Bacterial aetiology and antimicrobial susceptibility of osteoarticular infections at a tertiary-level paediatric unit in South Africa

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Background. Osteoarticular infections (OAI) are very common in children living in low- and middle-income countries, yet the bacterial aetiology and antibiotic susceptibility of OAI in children are not well described.
Objective. To determine bacterial aetiology and antibiotic susceptibility of OAI in paediatric patients in a regional hospital in Cape Town, South Africa.
Methods. The study included all patients who underwent surgery for OAI over a 3-year period, and those with organisms identified from tissue, pus, fluid or blood. Duplicate cultures from the same patient were excluded if the organism and antibiotic susceptibility profiles were the same. Patients were categorised by age and class of infection (septic arthritis, acute osteomyelitis, fracture-related infection, post-operative sepsis and chronic osteomyelitis) and organisms were stratified accordingly.
Results. We identified 132 organisms from 123 samples collected from 96 patients. Most cultured organisms were from children older than 3 years with acute haematogenous septic arthritis, osteomyelitis or both. Methicillin-sensitive *Staphylococcus aureus* (*S. aureus)* accounted for 56% (*n*=74/132) of organisms cultured. The Enterobacterales accounted for 17% (*n*=22/132) of organisms cultured, mostly in the fracture-related and postoperative infection groups. Of these, six each were extended-spectrum β-lactamase producers and AmpC producers, respectively. There were no carbapenemase-producing Enterobacterales.
Conclusion. Methicillin-sensitive *S. aureus* is the most common infecting organism in paediatric OAI and anti-staphylococcal penicillin is the most appropriate empiric treatment for haematogenous OAI in our environment. In fracture-related or postoperative infections, Enterobacterales were more frequently cultured, and treatment should be guided by culture and susceptibility results.

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Osteoarticular infections (OAIs) are a common cause of morbidity in paediatric patients. The incidence is reported to range from 1 in 800 to 1 in 5 000, with low- and middle-income countries (LMICs) reporting a higher incidence.[1] In contrast to adults, these infections are predominantly haematogenous and only rarely related to previous surgery or fractures.

The management of these infections, including septic arthritis and osteomyelitis, usually consists of surgical drainage of pus followed by empirical antibiotic treatment based on the patient's age, severity of illness and the most likely causative bacterial organisms, considering local resistance patterns. Antibiotic treatment is subsequently adjusted to directed therapy when causative organisms and susceptibility results from intraoperative samples become available.

Two recent South African (SA) studies investigated the bacterial aetiology and susceptibility of isolates in chronic osteomyelitis.[2,3] However, these studies included only adult patients, in whom the epidemiology of OAIs is different. In contrast, the bacterial aetiology and susceptibility of causative organisms for OAIs in children is not well described in SA, and local empirical antibiotic regimes are based on international data and anecdotal evidence. Findings from other sub-Saharan countries may also not apply to our context as SA has a more temperate climate than, for instance, Malawi[4] or Tanzania,[5] and our socioeconomic context is different.

This study aimed to identify the bacterial aetiology of OAIs in children at the Red Cross War Memorial Children's Hospital, Cape Town, South Africa, and to determine the antibiotic susceptibility of common infectious organisms to better inform the choice of empirical antibiotics for OAIs.

Methods

Following ethics approval from the University of Cape Town's Human Research Ethics Committee (ref. no. HREC 236/2021), we searched the prospectively maintained departmental database for all patients at our institution who underwent surgery for OAI between January 2018 and December 2020 (Fig. 1). Only patients operated at our paediatric hospitals were included, therefore excluding most patients older than 13 years as per local policy. The National Health Laboratory Service's (NHLS) database was searched to identify patients with positive culture results (blood, pus, and tissue fluid) during admission for OAI. Samples with no growth were excluded. Patients whose cultures yielded mixed growths, where no specific organism was identified, were also excluded. Duplicate isolates from the same patient were excluded if the cultures yielded growth of the same organism, with the same antibiotic susceptibility.

All samples were submitted to the NHLS microbiology laboratory at our institution for routine bacterial culture and susceptibility

testing. Identification and susceptibility testing of organisms were performed using the VITEK 2 automated system (bioMérieux, France), biochemical or antigen-detection methods and disc or gradient diffusion antibiotic susceptibility testing methods where appropriate. Results of antibiotic susceptibility tests were interpreted using the Clinical Laboratory and Standards Institute (CLSI) guidelines for the relevant year. In this review, antibiotic susceptibility was classified as either susceptible or non-susceptible, with the non-susceptible category including both the 'intermediate' and 'resistant' categories as defined by the CLSI guidelines.

For the analysis, OAIs were divided into six categories: acute haematogenous septic arthritis, acute haematogenous osteomyelitis, acute haematogenous osteomyelitis and septic arthritis, chronic osteomyelitis, fracture-related infection and postoperative infection. Acute haematogenous infections were defined as infections that arose *de novo* with no predisposing injury or insult such as trauma or surgery. Fracture-related infection was defined as per the international consensus criteria.[6] Postoperative infection was defined as infection arising at a previously sterile site following elective surgery. Patients were categorised into three age groups: those younger than 3 months, those between 3 months and 3 years and those who were 3 years and older. The age categorisation was based on published trends observed on the aetiology of OAIs based on age in children.[7]

Descriptive analysis was performed using Stata version 14.2 (StataCorp., USA) and Microsoft Excel (Microsoft Corp., USA). Categorical variables were described using absolute values and percentages.

Results

A total of 123 samples collected from 96 patients were included in the analysis. Patient ages ranged from 1 month to 15 years (mean=6.5 years) old. A total of 132 organisms were isolated from these samples (Table 1). The distribution of organisms based on infection and age categories is summarised in Tables 2 and 3, respectively. Most organisms were cultured from patients older than 3 years (81%; *n*=107/132) and those presenting with acute haematogenous septic arthritis, osteomyelitis, or both (83%; *n*=109/132).

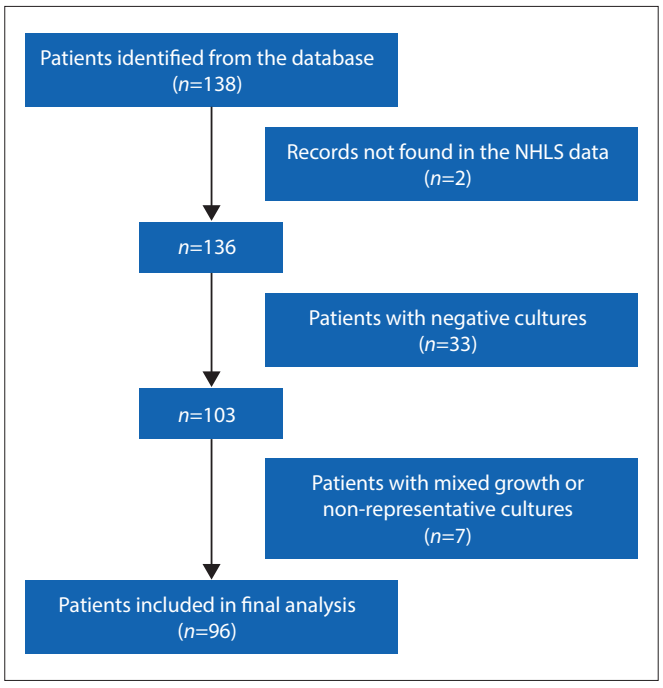

Fig. 1. Selection of patients eligible for inclusion in the analysis.

Bacterial aetiology and antibiotic susceptibility of commonly isolated or clinically relevant organisms

Staphylococcus aureus (*S. aureus*) accounted for 56% (*n*=74/132) of isolates cultured across the whole cohort. During the study period, no methicillin-resistant *S. aureus* was isolated. All *S. aureus* isolates were also susceptible to the following non-β-lactam antibiotics: clindamycin, vancomycin, linezolid and ciprofloxacin. Forty percent of *S. aureus* isolates were resistant to trimethoprim-sulfamethoxazole.

Enterobacterales were the second-most frequent cause of osteoarticular infection in our cohort, particularly in fracture-related infections (48%) and postoperative infections (50%), while only accounting for 17% (*n*=22/132) of all isolates. *Escherichia coli* (*n*=5) and *Enterobacter cloacae* (*n*=5) were the most frequently identified. Resistance to the β-lactam antibiotics due to AmpC-producing β-lactamases was identified in 6/22 (27%) isolates. Of these, all were susceptible to piperacillin-tazobactam, cefepime and trimethoprim-sulfamethoxazole, and five were susceptible to ciprofloxacin. Extended-spectrum β-lactamase (ESBL) producing Enterobacterales accounted for 6/22 (27%) isolates. Of these isolates, only three were susceptible to ciprofloxacin and one to trimethoprim-sulfamethoxazole. Carbapenem-resistant Enterobacterales (CRE) were not isolated in this cohort.

Bacterial aetiology and antibiotic susceptibility of infrequently isolated but clinically relevant organisms

Only 7/132 (5%) β-haemolytic streptococci were isolated. Of those, one was identified as *Streptococcus agalactiae* (Group B streptococcus) and, unsurprisingly, was isolated from an infant <3 months old. The rest were identified as *Streptococcus pyogenes* (Group A streptococcus). Three of these β-haemolytic streptococci were tested against and found to be susceptible to penicillin.

Streptococcus pneumoniae and *Haemophilus influenzae*, both of which have vaccines included in the childhood vaccination programme, were only isolated on one occasion each and both were tested against and found to be susceptible to penicillin and ampicillin, respectively.

Pseudomonas aeruginosa was isolated in 2% of isolates (*n*=3/132), two were from fracture-related infections and one from chronic osteomyelitis. All were susceptible to the anti-pseudomonal β-lactam antibiotics piperacillin-tazobactam, ceftazadime, cefepime, imipenem and meropenem and two were susceptible to ciprofloxacin.

Table 1. Summary of presenting characteristics of patients in whom organisms were identified

Variables	*n*
Organisms identified	132
Age category	
<3 months	7
3 months - 3 years	18
>3 years	107
Sex	
Male	79
Female	53
Type of infection	
Acute haematogenous septic arthritis	50
Acute haematogenous osteomyelitis	43
Acute haematogenous osteomyelitis and septic arthritis	16
Fracture-related infection	13
Chronic osteomyelitis	6
Postoperative sepsis	4

Mixed cultures

Infections where more than one organism was identified were present in 13 patients, of whom seven had haematogenous septic arthritis. Six patients had underlying conditions predisposing to infection or poor healing, such as spina bifida, open fractures, postoperative sepsis or a combination of the above.

Discussion

To our knowledge, this is the first SA study to investigate causative organisms and antibiotic susceptibility in paediatric osteoarticular infections.

Published data from LMICs are scarce and usually describe haematogenous infections only.[4,8-11] We included fracture-related and postoperative infections, and despite relatively low numbers of these types of infection, this allowed a better understanding of the bacterial aetiology of these infrequent conditions.

In accordance with published data from high- and low-income countries, *S. aureus* was the most frequently isolated organism in our patients, regardless of age. Interestingly, no cases of methicillin-resistant *S. aureus (*MRSA) were identified. The incidence of MRSA osteoarticular infections in children has been reported to be as high as 40% in the USA and Australia,[12-14] and rates of 29% and 17% have been reported in Japan and Thailand, respectively.[15] India, in particular, has classified MRSA as an endemic infection, with studies reporting an incidence as high as 55%.[8,16] In Africa, the reported incidence of MRSA is low, with many series also reporting no MRSA.[4,17] However, incidences of 9% and 15% have been reported in Tanzania and Tunisia, respectively.[5,11]

Kingella kingae (K. kingae) is considered the most frequent cause of osteoarticular infections in children between 3 months and 3 years of age.[18] *Kingella* is a fastidious, slow-growing Gram-negative bacillus that is difficult to culture using standard techniques. Positive cultures are more often obtained when inoculating samples into blood culture bottles. However, the gold standard for diagnosis is molecular methods, including PCR using specific gene targets from the *K. kingae* RTX toxin locus.[19] PCR testing for *K. Kingae* is not performed at our institution, which may explain why we had no cases of *K. kingae* in our cohort.

Enterobacterales, which include Gram-negative enteric bacteria such as *E. coli*, *E. cloacae, Salmonella* species and *Klebsiella pneumoniae*, are known to be frequent causes of bone and joint infections in neonates and young children.[8,9] In our cohort, Enterobacterales accounted for 17% of overall infections, but in patients older than 3 months. These children in our cohort tended to have infections secondary to fractures and trauma or prior surgery. However, the small number of cases precludes the identification of any definitive associations. *Salmonella* species was responsible for only three cases of osteoarticular infections in our cohort. This is in stark contrast to the published series by Lavy *et al.*[4] from Malawi, where *Salmonella* species accounted for more than 50% of culture-positive septic arthritis cases in their larger cohort of 204 children.

Antibiotic susceptibility for the Enterobacterales varied. There were no CRE isolated in our group, but six isolates were ESBL producers and another six were AmpC β-lactamase producers, conferring resistance to widely used and available β-lactam antibiotics.

There are several limitations to our study. The retrospective study design and our method of patient identification may have been inadequate to identify all cases of OAI during the study period. The subgroups 'fracture-related infection' and 'postoperative sepsis' included only a handful of patients, precluding any definitive antibiotic

Table 2. Organism frequency categorised by type of infection

Infection type	Organism class in order of frequency	%
ASA (*n*=50)	*Staphylococcus aureus*	48
	Enterobacterales	20
	β-haemolytic streptococci	8
	Coagulase-negative *staphylococcus*	6
	Bacillus species	4
	Other*	14
AHO (*n*=43)	*Staphylococcus aureus*	81
	Bacillus species	7
	Enterobacterales	5
	β-haemolytic streptococci	3
	Coagulase-negative *staphylococcus*	3
AHO and ASA (*n*=16)	*Staphylococcus aureus*	62
	Coagulase-negative *staphylococcus*	19
	Enterobacterales	13
	Other†	6
Chronic osteomyelitis (*n*=6)	*Staphylococcus aureus*	67
	Pseudomonas aeruginosa	11
	β-haemolytic streptococci	11
Fracture-related infection (*n*=13)	Enterobacterales	46
	Enterococcus species	23
	Pseudomonas aeruginosa	15
	Staphylococcus aureus	8
	β-haemolytic streptococci	8
Postoperative infection (*n*=4)	*Enterobacter*	50
	Other‡	50

ASA = acute haematogenous septic arthritis; AHO = acute haematogenous osteomyelitis.
**Acinetobacter, Enterococcus, Haemophilus influenzae, Streptococcus pneumonia, anaerobes.*
†Sphingomonas paucimobilis.
‡Streptococcus mitis, coagulase-negative *Staphylococcus.*

Table 3. Organism frequency categorised by age group

Age category	Organism class in order of frequency	%
<3 months (*n*=7)	*Staphylococcus aureus*	43
	Streptococcus agalactiae	14
	Streptococcus pneumoniae	14
	Enterococcus faecalis	14
	Coagulase-negative *staphylococcus*	14
3 months – 3 years (*n*=18)	*Staphylococcus aureus*	44
	Enterobacterales	22
	Streptococcus pyogenes	11
	Other*	23
>3 years (*n*=107)	*Staphylococcus aureus*	58
	Enterobacterales	17
	Coagulase-negative *staphylococcus*	7
	Streptococcus pyogenes	4
	Bacillus species	3%
	Enterococcus species	3%
	Pseudomonas aeruginosa	2%
	Other†	6%

**Haemophilus influenzae, Pseudomonas aeruginosa, Acinetobacter baumannii, Bacillus species.*
†Clostridium perfringens, Pseudomonas species, Spingomonas paucimobilis, Stenotrophamonas maltophilia, Streptococcus mitis.

recommendations. As we do not have access to PCR testing for *K. kingae*, we were unable to provide any information regarding this common pathogen.

Conclusion

Methicillin-sensitive *S. aureus* was the most frequently isolated organism causing haematogenous osteoarticular infections in our population. This was followed by a wide spectrum of Enterobacterales causing mostly fracture-related or postoperative infections. Empiric treatment of haematogenous OAI's consisting of an anti-staphylococcal penicillin such as cloxacillin is still recommended. For postoperative or fracture-related infections, the addition of a β-lactam with broad Gram-negative activity against AmpC-producing and ESBL Enterobacterales and *Pseudomonas aeruginosa* is recommended, due to the high incidence of Gram-negative organisms seen in these groups. Identification of the causative organisms in OAI remains essential and once established, antibiotic regimens should be adjusted accordingly.

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Author contributions. AH: Conceptualisation, data capture, write-up. CC: Data analysis. ML: Protocol development HT: Data analysis and oversight.

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