American Journal of Emergency Medicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Pediatric acute osteomyelitis in the postvaccine, methicillin-resistant *Staphylococcus aureus* era☆

Kristin Ratnayake, MD [a], Andrew J. Davis, MD [b], Lance Brown, MD, MPH [b], Timothy P. Young, MD [b,*]

[a] Division of Pediatric Emergency Medicine, Department of Pediatrics, Rady Children's Hospital, San Diego, CA
[b] Division of Pediatric Emergency Medicine, Department of Emergency Medicine, Loma Linda University Medical Center and Children's Hospital, Loma Linda, CA

ARTICLE INFO

Article history:
Received 26 February 2015
Received in revised form 6 July 2015
Accepted 6 July 2015
Available online xxxx

ABSTRACT

Objective: We sought to describe the causative organisms, bones involved, and complications in cases of pediatric osteomyelitis in the postvaccine age and in the era of increasing infection with community-associated methicillin-resistant *Staphylococcus aureus* (MRSA).
Methods: We reviewed the medical records of children 12 years and younger presenting to our pediatric emergency department between January 1, 2003, and December 31, 2012, with the diagnosis of osteomyelitis. We reviewed operative cultures, blood cultures, and imaging studies. We identified causative organisms, bone(s) involved, time to therapeutic antibiotic treatment, and local and hematogenous complications.
Results: The most common organism identified was methicillin-sensitive *S aureus* (26/55), followed by MRSA (21/55). Seventy-three bone areas were affected in 67 subjects. The most common bone area was the femur (24/73). Forty-six subjects had 75 local complications. The most common organism in cases with local complications was MRSA (49%). Three subjects had hematogenous complications of deep venous thrombosis, septic pulmonary embolus, and endophthalmitis. Subjects with complications had shorter time to therapeutic antibiotic treatment. When an operative culture was done after therapeutic antibiotics were given, an organism was identified from the operative culture in 84% of cases.
Conclusion: Treatment of pediatric osteomyelitis should include antibiotic coverage for MRSA. Most cases of pediatric osteomyelitis occur in the long bones. Hematogenous complications may include deep venous thrombosis and may be related to treatment with a central venous catheter. Operative culture yield when antibiotics have already been given is high, and antibiotic treatment should not be delayed until operative cultures are obtained.
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1. Introduction

Pediatric hematogenous osteomyelitis typically has a prolonged treatment course involving multiple specialties. Emergency physicians may treat children with osteomyelitis at various stages in the illness, including at diagnosis, at recurrence of disease, and when complications of the disease or its treatment arise. Historically, the long bones have been the major bones affected in pediatric osteomyelitis, and *Staphylococcus aureus* has been the most common causative organism, responsible for 66% to 70% of cases [1,2]. *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* have also been reported as causative agents [2–6].

Recently, increasing numbers of children with invasive infection caused by community-associated methicillin-resistant *S aureus* (MRSA) have been reported [7]. In the United States, rates of osteomyelitis caused by MRSA increased in children's hospitals during the first decade of this century, whereas those caused by methicillin-sensitive *S aureus* (MSSA) remained constant [8]. Children with osteomyelitis caused by MRSA experience more severe illness than do their MSSA counterparts, with greater need for procedures and longer hospitalizations [4,9]. Complications recently attributed to MRSA osteomyelitis include deep venous thrombosis (DVT), as well as problems at sites distant to the primary infection such as endocarditis and septic pulmonary emboli [5,10–12].

It is possible that changes in bacteriology have affected the distribution of site of infection in osteomyelitis. Prior to the era of MRSA, Craigen and colleagues [3] in the United Kingdom found that long bone infection (femur and tibia-fibula) was most common, but saw a decrease in long bone infection rate mirroring a decrease in *S aureus* infection. Infection rates at other sites remained constant. More recently, Saavedra-Lozano and colleagues [6] found increasing rates of infection with MRSA in Texas and that infection in the foot was more common than either the femur or tibia-fibula. Because of the rapidly changing nature of pediatric osteomyelitis, a more current description of its epidemiology and complications would benefit clinicians who diagnose and treat children with the disease.

We previously reported a high rate of MRSA in cases of septic arthritis at our institution [13] and became interested in examining

☆ The authors have no financial or other conflicts of interest related to the submission.
* Corresponding author at: Department of Emergency Medicine, Loma Linda University Medical Center, 11234 Anderson St, A-108, Loma Linda, CA 92354.
E-mail address: tpyoung@llu.edu (T.P. Young).

http://dx.doi.org/10.1016/j.ajem.2015.07.011
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Please cite this article as: Ratnayake K, et al, Pediatric acute osteomyelitis in the postvaccine, methicillin-resistant *Staphylococcus aureus* era, Am J Emerg Med (2015), http://dx.doi.org/10.1016/j.ajem.2015.07.011

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cases of osteomyelitis. At our institution, it is sometimes recommended that antibiotics be withheld until operative cultures are obtained in an effort to increase yield. Although adult studies suggest that preoperative antibiotics do not affect operative culture yield, there are less available data in the pediatric setting [14–16].

Our objective was to examine cases of acute culture- and/or imaging-proven osteomyelitis involving healthy prepubescent children seen in our pediatric emergency department. Our primary aim was to determine the rate of MRSA infection in cases of pediatric osteomyelitis. Our secondary aims were to determine organism susceptibilities for MRSA osteomyelitis, to describe site of involvement and rate of complications of osteomyelitis, to determine whether complications were associated with antibiotic discordance or time to antibiotic administration, and to evaluate the yield of operative cultures when antibiotics had already been administered.

2. Materials and methods

We performed a retrospective medical record review of children 12 years and younger presenting to the pediatric emergency department at our university-based, tertiary care institution between January 1, 2003, and December 31, 2012, with the diagnosis of osteomyelitis. We chose this age group to reflect the epidemiology and pathogenesis of a largely prepubertal sample of children. Gonococcal osteomyelitis has been reported in adolescents, and we aimed to avoid this entity [17]. Subjects were identified by the *Ninth Revision of the International Classification of Diseases* (*ICD-9*) diagnostic codes for osteomyelitis (730.00-730.99).

We used a standardized data collection form. Data were collected by a trained data abstractor. The data extracted from the medical records were the patient's age, sex, bone(s) involved, presence of comorbidities, previous diagnosis of bone infection, antibiotics given, results of bone aspirate culture and blood culture, and results of advanced imaging studies. A positive evaluation for osteomyelitis was defined by the presence of positive operative or blood culture for a known pathogen or advanced imaging studies indicating the presence of osteomyelitis. A known pathogen was considered to be any organism other than diptheroids. We included coagulase-negative staphylococcus (CONS) as a pathogen, as until 2008 our laboratory did not speciate CONS. Coagulase-negative staphylococcus has also been reported as a rare cause of osteomyelitis in healthy children [18]. We defined the presence of osteomyelitis on advanced imaging studies as a positive radiologic result for magnetic resonance imaging or nuclear medicine bone scan of the affected area. We defined the following as possible sites of infection: the hand, radius/ulna, humerus, scapula, foot, tibia/fibula, patella, femur, pelvis, spine, and cranium. We reviewed all cases of osteomyelitis for local and hematogenous complications. We defined local complications as abscess, myositis, or fasciitis seen on imaging studies or described in operative reports. We defined hematogenous complications as DVT, septic pulmonary emboli, or other infections at secondary locations attributed to the primary infection of osteomyelitis. Medical records were reviewed from initial presentation to the time of data collection for complications. We included DVTs related to catheters placed for long-term intravenous antibiotics as well as those without mechanical inciting factors. We reviewed cases with a pathogen-positive culture for antibiotic discordance. We defined antibiotic discordance as culture positive for one of the following: an organism explicitly resistant to the antibiotic(s) given prior to the culture result, an organism resistant to an antibiotic of the same class (eg, nafcillin and oxacillin), or an organism resistant to the antibiotic(s) administered according to the Sanford Guide in the year that the subject was treated. Our laboratory does not report sensitivities for all organisms and does not test all antibiotics. We recorded the day of illness that therapeutic antibiotics were given. We defined this as the day of illness at which an antibiotic was given that the organism was sensitive to in cases where an organism was identified, or the day of illness at which the first antibiotic was given in cases where there was no positive culture obtained. We also recorded the day of illness that an operative culture was obtained.

We excluded children with repeat visits, chronic osteomyelitis, a history of previous surgery on the affected bone, and chronic illness. We defined chronic illness as the presence of a ventriculoperitoneal shunt, the presence of an indwelling central venous catheter, and conditions such as sickle cell disease, spina bifida, extreme prematurity, complex congenital cardiac lesions, and cancer. Descriptive statistics were calculated using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA). Where 95% confidence intervals (CIs) are reported, the modified Wald (Agresti-Coull) method was used and was calculated using STATA IC 12 (Statacorp LP, College Station, TX). Subjects with complications were compared with those without complications with respect to both time to therapeutic antibiotic treatment and antibiotic discordance using a Mann-Whitney *U* test and a χ^2 test, respectively. Both were calculated in STATA, with an α level set at .05.

3. Results

We identified 194 patient encounters with an *ICD-9* code for osteomyelitis during the 10-year period. All medical records were complete. A total of 102 encounters met our exclusion criteria. This resulted in a group of 92 subjects who were evaluated for osteomyelitis. Twenty-five subjects had a negative evaluation for osteomyelitis. Therefore, our main study group consisted of the remaining 67 subjects (Fig. 1). After our exclusion criteria were applied to identify cases of interest for this study, the use of *ICD-9* codes had a 73% (67/92) positive predictive value for osteomyelitis as we defined it. All included subjects had either a positive imaging study or a positive operative culture. Forty subjects (60%) were male. The median age was 5 years (interquartile range [IQR], 2-10 years; range, 1 month to 12 years; Fig. 2). The most common pathogenic organism was MSSA, followed by MRSA (Table 1). The most common organism recovered by blood culture was MRSA (12/23; 52%), followed by MSSA (9/23; 39%). All isolates of MRSA were sensitive to vancomycin and trimethoprim-sulfamethoxazole. Two were resistant to clindamycin. The most common site was the femur (Fig. 3).

Forty-six subjects (69%) had a total of 75 local complications (Table 2). Three subjects had hematogenous complications (Table 3). Two of the subjects with hematogenous complications had infection with MRSA. All subjects with hematogenous complications also had local complications. For cases with complications in which the organism was identified, the most common organism was MRSA (19/39; 49%), followed by MSSA (16/39,; 41%). Subjects with complications had a median time to therapeutic antibiotics of 6 days (IQR, 4-9 days), whereas those without complications had a median time to therapeutic antibiotics of 8 days (IQR, 6-22 days; $P = .03$). For subjects without complications in which the organism was identified, the most common organism was MSSA (8/14; 57%), followed by MRSA (3/14; 21%). Subjects with and without complications did not differ regarding antibiotic discordance ($P = .50$). When an operative culture was done after therapeutic antibiotics were given, an organism was still identified from the operative culture in 42 (84%) of 50 cases (95% CI, 71%-92%). An organism was identified from operative cultures when therapeutic antibiotics had not been given prior to operative cultures in 4 (80%) of 5 cases (95% CI, 36%-98%).

4. Discussion

We found a 38% rate of infection with MRSA in cases of pediatric osteomyelitis at our institution, nearly equal to that of MSSA. Pediatric osteomyelitis most commonly affected the long bones. A high proportion of our subjects had complications (69%). Subjects with complications had a shorter time to therapeutic antibiotic administration. Operative culture yield was 84% when therapeutic cultures had already been given.

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