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Original article

Nutritional and metabolic characteristics of critically ill patients admitted for severe toxidermia

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SUMMARY

Introduction: Drug-induced toxidermia is an idiosyncratic adverse skin reaction that may become life-threatening in a small portion of patients, requiring intensive care unit (ICU) admission. The treatment recommendations are extrapolated from those of major burns, while prospective data remain sparse. The objective was to observe the application of these recommendations in patients treated in a burn ICU.

Method: Retrospective cohort study including patients requiring ICU between 2006 and 2020 in a tertiary university hospital. Inclusion criteria: Age >18 years. Patients were categorized as Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), or other toxidermia. Variables: severity scores, body surface area (BSA) involvement, nutritional and metabolic variables, trace element status, outcome variables. Descriptive statistics: median [IQR].

Results: Altogether 35 patients were included (27 *SJS/TEN and 8 "other"*), aged 58 [48; 69] years. Skin involvement was 45% [30; 60] of body surface, 17 patients required mechanical ventilation, and length of ICU stay was 16 [6.5; 26] days. Hospital mortality was 23%. Fluid resuscitation requirements were moderate, despite intense inflammation (admission CRP (144 [89; 218] mg/L). The first 2 weeks' energy and protein intakes were below recommendations ($p < 0.0001$), lowest with oral feeding. Indirect calorimetry showed high energy expenditure in 11 patients (30.4 [23.9; 35.5] kcal/kg) resulting in negative energy balances (mean −245 kcal/day). Copper and zinc levels were below reference range during the first week, the low copper values being a novel finding.

Conclusion: Trace elements should be monitored. The cohort was underfed with intakes lower than our ICU protocols, partly explained by short intubation times, and mucocutaneous involvement complicating the management and placement of feeding tubes. Oral feeding was least efficient and may become an indication for supplemental parenteral nutrition in the absence of an enteral feeding tube.

ClinicalTrials.gov Identifier: NCT05320653

1. Introduction

Toxidermia is defined as an adverse mucocutaneous reaction caused by drugs. Most of them (>90%) are benign but, in rare cases, patients may develop life-threatening forms with high mortality that requires highly specialized care. The Stevens-Johnson syndrome (SJS) is the least severe with involvement of less than <10% of the body surface area (BSA), while the toxic epidermal necrolysis (TEN) affects over 30% of the BSA, the SJS/TEN overlap being defined as a skin detachment involving 10–30% BSA [1,2]. SJS and TEN are mostly induced by medication although some are related to infections. The detailed pathophysiologic mechanisms are still debated but in general, acute TEN is considered a T-cell mediated, type IV hypersensitivity disorder, which leads to skin detachment leaving the dermis exposed, akin to a superficial 2nd-degree burn [3–5]. Besides this specific form, other forms of toxidermia can be encountered

Abbreviations: BSA, body surface area; EN, enteral nutrition; IC, indirect calorimetry; CRP, C-reactive protein; ICU, intensive care unit; NRS, nutrition risk screening score; PN, parenteral nutrition; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; EE, energy expenditure.

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[6]: they represent a heterogeneous group of conditions (e.g. acute generalized exanthematous pustulosis (AGEP), and drug reactions with eosinophilia and systemic symptoms (DRESS), including various clinical patterns that may involve large skin surfaces.

A systematic review showed that the management of epidermal destruction is highly variable [7]. The treatment of SJS/TEN requires hospitalization, the most severe forms requiring intensive care unit (ICU) care ideally to a specialized burn unit [2], in a private room with temperature and humidity control with a 1:1 nurse-to-patient [7], as the skincare requires specialized nursing teams, and eventually an air-fluidized bed. It generally includes fluid management, wound care, and often mechanical ventilation. Treatment focuses on stopping the cause (culprit-drug identification and withdrawal), pain medication, and supportive care, while the use of corticosteroids, immunoglobulins, and anti-cytokines is still debated. Infection surveillance, electrolyte management, oral and ocular care, thrombosis prophylaxis, stress ulcer prophylaxis, and nutrition are all integral parts of the supportive care [7].

The metabolic specificities, nutritional requirements, and management of these critically ill patients remain poorly described [2,7,8]. The largest study is a multicentric observational study including 171 patients which confirms the presence of difficulties in oral feeding resulting in 81% of the patients requiring enteral nutrition (EN) at some stage, with measured energy expenditure of 24.2 kcal/kg [9]. The latter value is much lower than in major burns patients to which the toxidermia patients are often compared: in addition the latter present large exudates which induce special nutritional requirements [10]. Already in the seventies the large volumes of burn exudates were shown to contain large amounts of proteins, electrolytes, and trace elements [11,12]: information regarding the composition of the SJS/TEN exudates however remains limited. A case report analyzing 10 blister samples and bloods of the same patients showed the presence of albumin, immunoglobulins, calcium and magnesium: volume was limited [13]. The comparisons of burn and TEN blister shows lower albumin and protein content in TEN blisters than in burns [13]: nothing is known about the trace element status and blister content.

The objectives of the study were to describe the fluid resuscitation requirements, and the applicability of the burn [14] and ICU nutritional protocol, with the metabolic and nutritional response to these protocols in patients admitted for extensive toxidermia in ICU settings.

2. Methods

This retrospective observational cohort study included all patients admitted for toxidermia to the adult Burn ICU of CHUV between 2006 and 2020. The study was approved by the ethics commission on human research of Canton de Vaud (N° CER-VD 2018–02268). ClinicalTrials.gov Identifier: NCT05320653.

2.1. Patients and variables

All patients over 18 years old and admitted to the burn ICU for toxidermia were included, whatever the skin surface involvement. Exclusion criteria were an ICU stay shorter than 24 h. The observation period was limited to the first 31 days of the ICU stay. The recorded variables were: demographic characteristics, body surface area (BSA) involved, severity scores (SAPSII, SCORTEN for SJS/TEN [1], nutrition risk screening (NRS) score [15]), fluid intakes and balance (exudate volume estimation not included) of the first 10 days, body weight during the stay, renal function (creatinine clearance calculated with Cockroft–Gault equation), length of mechanical ventilation and of ICU stay. Nutritional variables included the 24 h energy prescription and delivery, protein, glucose, and lipid intakes, propofol, insulin and indirect calorimetry (IC) studies. Laboratory blood results included glucose, prealbumin, albumin, C-reactive protein (CRP), triglycerides, creatinine, and trace elements (Cu, Se, Zn). Data were extracted from the electronic medical record (MetaVision®, ImdSoft, Tel Aviv, Israel, version 5.46.44).

2.2. Clinical protocols

Hemodynamic management: crystalloids and vasopressors were titrated to maintain a mean arterial pressure of ≥65 mmHg, and a minimal diuresis of 0.5 ml/kg/h as in other general ICU patients (no change over time). Albumin 20% solution were delivered in case of severe hypoalbuminemia (<21 g/L).

Wound management: the wounds were treated conservatively (no surgical debridement, nor grafting). Hydrotherapy was used in rare cases of wound infection (no change over time).

Nutrition protocol: Nutritional evaluation was based on the Nutrition Risk screening (NRS) score [16] calculated by the nurses or the dieticians (who are part of the ICU team). Admission body weight determined with a calibrated in-bed-stretcher scale was used for calculations. Adjusted body weight was only used if BMI exceed 30 kg/m^2. The general ICU protocol recommended enteral feeding as first route in intubated patients, using polymeric solutions with fiber. The initial energy targets have evolved: they were higher between 2006 and 2010 (30 kcal/kg/d becoming 20–25 kcal/kg/day thereafter, to be reached over 3 days. After day 4 targets had to be guided by indirect calorimetry in intubated patients. In non-intubated patients, oral feeding was proposed first in addition with oral nutrition supplements (ONS) if required. Supplemental PN was indicated when EN did not cover 60% of targets. In burns, the initial target was 30 kcal/kg. Protein target was 1.3 g/kg/day (for burns 1.5–2.0 g/kg) [14]. There was no systematic adjustment of the protein target or micronutrients supplementation in case of renal replacement therapy. Application of general ICU or burn protocol was determined according to the extent of skin involvement. Energy balance was calculated as the difference between prescribed target (or measured energy expenditure) and energy delivery which includes non-nutritional sources of energy. Oral food was prepared by standard recipe delivering 1800 kcal as a mean, enabling evaluation of energy intake based on plate quarter evaluation (camembert quarters). Blood glucose control was achieved with a continuous insulin infusion with a target of 6–8 mmol/L in non-diabetic [17], and of 6–10 mmoL/l in diabetic ICU patients.

2.3. Trace element and vitamin protocol

The ICU protocol proposes two different patterns of micronutrient additives. The first complement called “stress profile” for the critically ill general ICU patients includes a 6-day multi-micronutrient complement (containing 1 multi-trace element (Addaven®, Fresenius Kabi) and multi-vitamin (Cernevit®, Baxter), 100 mg thiamine, 500 mg vit. C, 10 mg Zn, 220 UI (5.5 μg) Vit. D3); from day 7 an enteral complement is added to the enteral feeds (Supradyn® (Roche) that covers 100% DRI and contains 200 UI (5.5 μg) Vit-D3): no additional Vitamin D supplement is proposed. The 2nd supplement for major burn patients (burns >20% BSA) called “burn profile” intended for patients with skin burn or detachment >20% BSA which provides an additional infusion of 3.75 mg copper, 38 mg zinc, and 300 μg selenium for a duration of 10–30 days depending on the involved surface [10]. The words “complement” (cover basal needs) and “supplement” (doses superior to DRI or PN guidelines) are employed according to ESPEN guidelines [18]. By analogy with major burns, enteral Intestamin®, which contains 300 μg Se, 20 mg Zn and 20 g glutamine is administered in patients with the most extensive skin involvement.

2.4. Statistics

Data are presented as median and interquartile ranges (IQR [25; 75]) due to their limited number and a non-normal distribution of several variables (visual appreciation of histograms). Continuous variables were tested using Wilcoxon rank test, while Chi2 test was used for discrete variables. Changes over time were tested with one-way ANOVA. Means were compared using Tukey–Kramer or Dunnett tests. Significance was considered at a level of $p < 0.05$. The statistical package was JMP version 15.0., SAS, California and Rstudio Version 1.3.1056. Integrated Development for R. RStudio, PBC, Boston.

3. Results

3.1. Patients

Altogether 35 patients were admitted to the Burn unit of the ICU during the study period, including 27 patients with a biopsy proven SJS/TEN and eight for other forms of toxidermia, and skin lesions including: 2 patients with SJS/TEN excluded with no other specifications available but just named toxidermia, 2 patients with pemphigus vulgaris, 1 patient with fixed disseminated pigmented erythema, 1 patient with linear IgA dermatosis, 1 patient with spongiform drug eruption, and 1 case of Staphylococcal toxic shock syndrome, which was maintained in the cohort due to his similar clinical evolution. The patient characteristics are summarized in Table 1, with a median age of 58 [48; 69] years, and an admission body weight of 75 [65; 86] kg: nine patients presented Diabetes mellitus (DM). There was a higher proportion of women in the *non-SJS/TEN* patients. The affected body surface was 45 [30; 60] % BSA: mucosal involvement was present in 16/26 SJS/TEN patients (62%) The patients were critically ill (median SAPSII 34 [27; 41]) and presented a high NRS 5 [4,6] on admission. Invasive mechanical ventilation was required in the 18 patients with respiratory failure: their intubation time was 19.5 [8.3; 24.5] days. Continuous renal replacement therapy was required in 3 patients, initiated on days 1, 9, and 17, for 12 days as a mean. The ICU mortality was 23% (n = 8), total hospital mortality was 34.3% (n = 12): 17 patients (48.6%) were discharged to home, the others to nursing homes, and 2 were lost to follow-up. Hospital stay after ICU was prolonged with 23 [13; 51] days.

3.2. Clinical management

Fluid management (Fig. 1): median 24Hr fluid intakes of the first 3 days were 3463 [2355; 4818] ml/day. Fluid balances were modestly positive with 1467 [477; 3017] ml/day. Fluid intakes and balances remained stable during the first 10 days, although positive, resulting in a modest, increase in body weight over the first 10 days ($p = 0.889$). Albumin 20% was infused to 17 patients in context of albuminemia <21 g/L: mean volume was 600 ml over 4–6 days.

Nutrition was started during the first 24 h in 14 patients including 5 on oral feeding. Analysis of the feeding route and nutritional intakes is available for 528 days (Fig. 2): EN was used in 65.2% of days, parenteral nutrition (PN) in 8%, combined enteral and PN in 8%, and oral in 9.1%. Oral feeding was associated with the largest energy intake variability, and the lowest median intake values (Fig. 3).

Energy targets were per general ICU protocol in most patients, i.e. 20 kcal/kg during the first week: indirect calorimetry (IC) was used in 11 (31%) patients with 22 values (Table 2): spontaneous breathing with oxygen dependence was the main reason for not realizing IC in still oxygen dependent patients. Median energy delivery was low during the first week, increasing over time (Fig. 4), with a large individual variability; Energy balances looked neutral when calculated with prescribed values. In patients with IC studies, energy balances were negative (mean −245 kcal/day).

Protein intakes were below the recommended values for critically ill patients, despite progression during the stay, with a mean value of 0.9 g/kg for the first week and a median dose not exceeding 1.49 g/kg/d at the end of the stay (Fig. 4). Exact data for oral feeding are not available.

3.3. Trace element data

Trace elements delivery duration and dose varied (Table 3): the *stress profile* was delivered to 27 patients for median 7days, and the *burn profile* to six TEN patients with a median 70% BSA involvement for a median of 6 days. Monitoring of blood copper, selenium and zinc values was realized in 12 patients (Fig. 5, Table 4). The three elements were negatively correlated with inflammation (CRP) (Fig. 6). Copper values were low and inversely correlated with CRP

Table 1
Patient characteristics (data as median IQR [25; 75]).

Variables	All (n = 35)	SJS/TEN (n = 27)	Other toxidermia (n = 8)	P-value
Age (years)	58 [48; 69]	58 [46; 70]	64 [55.75; 68.5]	0.479
Gender (n (%))				0.024*
Women	16 (46%)	11 (40.7%)	5 (62.5%)	
Men	19 (54%)	16 (59.3%)	3 (37.5%)	
Body Weight - admission (kg)	75 [65; 86]	75 [65; 85]	75.5 [58.25; 89.25]	0.753
Height (m)	1.7 [1.65; 1.75]	1.72 [1.65; 1.75]	1.68 [1.61; 1.75]	0.082
BMI (kg/m2)	23.88 [22.31; 29.41]	23.88 [21.85; 28.08]	25.34 [23.14; 33.28]	0.280
BSA (%)	45 [30; 60]	40 [30; 60]	55 [35; 74]	0.561
SCORTEN		4 [4; 5]		
Mucosal involvement		16/27 (62%)		
SAPS II	34 [27; 41]	38 [27; 45]	32 [23; 39]	0.335
NRS score	5 [4; 6]	5 [4; 6]	5 [3; 6]	0.486
CRRT	3 (8.6%)	2	1	0.664*
Required IMV (yes/no) (n)	18/17	14/13	4/4	0.927*
Length of IMV (d)	19.4 [8.3; 24.5]	17.4 [7.7; 25.0]	21.0 [10.8; 23.8]	0.804
Length of ICU stay (d)	16 [6.5; 26]	16.0 [6; 26]	14.5 [4.5; 28.3]	0.922
Length of Hospital stay after ICU discharge (d)	23 [13; 51]	23 [12.5; 51]	19.5 [13.25; 43]	
Outcome (n (%))				0.870*
ICU Alive/Died	27 (77%)/8 (23%)	21 (77.8%)/6 (22.2%)	6 (75%)/2 (25%)	
Hospital Alive/Died	23 (65%)/12 (35%)	18 (66.6%)/9 (33.3%)	5 (62.5%)/3 (37.5%)	

Statistics: Wilcoxon rank tests and *: Chi2 test, Abbreviations: d = day, IMV = invasive mechanical ventilation (i.e. intubation).

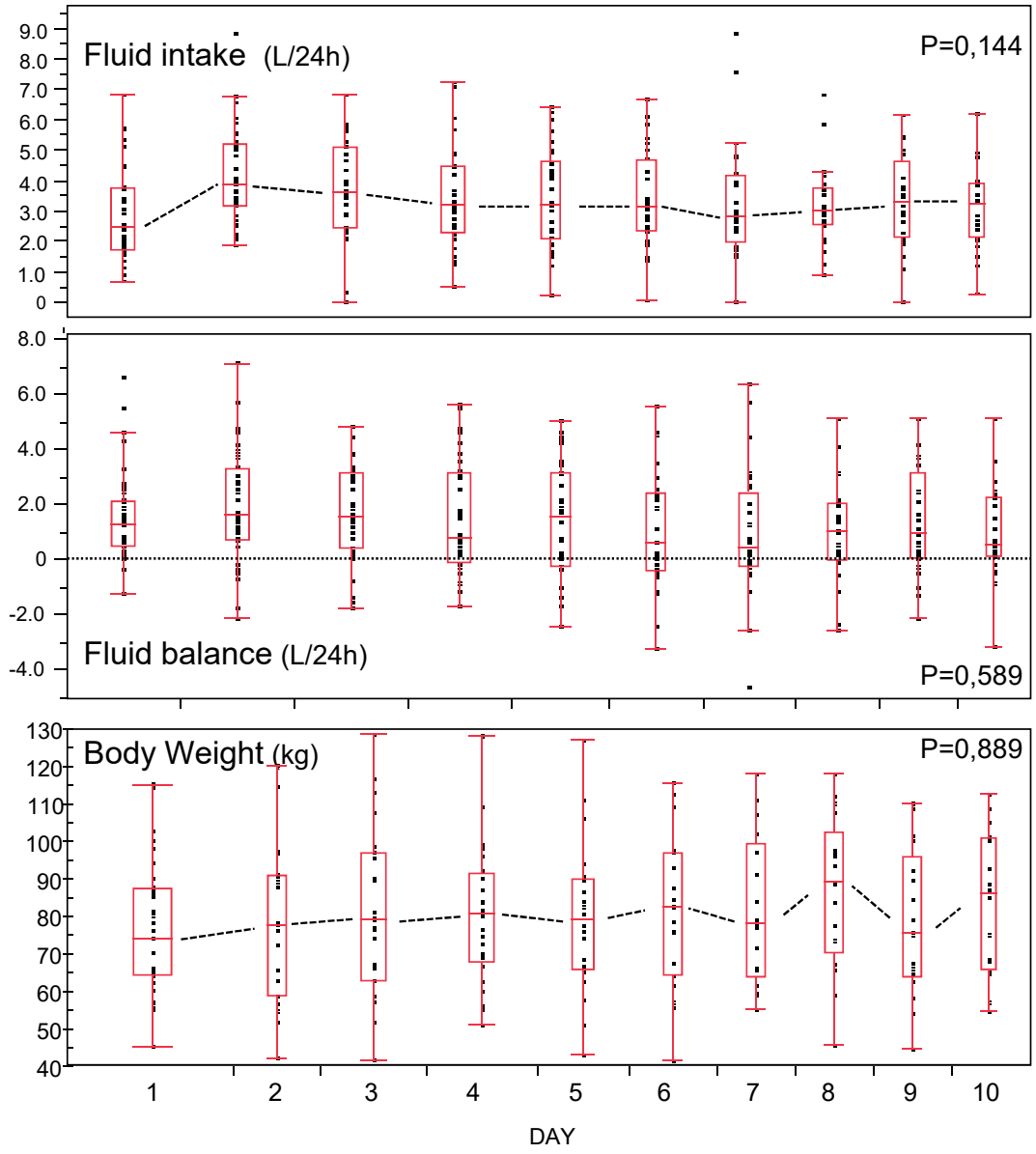

Fig. 1. Fluid intakes and balances during the first 10 days with evolution of body weight.

($p = 0.0006$, $R^2 = 0.437$). Selenium values were mostly within reference ranges and modestly correlated with inflammation ($p = 0.071$, $R^2 = 0.112$). Zinc values were below the reference range, and the decrease was inversely proportional to CRP ($p = 0.002$, $R^2 = 0.234$).

3.4. Laboratory variables (Table 4)

Blood glucose control required a median daily insulin dose of 24 UI/day (1UI/hour) over the first 3 weeks, being higher in diabetics patient: 19 [0; 53] IU/day in nondiabetics versus 45 [18; 83] IU/day in the 9 diabetics patients ($p < 0.0001$).

CRP was high on admission (144 [89; 218] mg/L) decreasing progressively without normalization (daily values Fig. 7). Albumin values were low through the stay. Prealbumin (determined weekly) was low during the first week and increased modestly over time but did not revert to normal.

4. Discussion

The results of this observational study highlight three aspects of TEN/SJS: the fluid management, trace element data and difficulties of the nutritional management.

4.1. Fluid management

Our observation of 35 patients shows that despite extensive skin lesions affecting a median 45% BSA, the fluid volumes required for hemodynamic stability were modest. Due to the extensive skin involvement in many patients, the guidelines recommend monitoring the fluid balance [19], as there might be evaporative of exudative fluid losses by analogy with burns. Major burn patients with similar skin surface involvement would have require 22.5 L by the Parkland formula during the first 24 h (equation guiding resuscitation in burns), versus 2.5 L in the present cohort: the

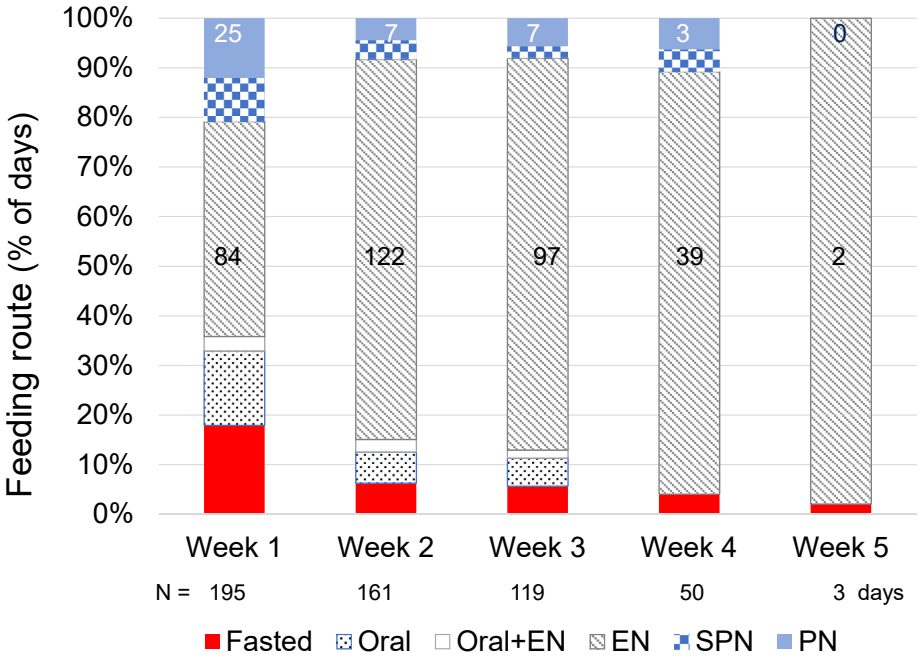

Fig. 2. Evolution of feeding route over time showing the preponderance of enteral nutrition (EN) from day 3.

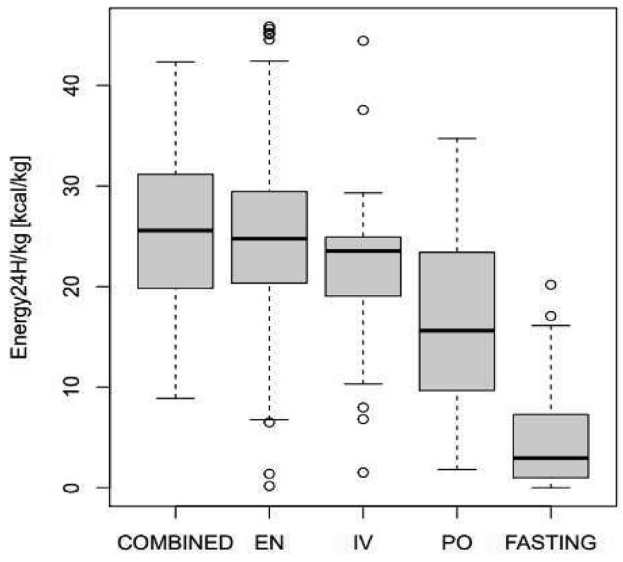

Fig. 3. Energy delivery (24hr means) according to the route of feeding showing that enteral (EN) parenteral (PN) and combined feeding achieve >20 kcal/day, while oral (po) food intake is highly variable.

median fluid balance was +1.25 L in 24hrs (Fig. 1). The fluid requirements remained modest for the first 10 days, resulting in slightly positive fluid balances associated with a non-significant increase in body weight. In major burns, the large early fluid requirements caused by capillary leak and exudative losses, result in major hemodynamic instability, not present in the toxidermia patients. Similarly with major burns, the patients were highly inflammatory with a median CRP value on admission of 142 [71; 236] mg/L, and a low albuminemia of 26 [22.5; 30.0] g/L probably explained by a capillary leak and resulting in 17 patients requiring albumin infusion during the first 10 days [20]: abnormal values levels persisted for several weeks.

4.2. Trace element data

The second original information in our study is the blood trace element data, with the unexpected low blood copper values appearing despite Cu supplements and reflecting copper deficiency [18]. We could not identify any trace element publication in SJS/TEN patients. While during an inflammatory response most trace elements decrease due to redistribution out of the blood compartment, the reverse is true for copper, which increases [21]. Contributing factor to deficiency may have been an unmeasured

Table 2
Energy expenditure (EE) measured by indirect calorimetry and energy delivery on same days.

	Week 1 (n = 8)	Week 2 (n = 5)	Week 3 (n = 5)	Week 4 (n = 2)
EE (kcal/day)	1925 [1557; 1983]	2180 [2072; 2970]	2270 [2255; 2267]	1881 [1821; 1942]
EE (kcal/kg/day)	25.5 [20.9; 34.7]	30.9 [29.8; 39.0]	33.6 [26.5; 36.3]	27.8 [24.1; 31.5]
Energy delivered (kcal/day)	1670 [1140; 1870]	2010 [1300; 2550]	2260 [1730; 2370]	1925 [1870; 1980]

Data as (median IQR [25; 75]).
Note: The 11 patients (5 women, 6 men) with IC were aged 55 [38; 66] years, weighed 75[57; 86] kg with a BMI 23.4 [20,8; 30,9] kg/m2; on Week 4 the two remaining patients were women aged 37 years (BMI 31.6) and 55 years (BMI 20.8).

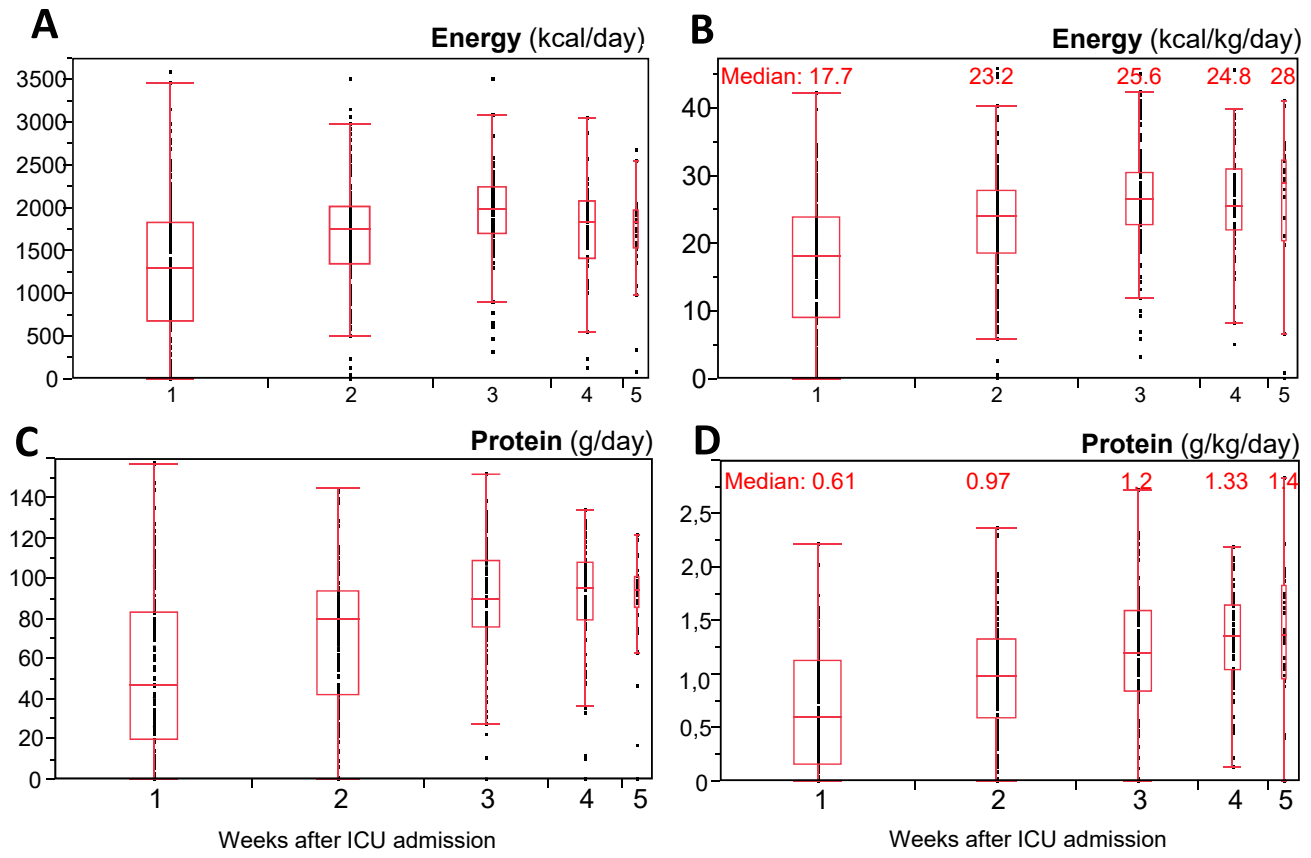

Fig. 4. Evolution of the weekly daily energy and protein delivery expressed (A) in kcal/day, (B) by kg body weight, C) protein gram/day and D) in gram/kg body weight. The increase over time is significant at the level of $p < 0.0001$ for all. The exact median value per kg is indicated for B) and D).

Table 3
Evolution of weekly nutritional daily intakes (median IQR [25; 75]).

Variables Intakes/day	Week 1 (n = 35)[a]	Week 2 (n = 27)[a]	Week 3 (n = 19)[a]	Week 4 (n = 11)[a]	Week 5 (n = 8)	P-value
Energy target (kcal)	1900 [1500; 2100]	1900 [1500; 2100]	2000 [1800; 2200]	2000 [1700; 2100]	1800 [1700; 2000]	ns
Energy delivery (kcal)	1277 [616; 1789]	1755 [1326; 2012]*	1973 [1680; 2245]*	1835 [1396; 2086]*	1840,5 [1534; 1982]**	<0.0001
(kcal/kg/d)	18.3 [8.3; 24.1]	22.4 [17.5; 27.2]*	26.0 [22.0; 30.6]*	24.3 [19.6; 31.1]*	29.3 [17.1; 32.4]**	<0.0001
Energy balance (kcal/d)	−371 [-1130; 50]	−1 [-221; 101]	49 [-86; 145]	−31 [-360; 80]	40 [-121; 80]	<0.0001
Proteins (g/d)	47 [12; 89]	78 [44.5; 94] *	90 [73; 109] *	94 [77.75; 106]*	94 [88; 101]**	<0.0001
(g/kg/d)	0.63 [0.16; 1.17]	0.94 [0.53; 1.29]*	1.20 [0.81; 1.62]*	1.31 [1.00; 1.58]*	1.40 [0.98; 1.86]**	<0.0001
Carbohydrates (g)	138 [55; 218]	196 [140; 252]*	217 [140; 252]*	200.5 [160; 246]*	199 [174; 230]**	<0.0001
(g/kg/d)	2.20 [0.86; 2.90]	2.66 [1.96; 3.23]*	3.03 [2.21; 3.49]*	2.87 [2.37; 3.37]*	3.40 [2.28; 3.69]**	<0.0001
Lipids (g/d)	32 [9; 55]	54 [35; 68]*	61 [45; 77]*	55 [41; 66]*	50.5 [43; 68]**	<0.0001
(g/kg/d)	0.56 [0.17; 0.74]	0.70 [0.49; 0.95]*	0.80 [0.62; 1.00]*	0.74 [0.58; 0.88]*	0.85 [0.63; 0.98]**	<0.0001
Copper (mg/d)	0.855 [0; 2.35]	1.99 [0; 2.99]	2.21 [0; 3]	2.01 [0; 2.77]	2.235 [0; 2.59]	<0.05
Selenium (μg/d)	173 [23; 224]	170 [42; 225]	65.5 [50; 222] @	62 [47; 123]@	59 [53; 69.5]@	<0.05
Zinc (mg/d)	19.9 [6.9; 29.6]	20.3 [12.8; 31.8]	19 [12.9; 32.4]	16.5 [13.7; 22.4] @	18.15 [15; 19.8] @	<0.05

*: $p < 0.0001$ different from week 1, using Tukey–Kramer or Dunnett tests.
*: $p < 0.01$ different from week 1, using Tukey–Kramer or Dunnett tests.
@: $p < 0.05$: lower intakes during weeks 3-4-5 versus weeks 1*2 using Tukey–Kramer or Dunnett tests.
[a] Number of patients present during the week. Statistics: One-way ANOVA, or Wilcoxon-rank test for skewed distribution.

local exudative loss, or migration into the wound, consumption of copper in the wound healing process, or loss with the necrotic tissues. The roles of copper include modulation of cytokines and growth factors, and involvement in all stages of the wound healing process. Platelet-derived growth factor (PDGF), required for several steps of the healing process is strictly dependent on copper ion availability [22]. Further copper binds and interacts with growth factors involved in vessel formation. Copper-based nanomaterials and nanoparticles have emerged for potential use in wound dressing, aiming at increasing the local delivery of copper, thus assisting tissue repair [23]. But no data are available regarding blood concentrations in the published wound healing studies. By analogy with burns, the patients with a skin detachment >20%BSA received from admission the "stress profile" complement and six patients the "burn profile" supplement which contains additional copper, selenium, and zinc: the infusions are delivered during the night shift and terminates about 3 h before the blood sampling, which therefore reflects status. The blood concentrations of selenium during the first 2 weeks, were surprisingly close to normal in presence of inflammation, and zinc values being modestly

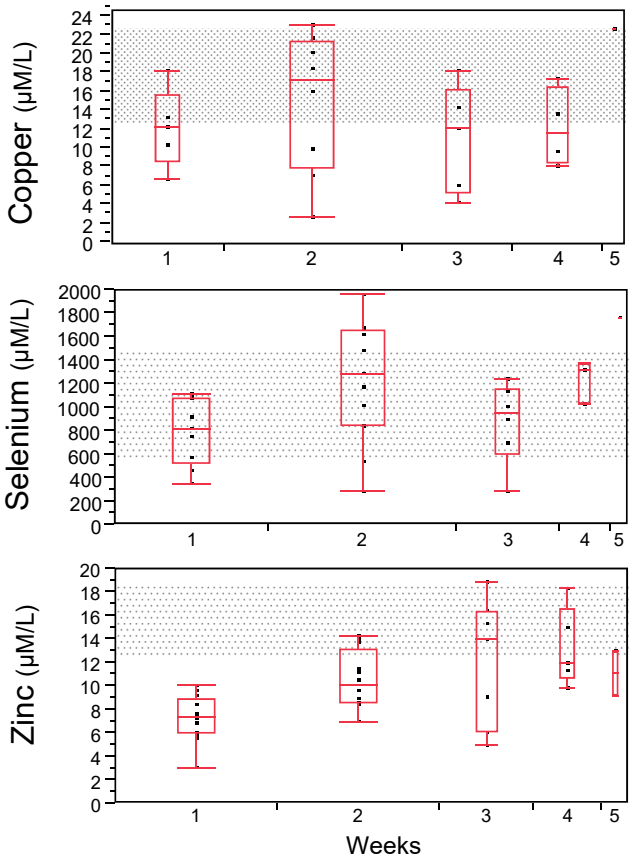

Fig. 5. Evolution of copper, selenium and zinc blood concentrations (the shaded areas show the reference ranges).

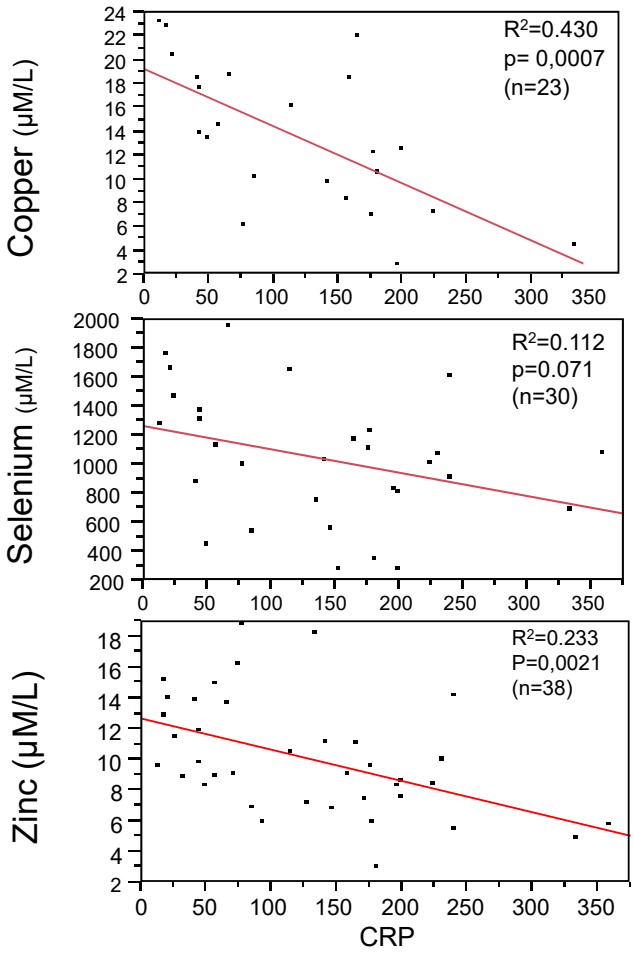

Fig. 6. Association between Cu, Se, and Zn levels by CRP (single regression) showing that with increasing inflammation all trace elements decrease, including copper, reflecting deficiency for the latter [18].

decreased: this can be interpreted as the delivered doses being sufficient to maintain status. For selenium and zinc, the values were not as strongly altered as in burnt patients [10]: the intravenous supplement doses seemed to address the needs and maintain blood

Table 4
Evolution of the blood laboratory variables.

Variables	Week 1	Week 2	Week 3	Week 4	Week 5*	P-Value	Ref range
Albumin (g/L)	22 [20; 26] (n = 35)	23 [21; 25] (n = 25)	23 [21.3; 25] (n = 18)	23 [22; 26] (n = 11)	27 [23.3; 30.8] (n = 7)	0.032	35–45
Prealbumin (g/L)	0.07 [0.06; 0.12] (n = 23)	0.10 [0.07; 0.14] (n = 23)	0.13 [0.06; 0.20] (n = 15)	0.11 [0.08; 0.14]* (n = 8)	0.14 [0.13; 0.26]* (n = 6)	0.024	0.2–0.4
CRP (mg/l)	144 [89; 218] (n = 35)	114 [60; 193] (n = 25)	91 [55; 144] (n = 18)	80 [53.25; 102.5]* (n = 12)	71 [38; 98]* (n = 7)	<0.0001	<10
Creatinine (µmol/l)	73 [52; 140] (n = 35)	74 [57; 111] (n = 25)	69 [47; 97] (n = 16)	61 [35; 86]* (n = 10)	43 [85; 76]* (n = 7)	<0.0001	F: 53–75; M: 62 –115 µmol/L
Creatinine clearance (ml/min)	90.9 [56; 132] (n = 32)	95 [63; 124] (n = 25)	101 [61; 157] (n = 16)	131 [82; 218]* (n = 10)	172 [85; 234]* (n = 7)	<0.0001	>60
Glucose mmol/l	7.2 [6.1; 8.8] (n = 33)	7.1 [6.08; 7.8] (n = 23)	7.2 [6.4; 8.4] (n = 17)	7.6 [6.7; 8.7] (n = 8)	6.8 [6.1; 7.2] (n = 5)	0.109	4.2–6.1
Insulin (UI/d)	19 [0; 54]	24 [3; 64]	24 [0; 60]	14 [0; 71]	11 [0; 31]	0.591	na
Copper (µmol/L)	12.5 [8.75; 15.97] (n = 5)	17.46 [8.03; 21.6] (n = 8)	12.3 [5.35; 16.53] (n = 5)	11.85 [8.68; 16.75] (n = 4)	–	0.427	12.4–22.4
Selenium (µmol/L)	808 [507; 1077] (n = 9)	1282 [833; 1654] (n = 11)	942 [588; 1154] (n = 6)	1308 [1026; 1372] (n = 3)	–	0.053	550–1500
Zinc (µmol/L)	7.4 [5.9; 8.9] (n = 12)	10.1 [8.45; 13.13] (n = 12)	13.9 [6.0; 16.3] (n = 7)	11.9 [10.5; 16.55] (n = 5)	11.0 [9.1; 12.9] (n = 2)	0.006	12.4–18.2

* Signals the values that differ significantly, using Tukey–Kramer or Dunnett tests.

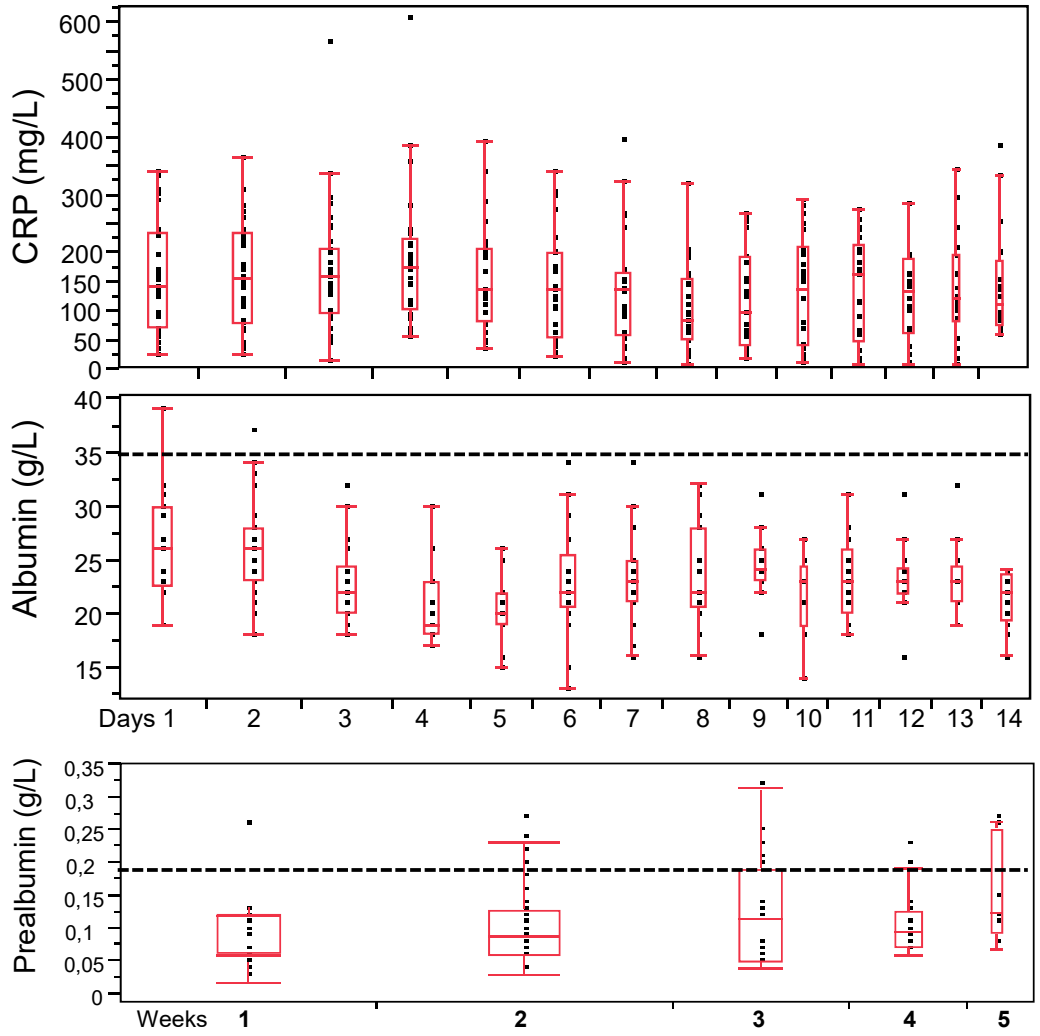

Fig. 7. Daily evolution of CRP levels and albuminemia during the first 14 days, showing persistent inflammation and very low albumin levels (—: lower normal reference range).

levels within references values. Without such supplements, the blood levels would likely have been lower.

4.3. Nutritional management

The patients started their ICU journey with a high nutritional risk, partly due to low food intakes before admission (median NRS 5). Our patients were prescribed the values that are applied to the general ICU patients (20–25 kcal/kg/day) for the first week, before energy expenditure (EE) can be measured by indirect calorimetry (IC). Based on phenotypic analogy with major burns, an increased EE has been hypothesized for SJS/TEN patients in several review articles [24,25]. In our cohort IC could be carried out in only 11 patients (31%) this low proportion being explained by only 17 patients requiring invasive mechanical ventilation, and a short intubation time in the others related to wound dressings. In the latter oxygen dependent spontaneously breathing patients canopy IC could not be realized. In those patients with IC, the EE values during the 1st week were 25.5 [20.9; 34.7] kcal/kg/day increasing modestly over the first 3 weeks to slightly over 30 kcal/kg. These values are a little higher than the empirical targets proposed in the UK guidelines for the early phase (up to 20–25 kcal/kg/day), or the 25–30 kcal/kg proposed in the anabolic phase [19]. These EE values are also a little higher than those observed by Graves et al.: measured EE was 24.2 [19.4–29.9] kcal/kg in the 34% of their patients with IC: [9]. The values in our cohort were significantly lower than those we measure in major burns patients with similar skin surface involvement [26].

Energy balances were equilibrated when calculated with the prescribed targets intended for the general ICU patients, reflecting the precise nurse work aiming at delivering the prescribed values (Table 3). But energy delivery did probably not cover the patients' real needs, the prescribed targets being lower than the available IC data. Indeed, in those patients with IC values, the balances were negative: the higher EE are probably explained by the extensive wound healing process.

Protein delivery was below our internal general ICU protocol recommendation and guidelines for critically ill [16], with a median value of 0.9 g/kg. In the patients on oral feeding, the protein intakes were probably even lower. Prealbumin was determined weekly by analogy with burns: in the latter, despite persistent inflammation, and increasing value is associated with the energy and protein delivery within targets [26]. In this cohort, despite inflammation slowly decreasing, prealbumin remained very low, possibly reflecting the insufficient cover of both energy and protein needs.

The US systematic review regarding SJS/TEN's nutrition recommends to maintain oral nutrition and to use a nasogastric tube

for EN only if necessary [7]: this may prove difficult considering the mucous membrane involvement in up to 95% of patients [24,27], and present in 16/27 SJS/TEN patients (62%) in our cohort. Medical nutrition therapy, i.e., EN, PN or their combination, was delivered in 65.1% of ICU days during the 1st week and 87.6% during the 2nd week, with a predominance of EN as encouraged by our protocol and guidelines, but also to the presence of mucous involvement. Enteral feeding tubes were often pulled out by the patients (episodes of agitation in non-intubated patients), resulting in intermittent underfeeding, motivating PN or supplemental PN in some patients.

The UK guidelines propose to exert blood glucose control [19], which was realized in the present cohort. As our patients were on the underfeeding side, the doses of insulin required to maintain blood glucose within 6–8 mmoL/l were moderate with 1 UI/h, being higher in the diabetic patients.

4.4. Limitations

Due to the retrospective nature of the study, several variables are incomplete. Moreover, the cohort spans over 15 years which exposes to changes in management procedures over time: the changes in practice were limited though, consisting mainly in a reduction of energy targets since 2011: they did not affect the wound management, nor the fluid management practice. Further, in this single center study the sample's size is small, and only large differences can be detected, reducing the external validity of our observations. Nevertheless, being monocentric has the advantage of a stable team over time, with homogeneity of treatment resulting from well-defined protocols in a burn ICU.

Due to this homogeneity, our study could identify specificities of SJS/TEN patients compared to major burns. Two are important in terms of ICU management, with limited fluid requirements for hemodynamic stability, and surprising low requirement for invasive mechanical ventilation. The latter characteristic complicated the nutritional management as feeding tubes were frequently displaced reducing EN efficacy, and energy expenditure could not be measured. Our study completes the observations by Graves et al. [9]. Finally, the length of hospital treatment after ICU discharge was prolonged, reflecting rehabilitation issues also compatible with underfeeding: the mortality was high with 35%, confirming the severity of this pathology.

5. Conclusion

The toxidermia patients are at high risk of undernutrition during their stay, with low oral food intake and presence of mucosal lesions that complicated handling of feeding tubes. The short intubation time in most of them, further complicated the process. Precisely estimating their energy requirements was possible only in 31% of them. The trace element data show that a weekly blood monitoring should be done and would reveal copper deficiency. When a feeding tube is not available, and the energy intake remains significantly below target, our ICU protocol proposes supplemental PN: we consider that we did not use this option enough. It might be appropriate to consider supplemental parenteral nutrition from day 4 on as in other critically ill patients. Tight monitoring is required to detect early feeding problems to avoid energy and protein deficits that will worsen wound healing.

Author involvement

MK, OP and MMB designed the study, MK, OP and MMB collected the data, MK and MMB realized the statistical outwork and the figures, MK and MMB wrote the first draft. MK, MMB, OP, OG and MMB reviewed the manuscript, and all authors approved the final version.

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Conflicts of interest

The authors do not declare any conflict of interest (see COI forms).

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