Chapter 7

Neonatal Osteomyelitis

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Abstract

Osteomyelitis in neonates is relatively uncommon, but burdened with an increased hospital stay and possible long-term sequelae if not diagnosed on time. It differs from that of older children for etiology, clinical and radiological findings, and treatment. Due to anatomic contiguity, osteomyelitis may coexist with septic arthritis. Soft-tissue swelling or joint effusion is often associated. Our aim is to review the literature to provide the most recent data related to epidemiology, clinical presentation, diagnosis, treatment, and outcome.

Keywords: neonatal osteomyelitis, septic arthritis, antibiotics, imaging studies, micro-organisms

1. Introduction

Osteomyelitis (OM) refers to an infection of the bone that affects around 8/100,000 children [1]. For neonatal OM, an estimated incidence of 1–7/1000 hospital admissions has been reported [2, 3]. Due to their immature immune response, neonates are more susceptible than older children. Preterm infants are at a higher risk because of frequent blood withdrawal, invasive monitoring, diagnostic and treatment procedures, parent's nutrition, ventilatory support, perinatal hypoxia and prolonged NICU stay [4–7]. The long bones are the most frequently affected sites, especially of lower extremities, femur and tibia. Sites less commonly involved include the upper limbs, the pelvis, the clavicle, and the rib [8]. The presence of interosseous collateral arteries makes vertebral bodies less susceptible to infarction from septic emboli and more able to clear bacteria secondary to septic embolization. This explains the low incidence of vertebral body infection in neonates compared to older children and adults [9]. Few studies have focused on race differences. In low-risk neonates with OM, an accompanying

fracture should be considered [10]. Sternal OM is extremely rare, but has been reported [11]. Neonates are most vulnerable to multifocal infection [12, 13]. **Pathophysiology.** Osteomyelitis in neonates is usually due to hematogenous spread of bacterial infections or less frequently to direct inoculation as a result of a trauma or puncture wounds or surgery, infected cephalohematoma [14–16]. In preterm infants, direct injection of bacteria can result from heel or venipuncture and artery or vein umbilical catheterization. Indirect contamination from a nearby infection, for example, cellulitis is also possible. Premature rupture of membranes, transplacental infection, and urinary tract infections has been described as risk factors too [17, 18]. A few cases of neonatal Gram-negative germ osteoarthritis have been reported, associated with a vesico-ureteral reflux (VUR) or hydronephrosis by the same microorganism [19, 20]. The most susceptible areas to haematogenous seeding of infection are metaphyseal of long bones, in particular the areas adjacent to the cartilaginous growth plate (physis) that is highly vascularized with slow intravascular flow. Abscess can result from the passage of bacteria through gaps from the sinusoidal veins to the capillaries into the tissue, where they are provided an ideal environment to grow. These abscesses frequently rupture into the joint [21]. Acute haematogenous OM and septic arthritis of the adjacent joint coexist in up to 76% of all cases as a result of a unique vascular anatomy characterized by the presence of vascular connections between the metaphysis and the epiphysis, particularly before the appearance of a secondary ossification center. Involvement of the shoulder or hip joints is noted when the intracapsular metaphyseal end of the humerus or femoral are involved from infection.

2. Symptoms

Asymmetric movement of extremities, irritability and poor feeding may be often the early and unspecific findings of OM [9, 22]. Common symptoms include bone pain, swelling, redness, guarding and failure to move the affected body part (pseudoparalysis). Fever may or may not be present because of an immature immune system. It is important to ascertain joint involvement through the detection of pseudoparalysis and pain during passive movements and signs of local inflammation [22]. Dierig et al. [23] reported a newborn with combined OM and suppurative arthritis caused by *Streptococcus pyogenes* giving rise to right brachial plexus palsy. Acute haematogenous OM is usually defined acute if the signs or symptoms are present for less than 14 days, and subacute if signs or symptoms are present for more than 14 days. In neonates, acute forms predominate [1].

3. Causative microorganisms

The causative agents of OM reflect those of neonatal sepsis, which vary from country to country and in many cases remain unknown. The most common pathogen is *Staphylococcus aureus*, found in 70–90% of culture positive cases [24, 25]. Other pathogens include *Streptococcus* mainly group B (*Streptococcus agalactiae*) and Gram-negative enteric bacteria (*Escherichia coli and Klebsiella pneumoni*a) *Pseudomonas aeruginosa* [26, 27]. Multi-drug resistant *S. aureus*

(MRSA), community-acquired strains of methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and *Kingella kingae* have emerged as being relevant in recent years and are responsible for serious infections [28]. *Candida albicans* OM needs to be considered in neonates, especially if preterms with specific risk factors. The presentation is more subtle and subacute, even in the absence of fever and elevated inflammatory markers. The progression is prolonged. OM from *Haemophilus influenzae* type b (Hib) has declined significantly; thanks to the introduction of the Hib vaccine.

4. Differential diagnoses

Differential diagnosis may be difficult and cellulitis, septic arthritis, subcutaneous abscess, fractures, and bone tumors should be taken into account. CNS disease (cerebral hemorrhage), trauma, scurvy, and child abuse are to be considered in the case of pseudoparalysis. Allagui et al. [29] described a case of acute OM of the clavicle in a 30-day-old newborn, with clinical symptoms simulating obstetric brachial plexus palsy. Laboratory tests are necessary to confirm a clinical diagnosis of OM. Neonates with OM may have a normal leukocyte count that is elevated in only half of the patients with or without thrombocytosis. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are almost always elevated (except in small bone infections). It is important to obtain blood, bone, or joint aspirate cultures if necessary, to identify the causative organism, before any antibiotics are given. Because OM usually is a consequence of sepsis, hence lumbar puncture should be considered. Any potential source of infection should be examined, including intravascular catheter tips. Serum procalcitonin may be used as a sensitive and specific marker in the diagnosis of acute OM [30] more suitable as an aid for rule-in diagnosis rather than for exclusion. Its diagnostic performance is better for a lower cut-off value compared to a conventional cut-off of 0.5 ng/ml which is specific but less sensitive [31]. A bone biopsy is advisable if the patient does not respond to the standard therapy.

5. Imaging studies

Imaging (computed tomography (CT) scan, radiography, bone scan, US and/or MRI) is used to identify the site of an infection, the presence of liquid collections for diagnostic aspiration and/or biopsy, to differentiate a unifocal from multifocal disease and to identify present or impending complications, such as joint or extradural involvement. Montgomery et al. [32] showed that the use of advanced imaging (CT scan, bone scan, and/or MRI) in infants younger than 4 months of age may shorten hospital stays, decrease the number of operative procedures required, and possibly limit infection-related sequelae. MRI has become the gold standard to evaluate musculoskeletal infection. It has the capability of assessing the osseous, articular and muscular structures simultaneously and does not require ionizing radiation. In particular MRI plays an important role in defining the extent of soft tissue involvement, defining drainable fluid collections and bone biopsy sites pre-operatively and thereby decreasing

the need for repeating the surgery. Increased marrow intensity with surrounding inflammation are the most suggestive signs of OM. MRI of the spine is useful in children not responding to therapy and/or to detect complications, such as extradural and paraspinal collections that will require surgical treatment because of causing spinal cord compression. The enhanced uptake of the radioisotope, distinguishes OM from deep cellulitis Gadolinium-enhanced fat-saturated T1-weighted sequences increase the confidence of the diagnosis of OM and may help also to distinguish edema from an abscess [33] and allows one to see the isolated involvement of the epiphyseal growth cartilage that is occult on radiographs and bone scintigraphy because of the paucity of growth cartilage ossification. The finding of hypo-enhancing foci in the growth cartilage suggests cartilage ischemia, necrosis or abscess as a consequence of infectious chondritis or septic thrombosis [34]. MRI may not be appropriate for monitoring the evolution of the lesions. Technetium bone scanning has a false-negative rate of as much as 20%, particularly in the first few days of illness. Indium-labeled leukocytes have limitations in newborns. Gallium scanning is not recommended because of lower specificity and exposure to higher levels of radiation. Ultrasonography: Although ultrasonography is an operator dependant technique with an inability to differentiate infectious fluid from traumatic ones, in able hands, it allows the detection of changes of acute OM as early as 48 h after the onset of infection. In the early stages ultrasound document deep soft tissue swelling (1–3 d), then the elevation of the periosteum by a thin layer of fluid, a definite subperiosteal collection, joint effusion and finally cortical erosion (2–4 w). In this last case it is used to guide needle drainage aspiration if necessary. Ultrasound images normalize by 4 weeks in the case of response to treatment [35]. Doppler venous ultrasonography is the first imaging study indicated in the case of clinical suspicion for deep vein thrombosis in patients with OM caused by CA-MRSA. A normal ultrasound scan does not exclude OM. Radiography is usually the first radiological investigation in a neonate with suspected OM, although it is reported that only 20% of the radiographs are abnormal at 10–14 days [36, 37]. Despite the low prevalence of abnormal features at presentation, it allows the exclusion of fractures and is useful to show long-term follow-up of complications. Initially it may reveal normal results, after 10–15 days signs of bone destruction, osteopenia, lytic lesions, and periosteal changes. Metaphyseal irregularities and periostitis (both non-specific) may be documented [37]. It has low sensitivity toward detection of a joint effusion or deep soft tissue swelling; the diagnosis of suspicion may include widening of the joint space with or without subluxation and soft tissues protruding that can be detected as early as 48 h after the onset of infection. Radiography may detect bone destruction when at least one-third of the matrix has been involved. Findings related to the spine may be limited to a loss of the normal lumbar lordosis, disc space narrowing, end plate erosions, pressure erosion of the superior and inferior margins of the adjacent vertebral body if the infection prolonged. Normally, other imaging tests are required. A bone scan is reserved for the cases in which radiographs and/or ultrasound are unclear, for suspected multifocal infection, chronic multifocal OM, and discitis. Bone scintigraphy is highly sensitive to the detection of OM in the early stages of the disease. In the first week of the disease, technetium (99mTc)-labeled bone scans revealed positive in 87% of the cases as compared with 42% diagnosed with radiography. Scintigraphy is useful for detecting multifocal diseases that are more common in neonates. A 99mTc-labeled phosphonate complex is the most used isotope. Scintigraphic study, even if non-specific, is useful to document through increased uptake of

all three phases: perfusion, blood pool activity and bone metabolism. Cold spots occur as a result of decreased blood flow secondary to edema and subperiosteal or articular infection. It may be a discriminating diagnosis in secondary bone infection in the case of persisting coagulase negative staphylococcus (CONS) bacteremia [38]. Computed tomography (CT) scan use is limited in the neonate. It is superior to MRI in chronic OM with cortical destruction, air and sequestra. It may also be used to guide aspiration and biopsy, especially when the spine and paraspinal soft tissues are involved [9].

6. Procedures

If signs and symptoms do not begin to resolve within 48–72 h of initiation of appropriate antimicrobial treatment, bone aspiration may be necessary to identify the pathogen and to drain the pus in accordance with the orthopedic surgeon. Bone and/or joint fluid aspirate for culture, can be bactericidal. Bone biopsy is necessary in the suspicion of tumors.

7. Management

It is a necessary antibiotic treatment, as soon as possible, in order to prevent the potentially adverse anatomic and functional consequences, preferably after obtaining blood and bone aspirates for culture. As cultures may be negative or difficult to obtain, empirical treatment is based on the local prevalence of organisms, resistance patterns taking account of the change over the years of the spectrum of organisms causing OM. The choice of an agent is generally either a penicillinase-resistant penicillin (e.g. nafcillin, oxacillin, flucloxacillin), which will be effective against S. aureus but may be of limited value against other organisms, or a broad-spectrum cephalosporin, which could have reduced the activity against *S. aureus.* Antibiotics against methicillin-sensitive *S. aureus* (MRSA) and streptococci (a penicillinase-resistant penicillin, first generation cephalosporin or clindamycin) must be incorporated into any empiric regimen for OM because *S. aureus*, *group A Streptococci* and group B streptococcus (GBS) and *S. pneuomoniae* together account for more than 90% of the cases of osteoarthritis in neonates [39]. Immunization rates worldwide have obviated the need to use antibiotics against Hib in many countries. Cefuroxime, a second-generation cephalosporin can be used as a single agent against both methicillin-sensitive *S. aureus* (MSSA) and Hib, if they are the suspected pathogens. The increasing incidence of penicillin-resistant S pneumoniae warrants the use of a clindamycin and cefotaxime/ceftriaxone combination. When treating neonatal OM, consider nafcillin and tobramycin or vancomycin and gentamicin combinations to provide coverage of bacteria from the Enterobacteriaceae family, in addition to group B streptococci and *S. aureus*. Vancomycin is preferred for proven or suspected MRSA-related septicaemia or known multi-drug resistant MRSA infection. The suspicion of enteric organisms justify additional therapy with an aminoglycoside, such as gentamicin, tobramycin or amikacin or an extended-spectrum, a Pseudomonas-active agent, such as cefepime [40]. In the case of acquired MRSA infections should be started vancomycin, rather than a penicillin antibiotic [5]. Daptomycin, Linezolid, and Quinupristin-dalfopristin have not been fully

evaluated or approved for use in neonates and should be employed when the neonate cannot tolerate vancomycin [40]. If B streptococcical infection is confirmed, combination therapy with penicillin G (or ampicillin) and gentamicin should be given for 2–5 days, after which time penicillin G (or ampicillin) alone is adequate. Monitoring serum acute-phase proteins, particularly the C-reactive protein, has been proposed as a useful way to determine resolution of infection and duration of therapy [40]. Management of *C. albicans* OM requires prolonged antifungal therapy. Society of America practices guidelines, including surgical debridement in selected cases and fluconazole therapy for 6–12 months, intravenous initially and then orally [26]. Amphotericin B is the most commonly used antifungal therapy. They are not provided clear guidelines on the optimum duration of treatment to eradicate infection. Even if by many are advocated shortened courses of antibiotic therapy because of morbidity and cost implications related to the prolonged therapy, the recommended entire duration of treatment still consists of at least 4–6 weeks until normalization of the C-reactive protein level [41]. Moreover it is typically recommended that infants under 3 months are given the full course of antibiotics parentally due to concerns over absorption and efficacy of oral antibiotics and to ensure adequate serum levels of the antibiotic. Recently some studies reported about oral therapy after a few days of intravenous therapy. Jagodzinski et al. [42] treated 70 children with intravenous therapy, converted after 3 (59%) or 5 (86%) days and continued for three weeks using temperature and C-reactive protein as parameters to response to therapy. The use of third-generation cephalosporins alone to treat OM is not recommended because they are not optimal for treating serious *S. aureus* infections. An earlier study by Vinod et al. [43] suggested that a reduced course of antibiotic therapy could be effective in the treatment of acute OM. Ecury-Goossen et al. [44] resolved clinical symptoms, microbiologic, and radiologic signs by using a short course of two weeks of intravenous antibiotics followed by 4 weeks of oral clindamycin, in selected preterm neonates with OM. The signs of continuing infection are persisting pain, fever, and rising hematologic markers that need prolonged antibiotics and repeated surgical intervention. While in children >3 months an early transition from intravenous to oral therapy (3–4 days) is suggested and a total course of 3 weeks in the treatment of acute OM, there are insufficient data on neonates to alter the current recommendation that a full course of at least 4 weeks of antibiotics be given parentally for neonatal OM due to concerns over absorption and efficacy of oral antibiotics [5]. Intraarticular administration of antibiotic is unnecessary. Some authors reported about successful treatment of newborns with oral dicloxacillin [45–47] fluclocacillin, fusidic acid and penicillin V for an additional period ranging from 14 to 42 days after an initial course of intravenous therapy. Despite everything, large, randomized controlled trials are needed to clarify the best practice in treating acute OM in children. It is important underline that OM and septic arthritis have a potential for life-long disability if treated insufficiently. Vertebral OM of the upper cervical spine requiring surgical treatment in children is rare. Glotzbecker et al. [48] described a surgery of stabilization of the upper cervical spine due to progressive instability caused by OM.

8. Consultations

The involvement of a multidisciplinary team of pediatricians, orthopaedists, and infectious disease specialists is helpful in the management of OM and results in a more efficient

diagnostic workup, and improved adherence to recommendations. An orthopedic and an intervention radiologist would be very helpful in determining the surgery for diagnosis and treatment and to obtain a bone biopsy under fluoroscopic guidance. The involvement of physiotherapists allows individualized rehabilitation programs, designed to improve the anatomical and functional characteristics of the affected bones. A prompt approach to obtaining tissue and blood specimens for the culture led to a higher rate of organism identification. Additionally a multidisciplinary team led to a shorter total length of hospital stay and a lower hospital readmission rate [3].

9. Prognosis and outcome

Considerable morbidity may be associated with neonatal OM. Joint effusion may lead to subluxation or dislocation of the affected joint, accumulation of inflammatory exudate within the joint causes vascular compression and may result in avascular necrosis of the affected epiphysis. Vein thrombosis and fractures are recently reported. Osteomyelitis may become responsible for permanent sequelae in 6–50% like joint disabilities, change in bone growth due to the damage of the cartilaginous growth plate, limb length discrepancies, arthritis, pathologic fractures, and rarely complete destruction of joints. Multiple risk factors are associated with bad outcomes in the long run. A delay in diagnosis and treatment can result in complications that include: damage to the growth plate with premature and/or asymmetrical closure of the growth plate; avascular necrosis of the femoral head with or without complete dissolution of the femoral head and neck; pseudoarthrosis; limb length discrepancies, angular deformities at joints; joint dislocations; joint arthrodesis; vertebra magna (with narrowing of the spinal canal); and block vertebrae. Other factors are: late in surgical drainage and appropriate antibiotic coverage, involvement of hip or shoulder, culture positivity and *S. aureus* isolation [3]. It has been documented that as many as 40% of children with septic arthritis of the hip will develop a serious complication, and a long-term follow-up is mandatory. Especially for concomitant septic arthritis and OM, the final outcome may be not evident until 9–10 years of age. Copley et al. [49] proposed criteria for discharge based on having a CRP < 2 mg/dL prior to discharge along with clinical improvement, resolution of fever, and having two sets of negative blood cultures for at least 48 h following any initial findings of bacteremia. Given the reported peripheral inserted central catheter complications (adverse drug reaction, a return emergency department visit or rehospitalization for adverse outcome), it should be considered the practice of oral antibiotic therapy instead of prolonged intravenous antibiotics after hospital discharge [50].

10. Conclusions

Acute OM, although rare in neonates, is a condition associated with morbidity and possible functional sequelae that need a prompt diagnosis and treatment. The implementation of evidence-based, clinical practice guidelines, a lower rate of initial bone scans, a faster change to oral antibiotics, a lower rate of presumptive drainage, and a shorter length of hospital stay are challenging objectives [51].

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