

Osteoarthritis in the neonate: risk factors and outcome

ABSTRACT

Objectives: The aim of this study was to identify the clinical, radiological, and bacteriological features, risk factors, and outcome of neonates with bone and joint infections. **Study design:** Observational, retrospective, and analytical study of 77 patients less than 2 months of age, admitted to a tertiary neonatal intensive care unit (NICU) with the diagnosis of bone or joint infection, based on clinical, radiological, and microbiological criteria. **Results:** Seventy-seven patients with 99 acute osteoarthritis foci in a 16 year period were included in the study. Risk factors for infection could be identified in 69% of the patients. The hip was the most frequent. *Staphylococcus aureus* was the main isolated microorganism. Twenty-nine infants (38%) had sequelae. Hip involvement, culture positive, and *Staphylococcus aureus* isolation were risk factors associated with sequelae. **Conclusion:** Osteoarticular infection is unusual in the neonate; however it is associated with an elevated incidence of sequelae. This mandates for a high degree of suspicion to diagnose this potentially disabling entity.

Keywords: osteoarthritis, neonate, *Staphylococcus aureus*.

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INTRODUCTION

Acute osteoarthritis (AO) in the neonatal period is uncommon. The estimated incidence is 1 to 3 cases per 1000 admissions in Neonatal Intensive Care Units¹ Clinical features, microbiology, and outcome differ from that of older children. Diagnosis may be difficult and delayed because of the paucity signs and symptoms. Poor outcome is related to its potential to cause permanent sequelae.^{2,3}

The aim of this investigation was to identify the clinical and radiological features, microbiology, risk factors for sequelae, and outcome of neonates with AO infection.

PATIENTS AND METHODS

We included all patients with less than two months of age admitted to the Neonatal Intensive Care Unit (NICU) of the Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan", Buenos Aires, Argentina, over a period of 16 years (1988–2004). This unit admits about 700 neonates per year and is a tertiary referral center in the country.

The diagnosis of bone or joint infection was based on clinical, radiological, and microbiological criteria. At least two of the following criteria had to be met for inclusion in the study: 1) clinical symptoms; 2) radiological changes; 3) positive blood or bone or joint cultures; 4) aspiration of pus from bone or joint.

Outcome was evaluated by an orthopedic surgeon, an infectologist, and a neonatologist on the basis of radiographic and clinical features. Sequelae included ambulatory disability, limb-length discrepancy, and bone growth abnormalities.

Mild sequelae were defined as local swelling or pain or limited motility and radiographic changes consisting of lytic lesions limited to less than one-third of the bone shaft, a periosteal reaction or sclerosis. Severe sequelae were defined as any symptom at the infection site and radiographic changes consisting of lytic lesions extending over one-third of the bone shaft or lesions within the growth plaque. Radiographic classification (I-V) proposed by Hunka *et al.* was used for hip infection.⁴

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STATISTICAL ANALYSIS

All data were entered and verified with the use of Epi-Info 6.0. Statistical Data are summarized as mean or median, range for continuous variables, frequency and percentages for categorical data. Comparative analyses of categorical data were performed by chi-square analysis. P-values < 0.05 were considered as statistically significant. Statistical analyses were calculated with 95% confidence intervals.

RESULTS

We included 77 patients with 99 AO foci. The mean age was 21 (range: 2-53) days, 42 patients (55%) were male. Mean gestational age at birth was 38 (range: 26-42) weeks. Of all patients, 49 (64%) had nosocomial infections, and at least one risk factor for infection was present in 53 (69%) patients: high-risk pregnancy in 19 (25%), prematurity in 15 (20%), birth weight less than 1500 g in 5 (7%), asphyxia in 16 (21%), central catheterization in 24 (31%), mechanical ventilation in 11 (14%), and previous antibiotics in 35 (45%). Less than 4% of patients had a history of surgery, necrotizing enterocolitis or steroid medication (Table 1).

Table 1. Characteristics of patients

Variable	n:77	
	n	Percentage
Age (median in days)	21 (r 2-53)	-
Male	42	55
Risk factor for infection	53	69
High risk pregnancy	19	25
Prematurity	15	20
BW < 1500 g	5	7
Asphyxia	16	21
Central catheter	24	31
Mechanical ventilation	11	14
Previous ATB	35	45
Nosocomial infection	49	64
Time to diagnosis	2 (r 1-15)	
Fever	39	50
Pain	69	90
ESD (median)	52 (r 5-145)	
Positive cultures	66	84
Initial abnormal Rx	29	38
Sequelae	29	38
Mortality	1	1

Fourteen patients (18%) had multiple joint involvement. The lower extremities were the most commonly affected with 79 foci (80%). The hip was the most frequent focus affecting 47 (60%), followed by the knee in 23 (30%). Nineteen foci were localized in the upper extremities (20%), 12 of them (66%) in the shoulder (Table 2).

Table 2. Distribution of affected bone and joint n: 99 sites in 77 newborn

Bone/joint	Number of sites	%
Hip	47	47.5
Knee	23	23.3
Shoulder	12	12.2
Ankle	8	8
Elbow	6	6
Others	3	3
Total	99	100

The median time to diagnosis was two days (range: 1-15). The most common clinical presentation was pain in 69 patients (90%), motor disability in 71 (96%), tenderness in 58 (75%), and erythema in 35 (45%). Fever and sepsis were present in 38 patients (50%). Forty-seven percent of the patients presented local signs of infection solely.

The median peripheral white blood cell count was 15.900/mm³ (r: 4.500 - 37.000) with 70% polymorphonuclear leukocytes. Erythrocyte sedimentation rates (ESR) were abnormal at initial evaluation in 72 patients (93%). Cultures were positive in 66 (84%): joint cultures in 53 (82%), and blood cultures in 35 (54%). The predominant causative organism was *Staphylococcus aureus* 37 patients (57%), 19 were methicillin susceptible (Table 3).

Table 3. Microbiology of bone and joint infection n: 66 isolation

Organisms	Number of cases	%
<i>Staphylococcus aureus</i>	37	56
Gram-negative enteric bacilli:	16	24.3
<i>Klebsiella pneumoniae</i>	8	-
<i>Pseudomonas aeruginosa</i>	3	-
<i>Serratia marscecens</i>	1	-
<i>Proteus mirabilis</i>	1	-
<i>Acinetobacter baumannii</i>	1	-
<i>Enterobacter cloacae</i>	1	-
<i>Escherichia coli</i>	1	-
<i>Streptococcus agalactiae</i>	10	15.2
<i>Staphylococcus epidermidis</i>	2	3
<i>Haemophilus influenzae type b</i>	1	1.5
Total	66	100

Forty-nine patients acquired infection at the hospital, 39 (80%) of them with microbiological isolation. Community infection were acquired in 28 patients, 27 (96%) of them with positive culture. Relationship between risk factors and etiology is showed in (Table 4).

Table 4. Risk factor and microbiological isolation

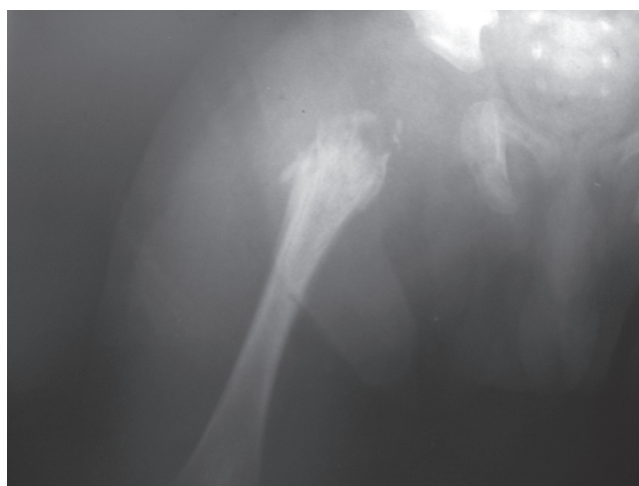
Organisms n = 66	Communi- ty Acquired	Noso- comial Infection	CVC	Mecha- nical ventilation	NEC	Cort
<i>S. aureus</i> (n = 37)	15 (40%)	22 (60%)	12 (33%)	6 (16%)	2 (5%)	2 (5%)
<i>S. epidermidis</i> (n = 2)	0	2 (100%)	2 (100%)	2 (100%)	0	0
Gram - negative) bacilli (n: 16)	1 (6%)	15 (94%)	6 (38%)	2 (13%)	0	0
<i>S. agalactiae</i> (n = 10)	10 (100%)	0	0	0	0	0
<i>H. influenzae</i>	1	0	0	0	0	0
n	27	39	20	10	2	2

CVC, Central vascular catheterization; NEC, necrotizing enterocolitis; Cort, steroid.

Considering nosocomial acquired infection (49), all of them presented with local symptomatology and only 23 patients (47%) with systemic manifestation such as fever and sepsis. The median time to the diagnosis was two days (r: 1-15d).

Bone radiological changes were observed in 29 patients (38%) at the initial evaluation; osteolytic lesions were the most frequently observed radiographic images (Figure 1).

Figure 1: Severe sequelae of neonatal bone-joint infection in the right hip.



All patients were treated with antibiotics for a median duration of 40 days. Surgical drainage was performed in 58 patients (75%). One patient (1%) died because of sepsis.

Twenty-nine infants (38%) had sequelae. Out of the 29 sequelae, eleven (38%) were mild and 18 (62%) severe, considering initial definitions.

By univariate analysis, the risk factors for sequelae were: hip involvement (RR = 3.15; 95% CI: 1.55-6.42; $p < 0.0005$), positive culture (RR = 5.25; 95% CI: 0.79-35; $p < 0.02$), and *Staphylococcus aureus* isolation (RR = 3.17; 95% CI: 1.09-9.34; $p < 0.03$).

DISCUSSION

In our study the incidence rate of AO was 7 cases per 1000 admissions, higher than that reported in literature. This may be explained because the Hospital Garrahan is a referral center, where neonates are referred for high risk and surgical management. The frequency of AO did not change along the 16 years of the study. Thus, it appears that neonatal AO continues to be an uncommon problem.

In the neonate, AO is usually due to a blood-borne spread of infection to bones or joints. Risk factors are therefore closely related to the risk of bacteremia.

Complications of pregnancy, labor, or delivery precede the occurrence of neonatal AO in one third to one half of patients.⁵ Associated risk factors included prematurity, low birth weight, asphyxia, bacteremia, and the presence of intravenous or umbilical catheter.^{6,7} In a review of more than 300 cases of neonatal AO, male infants predominate over females (1,6:1), and premature infants acquire osteoarthritis with a relatively greater frequency than do term infants.⁸ In our study, risk factors for infection were present in 53 patients (69%); mostly related to nosocomial infections, such as high-risk pregnancies and use of central catheters.

Clinical presentations in the neonate differ from older children. This can be explained partly by the neonate's blood supply to the bone. The metaphyseal vessels communicate with the epiphyseal vessels in the cartilaginous precursor of the ossific nucleus. This facilitates a rapid spread of the infection from the metaphysis to the epiphysis, which is often destroyed, offering a route of infection into the joint. This explains why in the neonate arthritis and osteomyelitis often coexist.⁹

The diagnosis of AO in neonates is often delayed because of nonspecific symptoms, and may be discovered accidentally in the course of routine radiographic examinations, or it may not be apparent until the formation of a local subcutaneous abscess. Local signs may be mild and systemic symptoms may be absent, being irritability the unique sign.^{10,11,12} Clinical presentation may be divided into two groups: The first is the "benign or mild form",

were preceding bacteremia is of low grade or transient, with a little or no evidence of infection other than local swelling or disability, and symptoms may last for several weeks. The other is the "severe form", where prolonged or intense bacteremia is frequent and systemic manifestations of sepsis predominate with an acute presentation with common multiple joint involvement.¹³

In our patients, as in other reports, the "benign form" was more frequent. Pain and limitation of motion were the most common clinical presentations (90% and 96% respectively). Other local signs such as swelling were present in 58 patients (75%) and erythema in 35 (45%). Fever was present in only 50% of the patients.

A report of 485 newborns with AO the lower extremities was involved in more than 70%, similarly to most reports.^{13,14} Eighty percent of our patients had lower extremities involvement (knee, hip, and ankle), the hip being the most frequent site of infection in 47 patients (60%) followed by the knee in 23 patients (30%). In the upper extremities, the shoulder was the most frequently involved site.

Multiple bone involvement is more frequent in the newborn, and has been reported in 20% to 50% of neonates with OA foci.¹⁵ In our study there was multifocal involvement in 18% of the cases.

Plain film radiographs are still the most useful means for establishing the diagnosis of neonatal OA. Neonates show definite signs of bone destruction by the 7th to 10th day of illness.¹³ The use of ultrasonography has been of increasing interest for bone and joint infections. Experience with CT and MRI is limited, as they are used in special situations after the other conventional methods. In our experience, abnormal radiographs were found in 29 patients (37%) at the initial evaluation.

The white blood cell count (WBC) is of little value in diagnosing neonatal AO. In more than 150 cases, in which these values were recorded, the median WBC count was 17.000 (r: 4.000-75.000); PMN leucocytes represented about 60% of WBC. The sedimentation rate is often elevated, and is helpful for diagnosis and follow-up when elevated, but cannot be used to rule out OA infection.¹⁷ It reacts slowly to resolution of inflammation; frequently, it still rises as clinical improvement occurs. Even when recovery is uneventful, normal rates are not reached until three weeks have elapsed. Alternatively, the C-reactive protein (CRP) is a rapid indicator of inflammation and tissue necrosis and may be useful as an acute phase reactant with more sensitivity in the follow-up. High serial CRP concentration is related with sequelae-prone patients.¹⁷⁻¹⁸

In our series, the median WBC count was 15.900/mm³ with neutrophil predominance (70%). ESR was elevated initially in 94% of the patients. C-reactive pro-

tein was not evaluated because it was not performed on a routine basis.

Clinical or radiological evidence of joint-space infection requires confirmation through needle aspiration of an inflammatory area, to establish a rapid means of diagnosis, in addition to the usual sepsis screening studies. In our experience, cultures were positive in 65 patients (84%), with blood and joint as the most frequent sites of isolation.

Because most cases arise as a consequence of an early bacteremia, the organisms responsible for AO reflected the etiology of neonatal sepsis. Gram-positive cocci are the most frequently cultured microorganisms representing more than 85% of isolations, being *Staphylococcus aureus* the most common. *Streptococcus agalactiae* have become increasingly prevalent, as a late-onset illness during the third and fourth week of life, usually with a mild presentation. AO caused by Gram-negative enteric bacilli is relatively uncommon despite the frequency of neonatal bacteremia.¹⁹ In Stockholm, during 1969 to 1979, *E. coli* and *Klebsiella-Enterobacter* were responsible for about 30% of neonatal septicemia, but only 5% of bone infections.⁵ In contrast, *S. aureus*, although also causing about 30% of neonatal bacteremia, was responsible for 75% of osteomyelitis.

In our experience, Gram-positive cocci represented 75% of all isolations. The predominant causative organism was *Staphylococcus aureus* in 37 patients (57%). Group B *Streptococcus* was cultured from 10 patients (15%), enteric gram-negative bacilli from 16 (24%), *Staphylococcus epidermidis* from two, and *Haemophilus influenzae* type b from one patient.

Emergence of new pathogens like community-acquired methicillin-resistant *Staphylococcus aureus* must be considered in newborns with bone and joint infection for empirical treatment.²⁰ Successful treatment of osteoarthritis depends on prompt clinical diagnosis and identification of the infectious agent. No controlled studies of type and duration of therapy of these infections exist. General recommendations for antibiotic treatment consider that it should be given by parenteral route initially and continued during 4 to 6 weeks. Peltola *et al.* propose shorter course of treatment in pediatric patients > 3 months old, but only few reports is written in newborn patients.^{21,22} Complications encountered during prolonged parenteral antibiotic treatment in children with acute OA infection are related, such as antimicrobial drug reactions and catheter related infections.²³ Sequential parenteral-oral therapy may be used with close follow-up. Nelson *et al.* showed that a shorter duration of parenteral therapy followed by an oral therapy based on patient's clinical response was not associated with any recurrence

of infection.²⁴ Longer IV treatments may be needed in those high-risk sequelae-prone patients, depending on localization and microbiology.²⁵

In our series, all patients received antibiotic treatment, and 75% (58) also needed open surgical drainage, especially for hip and shoulder localization.

Treatment duration had a median time of 40 days, with a mean of 21 days of intravenous treatment. Most patients (91%) received sequential parenteral-oral treatment. The minority (9%) received IV antibiotics alone.

The mortality related to AO is low and is associated with the presence of sepsis. In our experience only one patient died, and it was because of sepsis.

A number of studies document a poor outcome even with modern treatment facilities. Neonatal AO can lead to permanent joint disabilities or disturbances in skeletal growth secondary to damage to the cartilaginous growth plate. These include arthritis, decreased range of motion, limb-length discrepancy, and gait abnormalities. The reported incidence of permanent sequelae varies from 6% to 50%.^{3,6} Osteoarticular disabilities was found in 38% of our patients.

Multiple risk factors are associated with sequelae-prone cases: delay in diagnosis or surgical drainage, involvement of hip or shoulder, short duration of antimicrobial therapy, high serial serum CRP concentrations or high ESR, and slow clinical response to treatment.²⁶ Other studies reported that the presence of concomitant osteomyelitis and methicilin-resistant *Staphylococcus aureus* infection was associated with a significantly increased risk of sequelae.^{27,28}

We analyzed risk factors of sequelae in the 77 patients. Adverse outcome was associated with hip involvement, culture positivity, and *Staphylococcus aureus* isolation. The other evaluated factors were non-significant for adverse outcome.

CONCLUSIONS

Bone and joint infections are severe complications in the newborn period. There are risk factors associated with unfavorable outcomes. In our experience, hip involvement and microbiological isolation were risk factors for an unfavorable long-term outcome.

Considering the low incidence, paucity of symptoms, and associated morbidity, a high degree of suspicion is needed to diagnose AO in the newborn. Appropriate management with antibiotics and surgical drainage in selected cases are important to prevent long term morbidity.

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