Microbiological characteristics of acute osteoarticular infections in children

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This study aimed to describe the microbiological characteristics of acute septic arthritis (SA) and osteomyelitis (OM) in children. Cases of children (0–15 years) with SA/OM were identified through a retrospective search of hospital discharge codes over a six-year period. In addition, a systematic literature search and meta-analysis of studies reporting culture results of children with SA/OM was performed. In our retrospective chart review, we identified 65 cases of OM and 46 cases of SA. The most frequently cultured organisms in both conditions were Gram-positive cocci, primarily Staphylococcus aureus. On admission, most patients had a normal white blood cell count (WCC) but elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). Bacteraemia was associated with a longer mean length of hospitalization for both infections. Considering our results and the meta-analysis, we found low rates of culture-positivity in cases of clinically confirmed infection. In SA, articular fluid was culture-positive in 42.49 % [95 % confidence interval (CI) 28.39–57.23]. In OM, intra-operative samples were culture-positive in 52.65 % (95 % CI 30.54–74.22). Bacteraemia was detected in 23.91 % (95 % CI 8.40–44.24) of children with SA and 21.48 % (95 % CI 10.89–34.47) with OM. Despite appropriate sampling, a positive microbiological diagnosis is often lacking in paediatric acute osteoarticular infection using standard culture-based methods. This highlights the need for validation and use of more sensitive diagnostic methods, such as PCR.

INTRODUCTION

Septic arthritis (SA) and acute osteomyelitis (OM) are important infectious diseases in children, due to the risk of functional compromise if treatment with appropriate antimicrobials is delayed (Fabry & Meire, 1983; Gillespie & Mayo, 1981). Empirical antimicrobials should be selected carefully on the basis of local epidemiological data in order to cover the most likely aetiological pathogens and their resistance patterns. In order to practice proper antimicrobial stewardship, agents started for empirical cover must be changed to agents with a narrower spectrum of activity once an organism has been identified. At our institution, initial empirical treatment for SA and OM consists of intravenous flucloxacillin and clindamycin. Optimum management of these infections requires a microbiological diagnosis to be made consistently to enable the design of appropriate empirical regimens, as well as to allow de-escalation to pathogen-directed therapy during the management of individual patients.

The aims of this study were to describe the microbiological characteristics of SA and OM in a cohort of UK children through a retrospective chart review, and to perform a meta-analysis of published studies describing similar data.

METHODS

Retrospective chart review. We identified cases of children (0–15 years) presenting with acute SA or OM through a retrospective search of hospital discharge codes from January 2007 to September 2013 at the Royal Hospital for Sick Children in Edinburgh. The ICD-10 codes searched for OM were M86.0 (‘Acute haematogenous osteomyelitis’), M86.1 (‘Other acute osteomyelitis’), M86.9 (‘Osteomyelitis, unspecified’); and the codes searched for SA were M00.0 (‘Staphylococcal arthritis and polyarthritis’), M00.1 (‘Pneumococcal arthritis and polyarthritis’), M00.2 (‘Other streptococcal arthritis and polyarthritis’), M00.8 (‘Arthritis and polyarthritis due to other specified bacterial agents’), M00.9 (‘Pyogenic arthritis, unspecified’). No site code restrictions were applied.

To be included in our study as a case of OM, we required documentation of compatible clinical findings (pain around the affected site of less than two weeks’ duration), consistent imaging...
X-ray or magnetic resonance imaging (MRI) and a documented clinical improvement with antimicrobial therapy. For a case of SA to be included, we required documentation of compatible clinical findings (pain, swelling or reduced range of movement/weight bearing) plus one of: positive synovial fluid culture; positive blood culture (with no other identified focus of infection); purulent appearance of joint aspirate or white cells seen on microscopy of aspirate; or positive response to antimicrobials documented (Margaretten et al., 2007). Immunocompromised children were excluded from both categories. Electronic patient records were reviewed and laboratory data and microbiology culture results were obtained from the laboratory results computer system. We considered one set of paired aerobic and anaerobic blood cultures or a single joint aspirate or intra-operatively obtained bone sample to represent an appropriate microbiological sample.

Systematic literature search. We searched the Pubmed (MEDLINE), Embase and Cochrane databases using the following keywords: ‘septic arthritis’; ‘osteomyelitis’; ‘arthritis, infectious’; ‘child’; ‘aetiology’; ‘cause’; ‘organism(s)’; ‘detection’; ‘identification’; ‘diagnosis’; ‘culture’; ‘microbiology’; and ‘bacteriology’. We limited the search to articles published between January 2004 and May 2014, when the search was performed. All studies (excluding case series and case reports) investigating SA and OM in children at European centres were eligible. To be included, we required authors to report: (i) the proportion of patients with positive and negative culture results (as a proportion of patients who had had samples obtained); (ii) specimen details (was the specimen blood, joint aspirate or bone?; and to distinguish between these when presenting culture results); and (iii) to distinguish between SA and OM culture results. We excluded studies describing maxillofacial osteoarticular infections and studies with a sample size <10.

Analysis. Fisher’s exact test was used to compare categorical data. The unpaired t-test was used to compare mean values for laboratory results. Receiver operating characteristic (ROC) curve analysis was used to analyse the predictive value of C-reactive protein (CRP) concentration in predicting bacteraemia. Youden’s J statistic was used to derive a threshold CRP concentration that represented the value at which the sensitivity and specificity were maximal. We performed a meta-analysis of the proportion of culture-positive samples from studies identified by our systematic review. Cochran’s Q and the I² statistic were used to test for heterogeneity. MedCalc software, version 13.3, was used for statistical analysis. A P value of <0.05 was considered significant.

RESULTS

One hundred and eleven cases of acute osteoarticular infection in children were identified. These comprised 65 cases of OM and 46 cases of SA. Across both types of infection, 64 % of patients were male. The majority of patients were aged 3 years or under (range <1–16 years; Fig. 1).

Inflammatory markers

On admission, the majority of patients did not have an elevated white blood cell count (WCC) or neutrophil count, though cases of SA were more likely to have both a leucocytosis and neutrophilia than cases of OM (P=0.0299 and P=0.0088, respectively). Overall, patients were more likely to have a neutrophilia than a leucocytosis (P=0.0001) and this was true when SA and OM cases were considered individually. Thrombocytosis was present as often as leukocytosis in SA, and more often in OM (P=0.24). CRP was the most frequently elevated inflammatory marker. CRP was more often elevated in SA versus OM (P=0.0007) and was also detected at a higher average concentration in cases of SA (P=0.0196). Erythrocyte sedimentation rate (ESR) was also elevated in the majority of both infections, with no significant difference in the proportion of patients with an elevated ESR in SA compared with OM. On average, ESR was higher in cases of SA (P=0.0219). In patients with OM, ESR was more often raised than CRP (P=0.079). Laboratory results on admission are shown in Table 1.

Anatomical distribution

For both SA and OM, infections were more likely to involve the lower limb (Fig. 2). There were eight cases of mixed OM and SA, as follows. In four cases of SA of the hip there was concurrent OM of the pelvis (n=2), femur (n=1) and metatarsal (n=1, discussed below). In three cases of SA of the shoulder and in one case of SA of the elbow there was concurrent OM of the humerus.

Septic arthritis

An organism was identified in 27/46 (58.7 %) SA cases (from blood or joint aspirate culture). Gram-positive cocci accounted for the majority of culture-positive infections (23/27, 85.2 %) with meticillin-sensitive Staphylococcus aureus (MSSA) being the predominant pathogen (12/27, 44.4 % of culture-positive infections). There were no polymicrobial infections. Full culture results are shown in Table 2.

All 46 children with SA underwent joint aspiration, and culture of articular fluid was positive in 45.7 % (21/46) of cases. Only 84.8 % (n=39) of children had blood cultures drawn, and 33.3 % of these (13/39) were positive. Bacteraemia was due to Streptococcus pyogenes (n=5), Staphylococcus aureus (n=4), Streptococcus pneumoniae (n=2), Streptococcus agalactiae (n=1) and Escherichia coli (n=1). Of children who had both articular fluid and blood sent for culture, 17.9 % (7/39) grew an organism from both (the same organism in all cases). There were eight cases of SA with concurrent OM. All eight cases had positive articular fluid cultures (three Streptococcus pneumoniae, four Staphylococcus aureus and one Enterobacter cloacae), and four were bacteraemic (in all four cases with the same organism isolated from articular fluid: one Streptococcus pneumoniae and three Staphylococcus aureus). No intra-operative bone cultures were obtained from these patients with SA and concurrent OM. One of these patients had SA of the hip with concurrent metatarsal OM. Consistent with this being a metastatic infection with haematogenous seeding, blood cultures were positive (Streptococcus pneumoniae), though we do not know which focus of infection came first.
Bacteraemia was associated with a longer length of hospital stay (LOHS; mean LOHS 13 days for bacteraemic children and 7 days for children without bacteraemia, \( P=0.0327 \)), whereas having a positive articular fluid culture (in the absence of bacteraemia) was not associated with a significant difference in LOHS. There were no significant differences in WCC, neutrophil count, platelet count, CRP or ESR between culture-positive and -negative cases, or when bacteraemic children were considered separately.

Raised white cell counts were seen on microscopy of articular fluid in the majority of cases (Table 3). Overall, 43.5% of aspirates appeared blood-stained and only 23.9% were frankly purulent. There was no association between articular fluid culture results and macroscopic appearance or the presence of white blood cells on microscopy.

**Osteomyelitis**

In the patients with OM, an organism was identified in 18/65 (27.7%) cases overall, representing 30.5% (18/59) of cases where a sample (intra-operative or blood) was sent for culture. There were no polymicrobial infections. MSSA caused the majority of culture-positive infections (16/18, Table 1. Characteristics of patients with SA and OM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SA patients (n=46) (%) (n)</th>
<th>OM patients (n=65) (%) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>17.4 (8)</td>
<td>9.5 (6/63)</td>
</tr>
<tr>
<td>Elevated WCC</td>
<td>30.4 (14)</td>
<td>12.7 (8/63)</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>41.3 (19)</td>
<td>17.5 (11/63)</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>30.4 (14)</td>
<td>22.2 (14/63)</td>
</tr>
<tr>
<td>CRP &gt;8</td>
<td>91.3 (42)</td>
<td>62.5 (40/64)</td>
</tr>
<tr>
<td>ESR &gt;20</td>
<td>86.5 (32/37)</td>
<td>77.6 (45/58)</td>
</tr>
<tr>
<td>Male</td>
<td>65.2 (30)</td>
<td>61.5 (40)</td>
</tr>
<tr>
<td>Age &lt;3 years</td>
<td>56.5 (26)</td>
<td>53.8 (35)</td>
</tr>
<tr>
<td>Age &lt;1 year</td>
<td>19.6 (9)</td>
<td>13.8 (9)</td>
</tr>
<tr>
<td><strong>Positive cultures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (any sample)*</td>
<td>56.5 (26)</td>
<td>27.7 (18)</td>
</tr>
<tr>
<td>Blood†</td>
<td>33.3 (13/39)</td>
<td>15.4 (8/52)‡</td>
</tr>
<tr>
<td><strong>Site-specific</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Articular fluid</td>
<td>45.6 (21)</td>
<td>71.4 (10/14)</td>
</tr>
<tr>
<td>Intra-operative bone</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Blood and site-specific†</td>
<td>17.9 (7/39)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mean value (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg l(^{-1}))</td>
<td>71.7 (1–304)</td>
<td>43.7 (1–255)‡</td>
</tr>
<tr>
<td>ESR (mm h(^{-1}))</td>
<td>63.5 (5–150)§</td>
<td>47.1 (1–142)§</td>
</tr>
<tr>
<td>LOHS (days)</td>
<td>9.0 (2–47)§</td>
<td>5.3 (0–18)</td>
</tr>
</tbody>
</table>

Reference ranges were corrected for age of child.

LOHS, length of hospital stay.

*Considering all patients, irrespective of samples obtained.

†Proportion of positive cultures from cases where such a sample was obtained.

‡Denominators other than sample size are specified, apart from variables expressed as mean where: a, n=64; b, n=37; c, n=58; d, n=43.
Intra-operative bone cultures had a high positivity rate (10/14 cases, 71.4%) but surgery was only performed in 20.1% (14/68) of cases; therefore, these samples were infrequently obtained in our cohort. Blood cultures were drawn in 76.5% (52/68) of cases and eight (15.4%) of these patients were bacteraemic. Seven of these cultures were drawn in 76.5% (52/68) of cases and eight samples were infrequently obtained in our cohort. Blood cultures were performed in 20.1% (14/68) of cases; therefore, these culture-negative cases not reported or insufficient data presented about nature of samples). Cochrane’s Q and the I² statistic indicated the presence of heterogeneity in all meta-analyses, so results are expressed using a random effects model. The results of our meta-analysis are presented in Fig. 4 (Ferroni et al., 2013; Joshy et al., 2010; Moumile et al., 2005; Peltole et al., 2009; Rasmont et al., 2008; Riise et al., 2008; Shivarathre et al., 2009; Singhal et al., 2011; Weber-Chryschoou et al., 2007).

In patients with SA who underwent joint aspiration, culture of articular fluid was positive in 42.48% (95% CI 28.39–57.23; Fig. 4a) of cases. When blood cultures were drawn, 23.91% (95% CI 8.40–44.24; Fig. 4b) of patients were bacteraemic. When intra-operative samples were obtained from patients with OM, culture was positive in 52.65% (95% CI 30.54–74.22; Fig. 4c) of cases. Bacteraemia was detected in 21.48% (95% CI 10.89–34.47; Fig. 4d) of cases of OM when blood cultures were drawn.

**DISCUSSION**

This retrospective chart review and meta-analysis demonstrates that a microbiological diagnosis is often lacking in acute osteoarticular infections of children using standard culture-based diagnostic methods, even when appropriate samples are obtained (blood, articular fluid or intra-operative bone samples).

In children with SA, culture of articular fluid yielded no organism in more than half of cases. It is likely that the majority of children will have received at least one dose of intravenous antimicrobial prior to joint aspiration and this will contribute to false negative culture results. PCR relies upon the detection of bacterial DNA, not the presence of viable organisms, so may overcome this problem, and there is emerging evidence supporting the role of PCR assays in diagnosing common pathogens in SA (Choe et al., 2013; Ferroni et al., 2013; Kim et al., 2010; Rosey et al., 2007).

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**Fig. 2.** Anatomical distribution of SA (a) and OM (b). MTPJ, metatarsophalangeal joint.

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**Meta-analysis**

We performed a systematic literature search to identify studies from European centres reporting the culture results of children with SA or OM. The search identified 1228 articles, 1171 of which were excluded following review of the title and abstract, and a further 46 were excluded following full text review (study population from outwith Europe, sample size <10, atypical study population, culture-negative cases not reported or insufficient data presented about nature of samples). Cochrane’s Q and the I² statistic indicated the presence of heterogeneity in all meta-analyses, so results are expressed using a random effects model. The results of our meta-analysis are presented in Fig. 4 (Ferroni et al., 2013; Joshy et al., 2010; Moumile et al., 2005; Peltole et al., 2009; Rasmont et al., 2008; Riise et al., 2008; Shivarathre et al., 2009; Singhal et al., 2011; Weber-Chryschoou et al., 2007).

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**DISCUSSION**

This retrospective chart review and meta-analysis demonstrates that a microbiological diagnosis is often lacking in acute osteoarticular infections of children using standard culture-based diagnostic methods, even when appropriate samples are obtained (blood, articular fluid or intra-operative bone samples).
The fastidious *Kingella kingae* is now recognized as an important pathogen in paediatric SA, largely through the use of targeted PCR (Ceroni et al., 2010; Chometon et al., 2007; Ferroni et al., 2013; Rosey et al., 2007). All of the studies included in the meta-analysis, and the current study, used only culture to detect pathogens and *K. kingae* PCR was not performed.

In this study, there were no significant differences in inflammatory markers or LOHS between children with SA with positive or negative articular fluid cultures, suggesting the same clinical phenotype. In addition, there was no association between having a positive articular fluid culture and a positive blood culture. We believe these points strengthen the argument for a significant proportion of culture-negative articular fluid samples being attributable to false negative culture results, where there is true infection. This may be related to the insensitivity of culture (culturable bacteria present in the sample but not grown) and the presence of fastidious, unculturable bacteria.

In acute OM, culture of intra-operative samples has a higher positivity rate than articular fluid in SA, but is still often

### Table 3. Features of the joint aspirate in patients with SA (n=46)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients (%) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirate appearance</td>
<td></td>
</tr>
<tr>
<td>Blood-stained</td>
<td>43.5 (20)</td>
</tr>
<tr>
<td>Turbid</td>
<td>23.9 (11)</td>
</tr>
<tr>
<td>Purulent</td>
<td>23.9 (11)</td>
</tr>
<tr>
<td>No comment</td>
<td>8.7 (4)</td>
</tr>
<tr>
<td>White cells seen on microscopy</td>
<td>84.8 (39)</td>
</tr>
</tbody>
</table>

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In acute OM, culture of intra-operative samples has a higher positivity rate than articular fluid in SA, but is still often
negative. Surgery is not always indicated in OM and in our chart review we found only 20.1% of children underwent surgery and thus had bone samples obtained. Children are likely to have had several days of intravenous antimicrobials prior to surgery, and this is likely to have a significant adverse effect on the success of culture, though it is possible that poorer bone penetration may account for the higher culture-positivity rate in comparison with SA. The numbers in our chart review were too low to comment on the characteristics of intra-operative sample positive versus negative cases. A limitation of this study, and the studies included in the literature meta-analysis, is that the specific operative sampling technique and number/volume of samples obtained intra-operatively for culture were not known.

As demonstrated by the Cohran’s Q and $I^2$ statistics (Fig. 4), there is significant heterogeneity in the proportion of culture-positive patients between studies. Inter-laboratory variation in routine microbiological work-up of specimens, as well as non-standard articular and intra-operative sampling techniques, could contribute a degree of artefactual heterogeneity. It seems likely that real heterogeneity will be significant, however, due to differing timings of obtaining samples before/after antimicrobials, as well as differences in the bacterial load (in blood/articular fluid/bone) at the time of sampling due to differences in the timing of presentation and sampling, and efficacy of antimicrobials already administered. Overall, most organisms cultured in the included studies were Gram-positive cocci, so aetiology does not seem to be contributing to the observed heterogeneity in culture-positivity.

In both SA and OM, bacteraemia was found to be associated with a prolonged LOHS and may, therefore, be associated with a more severe course of disease or slower clinical response. The requirement for a longer duration of intravenous antimicrobials may also be a factor. *Staphylococcus aureus* was the pathogen predominantly responsible for bacteraemia in patients with OM, whereas

**Fig. 4.** Forest plots demonstrating proportions of culture-positive samples from meta-analysis. (a) SA: articular fluid ($Q=90.44$, $P<0.0001$, $I^2=92.26\%$, 95% CI for $I^2=87.12–95.35$). (b) SA: blood culture ($Q=59.43$, $P<0.0001$, $I^2=93.27\%$, 95% CI for $I^2=87.23–96.45$). (c) OM: intra-operative bone sample ($Q=21.73$, $P=0.002$, $I^2=81.59\%$, 95% CI for $I^2=57.34–92.06$). (d) OM: blood culture ($Q=12.46$, $P=0.006$, $I^2=75.93\%$, 95% CI for $I^2=33.74–91.26$). Proportion of culture-positive cases in each included study represented by filled squares, size proportional to weighting in meta-analysis. Filled diamonds indicate a summary measure of the proportion of culture-positive cases. Lateral tips of diamonds represent confidence intervals.
in SA, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Streptococcus pneumoniae* were all seen. Our meta-analysis found that bacteraemia was detected in 23.91% (95% CI 8.40–44.24) of patients with SA and 21.48% (95% CI 10.89–34.47) of patients with OM. Given the low incidence but potentially worse outcome we sought predictors of bacteraemia. No laboratory indices were associated with bacteraemia in SA but in OM, higher CRP concentrations were found to be associated. ROC curve analysis could not derive a threshold value with acceptable specificity and sensitivity for predicting bacteraemia. These findings are in agreement with those of Pa¨a¨kko¨nen et al. (2013). If bacteraemia is indeed associated with worse outcomes then future clinical trials should consider this and investigate whether these children should be treated differently. Given the prevalence of *Staphylococcus aureus* bacteraemia amongst bacteraemic children with SA and OM, it is interesting to note that adjunctive rifampicin may be associated with better outcomes than beta-lactam or glycopeptide monotherapy, and this is currently being investigated by the ARREST trial (Russell et al., 2014; Thwaites et al., 2012).

In summary, even when appropriate samples are obtained, a positive microbiological diagnosis is often lacking in paediatric acute osteoarticular infection when standard culture-based diagnostic methods are used. This may be due to initiation of antimicrobial therapy prior to joint aspiration (SA) or surgical intervention (OM), but this will often be inevitable considering that children with SA and OM often present unwell with evidence of sepsis syndrome, necessitating the early administration of antimicrobials before invasive diagnostic procedures. This highlights the need for validation and routine use of more sensitive diagnostic methods, such as PCR. An important consideration in the validation of such highly sensitive techniques is that the specificity is acceptable for use as a diagnostic test. A positive culture is still of significant value to the clinical decision-making process, since it allows antimicrobial susceptibilities to be determined. Therefore, the importance of thorough microbiological sampling (two sets of blood cultures before antimicrobials, obtaining joint aspirate or multiple intra-operative bone samples) cannot be understated, despite the potential to increase diagnostic yield through the introduction of PCR. Finally, considering the poor sensitivity of inflammatory markers, there is also a need for new infection-specific biomarkers to aid in diagnosis and monitoring the response to treatment. The frequent lack of pathogen identification has important implications, both for the management of individual patients and also for the design of empirical antimicrobial regimens.

**ACKNOWLEDGEMENTS**

We are grateful to Elaine Kaye for performing the electronic search of hospital discharge codes to identify cases for the study.

**REFERENCES**


