Osteoarticular Infections in Newborns: Prognostic Factors and Outcome

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Abstract

Purpose: To analyze clinical, laboratory, microbiologic, imaging and therapeutic data that contribute to outcome in newborn infants with osteoarticular (OSA) infection. Methods: Clinical course, imaging and follow-up data of 15 newborns with the diagnosis of OSA infection were retrospectively reviewed. Results: 15 newborns with 23 acute osteoarthritis foci were included: risk factors were identified in 73%, lower extremities were affected in 8 (53%) and more than half of the children had two-or multifocal involvement. The predominant causative agent was Staphylococcus aureus. While plain radiography showed osteolytic bone lesions in only 33%, scintigraphy was consistent with osteomyelitis in 74% of study infants. Magnetic resonance imaging revealed an inflammatory process even when other imaging modalities did not detect any OSA signs. All newborns underwent surgical and antibiotic treatment; the average time from admission to surgical treatment was 3.6 days. No bone and joint deformities or limb-length disturbances were found in the mean follow-up period of 8.5 years. Conclusion: Our study confirms that the most important prognostic factors in predicting a long-term favorable outcome are early diagnosis and therapy consisting of a combination of both surgical and appropriate antibiotic treatment.

Keywords
Osteoarticular infection, Newborn, Osteoarticular imaging, Outcome

1. Introduction

Osteoarticular (OSA) infection, although a rare condition, remains a diagnostic and therapeutic challenge and poses the infant at high risk for long-term morbidity [1–3]. The estimated incidence in neonatal intensive units is 1-3 cases per 1000 admissions [1, 2]. There are etiological, clinical, radiological and therapeutic differences between osteoarticular (OSA) infection in the newborn when compared to older children and adults [4, 5]. In the majority of cases the metaphysis of the long bone are the most commonly implicated sites, but due to the anatomy and blood supply in newborns, osteomyelitis may often spread to the contiguous epiphysis and joint [1]. In the neonatal period, OSA infection usually follows bacteremia, seldom after direct inoculation of bacteria or as a complication of soft tissue infections [5–9]. The diagnostics of OSA may be hindered in neonates, due to the manifestation of less clear-cut characteristic symptoms and signs compared to older children [1–3]. When OSA is suspected, imaging techniques used in association with blood and tissue cultures are the most reliable diagnostic tests [3, 10, 11]. While antimicrobial treatment should be administered at the time of clinical suspicion, opinions about surgical treatment are still debatable. Despite modern treatment facilities several studies have documented poor outcome with reported incidence of permanent sequela between 6% and 50%, including disturbances in bone growth secondary to damage to the cartilaginous growth plate, arthritis, decreased range of motion and pathologic fractures [12–14].

There are only few studies in which OSA has been studied in the neonatal period and the longest follow-up described in neonatal cohorts is 4.5 ± 1.2 years [15]. The aim of this study therefore was to analyze clinical
data, results of laboratory and imaging investigations and therapeutic management that contributed to long-term outcome in newborns with OSA.

2. Methods

A retrospective study included all newborns hospitalized at the Department of Neonatology, University Children’s Hospital, Ljubljana, Slovenia, between 1 January 2003 and 31 December 2012, due to the OSA infections. Medical records were reviewed retrospectively for prenatal and perinatal history, clinical presentation, and hospital course including physical assessment, imaging, laboratory and microbiology studies, treatment and follow-up.

Diagnosis of osteomyelitis/septic arthritis was established by clinical appearance (swelling, erythema, pain at movement, decreased range of motion of the involved joint, and/or pseudo paralysis of the involved extremity), results of imaging (plain radiographs, bone scintigraphy, magnetic resonance imaging, and ultrasonography), laboratory and microbiological findings (blood cultures or joint aspiration).

2.1 Follow-up evaluation

A regular follow-up by an orthopedic surgeon included clinical and radiological analysis. The first evaluation was performed a month and the second three months after discontinuation of the antibiotic therapy, and were afterwards continued annually; the longest follow-up was 13 years. A favorable outcome was defined if no clinical signs or symptoms, including pain, limited range of motion, limping, limb length or angle deformity were detected. In respect of the radiological evaluation, a favorable outcome was defined if no differences regarding the limb instability, length or angle, and no joint deformities or avascular necrosis were found.

No statistical calculations were performed but rather the absolute numbers of patients with each outcome of interest are reported.

3. Results

During the study period, 15 children, 6 (40%) girls and 9 boys (60%), with OSA infection were identified. Their birth weight ranged from 2500 g to 4600 g (mean 3670 g, SD 544.35); gestational age from 37 to 41 weeks (mean 39
### TABLE 2. Imaging characteristics in 15 osteoarticular infection.

<table>
<thead>
<tr>
<th>Case (n)</th>
<th>US</th>
<th>RTG</th>
<th>Triple-phase bone scan Tc(^{99m})_MDP</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>soft tissue abscess and thickened periosteum</td>
<td>osteolysis of the d. L femur</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>subperiostal and soft tissue abscess abscesses</td>
<td>normal</td>
<td>normal</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>normal</td>
<td>normal</td>
<td>not done</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>thickened periosteum, free liquid 3 mm</td>
<td>normal</td>
<td>not done</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>the shoulder joint effusion, structurally modified R humerus metaphysis</td>
<td>rarefaction of R humerus pr. metaphysis, hyperemia, swelling of the soft tissue</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>hypoehogen areal in R tibia</td>
<td>osteolysis of the R tibia</td>
<td>not done</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>slightly raised periosteum</td>
<td>periosteal reaction, swelling of the soft tissue</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>normal</td>
<td>normal</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>normal</td>
<td>normal</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>synovial effusions</td>
<td>osteolysis of the L tibia</td>
<td>not done</td>
<td>T1 hypointensitive signal in knee. T1 hypointensitive and STIR hyperintensive signal at L tibia metaphysis and in subperiosteal space</td>
</tr>
<tr>
<td>11</td>
<td>synovial effusions, thickened synovia</td>
<td>osteolysis of the R femur</td>
<td>not done</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>thickened synovia in the L knee</td>
<td>periosteal reaction</td>
<td>TU in all three phases</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>minimum synovial effusions</td>
<td>normal</td>
<td>normal</td>
<td>nd</td>
</tr>
<tr>
<td>14</td>
<td>synovial effusions</td>
<td>normal</td>
<td>not done</td>
<td>T1 hypointensitive signal in shoulder, soft tissue, wider axillar recesses. STIR hyperintensive signal at posterior and lateral part of R humerus metaphysis</td>
</tr>
<tr>
<td>15</td>
<td>normal</td>
<td>normal</td>
<td>TU in two phases</td>
<td>T2 hyperintensive and T1 hypointensitive signal in L shoulder and rotator muscles. Increased uptake in the synovia and soft tissue</td>
</tr>
</tbody>
</table>

*D, distal; L, left; ND, not done; R, right; STIR, short T1 inversion recovery sequences; TU, tracer uptake.*

weeks, SD 1.22). Mean age at admission was 19 days (6 – 31) and the duration of symptoms was 1.9 days (1 – 3). Risk factors for the development of OSA were present in 11 (73%) and are in detail presented in (Table 1).

### 3.1 Clinical signs and symptoms

The main presenting findings were irritability and feeding intolerance, followed by a limited range of motion in 87%. In two thirds limb pain and swelling were detected. Temperature was inconsistently present as 47% had fever. Flexion contracture was present in 27%, pseudoporalysis of the extremity in 20%, and warmth above the area of inflammation in 13%.
FIGURE 1. Image course of a 15-day old term newborn with a swollen and painful right shoulder.

A) Radiography of the anteroposterior projection: oedema of the soft tissue of the shoulder and steolytic defects in the metaphysis humerus (arrow). Not ossified epiphysis.

B) Ultrasound with a small oedema around the humerus neck (arrow) and tissue edema.

C) MR STIR of the right shoulder in the transverse plane: pronounced oedema of the soft tissue at the shoulder joint (white arrow) and modified bone signal (black arrow).

D) and E) MRI of the right shoulder T1 TSE FS with contrast media sequence in the coronal and transverse plane: contrast stained soft tissues of the shoulder joint, thickened and hyperemic synovium and effusion (white arrows).

3.2 Site of involvement

Unifocal bone and joint involvement was present in 6 newborns while in 9 two or multifocal site of infection was present. Lower extremities were affected more frequently; humerus and femur were the most frequently affected bones. Infection of the bone and joint simultaneously was present in almost half of the cases. All together, there were 23 foci of OSA infections in 15 newborns and in four (Table 1 and Table 2; cases no. 1, 2, 14 and 15) subcutaneous abscess formation was a sign of underlying OSA infection. Concomitant septic skin metastases were present in only one child (case no. 15).

3.3 Laboratory and microbiological findings

As regards inflammatory markers, a C-reactive peptide was elevated in 13 (87%) infants, non-segmented neutrophils above 10% were present in one third of newborns and mean thrombocyte count was 481 x 10⁹/l (151 – 698).

Blood culture was performed in all patients and confirmed a bacteriological diagnosis in 9 infants. The predominant causative agent was Staphylococcus aureus (S.
study, the frequency of OSA has been the same in the last incidence reported in the literature. Based on the reported per 1000 admissions, which is similar to the estimated differences in the length of the limbs were observed. Symptom free and no bone or joint deformities or years), with the longest follow-up of 13 years. All patients The mean follow-up period was of 8.5 years (range 4–13 3.6 Outcome 11 newborns surgery was performed in the first 72 hours, time from admission to surgical treatment was 3.6 days. In irrigation in the affected bone and/or joint. The average Surgical treatment included drainage of pus content and modified according to the results of bacterial sensitivity. All newborns underwent surgical treatment followed by antibiotic therapy with cefoxime and flucloxacillin, and the therapy was subsequently initially treated by empiric antibiotic therapy with cefo-

3.6 Outcome The mean follow-up period was of 8.5 years (range 4–13 years), with the longest follow-up of 13 years. All patients were symptom free and no bone or joint deformities or differences in the length of the limbs were observed.

4. Discussion The incidence of OSA infections in this study was 2.7 per 1000 admissions, which is similar to the estimated incidence reported in the literature. Based on the reported study, the frequency of OSA has been the same in the last twenty years, which confirms that this disease remains rare in newborns [1, 14, 16, 17]. Although the clinical presentation in the neonatal period is often mild in comparison to OSA infection in childhood, in the present case series, the symptoms and signs played a leading role in the initiation of further diagnostic procedures; all infants had non-specific signs and in the majority, a limited rate of motion was present. Non-specific signs in newborns frequently give rise to the suspicion of bacteremia or sepsis, and as the disease progresses, more specific signs appear, including disability, local swelling, erythema or pain, which limits movement of the involved extremity [3, 16, 18].

In this series, the leading causative organism was S. aureus. There were no cases of methicillin-resistant S. aureus as a result of the fact that the prevalence of methicillin-resistant strains of S. aureus in the community is less than 10% and the prevalence of clindamycin-resistant S. aureus < 10% [19, 20]. Several authors have reported that blood cultures in patients with OSA yield the causative pathogen in approximately 50%, which is similar to our study where 60% of newborns with OSA infection had a positive hemo-
culture [3, 18, 19].

X-ray should always be the initial test in all cases of OSA infections in order to exclude other diagnoses, such as fractures and dislocations, and for follow-ups [19]. Conventional imaging may show early signs of osteomyelitis, while early signs of bone destruction may not be evident on plain radiographs until about 14 days following the onset of symptoms [20]. However, Fisher pointed out that neonates showed signs of bone destruction much earlier than older children, with radiograph abnormalities appearing by 7 to 10 days after the onset of infection [1]. Our results probably comply with his findings, since less than half of the newborns already had pathological findings on X-ray imaging.

Although ultrasonography is regarded as a subjective and very limited method for the assessment of OSA infections, in our study it proved to be a highly sensitive in the detection of soft tissue infiltration, abscess formation and joint effusion early in the process: in two thirds of newborns positive US findings were observed. The value of bone scintigraphy in newborns with OSA has been controversial due to lower sensitivity than in older infants. However, in our study this investigation ruled out OSA inflammation process in all but one case [20–22]. Additionally, in our study it had a discriminative role in making a distinction between bone and soft tissue infection and it was useful in detection of multifocal OSA infections [23]. MR has emerged as the imaging modality of choice for diagnosing osteomyelitis due to its high sensitivity for detecting early infection [1, 18]. Despite the fact that MR was used only in three newborns in our series, this imaging modality had a high sensitivity for the detection of OSA infection, allowing imaging of bone marrow, soft tissue, subperiosteal and articular collections, abscess formation or arthritis.

In the cases presented, children were treated with antibi-
otics, 4-6 weeks. Peltola and coauthors proposed shorter
treatment in children older than 3 months, but for newborns a clear recommendation regarding the duration of treatment is still missing and no specific time markers are described in the literature [3, 17, 24]. Surgical drainage is indicated whenever there is collection of pus in the intraarticular space to relieve pressure and to preserve the joint structure [25]. However, the need of drilling the cortex to drain intramedullary collections of the pus remains controversial. In all children from our study surgical decompression, irrigation and drainage were conducted in a very short time after admission to the hospital.

Our study is one of the few in which only newborn infants with OSA were studied, and, to our knowledge, the follow-up period is longer than in the previous studies. Lee and coauthors studied newborns and infants younger than 18 months with OSA and followed them 74.4 months, while Li and coauthors studied newborns with septic arthritis and followed them for 4.5 ± 1.2 years [15, 26, 27]. As the final outcome may not be clinically apparent until the child reaches 9 or 10 years of age, it is important to follow children after OSA to that age. Contrary to the data in the literature where permanent sequelae following OSA infections were described, in our cohort children had no consequences. The average time from admission to surgical procedure was shorter than 3.6 days. Furthermore, in all infants the duration of disease from the clinical onset to the introduction of antibiotic therapy was shorter than 48h.

Although different factors have been recognized to influence outcome, a therapeutic delay is generally considered an important risk factor for sequelae; a 4-day delay has been suggested acceptable in the treatment of uncomplicated osteomyelitis [18, 28, 29]. Newborns with concomitant septic arthritis and osteomyelitis are especially at risk of long-term functional sequelae [25, 26]. In the study of 31 infants with septic arthritis of the hip, Lee pointed out that the duration of symptoms longer than 5 days before surgery significantly affected the radiological prognosis [26].

It is usually considered that imaging plays a crucial role in establishing a timely diagnosis and guides early management, with the aim of reducing long-term complications. On the other hand, it is interesting to note that the oldest children in our cohort, who had been diagnosed and treated at the time when we did not have opportunities to perform MRI, had the same favorable outcomes as those in whom imaging with MRI had been performed. Therefore, we can point out that early diagnosis based on full clinical work up, followed by surgery and antibiotic treatment, are essential prognostic components to prevent long-term sequelae.

In conclusion, our cohort of children with long term follow-up after neonatal OSA infection presented with better outcome than that reported in the literature. In comparison to previous studies, the therapy was introduced earlier and consisted of both antibiotic and surgical treatment, so we believe that the most important prognostic factor in predicting long-term outcome in neonatal OSA infection is early diagnosis, followed by both early surgical and antibiotic treatment.

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CONFLICT OF INTEREST
All authors declare that they have no conflict of interest.

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REFERENCES


