A 34-day-old previously healthy boy born full term presented to the emergency department with fever at home (38.1°C), fussiness, and decreased oral intake for 1 day. He had difficulty to console at home. He had decreased oral intake without emesis, diarrhea, or a change in urine output. He did not have rhinorrhea, cough, or increased work of breathing noted by parents. He lived at home with his parents and 13-year-old brother, did not attend day care, and had no sick contacts. On examination, he was fussy but consolable. He was febrile to 39.3°C, tachycardic (180 beats per minute), and tachypneic (64 breaths per minute), with mottling and a capillary refill of 3 seconds. The remainder of his examination was normal, without an infectious focus for his fever. A complete blood cell count with differential revealed leukocytosis. A basic metabolic panel was normal. A catheter urinalysis was normal. Cerebrospinal fluid examination yielded pleocytosis, low glucose, and elevated protein. Blood cultures were persistently positive with methicillin-sensitive *Staphylococcus aureus*, but cerebrospinal fluid cultures remained negative. We present his case, management, and ultimate diagnosis.
Fever is often the only presenting sign of a serious bacterial infection in an infant ≤60 days of age, and up to 12% of febrile infants in this age group have either a urinary tract infection, bacteremia, or bacterial meningitis. Although urinary tract infection is the most common, 1% to 3% have bacteremia or meningitis.1–4 The standard emergent evaluation for these infants includes obtaining blood, urine, and cerebrospinal fluid (CSF) studies and cultures, with subsequent risk assignment and management strategies based on age, clinical assessment, and diagnostic test results.

Empirical antibiotics to treat a possible bacterial infection should be considered for infants who do not meet low-risk criteria. There are several different published low-risk criteria, with most criteria involving a well-appearing, previously healthy infant with low white blood cell counts and negative Gram stain in the serum, urine, and CSF and no other focus of infection.1–3 Our patient was not considered low-risk from the time of his initial assessment, because he was not well appearing with tachycardia and poor perfusion. Thus, along with fluid resuscitation, antibiotics were initiated immediately after blood, urine, and CSF cultures were collected, before results were obtained, and he was admitted to the hospital. The choice of antibiotic treatment for children who do not meet low-risk criteria typically includes a combination of antibiotics targeting bacteria that differs with the age of the patient. Typically, ampicillin and an aminoglycoside (ie, gentamicin) or ampicillin and cefotaxime are given to infants <1 month old to treat presumptive bacteria such as Streptococcus agalactiae, Listeria monocytogenes, and gram-negative species such as Escherichia coli and Klebsiella. For infants >1 month old, a third-generation cephalosporin is given to treat presumptive bacteria, including Streptococcus pneumoniae, Neisseria meningitides, Streptococcus agalactiae, Haemophilus influenzae, and E coli. Vancomycin may be added if bacterial meningitis is suspected. Institutions and local community resistance patterns may alter these typical regimens.5

When evaluating a febrile neonate, there is no consensus in the literature regarding the addition of antiviral therapy (acyclovir) for empirical coverage of herpes simplex virus (HSV) infection. HSV encephalitis, though uncommon, has a similar prevalence to bacterial meningitis in infants ≤28 days old and has a high morbidity and mortality.6 Two-thirds of infants with HSV infection do not have a history of parental HSV.7–9 Therefore, some institutions recommend starting acyclovir in infants ≤14 days old who present with a fever.10 Given the inability to identify infants at low risk of HSV infection, it is practice in our institution to start acyclovir on infants ≤60 days of age who present with fever and skin vesicles, hepatitis, seizures, aseptic meningitis (CSF leukocytosis with negative Gram stain), sepsis, encephalitis, or focal neurologic findings.

For this patient, a complete blood cell count with differential revealed leukocytosis with 17700 white blood cells (56% neutrophils and 4% bands). A basic metabolic panel, catheter urinalysis, and chest radiograph were normal. CSF examination yielded pleocytosis (2113 white blood cells with 66% neutrophils and 34% monocytes), 424 red blood cells, hypoglycorrhachia (39 mg/dL), and elevated protein (534 mg/dL), which raised concern for meningitis. Blood cultures were persistently positive over 48 hours with methicillin-sensitive Staphylococcus aureus (MSSA).

The patient’s CSF results raised concern for meningitis, specifically bacterial meningitis. He had been empirically started on ampicillin, cefotaxime, and acyclovir. After CSF results were noted to be concerning for bacterial meningitis, ampicillin was changed to vancomycin to treat possible pneumococcal meningitis. The initial blood culture and a blood culture obtained 24 hours later resulted in positive identification of MSSA. A blood culture obtained 48 hours after presentation was negative. Urinalysis and CSF cultures remained negative.

Dr Yamada, how do you interpret the results of the CSF studies in the setting of a negative CSF culture but positive blood cultures for MSSA? Given the rarity of MSSA meningitis in this age group, what is your differential for the source of the infection?
had to look for a parameningeal source of infection.

Additionally, when we see a patient with *S. aureus* bacteremia without a source, we typically look for a musculoskeletal infection such as osteomyelitis, pyomyositis, and septic arthritis or for an intravascular infection such as endocarditis. These infections are almost always hematogenously spread, which more often occurs in neonates with prematurity in the NICU as opposed to healthy full-term infants. Unfortunately, given the rarity of *S aureus* parameningeal, musculoskeletal, and intravascular infections in infants, the incidence is not well described.

**Dr Horner**

The infant was noted to have a transient systolic murmur once admitted to the hospital. A transthoracic echocardiogram was normal. Although diagnosis of osteomyelitis in young infants is challenging, we thought it was unlikely in this infant because only 20% of infants <4 months old present without specific signs of bone involvement on examination.11

Dr Zuccoli, if osteomyelitis is suspected, what imaging modalities would you recommend for this age group?

**Dr Giulio Zuccoli (Pediatric Neuroradiologist)**

If osteomyelitis is suspected, plain radiography would be the first choice to evaluate for soft tissue swelling and changes in bone density. However, in cases of hematogenous osteomyelitis, it may take up to 2 weeks for plain radiography to reflect changes suggesting osteomyelitis. Therefore, plain radiography may be normal in the initial phase of the disease, which would have been the case for this infant presenting within the first few days of illness. Other methods to evaluate for osteomyelitis in infants include ultrasound, MRI, and scintigraphy. Ultrasound and MRI can detect changes several days earlier than plain radiography, although it is more useful if there is a suspected location of infection. Scintigraphy is more useful when the suspected location of osteomyelitis is unknown.12,13

**Dr Horner**

Because the infant did not have a suspected location of osteomyelitis, scintigraphy would have provided the highest yield, but given the CSF results with neutrophil-predominant pleocytosis, hypoglycorrhagia, and elevated protein with negative cultures, additional investigation was focused on the CNS to evaluate for a source of meningeal or parameningeal inflammation. A head computed tomography scan with contrast and brain MRI with venography did not show an intracranial infection such as a brain abscess. A spinal ultrasound was negative for a paraspinal abscess. A spine MRI with contrast was abnormal (Figs 1 and 2).

Dr Zuccoli, can you describe the MRI findings?

**Dr Giulio Zuccoli (Pediatric Neuroradiologist)**

The MRI of the cervical spine demonstrated an extradural fluid collection, which was isointense to the CSF on both T1- and T2-weighted.
images. On sagittal T2-weighted images the identification of the anatomic landmarks represented by the displaced dura mater confirmed the extradural nature of the collection (Fig 1A). In normal conditions the dura mater cannot be distinguished from the adjacent spinal canal on MRI. The administration of contrast material demonstrated ring enhancement typical of an organizing abscess, which was essential in confirming the infectious nature of this collection (Fig 1B). In fact, spontaneous extradural collections may be indistinguishable from an abscess based only on precontrast images. Furthermore, the presence of pathologic contrast enhancement in the posterior aspect of the vertebral body of C4 indicated the source of the infection (Fig 1B). Early infectious involvement of the spinal cord was also noted (Fig 2).

**Dr Horner**

The anterior portion of the spinal cord houses the anterior and lateral spinothalamic tracts and the anterolateral corticospinal tracts. Therefore, compression of this area, as noted on the MRI, may cause loss of motor function below the level of the injury and loss of pain and temperature sensation with preservation of fine touch and proprioception. Given the location in the cervical spine, there is additional concern about loss of respiratory drive because the phrenic nerve arises from C3–5 roots. Dr Vellody, upon discovering these results, did you have concern about a potential change in his clinical status?

**Dr Kishore Vellody (Pediatric Hospitalist)**

Yes, we certainly did. He looked very well on examination despite the impressive MRI spine findings. However, the location of the abscess indicated potential future neurologic deficits. A cervical spinal cord compression would be catastrophic for this young infant, with potential loss of his respiratory drive, leading to complete cessation of respiration. Additionally, there was concern that the underlying support structures and bones of the cervical spine may also be compromised, leading to greater instability in that area. We immediately consulted neurosurgeons for possible surgical management of the abscess. Concurrently, we arranged for transfer to the pediatric ICU for closer monitoring of his neurologic status.

**Dr Stephanie Greene ( Pediatric Neurosurgeon)**

This child’s laboratory studies raised concern about parameningeal inflammation but not meningitis, given the negative CSF culture. His MRI findings are most consistent with an epidural abscess. The inflammation (and secondary contrast enhancement) of the pia is probably secondary to the abscess on the outer side of the dura. Surgically evacuating a ventral epidural abscess would require an anterior cervical approach. This space is extremely small in infants, increasing the risk of injury to the recurrent laryngeal nerve (producing hoarseness and swallowing dysfunction, which in the worst case necessitates G-tube placement) and esophagus. An epidural abscess often produces a phlegmon, such that an attempt to evacuate it from a posterior approach could result in no decompression or microbiological specimen but rather a wound to heal in the setting of infection and the possible need for a spinal fusion from a post laminectomy kyphosis in the future. The risks of surgery greatly outweigh the benefits in this neurologically intact infant. To attempt to have interventional radiology drain the abscess carries additional risks of injury to the vertebral artery on the side of approach and possible introduction of bacteria into the thecal sac. Unfortunately, given the rarity of cervical spinal abscesses in neonates, the literature is inconclusive about the necessity for surgical intervention rather than antibiotics alone. There are reports of cases managed with surgical drainage but also with antibiotics alone. Notably, many of the case reports describing surgical drainage of the abscess involve patients with neurologic compromise, whereas only 1 case series described patients treated with antibiotics alone who had neurologic compromise. Expanding to the pediatric population in general, recent literature has demonstrated appropriate recovery of children with epidural abscess with antibiotics alone, especially in those without neurologic deficit. Given the absence of neurologic compromise in combination with the intradural involvement (noted on MRI), we thought empirical management with antibiotics was preferable to the sizable surgical risks.

**Dr Horner**

Dr Yamada, given the recommendations by the neurosurgeon, what is your approach to medical treatment in this case?

**Dr Masaki Yamada ( Pediatric Infectious Diseases)**

Fortunately, the patient was clinically stable, without persistent bacteremia or neurologic symptoms from cord compression at the time of diagnosis. Therefore, we agreed the risks outweighed the benefit, and we mutually decided to manage the abscess medically without
surgical intervention. After 14 days of antibiotics, repeat spinal MRI demonstrated a significant decrease in size of the abscess (Fig 3). We recommended a prolonged course of 6 weeks of intravenous nafcillin because there was no surgical intervention.

Dr Horner

This patient was found to have an extensive invasive infection with MSSA involving bacteremia, vertebral osteomyelitis, and epidural abscess at a very young age.

Dr Rosenberg, should we be concerned about an underlying immunodeficiency, which may increase his susceptibility to invasive S aureus infections?

Dr Stacy Rosenberg (Pediatric Allergy and Immunology)

It is important to consider an underlying immunodeficiency manifesting as a sentinel invasive S. aureus infection, because several immune deficiencies have increased susceptibility to this particular bacteria. Chronic granulomatous disease (CGD) can present with invasive infections with catalase-positive organisms. Because CGD is caused by mutations in the nicotinamide adenine dinucleotide phosphate oxidase complex, affected people are susceptible to organisms containing the enzyme catalase for respiration using oxygen (catalase positive), such as S aureus, Micrococci species, Pseudomonas aeruginosa, and E coli, as opposed to catalase-negative organisms such as Streptococcus and Enterococcus species. CGD is diagnosed through evidence of a defective phagocyte oxidative burst. Abscesses can be found in other disorders with phagocytic defects, including leukocyte adhesion deficiency and cyclic or congenital neutropenia. Leukocyte adhesion deficiency typically presents with delayed umbilical cord separation and leukocytosis. Defects in innate immunity, specifically toll-like receptor signaling, including IRAK4 deficiency and MyD88 deficiency, are disorders with increased susceptibility to S. aureus infections and have a high risk of mortality in the first decade of life. Finally, STAT3 deficiency (hyper-immunoglobulin E syndrome) has been commonly associated with S. aureus disease.

In our case, the patient’s young age and invasive infection prompted an immunologic workup to address these potential underlying problems. Ultimately, it was unrevealing. He had normal neutrophil counts, neutrophil oxidative burst assay, toll-like receptor assay, immunoglobulin G and M levels (immunoglobulin A was probably physiologically low), lymphocyte proliferation, and severe combined immunodeficiency newborn screen, and he did not have lymphopenia. He had many reassuring clinical findings that were not suggestive of an immunodeficiency, including normal weight gain, development, stooling pattern, and healing from a circumcision and umbilical stump separation. He lacked previous rashes or infections and had a normal physical examination with the presence of tonsils.

**FINAL DIAGNOSIS AND DISCUSSION: MSSA BACTEREMIA, CERVICAL VERTEBRAL OSTEOMYELITIS, AND EPIDURAL ABSCESS**

MSSA bacteremia is increasingly being documented in the literature and is a notable yet uncommon pathogen in infants. In healthy, febrile infants ≤90 days old with bacteremia, only 5% have S. aureus bacteremia. Neonates represent 7% to 31% of all children with S. aureus bacteremia,30–33 with 1 additional pediatric study reporting 61% of S. aureus bacteremia episodes occurring in neonates. S. aureus bacteremia occurs with or without a source of infection. For example, a source may be the presence of a central venous catheter, congenital heart disease or endocarditis, musculoskeletal infection, or CNS infection. Health care–associated sources of S. aureus bacteremia, including central lines, intravascular devices, and skin or mucous membrane.
bacteremia, specifically the rate of its occurrence in the NICU given the prevalence of central venous catheters, is commonly described in the literature.35,36 On the other hand, S. aureus bacteremia without a source is rare, and there is a paucity of literature. A prospective surveillance study demonstrated that S. aureus bacteremia without a source made up only 6% of the 631 S. aureus bacteremia events in the series and occurred more often in immunocompromised patients.33

More often, S. aureus bacteremia occurs with a source, typically a concomitant deep-seated infection, which carries severe consequences if left undiagnosed or undertreated.34,37 Thus, the diagnosis of a deep-seated infection is integral to appropriate treatment to decrease morbidity and mortality. In the absence of central venous catheters or congenital heart disease, the most common sources of S. aureus bacteremia are bone and joint infections (11%–42%),30,31,38 endocarditis (0%–20%),30–32,34 and skin abscesses or cellulitis (11%–56%).29–31,34,38 Less commonly, deep-seated infections occur in the musculoskeletal system (pyomyositis), CNS (brain abscess, epidural abscess, meningitis), and lung (pneumonia).30,31,34,38 Studies evaluating S. aureus bacteremia demonstrate that deep-seated infections are usually either clinically apparent at presentation or occur in children known to be at higher risk secondary to the presence of central venous catheters or congenital heart disease.30,31,34,37,39 For instance, the incidence of endocarditis in the setting of S. aureus bacteremia ranges from 0% to 20%, with a significantly higher risk in those with congenital heart disease, up to 50%.30–32,34,37 In fact, Valente et al32 showed that 9 out of 10 of their patients with S. aureus bacteremia and infectious endocarditis had congenital heart disease.

The percentage of bacteremia in children attributed to methicillin-resistant S. aureus as opposed to MSSA differs based on geographic location and varies widely in the limited existing literature, ranging from 8% to 90% in NICU patients34,35,40–42 and 6% to 33% in non-NICU patients.30–36,38 Some case series note methicillin-resistant S. aureus to be more common in health care–associated cases, whereas others do not note this difference.31–35,38,40–42

Vertebral osteomyelitis complicated with an epidural abscess is only occasionally seen in immunocompetent children.23,43 The majority are adolescents, with the most common location of infection being lower thoracic or lumbar spines, as opposed to the cervical spine in our patient. S. aureus is the most common bacteria found in epidural abscesses.23

Herein, we had a rare case of a cervical vertebral osteomyelitis with epidural abscess in an otherwise healthy, immunocompetent infant. The key points in making the diagnosis were that S. aureus is not a common pathogen for meningitis, and the discrepancy between the CSF analysis consistent with bacterial meningitis and a sterile CSF culture indicated parameningeal inflammation. Both factors suggested that additional evaluation to identify a deep-seated infection was warranted.

Our diagnostic steps were initially focused on intracranial infection, which was excluded with a head computed tomography scan and brain MRI with venography. Without spinal MRI, the accurate diagnosis could have been missed, which demonstrates the importance of thorough evaluation for a deep-seated infection with S. aureus bacteremia. Failure to diagnose the vertebral osteomyelitis with epidural abscess could have caused fatal spinal cord injury.

A review of the literature reveals 2 other neonatal cases of vertebral osteomyelitis and concomitant epidural abscess but with different bacterial organisms. One is a 3-week-old infant with fever noted to have CSF pleocytosis with negative CSF culture and Pasteurella multocida bacteremia. He was treated nonoperatively with intravenous antibiotics without sequelae.20 The other is a 3-week-old infant with fever, CSF pleocytosis, and negative blood and CSF cultures; however, the epidural abscess was cultured, revealing β hemolytic Streptococcus. This child underwent operative drainage of the abscess and recovered without sequelae.15

Worthy of special mention is that these 2 infants and our patient all had cervical osteomyelitis with adjacent epidural abscess. Given this unusual location, especially in this age group, we postulated that perhaps cervical injury with birth trauma or poor head control may increase susceptibility to bacterial infection in this location, although this causal relationship has not been proven previously, and there was no history supportive of birth trauma in any of the cases.

The standard therapy for epidural abscesses is antibiotics and surgical drainage, but conservative nonoperative management with antibiotics alone may be considered in patients without neurologic deficit, with extensive abscesses, or with high surgical risks.23–25 Generally, epidural abscesses do not always warrant antibiotic treatment at meningitic doses. However, we continued the high dosing as if this were bacterial meningitis because of the initial CSF findings and concern about potential spread of the infection from the undrained abscess. Given the anatomic complexity, indications for surgical treatment should be discussed for each case, individually. The patient uneventfully completed 6 weeks of intravenous nafcillin.
therapy and is doing well at 6 months of age without neurodevelopmental delay or other invasive infections at all follow-up visits.

ABBREVIATIONS

CGD: chronic granulomatous disease
CNS: central nervous system
CSF: cerebrospinal fluid
HSV: herpes simplex virus
MSSA: methicillin sensitive Staphylococcus aureus

REFERENCES

8. O’Riordan DP, Golden WC, Aucott SW. Herpes simplex virus infections in preterm infants. Pediatrics. 2006;118(6). Available at: www.pediatrics.org/cgi/content/full/118/6/e1612


A 34-Day-Old With Fever, Cerebrospinal Fluid Pleocytosis, and *Staphylococcus aureus* Bacteremia

Kimberly Horner, Masaki Yamada, Giulio Zuccoli, Stacy Rosenberg, Stephanie Greene, Kishore Vellody and Noel S. Zuckerbraun

*Pediatrics* 2016;137; DOI: 10.1542/peds.2015-1406 originally published online December 7, 2015;

| Updated Information & Services | including high resolution figures, can be found at: [http://pediatrics.aappublications.org/content/137/1/e20151406](http://pediatrics.aappublications.org/content/137/1/e20151406) |
| References | This article cites 39 articles, 5 of which you can access for free at: [http://pediatrics.aappublications.org/content/137/1/e20151406.full#ref-list-1](http://pediatrics.aappublications.org/content/137/1/e20151406.full#ref-list-1) |
| Subspecialty Collections | This article, along with others on similar topics, appears in the following collection(s): Infectious Disease [http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub](http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub), Neurology [http://classic.pediatrics.aappublications.org/cgi/collection/neurology_sub](http://classic.pediatrics.aappublications.org/cgi/collection/neurology_sub) |
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: [https://shop.aap.org/licensing-permissions/](https://shop.aap.org/licensing-permissions/) |
| Reprints | Information about ordering reprints can be found online: [http://classic.pediatrics.aappublications.org/content/reprints](http://classic.pediatrics.aappublications.org/content/reprints) |
A 34-Day-Old With Fever, Cerebrospinal Fluid Pleocytosis, and *Staphylococcus aureus* Bacteremia

Kimberly Horner, Masaki Yamada, Giulio Zuccoli, Stacy Rosenberg, Stephanie Greene, Kishore Vellody and Noel S. Zuckerbraun

*Pediatrics* 2016;137;
DOI: 10.1542/peds.2015-1406 originally published online December 7, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/1/e20151406