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Adult native septic arthritis: A review of 10 years experience and lessons for empirical antibiotic therapy

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Abstract

Objective:

Antibiotic stewardship programs include development of practice guidelines incorporating local resistance patterns. The purpose of our study was to review the epidemiology of native septic arthritis to establish local guidelines for empirical antibiotic therapy.

Methods:

We conducted a ten-year retrospective study based on positive synovial fluid cultures and discharge diagnosis of septic arthritis in adult patients. Microbiology results and medical records were reviewed.

Results:

Between 1999 and 2008, we identified 233 episodes of septic arthritis. The predominant causative pathogens were methicillin-susceptible *Staphylococcus aureus* (MSSA) and streptococci (respectively 44.6% and 14.2% of cases). Only 11 cases (4.7%) of methicillin-resistant *Staphylococcus aureus* (MRSA) arthritis were diagnosed, among which five (45.5%) occurred in known carriers.

For large joint infections, amoxicillin/clavulanate or cefuroxime would have been appropriate in 84.5% of cases. MRSA and *Mycobacterium tuberculosis* would have been the most frequently uncovered pathogens. In contrast, amoxicillin/clavulanate would have covered only 75.3% of small joint infections (82.6% if diabetics are excluded). MRSA and *Pseudomonas aeruginosa* would have been the main uncovered pathogens. Piperacillin/tazobactam would have been appropriate in 93.8% of cases ($p<0.01$ vs. amoxicillin/clavulanate). This statistically significant advantage is lost after exclusion of diabetics ($p=0.19$).

Conclusions:

Amoxicillin/clavulanate or cefuroxime would be adequate for empirical coverage of large joint septic arthritis. A broad-spectrum antibiotic would be significantly superior for small joints infections in diabetics. A systematic coverage of MRSA is not justified, but should be considered for known carriers. These recommendations are applicable to our local setting. They might also apply for hospitals sharing the same epidemiology.

Introduction

Septic arthritis represents the most serious condition in the differential diagnosis of a hot swollen joint.[1-4] The yearly incidence of septic arthritis varies from 2 to 10 per 100'000 patients in the general population,[2-5] but is up to ten times higher in high-risk patients such as those suffering from rheumatoid arthritis.[2,5,6] Preexisting joint disease, diabetes, immunosuppressive treatments, prosthetic joints, intravenous drug use, older age and infection at a distant site are known risk factors.[1-3,5] Attributed mortality ranges from 10 to 15%,[7-9] mostly because of concomitant bacteremia with virulent microorganisms.[2] Complications are frequent (around 30%), including loss of joint function subsequent to inflammation and release of lysosomal enzymes and bacterial toxins.[2,7-10] Several risk factors and a delayed or inadequate treatment worsen the outcome of septic arthritis.[9,10] Thus, prompt initiation of an adequate empiric treatment and drainage of purulent joint fluid (either surgically or by closed-needle aspiration) are of utmost importance to reduce morbidity and mortality.[1]

Clinical presentation of septic arthritis lacks specificity, especially for patients with underlying joint disease. The diagnostic performance of signs and symptoms was recently reviewed, concluding that history and physical examination are not able to substantially change the pretest probability of septic arthritis in patients with an acutely painful, swollen joint.[11] Sensitivity of fever in particular is only 57%. The arthrocentesis is most helpful in predicting septic arthritis. In particular, synovial white blood cells count and percentage of polymorphonuclear cells provide the best utility in identifying septic arthritis. Polymorphonuclear cell count of at least 90% suggests infection with a likelihood ratio of 3.4 (95% confidence interval, 2.8-4.2). Gram stain sensitivity is variable and has been estimated from 29 to 52%.[11] Although analysis of synovial fluid may be useful in increasing the pretest probability of septic arthritis, the initiation of an empiric antibiotic treatment is necessary while cultures are pending.

Guidelines for accurate and rapid management of a suspected septic arthritis were recently published, with proposal of an empiric antibiotic therapy.[12] These guidelines were mostly based on expert opinion, due to the paucity of well-designed studies answering the question of which empirical antibiotic therapy would perform better for septic arthritis.[13] The authors suggested confronting these recommendations with the local resistance pattern to ensure an

appropriate empiric therapy,[14] in accordance with guidelines for antibiotic stewardship.[15] While *Staphylococcus aureus* and streptococci are commonly the most frequent pathogens in published series,[1-5,16,17] other microorganisms show an obvious geographical variation (e.g. brucellosis, tuberculosis).[16,17] In addition, although the distribution of microorganisms responsible for septic arthritis has been reported as stable over time,[18] the incidence of multi-drug resistant microorganisms is generally increasing, exhibiting a remarkable geographical variability.[19] In particular, the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* infections are of concern for empiric therapy of septic arthritis.

In an era of increasing bacterial resistance, the aim of our study was to review the epidemiology of septic arthritis and the antibiotic susceptibility profile of predominant causative pathogens in Western Switzerland in order to develop practice guidelines for empirical antibiotic therapy.

Patients and methods

We conducted a retrospective study on consecutive adult patients admitted with septic arthritis of a native joint in the University Hospital of Lausanne, an 850-bed tertiary care hospital in Western Switzerland, between January 1999 and December 2008. The design of this study was in accordance with the ethical standards of our hospital ethics committee.

Case definition

A case of adult native septic arthritis was defined as a > 16 year-old patient with a positive culture of synovial fluid and/or a discharge diagnosis of infectious arthropathy. Prosthetic joint arthritis was excluded.

Cases were identified by reviewing positive cultures of synovial fluid samples in the microbiology database. Contaminations, bacteriological samples wrongly labeled as synovial fluid or alternative diagnosis (e.g. septic bursitis) were excluded. In addition, we reviewed hospital discharge diagnosis codes of infectious arthropathies (ICD-10, v.2007, codes M00.0 to M01.1). Medical records of identified cases were assessed to confirm the diagnosis of septic arthritis. Data on comorbidities and specific risk factors (namely diabetes, documented pre-existing joint disease as osteoarthritis or inflammatory arthritis, intra-venous drug use, joint surgery or intra-articular injection in the previous 3 months) were collected. A former

MRSA carriage was recorded from the infection control database. Hip, knee, shoulder, ankle, wrist, elbow, sternoclavicular and sacroiliac joints were classified as large joints. Joints of hands and feet were classified as small joints.

Microbiology

During the study period, a Gram stain was systematically performed on all synovial fluid samples. Samples were inoculated on standard blood agar, chocolate agar, McConkey agar and thioglycolate broth. The strains were identified at the species level using conventional phenotypic tests such as Vitek2 system (BioMérieux, Marcy l'Etoile, France) or the API system (BioMérieux). Antimicrobial susceptibility testing was performed using manuel disk diffusion methods according to CLSI (formerly NCCLS) guidelines or automated susceptibility testing using Vitek2 system (BioMérieux). When *Mycobacterium tuberculosis* arthritis was suspected on the basis of history and medical exam, fluorescent microscopy was applied on synovial fluid samples using acid fast stain (auramine). MGIT broth (Becton Dickinson, Sparks, Md.) and Lowenstein-Jensen medium were used for culture. Mycobacterial identification was performed using standard phenotypic and genotypic methods. The automated blood culture system was the Bactec 9240 (Becton Dickinson) with the Plus aerobic/F and Lytic anaerobic/F vials (Becton Dickinson).

Antibiotic susceptibility

Antibiotic susceptibility profile including amoxicillin, amoxicillin/clavulanate, cefuroxime, flucloxacillin and piperacillin/tazobactam of causative pathogens were reviewed for each case. These antibiotics were chosen according to the prescribing practice in our hospital and to recent guidelines.[1,12] Our local antibiotic policy does not recommend the use of quinolones and carbapenems as empiric choices.

During the study period, the proportion of MRSA in all clinical isolates of *S. aureus* increased from 4% in 1999 to 12% in 2008 in our hospital (mostly hospital-onset cases). Incidence of extended spectrum beta lactamases (ESBLs) producing gram-negative bacteria was low (2% of all *E. coli* isolates in 2009) and vancomycin-resistant enterococci remained extremely rare (<1%).

Statistical analyses

Categorical variables were compared using the chi-square or Fisher's exact tests when appropriate; continuous variables were compared using the Mann-Whitney test. Analyses were conducted using the GraphPad Prism software (v. 5.03).

Results

Cases and classification

During the ten-year study period, 233 cases of native septic arthritis were diagnosed in 231 adult patients. Two intravenous drug users (IVDUs) presented recurrent infections. One hundred and seven episodes (45.9%) were identified through positive synovial fluid cultures, and 126 (54.1%) additional cases through the hospital discharge diagnosis codes. Among these 126 cases, 89 had wrongly-labeled positive synovial fluid cultures (samples mostly named as surgical swabs without precision), 14 had synovial samples that were processed in an external laboratory before admission, 12 had positive concomitant blood cultures, one had a negative synovial culture with a positive PCR, and ten remained of unknown bacterial etiology.

Most septic arthritis involved large joints (147 episodes, 63.1%). Clinical characteristics of patients with large and small joint infections are presented in table 1. Only 4 (1.7%) polyarticular septic arthritis were observed, all involving large joints.

Based on the review of medical records, hematogenous spread was the most likely pathogenesis for large joint infections (112 cases, 76.2%). Evolution from a contiguous focus (e.g. osteomyelitis, soft tissue infection) was predominant in case of small joint infections (81 cases, 94.2%). Small joint septic arthritis concerned mostly foot joints in diabetic patients (33 out of 36 episodes, 91.7%).

Microbiology

As expected, the predominant causative pathogens were *Staphylococcus aureus* (n = 115, 49.4%) and streptococci (n = 33, 14.2%). Etiological agents differed between large and small joint infections (table 2). Small joint infections were more frequently polymicrobial (24.4% vs. 1.4%, $p < 0.001$). Only two cases of *Neisseria gonorrhoeae* infections were diagnosed, both involving large joints. In eleven patients, synovial fluid and/or other samples remained negative, mostly because of concomitant antibiotic therapy. In one of them, *Streptococcus*

dysgalactiae was identified thanks to a 16S rDNA broad-spectrum PCR. The ten other cases remained of undetermined etiology (no PCR performed). Eleven out of 115 (9.6%) *S. aureus* isolates were methicillin-resistant. Five (45.5%) of the 11 MRSA cases occurred in known carriers.

A percutaneous synovial fluid sample was available in 107 cases (72.8%) of large joint infections, and in 6 cases (7.0%) of small joint infections. Direct gram staining and microscopy was positive in only 33.6% of these 113 cases. In all cases of *M. tuberculosis* arthritis (n=7), auramine staining was negative. *M. tuberculosis* specific PCR was either negative or not performed.

Thirty-five episodes of septic arthritis (15.0%) occurred in 33 IVDUs. Among this subgroup of patients, methicillin-susceptible *Staphylococcus aureus* (MSSA) was by far the most commonly involved pathogen (25 cases, 71.4%). No MRSA and only one case of *P. aeruginosa* arthritis were observed.

Seventy episodes of septic arthritis (30.0% of all, 23.1% of large and 42.0% of small joint infections) occurred in diabetic patients. MSSA was also the main causative microorganism (28 cases, 40.0%). Gram-negative bacteria (namely 2 *Escherichia coli*, 1 *Enterobacter cloacae*, 3 *Morganella morganii*, 3 *Pseudomonas aeruginosa*, 1 *Pantoea* spp, and 2 *Proteus* spp) were responsible for 12 cases (17.1%). Eleven of these cases were polymicrobial (15.7%).

Antibiotic susceptibility

Overall antibiotic susceptibility profiles of causative pathogens to amoxicillin, amoxicillin/clavulanate, cefuroxime, flucloxacillin and piperacillin/tazobactam were systematically reviewed and are summarized in table 3. No Gram-negative bacteria produced ESBL.

Performances of various empirical antibiotic therapies

For large joint infections, amoxicillin/clavulanate or cefuroxime would have been appropriate in 84.5% of cases (table 4). MRSA (8 cases) and *Mycobacterium tuberculosis* (7 cases) would have been the most frequently uncovered pathogens. Addition of vancomycin in previously known MRSA carriers (4 patients) would have only slightly increased the global

appropriateness to 87.3%. Exclusion of *M. tuberculosis* cases would increase the appropriateness of empiric amoxicillin/clavulanate or cefuroxime to 88.8%. An anti-pseudomonal penicillin (piperacillin/tazobactam) would not have performed significantly better (88.0%, p=0.4 vs. amoxicillin/clavulanate or cefuroxime).

In contrast, empiric amoxicillin/clavulanate would have been appropriate in only 75.3% of all small joint infections. This rate would increase to 82.6% if diabetic patients are excluded. MRSA (3 cases, of which one occurred in a previously known carrier) and *P. aeruginosa* (9 cases, of which 7 are monomicrobial) would have been the main uncovered pathogens. Piperacillin/tazobactam would have been appropriate in 93.8% of cases of small joint infections ($p < 0.01$ vs. amoxicillin/clavulanate). This statistically significant advantage is lost after exclusion of diabetic patients (p=0.19 vs. amoxicillin/clavulanate). When considering only diabetic patients with small joint infections, piperacillin/tazobactam was appropriate in 94.3% of cases vs. 65.7% for amoxicillin/clavulanate (p=0.01).

Discussion

In order to establish guidelines for empirical antibiotic therapy, we reviewed the epidemiology of septic arthritis over the last ten years in Western Switzerland and assessed the overall antibiotic susceptibility profile of causative pathogens. Two hundred thirty-three consecutive cases were analyzed. Due to the high proportion of wrongly-labeled synovial fluid specimens, the additional review of hospital discharge diagnosis codes identified 54% of all cases and should therefore be included in a review process to be exhaustive. Most of the previous large series were published in the eighties and nineties, [4,5,7,9,10,16] and only scarce recent data are available.[8,17,18] Globally, the main pathogens are concordant with previous studies,[1-5,8-10] staphylococci and streptococci being the most frequently recovered microorganisms. Incidence and species of gram-negative pathogens differed between large and small joint septic arthritis and according to underlying comorbidities such as diabetes. Gonococcal and mycobacterial arthritis were rare in our setting. Mycobacterial infections were included in our analysis as clinical presentation of this pathogen may be indistinguishable from other causes of septic arthritis,[20]. Only ten septic arthritis cases (4.3%) remained of undetermined etiology.

Based on our local epidemiology, amoxicillin/clavulanate or cefuroxime are adequate for empirical treatment of large joint septic arthritis and can be recommended in local guidelines. An anti-pseudomonal antibiotic was not superior in this setting. In contrast, piperacillin/tazobactam performs significantly better in the subgroup of diabetic patients with small joint infections, mostly due to the higher incidence of *P. aeruginosa*. We could not reliably consider the possible impact of a previous antibiotic therapy or recent hospitalization due to the frequently missing information in medical records. In diabetic patients with small joint infections, most cases arose from a contiguous focus (100%, soft tissue and/or osteomyelitis) and concerned foot joints (91.7%). This argues for chronic infections and possible previous outpatient antibiotic treatment. The use of broad-spectrum antibiotic in this specific clinical setting is in agreement with recommendation of empirical therapy for severe diabetic foot infections.[21-23]Further data are needed to determine if a narrower spectrum antibiotic therapy may be adequate for diabetic patients with small joint acute infections without previous antibiotic therapy.

Septic arthritis due to MRSA remained also rare during the study period (11 cases, 4.7% of all episodes). Although resistant strains emerged soon after the introduction of methicillin in 1961 and progressively became endemic worldwide,[24] many series published between 1976 and 2007 do not mention the quantitative importance of MRSA in the setting of *S. aureus* arthritis.[1,5,6,8-10,16,17] Only some studies performed in high MRSA incidence areas report a proportion of septic arthritis due to MRSA ranging from 2 to 25% of all cases.[18,25-27] As clinical presentation, patients' demographics and comorbidities do not reliably permit to distinguish MRSA from MSSA septic arthritis,[27] guidelines for empirical antibiotic therapy have to consider the local epidemiology. Almost half of our cases were known carriers before the septic arthritis. This is in agreement with studies demonstrating the significant risk of subsequent infections in prevalent MRSA carriers.[28,29] If the global frequency of MRSA septic arthritis does not justify systematic empiric coverage of this pathogen in our setting, an adapted empirical treatment should be considered for known carriers.

Evaluation of septic arthritis in IVDUs showed that MSSA remained the leading etiological agent. *P. aeruginosa* septic arthritis has been reported mostly in small studies from the eighties including heroin addicts.[30,31] At that time, usage of pentazocine, a synthetic opiate dissolved and injected without heating, was frequently associated with bacteremia due to environmental bacteria like *P. aeruginosa*. The parenteral usage of pentazocine ended in 1983

when the manufacturer added naloxone to stop its narcotic use.[32] A serie of 180 sternoclavicular infections, a frequent localization in IVDUs, reported a drop of *P. aeruginosa* arthritis rate from 82% before 1981 to 14% after 1981, and its concomitant substitution by *S. aureus* infections.[33] Our results are in agreement with this general trend and allow us not to consider empiric coverage of *P. aeruginosa* in IVDUs. Although intravenous drug use has been locally recognized as a risk factor for infection with community-associated MRSA,[34] our data do not provide any evidence for dissemination of this pathogen in our population of IVDUs.

By definition, our recommendations are only applicable to our local setting, although they might also apply for hospitals sharing the same epidemiology of resistant pathogens. Due to the retrospective design of our study, a precise description of the clinical initial presentation and a meticulous review of some risk factors were not possible. In particular, we could not integrate the detailed immunosuppressive medication or anamnestic elements indicating a previous urinary bacteremia or risk factors for sexually transmitted diseases. Usage of broad-spectrum and pathogen specific PCR for negative synovial fluid cultures was not systematically available before 2002 (confirmer la date). However, this should not have biased our analysis in minimizing resistant pathogens.

In summary, this ten-year review of the epidemiology of septic arthritis in Western Switzerland allowed us to extrapolate an appropriate empirical therapy for this local setting. These recommendations are only applicable to our local setting, although they might also apply for hospitals sharing the same epidemiology of resistant pathogens. Due to the changing incidence of resistant pathogens over time, the adequacy of this proposal should be validated on a regular basis.

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Transparency declarations

None to declare.

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Table 1: Comparison of clinical characteristics between patients with large and small joint arthritis

	Large joints *N = 147*	**Small joints** *N = 86*	**P value**
Male gender	91 (61.9%)	57 (66.3%)	0.57
Mean age (years)	57.6	63.3	0.07
Co-morbidities			
Diabetes	34 (23.1%)	36 (41.8%)	< 0.01
IVDU[1]	28 (19.0%)	7 (8.1%)	0.04
Preexisting joint disease	62 (42.2%)	56 (65.0%)	< 0.01
Previous joint surgery/puncture	11 (7.5%)	1 (1.2%)	0.06
Localization			
Knee	57 (38.8%)	-	
Hip	26 (17.7%)	-	
Shoulder	24 (16.3%)	-	
Ankle	13 (8.8%)	-	
Wrist	13 (8.8%)	-	
Sternoclavicular	6 (4.1%)	-	
Elbow	3 (2.0%)	-	
Sacroiliac	1 (0.7%)	-	
Hand			
Metacarpo-phalangeal	-	12 (14.0%)	
Distal interphalangeal	-	9 (10.5%)	
Proximal interphalangeal	-	5 (5.8%)	
Foot			
Metatarso-phalangeal	-	28 (32.6%)	
Proximal interphalangeal	-	27 (31.4%)	
Distal interphalangeal	-	5 (5.8%)	
Polyarticular	4 (2.7%)	0	

[1]IVDU = intravenous drug user

Table 2: Causative pathogens

Pathogens	**Large joints** *N = 147*	**Small joints** *N = 86*	**Total** *N = 233*
Staphylococcus aureus			
MSSA	78 (53.1%)	26 (30.2%)	104 (44.6%)
MRSA	8 (5.4%)	3 (3.5%)	11 (4.7%)
Streptococcus spp	20 (13.6%)	13 (15.1%)	33 (14.2%)
Coagulase-negative staphylococci	3 (2.0%)	3 (3.5%)	6 (2.6%)
Other Gram-positive bacteria[1]	5 (3.4%)	2 (2.3%)	7 (3.0%)
Pseudomonas aeruginosa[2]	4 (2.7%)	7 (8.1%)	11 (4.7%)
Escherichia coli[2]	6 (4.1%)	0	6 (2.6%)
Neisseria gonorrhoeae	2 (1.4%)	0	2 (0.9%)
Other Gram-negative bacteria[2,3]	7 (4.8%)	6 (7.0%)	13 (5.6%)
Mycobacterium tuberculosis	7 (4.8%)	0	7 (3.0%)
Polymicrobial	2 (1.4%)	21 (24.4%)	23 (9.9%)
Unknown	5 (3.4%)	5 (5.8%)	10 (4.3%)

[1] Large joint infections: 2 *Propionibacterium acnes*, 3 *Streptococcus pneumonia* (penicillin-susceptible). Small joint infections: 1 *Enterococcus* spp (vancomycin-susceptible), 1 *Corynebacterium* spp

[2] No extended spectrum beta lactamases (ESBLs) producing gram-negative bacteria

[3] Large joint infections: 2 *Neisseria* spp, 1 *Proteus vulgaris*, 1 *Pantoea* spp, 1 *Haemophilus influenzae*, 1 *Enterobacter cloacae*, 1 *Brucella* spp. Small joint infections: 3 *Morganella morganii*, 1 *Enterobacter cloacae*, 1 *Fusobacterium nucleatum*, 1 *Proteus mirabilis*.

Table 3: Overall antibiotic susceptibility profiles of causative pathogens

Antibiotic	**Large joints** *N = 142*[1]	**Small joints** *N = 81*[1]	**Total** *N = 223*[1]
Amoxicillin	45 (31.7%)	27 (33.3%)	72 (32.3%)
Amoxicillin/clavulanic acid	120 (84.5%)	62 (76.5%)	182 (81.6%)
Cefuroxime	120 (84.5%)	59 (72.8%)	179 (80.3%)
Flucloxacillin	107 (75.4%)	54 (66.7%)	161 (72.2%)
Piperacillin/tazobactam	125 (88.0%)	76 (93.8%)	201 (90.1%)

[1]Ten septic arthritis cases remained of unknown etiology and were excluded from this analysis (5 large joint and 5 small joint infections).

Table 4: Performance of empirical antibiotic therapy on coverage of causative pathogens

	Amoxicillin/clavulanic acid	Piperacillin/tazobactam	**P value**
Large joints	120/142 (84.5%)	125/142 (88.0%)	0.4
Small joints	61/81 (75.3%)	76/81 (93.8%)	< 0.01
Diabetics	23/35 (65.7%)	33/35 (94.3%)	< 0.01
Non-diabetics	38/46 (82.6%)	43/46 (93.5%)	0.19
All	182/223 (81.6%)	201/223 (90.1%)	0.01