Frequency of Multifocal Disease and Pyogenic Arthritis of the Hip in Infants with Osteoarticular Infection in Three Neonatal Intensive Care Units

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Objective To describe the clinical features of osteoarticular infection in infants cared for in neonatal intensive care units (NICUs) and to assess the presence of multifocal infection.

Study design Retrospective medical record review with structured data abstraction of infants with osteomyelitis or pyogenic arthritis or both in NICUs at 3 children's hospitals over a 29-year period.

Results Of the 45 cases identified, 87% occurred in prematurely born infants, with a median gestational age of 27.4 weeks (IQR, 26, 31 weeks). Median postnatal age at diagnosis of infection was 33 days (IQR, 20, 50 days). Osteomyelitis was present without joint involvement in 53% and with joint involvement in 44% of cases. Methicillin-susceptible *Staphylococcus aureus* (71%) was the predominant pathogen, despite prevalent methicillin-resistant *S aureus* in community-associated infections. More than 1 bone was infected in 34% of cases. The femur (in 50% of patients) was the most frequently involved bone and the hip (in 20% of patients) was the most frequently involved joint. Bacteremia persisted for 4 or more days in 54% of patients with a positive blood culture despite active antimicrobial therapy.

Conclusions Among infants with osteoarticular infection in NICUs, multifocal disease is common and frequently is unsuspected. Search for additional sites of infection including the hip is warranted following the diagnosis of osteoarticular infection at a single site. Involvement of contiguous joints should be suspected in cases of osteomyelitis; conversely the presence of pyogenic arthritis usually indicates extant osteomyelitis in a contiguous bone. *(J Pediatr 2020;227:157-62)*.

Osteomyelitis and pyogenic arthritis are relatively common infections in children. In contrast, osteoarticular infection in infants cared for in neonatal intensive care units (NICUs) is an uncommon but serious infection. Compared with osteoarticular infection in older children, infection in these young and often premature infants can be associated with multifocal involvement,[1] a more varied microbiologic etiology,[2] and a higher risk for substantial long term sequelae, especially when pyogenic arthritis of the hip occurs.[3] Medical literature regarding osteoarticular infection in young infants from developed countries is limited and most primary case series were published more than 20 years ago.[1] Although the complex nature of osteoarticular infections in the neonate was described decades ago, we experienced as consultants the frequent delays in diagnosis and substantial resultant morbidity of such infections in the neonate. No series has been reported during the current era of high prevalence of community-associated methicillin-resistant strains of *Staphylococcus aureus* (MRSA). The purpose of this case series of osteoarticular infections among infants in the NICU is to provide contemporary data on the epidemiology and microbiology, including the proportion of cases with MRSA; and to assess the hypothesis that infection frequently is complicated and multifocal; with particular risk for pyogenic arthritis of the hip. The study was designed as a multicenter study to generate a sufficient sample size for analysis and to broaden the experience beyond that of a single institution.

Methods

Cases were identified from a search of medical records, NICU patient registries, and/or logs of infectious diseases consultations at 3 medical centers: Cohen Children's Medical Center of New York of Northwell Health, New Hyde Park, New York with cases emanating from 2 NICUs, 1 in New Hyde Park, New York and 1 in Manhasset, New York; St. Christopher's Hospital for Children, Philadelphia, Pennsylvanian; and Schneider Children's Medical Center of Israel, Petah Tikva,

GBS	Group B *Streptococcus*
MRSA	Methicillin-resistant strains of *Staphylococcus aureus*
NICU	Neonatal intensive care unit

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Israel. Cases were required to have suggestive clinical findings plus positive imaging findings or a positive culture of blood, joint fluid, or bone. The study time period was 1990 through 2018. Data were abstracted from the medical records of each patient by study investigators using a collaboratively planned structured format and were collected and managed using REDCap (Nashville, Tennesee) electronic data capture tools hosted at Northwell Health. The symptoms and complete blood count were recorded from the time the patient exhibited a change from her/his baseline clinical condition, generally at the time of the initial blood culture. This study was approved by the institutional review board at each institution.

Results

Forty-five infants with osteoarticular infection were identified from the 3 institutions (Table). All cases had retrieval of medical, laboratory, and imaging records. Fewer cases were identified during the arbitrarily defined 15-year period 1990 through 2004 than during the 14-year period 2005 through 2018; the demographics of the cases and distribution of pathogens during the time periods were similar (Table). The infants had a median birthweight of 1040 g with a range of 475-3195 g (Table); 47% had birthweight of <1000 g and an additional 29% had birthweight between 1000 and 1499 g. Overall, 87% were born prematurely (<37 weeks of gestation), with a median gestational age of 27.4 weeks; 64% of the infected infants were male. Prenatal testing detected maternal group B *Streptococcus* (GBS; *Streptococcus agalactiae*) colonization in 16% of the mothers of patients. Birth was by cesarean delivery in 78% (35) of infants.

The median postnatal age at onset of symptoms of infection was 30 days (Table), and the median age at diagnosis of infection was 33 days (IQR; 20, 50 days). At the onset of symptoms, 7 infants (16%) were requiring assisted ventilation with a mechanical ventilator. A central venous catheter was in place within 1 week prior to onset of symptoms of infection in 21 (47%) of patients, and 25 (56%) received parenteral nutrition within 1 week of onset of infection. A surgical procedure had been performed prior to the osteoarticular infection in 10 (22%) of 44 patients (data not available for one patient), which included cardiothoracic surgery in 5 and gastrointestinal surgery in 3, with a median time interval of 27.5 days (IQR; 24, 29 days) between surgery and infection.

Local symptoms or signs at an infected site were present at diagnosis in the majority of patients, with the presence of swelling in 29 (64%), erythema in 25 (56%), and reduced movement in 10 (22%); localized symptoms or signs less frequently present were tenderness or drainage from overlying skin, each in 4 patients (8.9%), and presence of a pustule or induration in 1 patient each. Systemic symptoms were present at diagnosis in 31 patients (69%) and most frequently included apnea, 24 (53%); temperature instability, 23 (51%); or bradycardia, 18 (40%). Less frequently present systemic symptoms were feeding intolerance or reduced enteral intake, 6 (13%); irritability, 5 (11%); lethargy, 2 (4.4%); poor perfusion requiring vasoactive medications for blood pressure support, 2 (4.4%); and hypotonia, 1 (2.2%). No systemic symptoms were present in 14 patients (31%).

Table. Demographic features of infants with osteoarticular infections

	Time period		
	Total: 1990 through 2018	1990 through 2004 (15 y)	2005 through 2018 (14 y)
Number of cases (total)	45	8	37
Hospital 1	24	3	21
Hospital 2	15	5	10
Hospital 3	6	0	6
Gestational age (wk, median; IQR)	27.4 (26, 31)	28 (26, 29)	27.3 (25.2, 32)
Birthweight (g, median; IQR)	1040 (805, 1249)	1280 (600, 1370)	1040 (805, 1750)
Postnatal age at onset of osteoarticular infection (d; IQR)	30 (15, 48)	14 (12, 27)	33 (18, 50)

Diagnostic Imaging

Standard radiographs were performed in 40 patients (91%) and demonstrated abnormal findings in 78%, periosteal reaction was identified in 21 patients (68%), a lytic lesion in 9 (29%), and joint swelling or effusion in 7 (23%). In 2 cases, the abnormal finding was an incidental finding on chest radiograph performed for systemic symptoms. Ultrasonography of joints or bone was performed in 23 (51%) of patients. An ultrasound examination of the hip was performed in 17 (38%) of patients with the following findings: no fluid in 11 (65%), simple effusion in 5 (29%), and complex effusion (nonhomogeneous signal) in 1 patient (5.9%). Magnetic resonance imaging was performed in 4 patients (9.1%) and showed abnormalities in 2 patients; one with bone marrow edema only and the other with bone marrow edema, periosteal reaction, and joint effusion.

Sites of Osteoarticular Infection

Of the 45 patients, 53% had osteomyelitis without joint involvement and 44% had both osteomyelitis and joint involvement. One patient was classified as joint infection (of the hip) without osteomyelitis, but it is uncertain if osteomyelitis was present because his only imaging was an ultrasound examination of the hip. In all patients classified as having osteomyelitis, the bone infection was documented by abnormal imaging. More than 1 noncontiguous distinct anatomic site of bone and/or joint infection was observed in 27% of patients with 2, 3, or 4 sites in 21%, 2.3%, and 4.5% of patients, respectively. Similarly, a single bone was infected in 19 (66%) patients and 2, 3, and 4 bones were infected in 10 (23%), 2 (4.5%), and 3 (6.8%) patients,

respectively. The femur was the bone most frequently affected overall and also was the first involved bone detected, followed by the humerus, tibia, and sternum (Figure 1, A). Among the 6 patients with osteomyelitis of the sternum, 5 had antecedent cardiac surgery involving cutting the sternum between 2012 and 2016 at one of the study hospitals. The 3 patients with gastrointestinal surgery had surgery 9, 25, and 27 days prior to the onset of symptoms of osteoarticular infection. For the patient who had gastrointestinal surgery 9 days prior to onset of symptoms of osteomyelitis, osteomyelitis of the femur was caused by a gram-negative bacillus, *Citrobacter koseri*.

The joint most frequently identified was the knee followed by the hip (Figure 1, B) and the first joint to be identified was also the knee. Five (23%) of the 22 patients with joint involvement had more than 1 joint involved, with 2 joints in 1 patient, 3 joints in 3 patients, and 4 joints in 1 patient. The hip joint was involved (ie, effusion on imaging and/or surgically drained) in 9 patients (20%) patients, and in 4 patients (44%) the diagnosis of hip involvement was not made during the first 48 hours after onset of symptoms of osteoarticular infection.

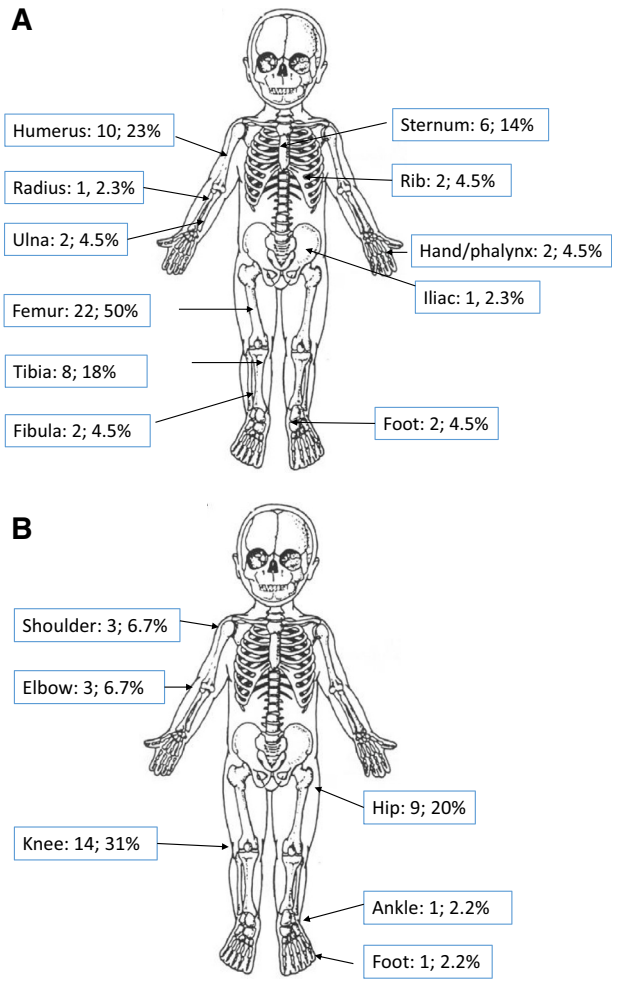

Figure 1. Sites of involvement of bones (**A,** among 44 patients) and joints (**B,** among 22 patients) in 45 infants in NICUs with osteoarticular infections. Percentages reflect the proportion of patients with **A,** bone infection or **B,** joint infection affected at each body site.

Laboratory Test Results

The median blood leukocyte count was 18 200 cells/μL (IQR; 13 500, 23 800; range 1600-47 900 cells/μL). Eight patients had a leukocyte count of >30 000 cells/μL and 2 had a leukocyte count of <6000 cells/μL. Few patients had joint fluid cell counts reported. Cultures grew a pathogen in 38 (84%) patients. Blood culture was positive in 37 (82%) of the 45 patients in whom it was performed, joint fluid culture was positive in 11 (85%) of 13 patients with cultures of joint fluid; and culture of bone was positive in 4 (33%) of the 12 cases who underwent surgical drainage of bone. *S aureus* was the etiologic agent in 34 (89%) cases, with methicillin-susceptible *S aureus* cases predominating (27 cases, 79% of *S aureus* cases) and with MRSA accounting for 7 cases (21% of *S aureus* isolates; Figure 2). Gram-negative bacilli cases comprised 3 (7.9%) isolates, coagulase-negative staphylococci, 1 (3%; patient with 2 positive blood cultures and a central venous catheter), and Candida spp, 1 (3%).

Treatment

Of 45 patients, 19 (42%) underwent a surgical drainage procedure, with drainage of both bone and joint in 6 patients, drainage of bone alone in 6 patients, and drainage of joint alone in 7 patients. The hip joint was drained in 8 of 9 cases with hip involvement. Intravenous antibiotics were administered in all 45 cases. The antibiotics used for definitive therapy were nafcillin/oxacillin (27 patients, 63%), cefazolin (5 patients, 12%), vancomycin (8 patients, 19%), rifampin (used in combination with nafcillin/oxacillin in 4 and in combination with vancomycin in 2, 14%), and 1 patient each received cefotaxime, meropenem, piperacillin/tazobactam, and amphotericin. No patient was treated with clindamycin. Excluding 1 patient who expired on day 7 of antimicrobial therapy, the median duration of antibiotic therapy was 32 days (range, 28-42 days; IQR, 25, 75).

Bacteremia was often prolonged despite antimicrobial therapy. Of the 37 patients with a positive blood culture, the median number of days of positivity was 4. Twenty patients (54%) had positive blood cultures for 4 or more days and 4 patients had blood cultures positive for more than 7 days; only 5 patients had a single day with a positive blood culture. The association between surgical drainage of bone and/or joint and duration of blood culture positivity was examined. Among patients with positive blood cultures for less than 4 days, the proportion who underwent surgical drainage was 67% compared with 54% who had blood cultures positive for 5 or more days; this difference was not statistically significant (P = .71, Fisher exact test, 2-tailed). In the cases with *S aureus* bacteremia, in only 59% (19 of 34)

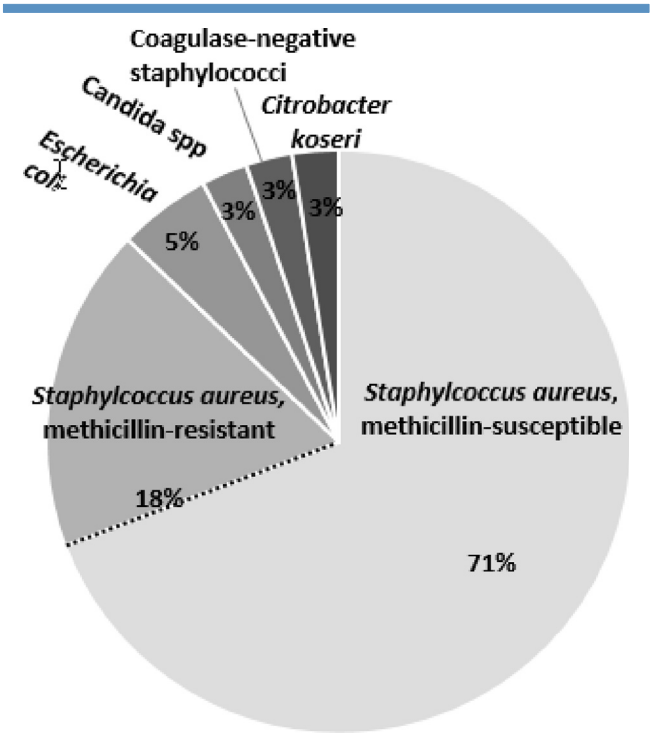

Figure 2. Distribution of pathogens causing osteoarticular infections in the 38 of 45 infants in NICUs with a positive culture.

of cases was there a central venous catheter present at the time of bacteremia or during the preceding week.

Outcome

No patient experienced a relapse of infection. Six patients expired prior to hospital discharge but in only 1 case was death due to infection. Six or more months of follow-up data were available for 6 patients, 4 of whom had clinically significant orthopedic sequelae: 2 patients with knee joint deformity and leg length discrepancy and 1 patient each with hip deformity; and leg length discrepancy. An additional 3 patients had follow-up data for less than 6 months but were noted to have the following orthopedic sequelae: elbow joint deformity, at 63 days; knee joint deformity with leg length discrepancy, at 54 days; and hip joint deformity with aseptic necrosis of femoral head and leg length discrepancy, at 33 days. Five of the 7 patients with sequelae of infection had undergone a surgical drainage procedure.

Discussion

This case series of osteoarticular infections among infants in three NICUs has 3 notable major findings: (1) the large proportion of patients with multifocal involvement; (2) the presence of concurrent contiguous osteomyelitis in almost all cases of joint involvement; and (3) the relatively large proportion of patients with hip involvement. The typical case was an infant born extremely prematurely who had the clinical onset of infection at the age of ~1 month. An explanation for the markedly higher number of cases identified during the latter period of 2005-2018 compared with 1990-2004 is unclear but the disparity occurred at all 3 sites. Speculative causes could include host, microbiologic, environmental, and ascertainment factors; however, we cannot conclude that the rate of infection increased because we lacked the data necessary to calculate infection rates.

Nearly two-thirds of the infants with osteoarticular infection were male, as is the case for osteomyelitis in older children.[4] Similarly, from India, Narang et al reported a 2:1 male predominance among 25 neonates, 40% of whom had a history of prematurity, and from Denmark, Frederiksen et al reported male sex in 14 (64%) of 22 premature infants with osteoarticular infection.[5,6] However, another study from India found that only 41% of 29 infants with neonatal osteoarticular infection were male, with prematurity noted in 69%.[7] Male infants accounted for 52.3%, with a birth weight of less than 1500 g in NICUs reported by Stoll[8] and 54.8% of infants admitted to the NICU at Cohen Children's Medical Center of New York during the 10 years from 2009 through 2018 (L Rubin, unpublished observation). Furthermore, the reported occurrence by sex of late-onset sepsis among those with a birth weight of 500-1500 g, 25% in male and 24% in female infants, did not differ significantly.[9] Among infants in 1 NICU who became colonized with *S aureus*, Ibukunoluwa et al found that 48% were male.[10] Thus, there is a male predominance in neonates with osteoarticular infection, but it does not appear to be explained by a male predominance among the NICU population or a sex-related risk for late-onset sepsis or *S aureus* colonization.

The diagnosis of osteomyelitis generally was not established at an early stage of infection. This is evidenced by the large proportion of patients whose radiographic abnormalities included periosteal reaction or lytic lesions, which require a minimum of 7-10 days after the onset of infection to be visible on plain radiographs.[11,12] In cases with both osteomyelitis and pyogenic arthritis, it is likely that in most cases hematogenous osteomyelitis occurred first, followed by contiguous spread leading to pyogenic arthritis. Local findings of swelling (in 64%) and erythema (in 56%) were commonly observed at diagnosis and likely reflect infection that has advanced from the bone to soft tissue. These observations suggest that most cases of osteomyelitis in infants in a NICU may be difficult to recognize and the first "obvious" clinical finding is a complication of osteomyelitis.

Although involvement of more than a single bone occurs in less than 5% of cases of osteomyelitis in older children,[4] multifocal infection was present in 27% in our NICU infants with osteoarticular infections. Ish-Horowicz et al reported multifocal infection in 55% of 20 cases of MRSA osteomyelitis in one NICU.[13] Others have reported multifocal infection in 41%-47% in case series of osteoarticular infections in neonates, although in these reports many of the patients were outpatients at the time of presentation.[1,14]

Unlike in older children, the intracapsular location of the metaphyses of long bones in neonates, the venous channels

that perforate the growth plate, and the communication between the blood supply of the metaphysis and epiphysis lead to bone infection frequently being complicated by contiguous pyogenic arthritis in neonates. Osteomyelitis was associated with infection in a contiguous joint in 44% of infants in our case series and in 71% of neonates in another series.[14] Infection of the hip joint is associated with substantial clinical sequelae[15] and delayed management of hip infections is a predictor of long term sequelae.[16] As noted above, among the 9 cases with hip involvement in our case series, 4 (44%) cases were not detected within 48 hours of the onset of symptoms. Because of frequent involvement of the hip as well as multiple sites of infection in our series and others,[5] and in light of insensitivity of clinical examination, it may be prudent to perform ultrasound examination of both hips when an infant in a NICU has evidence of osteoarticular infection at any body site.[3] This strategy is an attempt to diagnose pyogenic arthritis of the hip promptly, to afford the earliest opportunity to decompress a closed space and reduce the likelihood of ischemia/avascular necrosis, and to provide drainage to hasten control of infection. In our series, 62% of patients did not have an ultrasound of the hip(s). Irreparable damage to the hip can be caused directly by the infection or the host response or both, or as a consequence of elevated pressure within the joint capsule leading to impairment of vascular supply and aseptic necrosis of the femoral head.

Despite the high proportion of community-associated *S aureus* infections caused by MRSA infections in the US during the study period with an onset during the 1990s and a peak proportion during the first decade of 2000 of 63%-70% among older children with *S aureus* osteoarticular infections,[17,18] Methicillin-susceptible Staph aureus remained the most common osteoarticular pathogen in the NICUs we studied. However, MRSA was the predominant pathogen of osteoarticular infection in a case series reported from a single NICU during the early 1990s.[13] It is noteworthy that gram-negative bacilli were uncommon causes of osteoarticular infection in our series. In addition, no case was due to GBS. Most cases of GBS occur in a different population, namely as late onset disease in infants who were born at term, when infection usually is limited to a single bone or joint.[19] Coagulase-negative staphylococci were the most common causes of bloodstream infections in NICUs during the study period[20,21] yet were a rare cause of osteomyelitis. The recognition of *S aureus* as the predominant pathogen and that such infections are hospital-acquired provides an opportunity to prevent osteoarticular infections in NICUs through infection prevention strategies that can reduce colonization and transmission.[22]

The occurrence of cases with prolonged bloodstream infection (ie, cultures positive for ≥5 days) despite treatment with an antimicrobial to which the pathogen was susceptible raises the question of whether inadequate source control (ie, drainage of the bone and/or joint) was responsible. However, infants without prolonged positive blood cultures (ie, <5 days) were not substantially more likely to have surgical drainage than infants with prolonged bacteremia (67% vs 54%, respectively). Infection of a vascular catheter could result in bacteremia and lead to osteomyelitis as well as potentiate bacteremia but only 47% of infants had a central venous catheter in place within 1 week of the onset of infection; however, the proportion of patients in the NICU population with a central venous catheter during the study period was not tabulated. Immaturity of host defense, limiting the ability to rapidly localize or eliminate pathogens, especially *S aureus,* likely contribute to dissemination and persistence of infection in this vulnerable population.

Although a systematic examination of orthopedic sequelae was not performed, sequelae were common in the subgroup of our patients for whom we had data, and sequelae have been common in reported series.[23] Among cases with pyogenic arthritis, the hip joint is most prone to sequelae,[16] which frequently has a high negative impact on quality of life and requires subsequent surgical interventions.

Our study has the limitations intrinsic to retrospective case series. Although all infants were being cared for under neonatal intensive care with daily recorded examinations reviewed, symptoms and signs may not have been fully reported. Medical and surgical interventions and imaging were at the discretion of care providers. Use of a template for data retrieval mitigated some variability and permitted recording of the performance and results of relevant clinical events, findings, laboratory, and imaging studies but the timing of surgical drainage procedure(s) was not recorded. Follow-up was limited and may bias outcomes toward severely affected cases. Although ours is a summative case series from 3 NICUs, the findings may not be generalizable.

Osteoarticular infections in the NICU are highly consequential nosocomial events. Avoidance will require focus on infection prevention methods to reduce transmission of pathogens, particularly *S aureus* and optimization of patient management to reduce the likelihood of their invasion. If osteoarticular infection is diagnosed at one body site in the NICU setting, the high frequency of multifocal disease mandates the careful clinical evaluation for infection at other sites. Involvement of contiguous joints should be suspected in cases of osteomyelitis; conversely the finding of pyogenic arthritis usually indicates a contiguous site of established osteomyelitis. Pyogenic arthritis of the hip is commonly associated with neonatal osteomyelitis, either as a complication or occasionally as an antecedent event, and requires urgent drainage to optimize outcome. Therefore, ultrasound examination of the hips should be performed on infants in a NICU with suspected contiguous osteomyelitis and should be considered when bone or joint infection is evident at any body site. ■

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