J Antimicrob Chemother 2011; **66**: 1168–1173
doi:10.1093/jac/dkr047 Advance Access publication 22 February 2011

Journal of Antimicrobial Chemotherapy

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

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Received 18 October 2010; returned 14 December 2010; revised 14 January 2011; accepted 28 January 2011

Objectives: To review the epidemiology of native septic arthritis to establish local guidelines for empirical antibiotic therapy as part of an antibiotic stewardship programme.

Methods: We conducted a 10 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 *S. aureus* (MRSA) arthritis were diagnosed, among which 5 (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 frequent pathogens that would not have been covered. In contrast, amoxicillin/clavulanate would have been appropriate for only 75.3% of small-joint infections (82.6% if diabetics are excluded). MRSA and *Pseudomonas aeruginosa* would have been the main pathogens not covered. Piperacillin/tazobactam would have been appropriate in 93.8% of cases ($P<0.01$ versus 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 in our area. A broad-spectrum antibiotic would be significantly superior for small-joint infections in diabetics. 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 to hospitals sharing the same epidemiology.

Keywords: osteoarticular infections, antibiotic stewardship, practice guidelines

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 10 times higher in high-risk patients such as those suffering from rheumatoid arthritis.[2,5,6] Pre-existing 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 bacteraemia with virulent microorganisms.[2] Complications are frequent (~30%), including loss of joint function subsequent to inflammation and release of lysosomal enzymes and bacterial toxins.[2,7–10] Several risk factors and delayed or inadequate treatment worsen the outcome of septic arthritis.[9,10] Thus, prompt initiation of adequate empirical treatment and drainage of purulent joint fluid (either surgically or by closed-needle aspiration) are of the utmost importance in reducing 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%. Arthrocentesis is most helpful in identifying septic arthritis. In particular, synovial white blood cell

count and percentage of polymorphonuclear cells are the best identifying factors for 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's stain sensitivity is variable and has been estimated as ranging from 29% to 52%.[11] Although analysis of synovial fluid may be useful in increasing the pretest probability of septic arthritis, the initiation of empirical antibiotic treatment is necessary while cultures are pending.

Guidelines for accurate and rapid management of suspected septic arthritis have recently been published, with a proposal of an empirical antibiotic regimen.[12] These guidelines were mostly based on expert opinion, owing to the paucity of well-designed studies addressing the question of which empirical antibiotic therapy would perform best for septic arthritis.[13] The authors suggested comparing these recommendations with the local resistance pattern to ensure selection of an appropriate empirical 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 multidrug-resistant microorganisms is generally increasing, exhibiting remarkable geographical variability.[19] In particular, the frequency of methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa* infections is of concern for empirical 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 the 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 labelled 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–M01.1). Medical records of identified cases were assessed to confirm the diagnosis of septic arthritis. Data on co-morbidities and specific risk factors (namely diabetes, documented pre-existing joint disease such as osteoarthritis or inflammatory arthritis, intravenous drug use, joint surgery or intra-articular injection in the previous 3 months) were collected. 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, Gram's staining was systematically performed on all synovial fluid samples. Samples were inoculated on standard blood agar, chocolate agar, MacConkey agar and in thioglycolate broth. The strains were identified at the species level using conventional phenotypic tests such as the Vitek2 system (BioMérieux, Marcy l'Etoile, France) or the API system (BioMérieux). Antimicrobial susceptibility testing was performed using manual disc diffusion methods according to CLSI (formerly NCCLS) guidelines or automated susceptibility testing using the Vitek2 system (BioMérieux). When *Mycobacterium tuberculosis* arthritis was suspected on the basis of history and medical examination, fluorescent microscopy was applied on synovial fluid samples using acid-fast stain (auramine). MGIT broth (Becton Dickinson, Sparks, MD, USA) 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 profiles including those for 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 recent guidelines.[1,12] Our local antibiotic policy does not recommend the use of quinolones and carbapenems as empirical 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). The incidence of Gram-negative bacteria producing extended-spectrum β-lactamases (ESBLs) was low (2% of all *Escherichia coli* strains in 2009) and vancomycin-resistant enterococci remained extremely rare (<1%).

Statistical analyses

Categorical variables were compared using the χ^2 or Fisher's exact test when appropriate; continuous variables were compared using the Mann–Whitney test. Analyses were conducted using GraphPad Prism software (v. 5.03).

Results

Cases and classification

During the 10 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 labelled 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, 1 had a negative synovial culture with a positive PCR and 10 remained of unknown bacterial aetiology.

Most septic arthritis involved large joints (147 episodes, 63.1%). Clinical characteristics of patients with large- and small-joint

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	28 (19.0)	7 (8.1)	0.04
pre-existing 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	

Data are *n* (%).

infections are presented in Table 1. Only four (1.7%) polyarticular septic arthritis cases were observed, all involving large joints.

Based on the review of medical records, haematogenous 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 the 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 *S. aureus* ($n=115$, 49.4%) and streptococci ($n=33$, 14.2%). Aetiological agents differed between large- and small-joint infections (Table 2). Small-joint infections were more frequently polymicrobial (24.4% versus 1.4%, $P<0.001$). Only two cases of *Neisseria gonorrhoeae* infections were diagnosed, both involving large joints. In 11 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 other 10 cases remained of undetermined aetiology (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.

Table 2. Causative pathogens

Pathogen	Large joints ($n=147$)	Small joints ($n=86$)	Total ($n=233$)
S. 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[a]	5 (3.4)	2 (2.3)	7 (3.0)
P. aeruginosa	4 (2.7)	7 (8.1)	11 (4.7)
E. coli[b]	6 (4.1)	0	6 (2.6)
N. gonorrhoeae	2 (1.4)	0	2 (0.9)
Other Gram-negative bacteria[b,c]	7 (4.8)	6 (7.0)	13 (5.6)
M. 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)

Data are *n* (%).
[a]Large-joint infections: two *Propionibacterium acnes*; three *Streptococcus pneumoniae* (penicillin susceptible). Small-joint infections: one *Enterococcus* spp. (vancomycin susceptible); one *Corynebacterium* spp.
[b]No ESBL-producing Gram-negative bacteria.
[c]Large-joint infections: two *Neisseria* spp.; one *Proteus vulgaris*; one *Pantoea* spp.; one *Haemophilus influenzae*; one *E. cloacae*; one *Brucella* spp. Small-joint infections: three *M. morganii*; one *E. cloacae*; one *Fusobacterium nucleatum*; one *Proteus mirabilis*.

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's staining and microscopy were 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 *S. 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 two *Escherichia coli*, one *Enterobacter cloacae*, three *Morganella morganii*, three *P. aeruginosa*, one *Pantoea* spp. and two *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.

Table 3. Overall antibiotic susceptibility profiles of causative pathogens[a]

Antibiotic	Large joints ($n=142$)	Small joints ($n=81$)	Total ($n=223$)
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)

Data are *n* (%).
[a]Ten septic arthritis cases remained of unknown aetiology and were excluded from this analysis (five large-joint and five small-joint infections).

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

Location	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

Data are *n* (%).

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 (eight cases) and *M. tuberculosis* (seven cases) would have been the most frequently uncovered pathogens. Addition of vancomycin in previously known MRSA carriers (four patients) would have only slightly increased the global appropriateness to 87.3%. An anti-pseudomonal penicillin (piperacillin/tazobactam) would not have performed significantly better (88.0%, $P=0.4$ versus amoxicillin/clavulanate or cefuroxime). Exclusion of *M. tuberculosis* cases would increase the appropriateness of empirical amoxicillin/clavulanate or cefuroxime to 88.8%.

In contrast, empirical 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 were excluded. MRSA (three cases, of which one occurred in a previously known carrier) and *P. aeruginosa* (nine cases, of which seven were monomicrobial) would have been the main pathogens not covered. Piperacillin/tazobactam would have been appropriate in 93.8% of cases of small-joint infections ($P<0.01$ versus amoxicillin/clavulanate). This statistically significant advantage is lost after exclusion of diabetic patients ($P=0.19$ versus amoxicillin/clavulanate). When considering only diabetic patients with small-joint infections, piperacillin/tazobactam was appropriate in 94.3% of cases versus 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 10 years in Western Switzerland and assessed the overall antibiotic susceptibility profile of causative pathogens. Two hundred and thirty-three consecutive cases were analysed. Owing to the high proportion of wrongly labelled synovial fluid specimens, the additional review of hospital discharge diagnosis codes identified 54% of all cases and should therefore be included in an exhaustive review process. Most of the previous large series were published in the 1980s and 1990s,[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 co-morbidities such as diabetes. Gonococcal and mycobacterial arthritis were rare in our setting. Mycobacterial infections were included in our analysis as the clinical presentation of this pathogen may be indistinguishable from other causes of septic arthritis.[20] Only 10 septic arthritis cases (4.3%) remained of undetermined aetiology. Although we could not definitely conclude that they were infectious arthritis, many previous studies of septic arthritis include cases of unknown origin,[5,6,10,16,17] probably secondary to previous antibiotic therapy.

Based on our local epidemiology, amoxicillin/clavulanate or cefuroxime is 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 previous antibiotic therapy or recent hospitalization due to 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 a broad-spectrum antibiotic in this specific clinical setting is in agreement with recommendations of empirical therapy for severe diabetic foot infections.[21–23] Further data are needed to determine whether narrower spectrum antibiotic therapy may be adequate for diabetic patients with small-joint acute infections without previous antibiotic therapy.

Septic arthritis due to MRSA also remained 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, patient demographics and co-morbidities do not reliably 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 incidence of MRSA septic arthritis does not justify systematic empirical 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 aetiological agent. *P. aeruginosa* septic arthritis has been reported mostly in small studies of heroin addicts from the 1980s.[30,31] At that time, usage of pentazocine, a synthetic opiate dissolved and injected without heating, was frequently associated with bacteraemia due to environmental bacteria such as *P. aeruginosa*. The parenteral usage of pentazocine ended in 1983 when the manufacturer added naloxone to stop its narcotic use.[32] A series of 180 sternoclavicular infections, a frequent localization in IVDUs, reported a drop in the *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 empirical 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 to hospitals sharing the same epidemiology of resistant pathogens. Owing 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 bacteraemia or risk factors for sexually transmitted diseases. Usage of broad-spectrum and pathogen-specific PCR for negative synovial fluid cultures was not systematically available. However, this should not have biased our analysis in minimizing resistant pathogens.

In summary, this 10 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 to 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.

Acknowledgements

We thank Ms Johanne Chevalier Parisod for her help in the review of hospital discharge diagnosis codes of infectious arthropathies.

Funding

This work was carried out as part of the routine work in our establishment.

Transparency declarations

None to declare.

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