CLINICAL PRACTICE

Vertebral Osteomyelitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 57-year-old man presents with fever, chills, and new lumbar back pain 2 weeks after undergoing a prostate biopsy because of an increased prostate-specific antigen level. His temperature is 39.7°C; he has an enlarged, tender prostate and lumbar spine tenderness. His white-cell count is 9100 per cubic millimeter, and the C-reactive protein level is 343 mg per liter. Urine and blood cultures reveal multidrug-resistant, extended-spectrum β-lactamase–producing *Escherichia coli* susceptible to imipenem. How should he be evaluated and treated?

THE CLINICAL PROBLEM

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Vertebral osteomyelitis (also termed spinal osteomyelitis, spondylodiskitis, septic diskitis, or disk-space infection) may be acute (i.e., evolving over a period of a few days or weeks) or subacute or chronic (i.e., lasting for weeks or months before antimicrobial therapy is initiated). Acute vertebral osteomyelitis is the focus of this article.

The incidence of vertebral osteomyelitis has been estimated at 2.4 cases per 100,000 population, with the incidence increasing with increasing age (from 0.3 per 100,000 among persons younger than 20 years of age to 6.5 per 100,000 among persons older than 70 years of age).[1] Vertebral osteomyelitis most often results from hematogenous seeding, direct inoculation at the time of spinal surgery, or contiguous spread from an infection in the adjacent soft tissue.[2] *Staphylococcus aureus* is the most common microorganism implicated in pyogenic vertebral osteomyelitis, followed by *E. coli*.[2-6] Coagulase-negative staphylococci and *Propionibacterium acnes* are the microorganisms that are almost always the cause of exogenous osteomyelitis after spinal surgery, particularly if fixation devices are used.[2,4,7] However, in the case of prolonged bacteremia (e.g., infection associated with pacemaker electrodes), hematogenous vertebral osteomyelitis due to low-virulence microorganisms (e.g., coagulase-negative staphylococci) has been described.[8] In a study involving 253 patients with vertebral osteomyelitis, the primary focus of infection, identified in 51% of the patients, was the urinary tract, skin, or soft tissue; a site of vascular access; or endocarditis, bursitis, or septic arthritis.[2] Most patients with hematogenous pyogenic vertebral osteomyelitis have underlying medical diseases — especially diabetes, coronary heart disease, immunosuppressive disorders, cancer, or renal failure requiring hemodialysis — or use intravenous drugs.[4,5,9-11]

Vertebral osteomyelitis can be complicated by direct seeding in different compartments, resulting in paravertebral, epidural, or psoas abscesses. In one study, vertebral osteomyelitis was complicated by epidural abscess in 17% of cases, by paravertebral abscess in 26%, and by a disk-space abscess in 5%.[2] In one fourth of the patients, motor weakness or paralysis developed, with particularly high rates among patients with cervical spine osteomyelitis. Neurologic complications have been reported in 38% of patients with vertebral osteomyelitis.[3] In an analysis of 14 case

series, an episode of vertebral osteomyelitis was followed by relapse in 8% of the cases and by death in 6%.[4]

STRATEGIES AND EVIDENCE

EVALUATION

Clinical Features

Back pain is the most common initial symptom of vertebral osteomyelitis; in the analysis of 14 case series, back pain was reported in 86% of the cases.[4] Fever is not invariably present (reported frequency, 35%[5] to 60%[4]), probably because patients are usually taking analgesic medications. The location of the pain depends on the site of infection. The most common site is the lumbar spine (58%), followed by the thoracic spine (30%) and the cervical spine (11%).[4] Neurologic impairment, such as sensory loss, weakness, or radiculopathy, is reported in one third of cases. Tenderness of the spine on percussion was reported in fewer than a fifth of the patients in one study.[5] Particularly severe, sharp, or lancinating back pain suggests the presence of an epidural abscess[12]; in one study, the rates of this complication in the cervical, thoracic, and lumbar spine were 28%, 22%, and 12%, respectively.[2]

Since vertebral osteomyelitis is in most cases a secondary complication of a distant infection with hematogenous seeding, the symptoms and signs of osteomyelitis may initially be dominated by manifestations of the primary infection. A source of infection is detected in about half the cases.[4] Endocarditis is diagnosed in up to a third of cases of vertebral osteomyelitis.[3] Less commonly, patients who are known to have endocarditis are found secondarily to have vertebral osteomyelitis as well, a finding that is consistent with seeding of the bone in the setting of continuous bacteremia.[8]

The differential diagnosis of back pain in a febrile patient is broad and includes a viral syndrome, pyelonephritis, and pancreatitis, among other causes. In the absence of fever, back pain may be attributed to multiple other causes (e.g., osteoporotic fracture, spondylarthritis, degenerative disk disease, or spinal stenosis). As a result of the nonspecific nature of many signs and symptoms of vertebral osteomyelitis and the frequent absence of fever, there is often a considerable delay between the onset of symptoms and diagnosis (a range of 42 to 59 days in five studies).[13-17]

Testing

An increased leukocyte count or a high percentage of neutrophils (>80%) does not have high sensitivity for the diagnosis of osteomyelitis.[18,19] In a series of patients with staphylococcal vertebral osteomyelitis, these findings were present in only 64% and 39% of the patients, respectively.[18] In contrast, increases in the erythrocyte sedimentation rate and C-reactive protein level are highly sensitive and have been reported in 98% and 100% of cases, respectively.[18,20] The C-reactive protein level is more closely correlated with the clinical response to therapy than is the erythrocyte sedimentation rate and is therefore the preferred marker of infection, at least in the case of postoperative spinal wound infections.[20]

Blood cultures are crucial in the evaluation of vertebral osteomyelitis. A positive culture precludes the need for more invasive procedures. In a systematic review of studies of vertebral osteomyelitis, positive blood cultures were reported in 58% of the cases (range across studies, 30 to 78%).[4] If vertebral osteomyelitis is suspected after imaging is performed (see below) and blood cultures do not show growth of microorganisms, a biopsy is generally warranted. If polymicrobial osteomyelitis is suspected (e.g., intraabdominal sepsis), a biopsy should be performed regardless of whether the blood cultures are positive.[21] If the patient has a paravertebral, epidural, or psoas abscess, drainage guided by computed tomography (CT) (with subsequent staining and culturing of the specimen) may make a bone biopsy unnecessary.

A culture of a biopsy specimen, whether the specimen is obtained with the use of a CT-guided or an open technique, has a higher overall diagnostic yield than does a blood culture (77%; range across studies, 47 to 100%).[4] Bone samples should be cultured for aerobic and anaerobic bacteria and for fungi. Among patients with a suggestive history (e.g., a stay in a region in which relevant bacteria are endemic or a subacute presentation), cultures should also be performed for mycobacteria and brucella species.[14,22] In addition, histopathological analysis is useful, because the presence of leukocytes in the specimens distinguishes infection from contamination. Furthermore, the presence of granulomas suggests particular causes, such as brucellosis or tuberculosis. The choice between open and CT-guided biopsy depends on the availability of
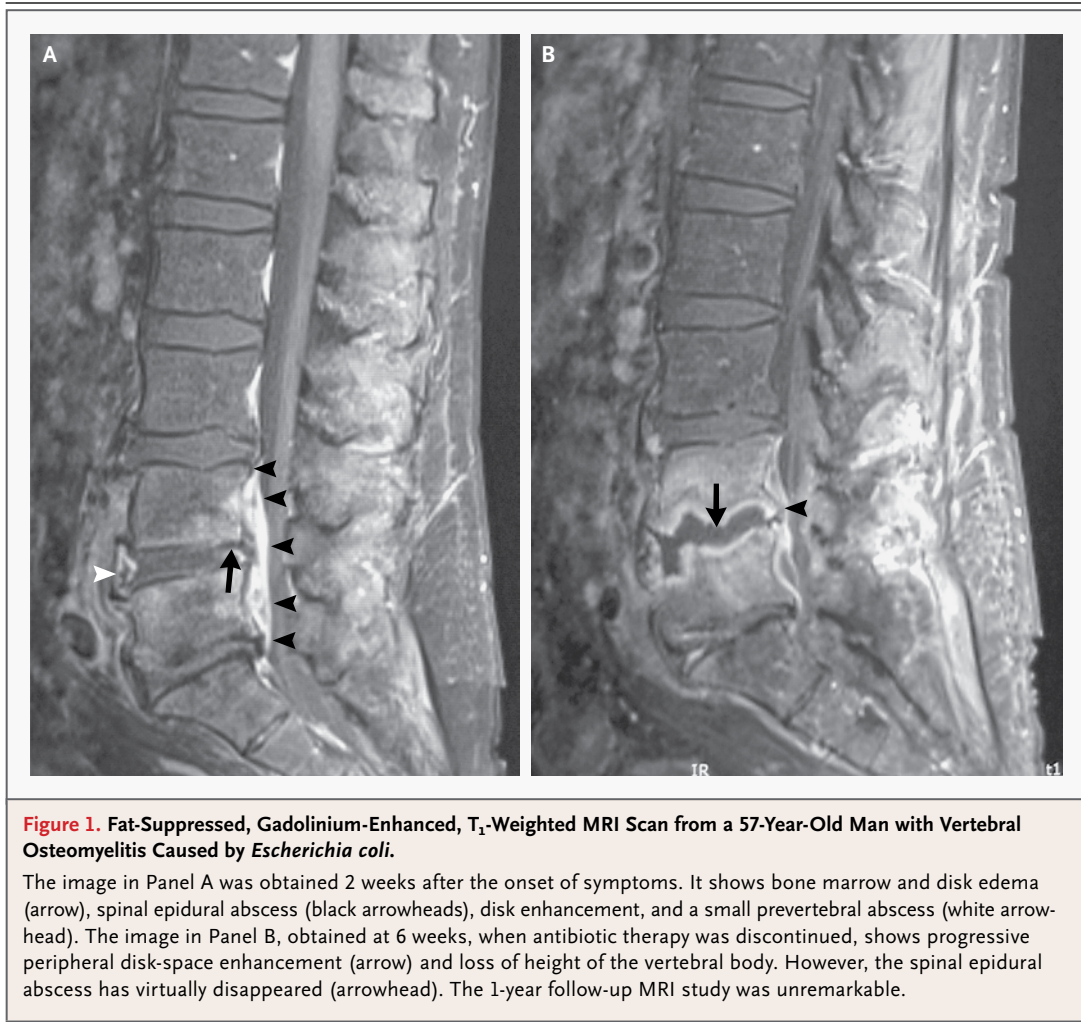
Figure 1. Fat-Suppressed, Gadolinium-Enhanced, T$_1$-Weighted MRI Scan from a 57-Year-Old Man with Vertebral Osteomyelitis Caused by *Escherichia coli*.

The image in Panel A was obtained 2 weeks after the onset of symptoms. It shows bone marrow and disk edema (arrow), spinal epidural abscess (black arrowheads), disk enhancement, and a small prevertebral abscess (white arrowhead). The image in Panel B, obtained at 6 weeks, when antibiotic therapy was discontinued, shows progressive peripheral disk-space enhancement (arrow) and loss of height of the vertebral body. However, the spinal epidural abscess has virtually disappeared (arrowhead). The 1-year follow-up MRI study was unremarkable.

the latter and the respective yield at a given center. If the suspicion of vertebral osteomyelitis is high despite a negative result of a CT-guided biopsy, an open biopsy should be considered. False negative blood cultures or biopsy samples are especially frequent among patients who have been treated with antibiotics before the culture or biopsy sample is obtained. If the patient is not critically ill (i.e., has no overt signs of sepsis or abscess), antimicrobial therapy should be started only after microbial growth has been documented in either blood cultures or bone-biopsy samples.

If antibiotic therapy has been initiated but the patient's condition is clinically stable, a biopsy should be postponed for at least 48 hours after the most recent antibiotic dose has been administered in order to increase the yield; an antibiotic-free interval of 1 to 2 weeks would allow a higher yield but for safety reasons is generally not advisable in cases of acute osteomyelitis.

Imaging

Imaging is used to rule out other diseases as a cause of symptoms and signs on presentation, to identify findings that may be suggestive of osteomyelitis, to localize the infection, and to look for pyogenic complications, such as an epidural, paravertebral, or disk-space abscess. Plain radiography is helpful as a first step, since it is widely available and may reveal an alternative diagnosis (e.g., bone metastases or an osteoporotic fracture); however, it is not a sensitive test for osteomyelitis. In patients with neurologic impairment, magnetic resonance imaging (MRI) should be the first diagnostic step, to look for spinal epidural abscess and to rule out a herniated disk. MRI has a high accuracy (90%) for diagnosing spinal osteomyelitis.[23] It typically shows high signal intensity within the disk on T$_2$-weighted sequences and loss of the intranuclear cleft. The vertebral end plates are rapidly destroyed and high-signal-inten-

Figure 2. Fat-Suppressed, Gadolinium-Enhanced, T_1-Weighted MRI Scan from a 71-Year-Old Woman with Chronic Lumbar Pain.

The image in Panel A, obtained during a period of exacerbation of acute pain, suggests vertebral osteomyelitis because of gadolinium enhancement in the vertebral bodies (arrows) and disk (arrowhead). However, an MRI scan obtained 20 months earlier (Panel B) shows a similar picture, thus confirming a degenerative origin (erosive osteochondrosis) rather than an infectious origin.

sity marrow edema is visible (Fig. 1).[23] Typically, the disk space and two adjacent vertebral bodies are involved. MRI is more sensitive than CT for the early detection of osteomyelitis. Therefore, CT is generally indicated only if the patient has a contraindication to MRI or if CT is needed to guide a percutaneous biopsy. Neither CT nor MRI has 100% specificity; the diagnosis that is most difficult to differentiate from vertebral osteomyelitis on imaging studies is erosive osteochondrosis, because its features may mimic those of vertebral osteomyelitis (Fig. 2).[24]

Three-phase technetium-99m bone scans are typically positive within a few days after the onset of symptoms, but the findings are nonspecific; the reported accuracy in the case of vertebral osteomyelitis is 67%.[25] The accuracy of Ga-67 scintigraphy with single-photon-emission CT (SPECT) is 92%, which is higher than that of technetium-99m scanning[25] and similar to that of MRI, but it is less sensitive for the detection

of an epidural abscess. Indium-111–labeled leukocyte scintigraphy and antigranulocyte scintigraphy are more specific for this diagnosis but have a low sensitivity for vertebral osteomyelitis (<20%).[23,26] Therefore, these tests have been replaced by MRI in most centers. Positron-emission tomographic (PET) scanning with ^{18}F-fluorodeoxyglucose has a diagnostic accuracy similar to that of MRI and may be a better choice when the patient has metallic implants.[23] However, this technique is not generally available, and experience with it is still limited.[27]

TREATMENT

Antimicrobial Treatment

Whenever possible, antimicrobial therapy of vertebral osteomyelitis should be directed against an identified microorganism. This is possible in most cases, provided that the patient did not receive antimicrobial therapy before samples were obtained for culturing. Data from randomized,

controlled trials that were specifically focused on antimicrobial therapy for vertebral osteomyelitis are lacking, and information on cure rates is derived largely from observational studies involving (but not necessarily limited to) patients with vertebral osteomyelitis. In one retrospective study involving 120 patients who had vertebral osteomyelitis due to different types of microorganisms and who were treated with various intravenous regimens for a mean duration of 32 days, the cure rate at 6 months was 91%.[28] In a study involving 253 patients, of whom more than 90% were treated with intravenous antibiotics for at least 4 weeks, the rate of survival without relapse at 1 year was 88%.[2] In an observational study comparing the outcomes in 28 patients with and 63 without concomitant endocarditis, the rate of death was similar in the two groups (7.1% and 12.7%, respectively), but among survivors, those with endocarditis had a higher rate of relapse of vertebral osteomyelitis than did those without endocarditis (8% vs. 1.9%).[3]

In a meta-analysis of 22 randomized trials of antibiotic therapy for various types of bone and joint infections, with data on 1-year follow-up, the eradication rate was 79% (95% confidence interval, 66 to 94).[29] With the exception of infections associated with orthopedic devices (for which regimens including rifampin appeared to be superior), there were no significant differences in the outcome according to the specific antibiotic therapy used.[29,30] The results of seven controlled trials involving patients with osteomyelitis, reported between 1987 and 1999, also showed no significant difference in the outcome between patients who received intravenous therapy and those who received oral fluoroquinolones.[29,31] However, more recent changes in resistance patterns of staphylococci render these trials outdated. Although fluoroquinolones are still the first choice in the treatment of osteomyelitis due to gram-negative bacilli, the rapid emergence of resistance to these drugs precludes their use as single agents against S. aureus.[30,32]

Table 1 provides a summary of suggested antibiotic regimens for the most common microorganisms; suggestions are based primarily on observational studies and expert opinion.[2-7,12,18,29,35-38] Antimicrobial agents should be chosen according to the type of microorganism and its susceptibility. Intravenous therapy is still the standard mode of treatment for gram-positive bacteria.

However, oral bactericidal drugs with excellent bioavailability, such as fluoroquinolones, allow for the possibility of an early switch to the oral route (e.g., the combination of a fluoroquinolone and rifampin for the treatment of staphylococcal osteomyelitis).[33,39] In a randomized trial involving patients in Europe with deep-seated or bacteremic staphylococcal infection, including 35 patients with acute bone or joint infection, the combination of an oral fluoroquinolone and rifampin resulted in cure rates that were similar to those with the standard intravenous therapy.[33] Clindamycin has good bioavailability but is bacteriostatic only against staphylococci. It is adequate for long-term treatment of chronic S. aureus osteomyelitis, but data from trials of clindamycin for the treatment of acute S. aureus osteomyelitis in adults are lacking. β-Lactam antibiotics should not be given orally for the treatment of osteomyelitis because of their low bioavailability.

There are no data from controlled trials that suggest the optimal duration of therapy. The recommended duration ranges from 4 to 6 weeks[28,40] to 3 months.[22,41] In an observational study comparing the outcomes in patients treated for various periods, the rates of recovery, relapse, and death when the duration of treatment was 6 weeks or less (36 patients), as compared with a duration of more than 6 weeks (84 patients), were similar[28]; the two study groups appeared to have similar characteristics, except that patients receiving treatment for more than 6 weeks were older. Prolonged antibiotic treatment is recommended in the case of patients who have abscesses that have not been drained and in the case of patients who have spinal implants.[7,30,38]

Surgical Treatment

Acute hematogenous osteomyelitis can usually be successfully treated with antibiotics alone. Surgery is required mainly for diagnostic purposes (open biopsy).[4] In addition, surgery may be needed to drain an abscess, although drainage with the use of a CT-guided catheter is sufficient in many cases. Surgery is often not required in the case of spontaneous vertebral osteomyelitis, but surgical débridement is always required in the case of infection associated with a spinal implant.[7] In cases of late-onset infection (symptoms developing more than 30 days after spinal-implant surgery), retention of the implant is associated with an increased risk of treatment failure, and

Table 1. Suggested Antibiotic Regimens for Common Causes of Osteomyelitis in Adults.*

Microorganism	First Choice†	Alternative Choice
Staphylococcus aureus or coagulase-negative staphylococci (methicillin-sensitive)	β-Lactam at high dose (e.g., nafcillin or oxacillin, 2 g administered intravenously every 6 hr, or cefazolin, 1–2 g administered intravenously every 8 hr)‡	Fluoroquinolone plus rifampin[33] (e.g., levofloxacin, 750 mg taken orally once daily, plus rifampin, 300 mg taken orally every 12 hr)§
S. aureus or coagulase-negative staphylococci (methicillin-resistant)	Glycopeptide (e.g., vancomycin, 1 g administered intravenously every 12 hr¶)[34]	Daptomycin, ≥6 mg/kg of body weight once daily,[35,36] or rifampin, 300 mg taken orally every 12 hr, plus levofloxacin, 750 mg taken orally once daily, or one double-strength tablet containing trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, taken orally every 8 hr, or fusidic acid, 500 mg taken orally every 8 hr
Streptococcal species	Penicillin G, 5 million units administered intravenously every 6 hr‡	Ceftriaxone, 2 g administered intravenously once daily
Enterobacteriaceae, quinolone-susceptible	Fluoroquinolone (e.g., ciprofloxacin, 750 mg taken orally every 12 hr)	Ceftriaxone, 2 g administered intravenously once daily
Enterobacteriaceae, quinolone-resistant, including extended-spectrum β-lactamase–producing *E. coli*	Carbapenem (e.g., imipenem, 500 mg administered intravenously every 6 hr)‖	
Pseudomonas aeruginosa	Cefepime or ceftazidime, 2 g every 8 hr (consider a combined regimen with an aminoglycoside), for 2 to 4 wk, followed by ciprofloxacin, 750 mg taken orally every 12 hr**	Piperacillin–tazobactam, 4.5 g every 6 hr (consider a combined regimen with an aminoglycoside), for 2 to 4 wk, followed by ciprofloxacin, 750 mg taken orally every 12 hr**
Anaerobes	Clindamycin, 300–600 mg administered intravenously every 6–8 hr	Penicillin G, 5 million units administered intravenously every 6 hr, or ceftriaxone, 2 g administered intravenously once daily, against gram-positive anaerobes (e.g., *Propionibacterium acnes*); metronidazole, 500 mg taken orally every 8 hr, against gram-negative anaerobes (e.g., bacteroides species)

* Regimens are shown for common causes of osteomyelitis, not including infection from spinal implants. The list is not intended to be comprehensive. All doses are for adults, assuming normal renal function.
† The choice of antibiotic should be based on in vitro sensitivity data. The total duration of antimicrobial treatment is generally 6 weeks.
‡ In patients with delayed hypersensitivity, cefazolin (1 to 2 g administered intravenously every 8 hours) can be used. In patients with immediate hypersensitivity, penicillin should be replaced by vancomycin (1 g administered intravenously every 12 hours).
§ There is less experience with oral regimens for staphylococcus than with intravenous regimens, but oral regimens are used, particularly in Europe, and often after a short initial course of intravenous antibiotics.
¶ The trough vancomycin concentration should be 15 to 20 μg per milliliter.[34]
‖ The failure of ertapenem treatment has been reported.[37]
** The rationale for starting ciprofloxacin only after pretreatment with a β-lactam (plus an aminoglycoside) is the increased risk of emergence of quinolone resistance in the presence of a high bacterial load.

removal is recommended whenever possible.[7] In a minority of patients, reconstruction and stabilization of large defects may be needed.[42,43] If bone imaging shows substantial destruction of the bone, an orthopedist should be consulted regarding the use of a fitted back brace or internal fixation.

Follow-up Assessment during Therapy

Clinical assessment at 4 weeks is useful for assessing the response to treatment. Lack of improvement in symptoms (continued fever and no reduction in pain) or a persistently elevated C-reactive protein level (above 30 mg per liter) is a predictor of treatment failure.[20,44] MRI is less

useful, since there is a poor correlation between clinical healing and improvement on MRI. In one study,[44] all the patients who had improvement on MRI had clinical improvement as well, but 85% of those whose MRI findings were unchanged or worse at 4 to 8 weeks also had clinical improvement. Follow-up MRI is warranted only if there is no indication of clinical improvement at 4 weeks (i.e., no reduction in symptoms or the C-reactive protein level) or if an epidural abscess is suspected (on the basis of increasing back pain or new neurologic symptoms) at any time during treatment.[12] In the case of a large abscess that has not been surgically treated, its resolution should be confirmed by repeat MRI before antibiotic therapy is discontinued.

AREAS OF UNCERTAINTY

Molecular diagnosis is not currently a standard diagnostic tool in the evaluation of osteomyelitis. Nevertheless, when blood and tissue cultures are negative, broad-range polymerase-chain-reaction (PCR) analysis of specimens obtained by means of biopsy or puncture should be considered if this technique is available,[45] since it may allow the detection of microorganisms that are difficult to identify, such as *Kingella kingae*, anaerobic bacteria, streptococcus species, bartonella species, brucella species, and *Tropheryma whippelii*.[45,46] However, conventional broad-range PCR has suboptimal sensitivity and specificity (due to contamination) and cannot provide information on the susceptibility of the microorganisms to antibiotics.

There are no data from randomized, controlled trials to guide decisions about specific antimicrobial regimens for vertebral osteomyelitis or the duration of therapy. Extrapolation from observational studies is hampered by the possibility of bias. For example, the choice and duration of therapy may be associated with the severity of the disease or with characteristics of patients that independently affect outcomes.

GUIDELINES

There are no U.S. guidelines for the management of vertebral osteomyelitis. Recent professional guidelines regarding the need to monitor vancomycin therapy during treatment are noted in Table 1.[34]

CONCLUSIONS AND RECOMMENDATIONS

Back pain and fever developed in the patient in the vignette after he underwent a prostate biopsy. MRI is warranted to look for changes consistent with vertebral osteomyelitis as well as epidural or other abscesses. Treatment should be guided by the results of the culture, and if the patient's condition remains clinically stable, treatment should not be started until the infecting agent is identified. A CT-guided or open bone biopsy is warranted if blood cultures are negative but MRI suggests osteomyelitis; however, a bone biopsy would be unnecessary in the case in the vignette given the positive blood cultures. Fluoroquinolone resistance precludes the use of oral therapy in this case. Because data are lacking to support the use of ertapenem (a medication taken once daily) for osteomyelitis (and failure of ertapenem treatment has been reported in a patient with osteomyelitis due to extended-spectrum β-lactamase–producing *E. coli*,[37]) I would treat this patient with imipenem. Although controlled trials are lacking, a treatment duration of 6 weeks is generally recommended, with longer courses recommended for persons with complicated infections and for persons who have spinal implants.

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