfolane on CYP activity and expression in HepaRG cells.
Conclusion: The association between sulfolane levels and the incidence of HC in pediatric patients receiving busulfan-cyclophosphamide conditioning regimen prior to hematopoietic stem cell transplantation does not seem to involve CYP modulation.

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Pharmacokinetics of transdermal etofenamate and diclofenac in healthy volunteers

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Background and aims: Little is known about the course of the plasma concentration and the bioavailability of non-steroidal anti-inflammatory drugs (NSAIDs) contained in dermal patches. In order to obtain more information about this subject, we determined the plasma concentration-time profile of diclofenac epolamine (from a commercially available dermal patch) and of etofenamate (from a prototype dermal patch) in 24 healthy human subjects. In order to calculate the bioavailability, we compared drug exposure following patch application to exposure after i.m. application of diclofenac or etofenamate in the same subjects.
Methods: Subjects were treated using a parallel design (n = 12 per stratum) with a single dermal patch (removed after 12 hours) followed by (after 48 hours) 8 consecutive dermal patches every 12 hours to reach steady state conditions. The patches contained 10 mg/g diclofenac (Flector®; weight 14 g, 140 cm^2) or 50 mg/g etofenamate (patent EP 1833471; weight 14 g, 140 cm^2). The i.m. applications contained 75 mg diclofenac (Voltaren®) or 1 g etofenamate (Rheumon®). Plasma concentrations were determined using a validated LC/MS method. Bioavailability was calculated as the ration of the AUCs with dose adjustment.
Results: One subject treated with etofenamate developed an allergic contact dermatitis; otherwise the patches were well tolerated. After the first patch, C_{max} was 0.81 ± 0.38 (95%CI) ng/mL (reached 12 hours after patch removal) for diclofenac and 31.3 ± 8.5 ng/mL for flufenamate (reached at patch removal), the main metabolite of etofenamate. Etofenamate was not detectable. After repetitive dosing, trough plasma concentrations after the eighth dose were 1.72 ± 0.72 (95%CI) ng/mL for diclofenac and 48.7 ± 14.8 ng/mL for flufenamate. C_{max} for the i.m. applications were 1790 ± 280 (95%CI) ng/ml for diclofenac and 5810 ± 1450 ng/ml for etofenamate (measured as flufenamate). Bioavailabilities (single dose) relative to i.m. applications were 0.22 ± 0.09% (95%CI) for diclofenac and 1.15 ± 0.13% for flufenamate.
Conclusions: Etofenamate is rapidly converted to flufenamate and has a higher bioavailability (as flufenamate) than diclofenac after topical administration. The bioavailability of both drugs is low compared to i.m. application. The plasma concentrations reached are well below the IC_{50} values for COX-1 and COX-2 inhibition of these drugs, explaining the absence of dose-dependent toxicities after dermal application.

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Multiplex liquid chromatography-tandem mass spectrometry assay for the simultaneous monitoring of Bosentan and Macitentan and their metabolites, together with Sildenafil and Tadalafil in patients with pulmonary arterial hypertension

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Introduction: Among the last generation endothelin receptor antagonists (ERAs) only Macitentan has shown a reduction in morbidity-mortality endpoints in pulmonary arterial hypertension (PAH) as compared to placebo. Moreover, compared to the previous ERA Bosentan, Macitentan may have higher clinical efficacy due to: (i) enhanced safety profile, (ii) less liver toxicity, (iii) reduced drug-drug interaction potential and (iv) improved tissue penetration properties as well as ER affinity [1]. Therefore, stable PAH patients currently on Bosentan may benefit from a switch to Macitentan. Yet, Bosentan moderately induces cytochromes CYP3A4 and CYP2C9, both enzymes also implicated in the biotransformation of Macitentan into its active metabolite. Then, switching from Bosentan to Macitentan may yield transiently subtherapeutic drug levels in patients, which have never been investigated before. Possible adverse effects may however be attenuated in patients under bi-therapy with PDE5-inhibitors. The

SWITCH clinical study has been initiated to examine in 25 PAH patients the evolution of plasma levels of drugs and principal active metabolites during the switching process from Bosentan to Macitentan. A sensitive and accurate mass spectrometry assay was needed to this end.
Methods: A multiplex liquid chromatography-tandem mass spectrometry was developed for the quantification in human plasma of Bosentan, Desmethylbosentan, Hydroxybosentan, Macitentan, Despropylmacitentan, Sildenafil and Tadalafil. Generic plasma protein precipitation with methanol was employed. Matrix-matched calibration in plasma was established over the respective clinically relevant range of concentrations. Stable isotopically-labelled internal standards were employed to circumvent matrix-effect and control the method variability.
Results: Baseline chromatographic separation of the seven analytes was achieved in less than 5 min. Optimal *multiple reaction monitoring* traces were applied for their selective detection using triple quadrupole MS. The required sensitivity was reached by optimizing electrospray ionization source parameters. The developed assay complies with the current recommendations of the FDA guidelines on bioanalytical methods validation.
Conclusion: The validated bioanalytical methodology has been found suitable for its application to plasma samples collected within the frame of the *SWITCH* clinical study.

Reference:
1 Pulido T, et al. N Engl J Med. 2013;369:809–18.

P523

Tailoring a clinical decision support tool to a hospital's needs

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Introduction: A large number of commercially available Clinical Decision Support Systems (CDSS) exist. Most commonly, they are embedded in an electronic prescribing software program and their quality is variable. According to the software developer, the embedded CDSS used in our hospital has approximately 21'000 "severe" or contraindicated drug-drug interactions depicted, based on trade-names and generic names. Such alerts "pop-up" automatically during the prescribing process.
Methods: Automatically generated warnings regarding drug-drug combinations which could result in patient harm ("severe"), or which were contraindicated according to the drug label were assessed prospectively during routine patient care by pharmacologists, pharmacists and internists between May 2015 and September 2016. Unsatisfactory warnings were recorded in a local electronic spreadsheet and reported to the company along with the requested alteration every 3–4 months.
Results: During the 16-month period, 137 problematic alerts regarding severe or contraindicated drug-drug interactions were identified and reported to the company. Of these, 60% were changed by the company as requested, within an average of 59 days. The following reasons for not adopting the experts' requests for optimization were given: technical difficulty, difference of opinion and inability to undertake country-specific changes to the database.
Conclusion: Close co-operation between treating physicians, pharmacologists, pharmacists, IT-specialists and the software company is needed to tailor a CDSS to a hospital's needs and quality standards. The process is time- and resource-consuming and does not achieve complete implementation of local expert's desired customizations.