Epidemiology and Management of Acute Hematogenous Vertebral Osteomyelitis and Discitis in Children

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Original Research

PEER REVIEWED

Danielle Comeaux, MPAS, PA-C
Teena Hadvani, MD
Shelley Kumar, MSc, MS
Nicole Wunderlich, PA-C
Angela Foyt, PA-C
Megan James, BSN, RN, CPN
Ankhi Dutta, MD, MPH

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ABSTRACT:

Background. Acute hematogenous vertebral osteomyelitis (AVOM) is a rare condition that causes significant morbidity in in the pediatric population owing to non-specific presentation and delayed diagnoses. The clinical management of AVOM is variable among providers. The objective of this study was to determine the epidemiology, clinical presentation, and variability in the management of AVOM in the pediatric population.

Methods. In this retrospective, observational study, we used descriptive statistics to describe the epidemiology, clinical presentation, diagnosis, and management of AVOM in children admitted to a quaternary hospital in the United States from 2010-2021. Pediatric patients (0-18 years) who were admitted to the hospital with AVOM as per ICD 9 and ICD 10 codes and confirmed AVOM by X-ray and/or magnetic resonance imaging were included in this study. Information regarding demographic, clinical, laboratory, microbiological, radiological, antibiotic use, surgical intervention, and outcome were collected from electronic medical records.

Results. A total of92 patients met the inclusion criteria. The median age of patients was 9.9 years (2.2-14.4 years), with 43.5% girls (n = 40). Out of the 92 patients, 31 patients (34%) were Hispanic, 57 patients (62%) non-Hispanic, and four patients were unknown (4%). The most common clinical presentation was fever (n = 52 patients; 56.5%) followed by back pain (n = 32 patients; 34.8%). Forty-six patients (50%) had either a wound, tissue, or a bone culture performed. Twenty-nine of these patients (31.5%) had no growth. Blood cultures were positive in 21 patients (25.6%). The most common isolated bacterial pathogen was *Staphylococcus aureus* (S aureus) (n = 29). The most administered empiric intravenous (IV)

antibiotic was vancomycin (n = 56; 60.9%), while clindamycin (n = 30; 32.6%) was the most administered oral antibiotic. The total median duration of IV antibiotics was 13.5 days (0-84 days) and 28 days (0-539 days) for oral antibiotics.

Conclusion. Delayed diagnosis is common among children with AVOM. In children with back pain and/or hip pain with fever, AVOM should be considered and MRI ordered. Of those with positive cultures, S aureus was the most common.

Introduction. Acute hematogenous vertebral osteomyelitis (AVOM) with and without discitis is defined as the inflammation of the intervertebral disc and vertebrae of the spine due to an infection.[3] This spinal condition is rare in the pediatric population, but it can have serious health implications owing to its non-specific clinical presentation, delayed diagnosis, and management. Furthermore, radiographic evidence of AVOM with or without discitis often occurs late in the disease, further delaying the diagnosis.[1-13] There is also a wide variability in antibiotic use in this population, including the antimicrobial class, route, and durations. This often leads to prolonged hospital stay and high costs for both the patient and the hospital.

Acute hematogenous vertebral osteomyelitis and discitis account for 3% of all osteoarticular infections admitted to the hospital In industrialized countries.[1] The most frequent age group presenting with AVOM is generally between 0.5-11 years, with children younger than 5 years of age presenting with discitis and older children presenting with vertebral osteomyelitis.[2] Although complications related to AVOM, namely, subdural abscess, epidural abscesses, and venous thrombosis are rare, they often increase morbidity and length of stay.[1] The etiology of discitis in children is less well known since a diagnostic biopsy is not always attempted among this patient population. For patients with positive cultures, the most common bacteria are *Staphylococcus aureus* (S aureus).[1-13] *Kingella kingae* is common among patients with spondylodiscitis and children younger than 4 years, while *Salmonella* species is reported in patients with sickle cell disease.[3] Tuberculosis is another cause of vertebral osteomyelitis in children living in endemic regions.[1] Other rare causes include fungi, parasites, *Brucella species* and *Bartonella species*.[1,3]

There is no consensus regarding the management of AVOM in children, including the choice of empiric antibiotics and duration of therapy, especially for patients with negative cultures. The European Society for Pediatric Infectious Diseases (ESPID) and the Infectious Diseases Society of America (IDSA) guidelines for acute hematogenous osteomyelitis (AHOM) recommend isolation of a microorganism from bone, joint, or blood with a clinical or radiological syndrome consistent with bone and joint infection, followed by starting empiric antibiotic therapy, which should include antistaphylococcal coverage.[4,5] Methicillin Resistant *Staphylococcus aureus* (MRSA) coverage is recommended if the MRSA rates in the geographic area are more than 10%. Oral therapy following intravenous (IV) antibiotic therapy is recommended if the patient is clinically improving, the bacteremia has cleared, no

metastatic foci exist, and inflammatory markers are decreasing. However, the guidelines are not specific for AVOM with or without discitis. Blood and tissue culture yields are variable in AVOM.[4,5] Blood culture positivity ranges between 33% to 57% of children with AVOM, with bone biopsies having an even lower yield.[1,2] The median total duration of IV antibiotics used in AVOM in pediatric studies is 25 days (19-32 days) with oral therapy to be 20 days (13-52 days).[1,2] The median total duration of both IV and oral antibiotics is typically reported to be between 6-12 weeks.[1,8]

With recent advances in diagnostic procedures and antimicrobial stewardship, we aim to evaluate the epidemiology, clinical presentation, and variability in the management of AVOM in children with/without discitis in a single institution. This would help develop a more standardized approach in the absence of specific guidelines for AVOM.

Methods. This is a retrospective, observational, single-center study at a quaternary hospital in the United States from 2010-2021. Pediatric patients (0-18 years) who were admitted to the hospital with AVOM with or without discitis as per ICD 9/10 coded and had confirmed AVOM by either X-ray and/or magnetic resonance imaging (MRI) were included in this study.

Patients were excluded if they had any spinal devices, pressure ulcers, or a secondary source (e.g. penetrating trauma, open wounds) that led to AVOM. Patients with discitis alone were excluded as well. In addition, any patient with spondylodiscitis due to non-infectious causes or not confirmed by imaging (X-ray or MRI), who were immunocompromised and those with isolated spinal abscesses without radiological confirmation of AVOM were excluded.

Information regarding demographic, clinical presentation, laboratory and microbiological studies, choice, route and duration of antibiotics, surgical intervention, and outcome were collected from the electronic medical record of patients who met the inclusion criteria. The diagnosis of vertebral osteomyelitis, discitis, spinal osteomyelitis, and spondylodiscitis was obtained per ICD 9/10 codes. Clinical data included the presence of fever, pain, other systemic symptoms, and duration of symptoms prior to admission. Laboratory studies included white blood count (WBC), C-reactive protein (CRP), and absolute neutrophil count (ANC). Microbiological cultures included blood, wound, tissue and bone cultures, histopathology, and any molecular tests performed on the samples. Molecular tests included microbial cell free DNA (mcDNA) testing in the blood and bacterial identification of 16s rRNA gene from tissue and/or sterile fluid. Positive cultures refer to patients with blood, wound, tissue, bone culture, and/or molecular testing that yielded an organism was considered an etiology of the AVOM/discitis. Negative cultures refer to patients with any of the above cultures not yielding any organisms. A favorable clinical outcome was defined as clinical resolution of presenting signs and symptoms. Any readmission within 30 days of discharge was documented

Results. During the study period, 203 children were identified with AVOM with or without discitis. Ninety-two patients met the inclusion criteria (Table 1).

Table 1. Demographics, clinical presentation, microbiological etiology, diagnosis, and treatment of patients with acute vertebral osteomyelitis with/without discitis

Age in years: Median (First quartile-third quartile)	9.9 (2.2-14.4)
Female (n, %)	40 (43.5)
Race (n, %)	70 (76.1)
White	10 (10.9)
Black	6 (6.5)
Asian	1 (1.1)
Pacific Islander Unknown	5 (5.4)
Ethnicity (n, %)	31 (33.7)
Hispanic	57 (62.0)
Non-Hispanic	4 (4.4)
Unknown	
Presence of fever (n, %)	52 (56.5)
Median fever Duration in days (first quartile to third quartile)	1 (0-5)
Presence of pain (n, %)	90 (98)
Refusal to bear weight (n, %)	22 (23.9)

Location of pain (n, %)	32 (34.8)
Back pain	22 (23.9)
Lower extremity pain	25 (27.2)
Multi-location symptoms	13 (14.1)
Others	
White cell count on admission Mean (First quartile to third quartile)	11.21x 10^3/uL (range 3.92-29.82 x10^3/uL)
C-Reactive Protein on admission Median (First quartile to third quartile)	4.1 mg/dL (<0.5-40.4mg/dL)
Blood Culture (n,%)	61 (74.3)
No Growth	14 (17)
Methicillin sensitive *S aureus*	4 (4.8%)
Methicillin resistant *S aureus*	2 (2.4%)
Salmonella species	1
Others	10
Not Done	
Bacterial etiology (n, %)	51 (55.4)
No growth	21 (22.8)
Methicillin sensitive *S aureus*	6 (6.5%)
Methicillin resistant *S aureus*	4 (4.3%)
Salmonella species*	3 (3.2%)
Group A Streptococcus*	2 (2.2%)
*Kingella kingae**	5 (5.4%)
Others*	

Location of vertebral osteomyelitis (n, %)	28 (30.4)
Lumbar	11 (12)
Sacral	6 (6.5)
Thoracic	8 (8.7)
Cervical	35 (38)
Multi-level	
Findings on MRI (n,%)	46 (50)
Associated myositis	40 (43.5)
Paraspinal abscess/phlegmon	18 (19.6)
Epidural extension or abscess	34 (37.4)
Associated discitis	4 (4.3)
Other abscesses	
Most common Antimicrobials used (n,%)	56 (60.9)
Intravenous	33 (35.9)
Vancomycin	38 (41.3)
Clindamycin	30 (32.6)
Ceftriaxone	20 (21.7)
Oral	23 (25.0)
Clindamycin	
Bactrim	
Cephalexin	
Clinical Outcomes (n, %)	81 (88)
Clinical Resolution	10 (10.8)
Readmission**	1 (1.1)
Unknown	

*These organisms were identified either by culture, polymerase chain reaction (PCR) through our standardized institutional PCR, metagenomics next generation sequencing (mngs) of microbial cell-free DNA (mcfDNA) or bacterial identification through universal PCR technique or serology. **Four were readmitted unrelated to their AVOM—two for side effects related to antibiotics and one for central line related complications.

The most common clinical presentations were fever among 52 patients (56.5%) followed by back pain among 32 patients (34.8%). Twenty-nine patients (90.6%) who reported back pain were older than 5 years of age compared with only three patients younger than 5 years of age (9.4%). In children 5 years of age or younger, 34 (37%) could localize their pain compared with 58 (63%) children older than 5 years of age.

Researchers recorded the WBC, ANC, and CRP for all patients. Blood cultures were performed in 82 patients (89%). Of these, 21 were positive (25.6%). Forty-six patients (50%) had either a wound, tissue, or a bone culture done. Twenty-nine of these patients (31.5%) had no growth. The most common bacterial pathogens isolated from cultures (any cultures including blood, wound, tissue or bone culture) were S aureus (n = 29).

Of the patients with a positive tissue/bone culture, concomitant bacteremia was present in seven patients (15.5%). Four of these patients grew Methicillin Sensitive *Staphylococcus aureus* (MSSA) and three grew MRSA. Among the eight patients with negative blood culture, a wound/tissue, or bone biopsy yielded an etiology (MSSA = 6, MRSA = 1 and salmonella = 1). The most common empiric IV antibiotic administered was vancomycin (60.9%, n = 56). Combination therapy was used in 68 patients (73.9%) and monotherapy in 14 (15.2%). The most common combination antimicrobials were vancomycin and ceftriaxone. The total median duration of the IV and oral antibiotics administered was 62.89 days (1-554 days). The total median duration of IV antibiotics was 13.5 days (0-84 days) and total median duration of oral antibiotics was 28 days (0-539 days).

Surgical intervention in the operating room or intervention radiology occurred in 50% (n = 46) of patients. Seventeen patients (36.9%) had a bacterium isolated on cultures. Since the most common antibiotic used in AVOM was vancomycin, we set out to determine the etiology of AVOM in patients started on empiric vancomycin. Of the 56 patients administered vancomycin, 26 (46.4%) had no growth, 17 (30.3%) grew MSSA, five (8.9%) grew MRSA, three (5.3 %) salmonella, and four (7%) grew other miscellaneous organisms. Of the 36 patients who were not on empiric vancomycin therapy, only one patient had MRSA. Among the patients who received empiric IV vancomycin therapy, most patients were switched to either oral clindamycin (n=15, 26.7%), TMP-SMX (n=16; 28.5%) or cephalexin (n=13, 23.2%) on discharge.

Comparing patients with culture positive versus culture negative AVOM. Patients with positive cultures were more likely to be older, with a mean age of 12.3 years (4.9-14.8 years) versus 7.9 years (1.7-14.2 years) (P = 0.03) in culture negative AVOM. Patients with culture

positive AVOM were also more likely to have fever at presentation (n = 31; 75.6%) compared with patients with culture negative AVOM (n = 21; 41.2%; *P* = 0.0009). Compared with those with negative cultures, patients with culture positive AVOM had a longer length of stay (median 8 days versus 6 days; *P* = 0.0017) increased median duration of fever (3 days versus 0 days; *P* = 0.0063), and increased CRP (mean = 14.4 mg/dl versus 3.4 mg/dL; *P* < 0.0001). There was no difference in race/ethnicity, presenting symptoms of pain, presence of abscesses, WBC or requirement of surgical intervention. Patients with a positive culture were less likely to have discitis at presentation (n = 6; 17.6%) when compared to those with negative cultures (n = 28; 82%, *P* <0.0001).

Discussion. Our study shows that there is a wide variability in the management of pediatric AVOM with/without discitis. This is not surprising, as microbiological etiology is hard to obtain in children with AVOM despite the advances in diagnostic modalities. Therefore, broad-spectrum antibiotics like vancomycin continue to be the primary empiric therapy pediatric AVOM. There are few points worth noting in our study that could help clinicians formulate a management plan in these patients. A high index of suspicion is required when diagnosing AVOM, especially in children younger than 5 years of age as they are less likely to report back pain. MRI of the spine in these situations, in the absence of an alternate etiology would be helpful to prevent diagnostic delays. This is consistent with other pediatric studies, where plain radiographs were less diagnostic than MRI and delayed diagnosis of AVOM occurred, especially in the younger age group.[1,2] Second, clinicians should be aware that diagnostic yield of cultures is low in pediatric AVOM. Like other pediatric studies, where reported blood culture positivity is 20%-57%, our blood cultures were positive in only 25.6%. Tissue cultures are less commonly performed in most pediatric studies (14%-24%) and positivity rates range between 20-80%.[1,2,6,7]

In our study, tissue cultures were attempted in 50% of patients and 36.9% were positive. Using molecular methods, we were able to identify patients with additional bacterium, two with *Kingella kingae* and one *Streptococcal pneumoniae* through our institutional limited 16s rRNA bacterial fluid PCR. In addition, *Kingella kingae* was isolated in one patient through mfDNA testing. All 10 of the expanded universal 16s rRNA bacterial identification for bacteria were negative. Given the prevalence of *Kingella kingae* in AVOM in preschool children,[3] there could be an underestimation of its role in AVOM and discitis. In this age group, it is reasonable to include this test in diagnostic studies if a biopsy is being done. Since all the universal bacterial PCRs in our study were negative, the utility on this costly test is debatable and should be used judiciously. Given the low diagnostic yield of all the microbiological methods in AVOM and discitis, the use of multimodal diagnostic approach should be attempted in children with AVOM. In our study, microbiological etiology was more common in children who presented with fever, older children and those with a higher CRP. Third, our study showed that although S aureus continued to be the most common pathogen, MRSA was not commonly isolated. It is interesting that while our community MRSA rates are more than 10%, we did not encounter an increase in MRSA rates with AVOM and discitis. Even

among those with negative cultures, definitive therapy did not require vancomycin. Short parenteral courses on IV therapy followed by oral therapy with either clindamycin or TMP-SMX with close follow-up with an infectious diseases specialist should be reasonable for those with clinical improvement. The total duration of antibiotic therapy in our study is comparable to previous research suggesting a range of 6-12 weeks of oral and IV antibiotics.[1-8]

Our study has several limitations. This is a retrospective study, so we could not determine the definitive choice of antibiotic therapy especially in a culture negative patient. Similarly, a clear recommendation for total duration of therapy cannot be made, though it seems reasonable to do a shorter course of IV therapy followed by 4-6 weeks on oral therapy in patients with AVOM who are clinically improving. Bone biopsy is an invasive procedure and given the lower yield in AVOM, we are unable to make a strong recommendation in all patients with AVOM especially if they are clinically improving. Lastly, since this is a single center study, the results may not be generalized to the rest of the US population.

Conclusion. Our study highlights the difficulty in finding an etiological diagnosis of AVOM with/without discitis in children and the variability of antibiotic management in a single institution. Short parenteral courses of IV therapy followed by oral therapy for 4-6 weeks seems to be adequate for uncomplicated cases of AVOM. The role of molecular methodology in identifying additional pathogens was not high-yield in our study, although the identification of *Kingella kingae* may be underestimated.

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AUTHORS:

Danielle Comeaux, MPAS, PA-C[1,6] • Teena Hadvani, MD[2,4] • Shelley Kumar, MSc, MS[5] • Nicole Wunderlich, PA-C[1,6] • Angela Foyt, PA-C[6] • Megan James, BSN, RN, CPN[2,3] • Ankhi Dutta, A, MD, MPH[2,3]

AFFILIATIONS:
[1]Texas Children's Hospital and Baylor College of Medicine, Department of Orthopedic Surgery, Houston, TX
[2]Texas Children's Hospital and Baylor College of Medicine Department of Pediatrics, Houston, TX
[3]Texas Children's Hospital and Baylor College of Medicine Division of Infectious Disease, Houston, TX
[4]Texas Children's Hospital and Baylor College of Medicine Division of Pediatric Hospital Medicine, Houston, TX
[5]Texas Children's Hospital and Baylor College of Medicine Department of Academic General Pediatrics, Houston, TX
[6]Texas Children's Hospital and Baylor College of Medicine Department of Pediatric Surgery, Houston, TX

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CORRESPONDENCE:

Danielle Comeaux, MPAS, PA-C, 17580 I-45 South, The Woodlands, TX 77384 (dscomeau@texaschildrens.org)