PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2022) **64**, e15212 doi: 10.1111/ped.15212

Original Article

Osteoarticular infections in infants under 3 months of age

Joana Branco,[1] Mariana Duarte,[1] Susana Norte,[2] Joana Arcangelo,[2] Pedro Alves,[3] Maria Brito,[1] Delfin Tavares[2] and Catarina Gouveia[1,4]

[1]*Infectious Diseases Unit,* [2]*Pediatric Orthopedic Unit,* [3]*Centro Tecnológico e Biomédico, Radiodiagnóstico, Hospital de Dona Estefânia, CHULC – EPE,* [4]*Nova Medical School, Faculdade de Ciências Médicas, Lisbon, Portugal*

Abstract

***Background*:** Acute osteoarticular infections (OAI) in infants under 3 months of age (≤3M) are rare and remain a diagnostic challenge. Orthopedic complications and functional sequelae have been less well described in this age group. Our aims were to evaluate trends in aetiology, management, and outcomes of OAI ≤ 3M, and to compare these younger children who have OAI with older children.

***Methods*:** A longitudinal observational study was conducted of OAI cases admitted to tertiary care pediatric hospital from 2008 to 2018. OAI ≤ 3M was compared with children above 3 months. Clinical, microbiological, imaging, and outcome data were analyzed.

***Results*:** We identified 24 (9.1%) of the 263 OAI in children under 3 months. Analyzing OAI ≤ 3M there was a twofold increase since 2014; 54% were males with a median age of 28 days (IQR: 13.5–60.0), 10 (41.7%) were premature and nine (37.5%) had healthcare-associated infections. Microbiological causes were identified in 87.5%, mostly *Staphylococcus aureus* (57.1%) and Group B *Streptococcus* (23.8%), and 25% were multidrug-resistant (5 methicillin-resistant *S. aureus* and 1 *Enterobacter cloacae*). Bacteremia (100% vs 36.8%, $P = 0.037$), multidrug resistant bacteria (75% vs 16, $P = 0.04$), and healthcare-associated infections (100% vs 26.3%, $P = 0.014$) were associated with sequelae. Comparing OAI ≤ 3M with older children, OAI ≤ 3M were treated with longer antibiotic courses, had more complications and sequelae (17.4% vs 3.2%, $P = 0.002$).

***Conclusions*:** *S. aureus* is still the most common cause of OAI ≤ 3M, and 25% of causative bacteria were multidrug-resistant bacteria. Complications and sequelae were more frequent in OAI ≤ 3M when compared with older children.

Key words infant, newborn, osteoarticular infection, *Staphylococcus aureus*.

Osteoarticular infections (OAI) are commonly considered to be bacterial infections of the bones and joints. They are uncommon in infants up to 3 months of age but represent a serious disorder, with high morbidity.[1–3] In young infants they are usually acute, spread by the hematogenous route, and more difficult to diagnose than in older children due to the scarcity of signs and symptoms.[1] The long tubular bones of the lower limbs are more commonly affected and quite often the hip is involved, contributing to the increased number of permanent sequelae.[4,5]

Since the 1980s, *Staphylococcus aureus* has remained the most frequent pathogen of OAI in infants below 3 months (OAI ≤ 3M), ranging from 22 to 76%.[1,5–7] In high-risk, hospitalized, premature infants, methicillin-resistant *S. aureus* (MRSA) and coagulase negative *staphylococci* are also a concern, associated with a worse prognosis.[8] However, in some countries, Gram-negative organisms or even Group B *Streptococcus* (GBS) are becoming more prevalent in the first months of life, even after labor prophylaxis in GBS colonized mothers.[1,4–6]

Few studies have analyzed OAI in young infants, and the type and duration of antibiotic treatment is still a matter of debate.[6,9,10] Although orthopedic complications and functional sequelae seem to occur more often at this young age, more data are needed.[1,11] Our aim is to evaluate trends in aetiology and management of OAI ≤ 3M, and to compare complications and sequelae with older children.

Methods

We performed a longitudinal observational data analysis of children with OAI admitted to a tertiary care pediatric hospital from January 2008 to December 2018. Children with OAI ≤ 3 M were compared with a cohort of children older than 3 months (OAI > 3 M). Data were registered retrospectively

Correspondence: Catarina Maria Machado França Gouveia, MD, Hospital Dona Estefânia, CHULC – EPE, Rua Jacinta Marto, 1169-045 Lisbon, Portugal.
Email: cmfgouveia@gmail.com
The work was carried out in Hospital Dona Estefânia, CHULC – EPE, Rua Jacinta Marto, 1169-045 Lisbon, Portugal.
Joana Branco and Catarina Gouveia are cofirst authors.

Received 11 November 2021; revised 18 February 2022; accepted 5 April 2022.

until 2014 and prospectively since then. Patients were evaluated by a multidisciplinary team including infectious diseases, orthopedic and radiology pediatric consultants. Demographic, clinical, microbiological, imaging, treatment, type of surgical care, and follow-up data were obtained from medical records.

The diagnosis of acute osteomyelitis (AOM) and septic arthritis (SA) was based on clinical findings – fever, limited range of movement (ROM), pseudoparalysis, painful movement and local inflammatory signs – with compatible radiological signs with or without microbiologic isolation.[2] The diagnosis of concomitant bone and joint involvement was defined as an association of SA and adjacent AOM. Healthcare-associated infections (HAIs) were categorized using criteria proposed by Friedman *et al.*[12]: invasive procedures or exposure to a hospital in the previous 30 days, hospitalization for more than 2 days in the previous 90 days, treatment with broad spectrum antibiotics in the previous 30 days. Multidrug resistant bacteria (MDR) were defined following Magiorakos *et al.*[13]

First-line intravenous treatment in children under 2 months consisted of third-generation cephalosporin whereas in children above 2 months of age flucloxacillin or second-generation cephalosporin was prescribed. Gentamicin was added for synergy. We carried out early joint drainage in SA but bone surgical intervention only when a complication was identified. Complications included dislocation, avascular necrosis, abscesses, pyomyositis, deep venous thrombosis (DVT), disseminated infection, pathologic fractures, or chronic osteomyelitis as previously reported.[14] All patients were followed up for at least 12 months. Sequelae considered were pain, ROM limitation, stiffness, angular deformity, or limb length discrepancy (LLD) with more than 12 months' duration. Microorganism identification and antimicrobial susceptibility were performed on the BacT/ALERT® Microbial Detection System by the hospital microbiology laboratory.

SPSS Statistics® version 24 (IBM Corp, New York, NY, USA) was used to perform data analysis. An independent samples *t*-test or Mann–Whitney *U*-test was used to compare continuous variables, while a χ^2 test or Fisher exact test were used to compare categorial variables. $P < 0.05$ was considered statistically significant. The study was subject to our hospital Ethics Committee approval.

Results

Children under 3 months

Yearly distribution

Of the 263 children with OAI, 24 (9.1%) had OAI ≤ 3 M, with a twofold increase since 2014. The yearly distribution of cases is shown in Figure 1.

Patient characteristics

Most (54%) children with OAI ≤ 3 M were males, with a median age of 28 days (IQR: 13.5–60.0). Fifteen had a risk factor for OAI: cutaneous lesion in 8 (33.3%; all due to previous vascular access and one of them with a concomitant phlebitis); prematurity in 10 (41.7%); previous trauma in one (4.2%) or preceding respiratory tract infection in another (4.2%). Of the 10 premature infants (range 31–36 weeks of gestation, with a mean of 35 weeks), eight had HAIs. The other case of HAIs (nine in total) was a patient with aortic coarctation, who developed OAI after cardiac surgery.

Clinical manifestations

The median duration of symptoms to diagnosis was 2 days (IQR: 1–3). The most frequent findings were ROM (83.3%), local inflammatory signs (66.7%), pain (70.8%), pseudoparalysis (58.3%), irritability (58.3%), fever (tympanic ≥ 38.2°C) (50%), toxic appearance (29.7%), and poor feeding (25%). The diagnoses were SA (70.8%), AOM (62.5%), and eight patients (33%) had concurrent SA and AOM. The most common affected bones were the femur (7/15;46.7%), humerus (3/15;20%), tibia (2/15;13.3%), radius and clavicle (1/15; 6.7% each) and the most affected joints were knee (8/17;47%), hip (6/17;35.3%), shoulder (2/17;11.8%), and elbow (1/17;5.8%). Bone involvement affected the epiphysis in 26.7% (4/15). Two (8.3%) patients had multifocal involvement (one multidrug-resistant *Enterobacter cloacae* and one MRSA). A secondary diagnosis was present in 54.2% (67% were newborns): myositis (7), cellulitis (6), sepsis (3), and pneumonia (1). One premature baby, with nosocomial MRSA infection, had concomitant meningitis, endocarditis, and hepatic abscesses.

Plain radiography and ultrasound were performed in all patients: 22 (91.7%) had significant ultrasound alterations, 10 (41.7%) had radiographic alterations, 8 (33.3%) at diagnosis (periosteal reaction or increased interarticular space) and 7 (29.2%) at 2-4 weeks after admission (lytic lesions, avascular necrosis or subluxation). Magnetic resonance imaging was performed overall in 58.3% (10/15 AOM and 4/9 with isolated SA) and it detected concomitant arthritis in three additional infants.

Microbiology

Microbiologic causes were determined in 87.5%, all with positive cultures, with no difference before and after 2014. Blood cultures (peripheral or central catheter) were performed in 100% and 45.8% of them were positive, synovial fluid cultures in 62.5% with 86.7% positive results (with no difference after 2014) and bone culture in 25% of patients and 50% were positive. The identified bacteria were *S. aureus* (12/21; 57.1%), GBS (5/21; 23.8%), *Escherichia coli* (2/21; 9.5%), *Klebsiella aerogenes (1/21; 5.3%)*, and *Enterobacter cloacae* (1/21; 5.3%). Six (25%) were MDR, 83.3% (5/6) were MRSA, all in newborns, four of them were HAIs and one was simultaneously resistant to clindamycin, and one multidrug-resistant Gram-negative bacteria (*E. cloacae*), only sensitive to meropenem and amikacin. These MDR infections had longer length of stay (LOS) (median 43, range 28–88 vs. 18.5, 14–21 days, $P = 0.002$) and more sequelae at 12 months follow-up (50% vs

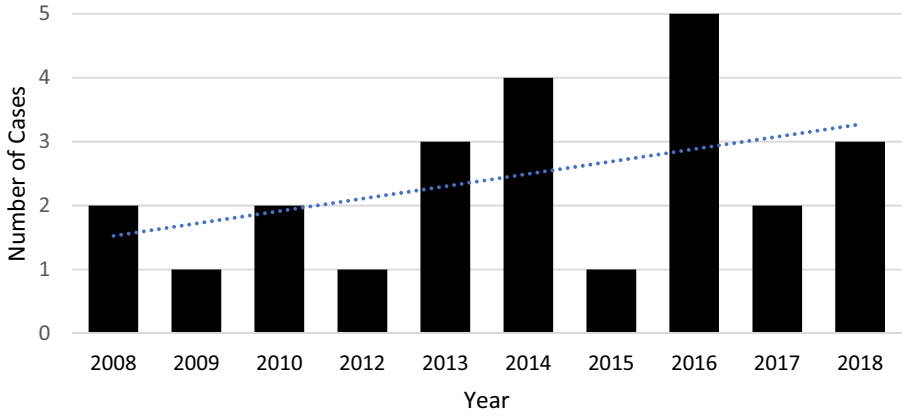

Fig. 1 Yearly distribution of the number of cases. Note the ascending trendline (dot line).

5.9%, $P = 0.04$). Seven patients (four with *S. aureus*) had persistent positive cultures (two blood cultures and five synovial fluid cultures), range 2–9 days after adequate antibiotic treatment.

Infants with *S. aureus* OAI ($N = 12$) had a known risk factor in 83.3% (10/12; 7 with vascular accesses), most had HAIs and were premature (7/12 respectively; 58.3%), and the majority had fever and bacteremia. Six (three MRSA) had complications and 2/11 patients (18.2%) had sequelae at 12 months' follow up.

All babies with OAI caused by GBS were delivered by vaginal birth, all but one were full-term newborns, with a median age of 26 days (IQR: 21.5–45) and only one had a positive screening for GBS, without adequate prophylaxis. All presented with pseudoparalysis, 80% had fever, and 40% bacteremia. Four (80%) had complications, mostly myositis (3/4) and subperiosteal abscesses (1/4) but none had sequelae.

Management

Empirical treatment included flucloxacillin (29.2%), third-generation cephalosporin (41.7%), or second-generation cephalosporin (25%), all with added gentamicin. Third-generation cephalosporin was mostly used in infants under 30 days of age (58.3%) and vancomycin was administered empirically in 16.7% (4/9 HAI cases). In 14.3% (3/21 cases) the isolated bacteria were resistant to the initial empirical treatment. The median IV and total antibiotic treatment duration is presented in Table 2. Seventeen (70.8%) were submitted to surgery, mainly joint drainage (14/17 SA, 82.3%) or bone drainage (4/15 AOM, 26.7%), due to intraosseous or subperiosteal abscesses, and only one (1/17, 5.9%) needed more than one intervention for persistent joint effusion/abscess. A switch to oral antibiotic was possible in 19 patients with flucloxacillin (29.9%), amoxicillin (20.8%) or cefuroxime (16.7%) based on antimicrobial susceptibility.

Complications and sequelae

Thirteen patients (54.2%) presented complications: four subperiosteal/intraosseous abscess, seven myositis, one femoral avascular necrosis, one pathological fracture of the femoral bone and two luxation of knee and hip joints. Only four (16.7%) needed pediatric intensive care unit (PICU) admission.

At discharge, five (20.8%) had residual symptoms, specifically limited ROM. One patient was lost to follow up. At 12-months' follow up 4/23 (17.4%) patients presented with sequelae, all observed for at least 2 years, two of them clinical (LLD and angular deformity) and all of them radiological (three asymmetrical centers of ossification and two deformities).

Comparing OAI ≤ 3 M with or without complications and sequelae, concomitant AOM (92.3% vs 27.3%, $P = 0.02$) was associated with complications and bacteremia (100% vs 36.8%, $P = 0.037$; OR: 15, range 0.7–319) and MDR (75% vs 16, $P = 0.04$) and HAIs (100% vs 26.3%, $P = 0.014$, OR: 23.7, range 1.1–517) were associated with sequelae at 12 months follow up.

Comparison of OAI ≤ 3 M with older children

Comparisons of OAI ≤ 3 M with children above 3 months are shown in Tables 1 and 2. Children with OAI ≤ 3 M more often had previous vascular accesses (33.3% vs 0%, $P = 0.000$), bone involvement, and other associated diagnoses, mainly myositis, cellulitis, and sepsis. Younger infants more often had irritability, septic appearance (29.1% vs 6.3%, $P < 0.001$) and radiographic alterations (37.5% vs 16.3%, $P = 0.005$). Bacteremia, a higher rate of pathogen identification, and *S. aureus* infection were also more common. Although they were treated with longer IV and total antibiotic courses, complications were more frequent, as were sequelae (Table 2).

Discussion

The present study, although single centered, involves a sizeable cohort, and describes aetiology and management of OAI among infants under 3 months old in Lisbon, comparing them

Table 1 Clinical and laboratory presentation of OAI according to age (≤3 M vs >3 M)

	≤3 M (n = 24)	>3 M (n = 239)	P
Male gender, *n* (%)	13 (54.2)	139 (58.2)	0.7
Duration symptoms at presentation, days, median (IQ)	2 (1–3)	3.5 (2–7)	0.054
Identified risk factor, *n* (%)	15 (62.5)	116 (48.5)	0.36
Fever on presentation, *n* (%)	12 (50)	149 (62.3)	0.419
Irritability, *n (%)*	14(58.3)	28 (11.7)	<0.001
Leucocytes peak > 15 000, *n* (%)	11 (45.8)	75 (31.4)	0.3
Platelets > 450 000, *n* (%)	20 (83.3)	59 (24.7)	<0.001
CRP† peak > 20 mg/L, *n* (%)	17 (70.8)	185 (77.4)	0.27
ESR‡ peak >20 mm/h, *n* (%)	18 (75)	217 (90.8)	0.059
Osteomyelitis, *n* (%)	15 (62.5)	78 (32.6)	0.004
Septic arthritis, *n* (%)	17 (70.8)	195 (81.6)	0.2
Concurrent septic arthritis and osteomyelitis, *n* (%)	8 (33.3)	34 (14.2)	0.015
Other diagnosis, *n* (%)	13 (54.1)	52 (21.8)	<0.001

†CRP-C-reactive protein; ‡ESR- eritrocyte sedimentation rate.

Table 2 Microbiology and outcomes OAI* according to age (≤3 M vs >3 M)

	≤3 M (n = 24)	**>3 M** (n = 239)	P
Bacteremia, *n* (%)	11 (45.8)	37(14.9)	0.001
Pathogen positive infection, *n* (%)	21 (87.5)	89 (37.2)	<0.001
Staphylococcus aureus, *n* (%)	12 (50)	32 (13.4)	<0.001
Days IV§ antibiotic, median (IQ)	21 (15–28)	10 (7–15)	<0.001
Days total antibiotic, median (IQ)	37.5 (30.5–44.3)	26 (21–35)	0.003
Hospital stay, days, median (IQ)	22 (16–32.3)	10 (8–16)	0.07
Surgical procedures, *n* (%)	17 (70.8)	180 (75.3)	0.63
ICU admission, *n* (%)	4 (13.6)	6 (2.5)	0.001
Complications, *n* (%)	9 (37.5)	47 (19.7)	0.042
Sequelae 12 M FU††, *n* (%)	4/23 (17.4)	7/221 (3.2)	0.002

*OAI, osteoarticular infections; §IV- intravenous; ††FU, follow up.

with older children. During the 11-year study period, the proportion of OAI ≤ 3 M was 9.1%, which is higher than reported in the literature (0.02%–1.4%).[1,4–7,11] This may be due to the fact that our hospital is a referral center for high-risk young infants and neonates needing surgical management. As previously reported in older children in our center,[14,15] the incidence of OAI ≤ 3 M has increased twofold after 2014. It seems reasonable to assume that prospective enrolment but also better acknowledgement of the condition and improved imaging, might have contributed to this trend. Furthermore, several authors have reported a rising incidence of OAI in Europe in children.[16,17]

The rate of microbiological isolation was 87.5%, much higher than in older children (37.2%) and even higher than reported by others (29.8–85.7%).[1,4,5,7] The improved microbiologic diagnosis in recent years,[9,18] by upgraded laboratory automatized systems, probably account for this difference. Although direct inoculation of synovial fluid into blood bottle vials seems to improve bacterial isolation,[19] this was not the case in OAI ≤ 3 M. Indeed, after 2014 (when all synovial samples were sent into blood bottle vials) the rate of synovial isolation was similar in infants under 3 months. It is probable that *Kingella kingae*, a bacterium that is common only between the ages of 6 to 48 months, might account for this difference,[14] with the typical pathogens in younger children isolated equally by both methods.

According to the literature, the most commonly isolated pathogen was *S. aureus,* ranging from 22% to 76.6%,[1,7,17] which accounted for 57% of pathogens in our cohort, of which five (41.7%) were MRSA. Indeed, *S. aureus* is an important cause of bacteremia in this age group, with known bone and joint tropism. The presence of *S. aureus* in the blood should prompt a consideration of OAI in infants under 3 months, even without significant localizing symptoms. The high rate of HAIs in our OAI ≤ 3 M (37.5%; with 77.8% caused by *S. aureus*), which is similar to other series (15.5% to 64%),[1,4] can also explain the predominance of *S. aureus*. Furthermore, *S. aureus* was implicated in all patients admitted to the ICU, and most (85.7%) infants with previous vascular catheters.

GBS and Gram-negative organisms such as *E. coli* are more common in neonates and young infants, and in one series accounted for 60% of OAI before 3 months of age.[20] Mediamole *et al.*[1] also reported an increase in GBS isolation, this being the predominant pathogen in their study. However, in our study GBS was the second most frequent agent (23.8%), similar to other series.[5,7,8] Although GBS is the most common cause of early onset neonatal sepsis, in our study all GBS OAI were late-onset infections, with a median age of onset at 26 days of life (range 19–60 days), similar to other studies.[1] The recommended maternal intrapartum antibiotic prophylaxis probably explains the significantly decrease in early onset infections; however, with no impact on late-onset disease.[21] Multidrug resistant bacteria were present in 25% of our OAI ≤ 3 M cases, mostly MRSA. These MDR infections are becoming more prevalent and are associated with longer LOS and worse outcomes,[22] as occurred in our OAI ≤ 3 M infants.

Although the European Society for Pediatric Infectious Diseases proposes shorter treatment courses in older children,

they still suggest longer 2–3 weeks IV, and total 4–6-weeks antibiotic regimens for high-risk younger infants, although some suggest early oral switching, especially after the neonatal period.[10,19,23] We had a median of 21 days IV treatment, similar to Berberian *et al*.,[4] but shorter total courses, when compared with other series (36.5–45 days),[1,4] without worsening the sequelae rate. However, most of these studies were from the early 2000s or 1990s, when treatment durations were longer.

In major joint SA, joint drainage is the rule, justifying the high surgical intervention rate (70.8%).[1,4,9,24] For AOM, the role of surgery remains controversial, although a conservative approach is usually advised in older children.[9,23,25] However, in infants under 3 months the cortical bone is weak and soft, and the periosteum is loose, which facilitates the development of abscesses and concomitant limb swelling.[7] Indeed, 4/15 (26.5%) cases of AOM were submitted to bone drainage due to intra or subperiosteal abscesses. Furthermore, in two preterm babies with bone sequelae (both MRSA), the diagnosis of bone involvement was made by radiograph alone, it being probable that bone abscesses could be present if MRI was used. We cannot predict if the prognosis would have been better if bone drainage was undertaken in these cases. Probably, in infants under 3 months, the development of complications, such as bone abscesses, should lower the threshold for intervention.

Sequelae at 12-months follow up (17.4%) were higher in infants under 3 months in agreement with the literature (5.6–38%).[1,4,5,11] However, only one was severe (femoral head deformity and dislocation). Predictors of poor outcome usually include hip and shoulder involvement, concomitant osteomyelitis, bacteremia and *S. aureus* infection, mostly MRSA.[18,26–28] In our series, bacteremia, HAIs and symptoms at discharge were all associated with sequelae. Moreover, although not statistically significant, three of the four patients with sequelae had femoral bone osteomyelitis, two with concomitant hip arthritis.

Our study had some limitations such as the fact that it was a partial retrospective, single-center study, and the small sample size for OAI ≤ 3 M.

Conclusions

Saureus was the most frequent pathogen of OAI ≤ 3 M, with MDR bacteria implicated in 25% of cases. Our study confirmed that children under 3 months have more severe infections, with more frequent complications and sequelae, and those sequelae were associated with bacteremia, MDR, and HAIs.

Disclosure

The authors declare no conflict of interest.

Author contributions

J.B., M.D., and C.G. collected and analyzed the data. J.B., M.D., and C.G. performed the statistical analysis. J.B., M.D., and C.G. wrote the manuscript and S.N., J.A., P.A., M.B., D.T., and C.G. reviewed the manuscript. All authors have read and approved the final manuscript.

References

1 Mediamolle N, Mallet C, Aupiais C *et al*. Bone and joint infections in infants under three months of age. *Acta Paediatr.* 2018; **108**: 933–9.
2 Arnold JC, Bradley JS. Osteoarticular infections in children. *Infect. Dis. Clin. North Am.* 2015; **29**: 557–74.
3 Krogstad P. Osteomyelitis. In: Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ (eds). *Feigin and Cherry's Textbook of Pediatric Infectious Diseases*. 8th edn. Elsevier Inc, Philadelphia, PA, 2019; 516–29. e5.
4 Berberian G, Firpo V, Soto A *et al*. Osteoarthritis in the neonate: Risk factors and outcome. *Braz. J. Infect. Dis.* 2010; **14**: 413–8.
5 Frederiksen B, Christiansen P, Knudsen FU. Acute osteomyelitis and septic arthritis in the neonate, risk factors and outcome. *Eur. J. Pediatr.* 1993; **152**: 577–80.
6 Narang A, Mukhopadhyay K, Kumar P, Bhakoo ON. Bone and joint infection in neonates. *Indian J. Pediatr.* 1998; **65**: 461–4.
7 Wong M, Isaacs D, Howman-Giles R, Uren R. Clinical and diagnostic features of osteomyelitis occurring in the first three months of life. *Pediatr. Infect. Dis. J.* 1995; **14** (12): 1047–53.
8 Dessì A, Crisafulli M, Accossu S *et al*. Osteo-articular infections in newborns: Diagnosis and treatment. *J. Chemother.* 2008; **20**: 542–50.
9 Saavedra-Lozano J, Falup-Pecurariu O, Faust SN *et al*. Bone and Joint Infections. *Pediatr. Infect. Dis. J.* 2017; **36**: 788–99.
10 Faust SN, Clark J, Pallett A, Clarke NMP. Managing bone and joint infection in children. *Arch. Dis. Child.* 2012; **97**: 545–53.
11 Kabak S, Halici M, Akcakus M, Cetin N, Narin N. Septic arthritis in patients followed-up in neonatal intensive care unit. *Pediatr. Int.* 2002; **44**: 652–7.
12 Friedman ND, Kaye KS, Stout JE *et al*. Health care–associated bloodstream infections in adults: A reason to change the accepted definition of community-acquired infections. *Ann. Intern. Med.* 2002; **137**: 791–7.
13 Magiorakos A-P, Srinivasan A, Carey RB *et al*. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance Background Emergence of resistance to multiple antimicrobial agents in pathogenic bac. *Clin. Microbiol. Infect.* 2012; **18**: 268–81.
14 Gouveia C, Duarte M, Norte S *et al*. Kingella kingae displaced *S. aureus* as the most common cause of acute septic arthritis in children of all ages. *Pediatr. Infect. Dis. J.* 2021; **40**: 623–7.
15 Gouveia C, Branco J, Norte S *et al*. Acute haematogenous osteomyelitis in Lisbon: an unexpectedly high association with myositis and arthritis. *An. de Pediatr.* (English Edition). 2022; **96**: 106–114.
16 Samara E, Spyropoulou V, Tabard-Fougère A *et al*. Kingella kingae and osteoarticular infections. *Pediatrics* 2019; **144**: e20191509.
17 Bréhin C, Claudet I, Dubois D *et al*. Assessing the management of pediatric bone and joint infections according to French guidelines. *Med. Mal. Infect.* 2020; **50**: 515–9.
18 Branson J, Vallejo JG, Flores AR *et al*. The contemporary microbiology and rates of concomitant osteomyelitis in acute septic arthritis. *Pediatr. Infect. Dis. J.* 2017; **36**: 267–73.

19 Saavedra-Lozano J, Falup-Pecurariu O, Faust SN *et al*. Bone and joint infections. *Pediatr. Infect. Dis. J.* 2017; **36**: 788–99.
20 Offiah AC. Acute osteomyelitis, septic arthritis and discitis: Differences between neonates and older children. *Eur. J. Radiol.* 2006; **60**: 221–32.
21 Jordan HT, Farley MM, Craig A *et al*. Revisiting the need for vaccine prevention of late-onset neonatal group b streptococcal disease. *Pediatr. Infect. Dis. J.* 2008; **27** (12): 1057–64.
22 Flokas ME, Karanika S, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in pediatric bloodstream infections. A systematic review and meta-analysis. Simeoni U, Ed. *PLoS One* 2017; **12**: e0171216.
23 Peltola H, Pääkkönen M. Acute osteomyelitis in children. *N. Engl. J. Med.* 2014; **370**: 352–60.
24 le Saux N. Diagnosis and management of acute osteoarticular infections in children. *Paediatr. Child Health* 2018; **23**: 336–43.
25 McNeil JC, Kaplan SL, Vallejo JG. The influence of the route of antibiotic administration, methicillin susceptibility, vancomycin duration and serum trough concentration on outcomes of pediatric *Staphylococcus aureus* bacteremic osteoarticular infection. *Pediatr. Infect. Dis. J.* 2017; **36**: 572–7.
26 Calvo C, Núñez E, Camacho M *et al*. Epidemiology and management of acute, uncomplicated septic arthritis and osteomyelitis. *Pediatr. Infect. Dis. J.* 2016; **35** (12): 1288–93.
27 Liu C, Bayer A, Cosgrove SE *et al*. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin. Infect. Dis.* 2011; **52**: 208–11.
28 Saavedra-Lozano J, Mejías A, Ahmad N *et al*. Changing trends in acute osteomyelitis in children: Impact of methicillin-resistant *Staphylococcus aureus* infections. *J. Pediatr. Orthop.* 2008; **28**: 569–75.