2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults[a]

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These guidelines are intended for use by infectious disease specialists, orthopedic surgeons, neurosurgeons, radiologists, and other healthcare professionals who care for patients with native vertebral osteomyelitis (NVO). They include evidence and opinion-based recommendations for the diagnosis and management of patients with NVO treated with antimicrobial therapy, with or without surgical intervention.

Keywords. spondylodiscitis; osteomyelitis; *Staphylococcus aureus*; spine infection; discitis.

EXECUTIVE SUMMARY

Native vertebral osteomyelitis (NVO) in adults is often the result of hematogenous seeding of the adjacent disc space from a distant focus, as the disc is avascular [1, 2]. The diagnosis of NVO can often be delayed several months and may initially be misdiagnosed and mismanaged as a degenerative process [3, 4]. NVO is typically diagnosed in the setting of recalcitrant back pain unresponsive to conservative measures and elevated inflammatory markers with or without fever. Plain radiographs of the spine are not sensitive for the early diagnosis of NVO. Magnetic resonance imaging (MRI) of the spine is often required to establish the diagnosis. Except in septic patients or patients with neurologic compromise, empiric antimicrobial therapy should be withheld, when possible, until a microbiologic diagnosis is confirmed. An image-guided or intraoperative aspiration or biopsy of a disc space or vertebral endplate sample submitted for microbiologic and pathologic examination often establishes the microbiologic or pathologic diagnosis of NVO [5]. NVO is commonly monomicrobial and most frequently due to *Staphylococcus aureus* [6–8]. The concomitant presence of *S. aureus* bloodstream infection within the preceding 3 months and compatible spine MRI changes preclude the need for a disc space aspiration in most patients [1, 9, 10]. Definitive therapy should be based on the results of culture and in vitro susceptibility testing. The majority of patients are cured with a 6-week course of antimicrobial therapy, but some patients may need

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[a]Guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

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surgical debridement and/or spinal stabilization during or after a course of antimicrobial therapy [7, 11–13]. Indications for surgery may include the development of neurologic deficits or symptoms of spinal cord compression and evidence of progression or recurrence despite proper antimicrobial therapy [6]. Most patients can be followed symptomatically and by monitoring laboratory parameters such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [14]. Repeat imaging studies should be reserved for patients failing to show clinical and or laboratory improvement [15, 16].

Summarized below are the Infectious Diseases Society of America (IDSA) recommendations pertaining to the diagnosis and management of patients with NVO. The expert panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [17–20] (Table 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines.

RECOMMENDATIONS FOR CLINICAL DIAGNOSTICS

I. When Should the Diagnosis of NVO Be Considered?

Recommendations

1. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and fever (strong, low).
2. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and elevated ESR or CRP (strong, low).
3. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and bloodstream infection or infective endocarditis (strong, low).
4. Clinicians may consider the diagnosis of NVO in patients who present with fever and new neurologic symptoms with or without back pain (weak, low).
5. Clinicians may consider the diagnosis of NVO in patients who present with new localized neck or back pain, following a recent episode of *Staphylococcus aureus* bloodstream infection (weak, low).

II. What Is the Appropriate Diagnostic Evaluation of Patients With Suspected NVO?

Recommendations

6. We recommend performing a pertinent medical and motor/sensory neurologic examination in patients with suspected NVO (strong, low).
7. We recommend obtaining bacterial (aerobic and anaerobic) blood cultures (2 sets) and baseline ESR and CRP in all patients with suspected NVO (strong, low).
8. We recommend a spine MRI in patients with suspected NVO (strong, low).
9. We suggest a combination spine gallium/Tc99 bone scan, or computed tomography scan or a positron emission tomography scan in patients with suspected NVO when MRI cannot be obtained (eg, implantable cardiac devices, cochlear implants, claustrophobia, or unavailability) (weak, low).
10. We recommend obtaining blood cultures and serologic tests for *Brucella* species in patients with subacute NVO residing in endemic areas for brucellosis (strong, low).
11. We suggest obtaining fungal blood cultures in patients with suspected NVO and at risk for fungal infection (epidemiologic risk or host risk factors) (weak, low).
12. We suggest performing a purified protein derivative (PPD) test or obtaining an interferon-γ release assay in patients with subacute NVO and at risk for *Mycobacterium tuberculosis* NVO (ie, originating or residing in endemic regions or having risk factors) (weak, low).
13. In patients with suspected NVO, evaluation by an infectious disease specialist and a spine surgeon may be considered (weak, low).

III. When Should an Image-Guided Aspiration Biopsy or Additional Workup Be Performed in Patients With NVO?

Recommendations

14. We recommend an image-guided aspiration biopsy in patients with suspected NVO (based on clinical, laboratory, and imaging studies) when a microbiologic diagnosis for a known associated organism (*S. aureus*, *Staphylococcus lugdunensis*, and *Brucella* species) has not been established by blood cultures or serologic tests (strong, low).
15. We advise against performing an image-guided aspiration biopsy in patients with *S. aureus*, *S. lugdunensis*, or *Brucella* species bloodstream infection suspected of having NVO based on clinical, laboratory, and imaging studies (strong, low).
16. We advise against performing an image-guided aspiration biopsy in patients with suspected subacute NVO (high endemic setting) and strongly positive *Brucella* serology (strong, low).

IV. How Long Should Antimicrobial Therapy Be Withheld Prior to an Image-Guided Diagnostic Aspiration Biopsy in Patients With Suspected NVO?

Recommendations

17. In patients with neurologic compromise with or without impending sepsis or hemodynamic instability, we recommend immediate surgical intervention and initiation of empiric antimicrobial therapy (strong, low).

Table 1. Strength of Recommendations and Quality of the Evidence

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation, very-low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

Abbreviation: RCT, randomized controlled trial.

V. When Is It Appropriate to Send Fungal, Mycobacterial, or Brucellar Cultures or Other Specialized Testing Following an Image-Guided Aspiration Biopsy in Patients With Suspected NVO?

Recommendations

18. We suggest the addition of fungal, mycobacterial, or brucellar cultures on image-guided biopsy and aspiration specimens in patients with suspected NVO if epidemiologic, host risk factors, or characteristic radiologic clues are present (weak, low).
19. We suggest the addition of fungal and mycobacterial cultures and bacterial nucleic acid amplification testing to appropriately stored specimens if aerobic and anaerobic bacterial cultures reveal no growth in patients with suspected NVO (weak, low).

VI. When Is It Appropriate to Send the Specimens for Pathologic Examination Following an Image-Guided Aspiration Biopsy in Patients With Suspected NVO?

Recommendation

20. If adequate tissue can be safely obtained, pathologic specimens should be sent from all patients to help confirm a diagnosis of NVO and guide further diagnostic testing, especially in the setting of negative cultures (strong, low).

VII. What Is the Preferred Next Step in Patients With Nondiagnostic Image-Guided Aspiration Biopsy and Suspected NVO?

Recommendations

21. In the absence of concomitant bloodstream infection, we recommend obtaining a second aspiration biopsy in patients with suspected NVO in whom the original image-guided aspiration biopsy specimen grew a skin contaminant (coagulase-negative staphylococci [except *S. lugdunensis*], *Propionibacterium* species, or diphtheroids) (strong, low).
22. In patients with a nondiagnostic first image-guided aspiration biopsy and suspected NVO, further testing should be done to exclude difficult-to-grow organisms (eg, anaerobes, fungi, *Brucella* species, or mycobacteria) (strong, low).
23. In patients with suspected NVO and a nondiagnostic image-guided aspiration biopsy and laboratory workup, we suggest either repeating a second image-guided aspiration biopsy, performing percutaneous endoscopic discectomy and drainage (PEDD), or proceeding with an open excisional biopsy (weak, low).

RECOMMENDATIONS FOR CLINICAL THERAPY

VIII. When Should Empiric Antimicrobial Therapy Be Started in Patients With NVO?

Recommendations

24. In patients with normal and stable neurologic examination and stable hemodynamics, we suggest holding empiric antimicrobial therapy until a microbiologic diagnosis is established (weak, low).
25. In patients with hemodynamic instability, sepsis, septic shock, or severe or progressive neurologic symptoms, we suggest the initiation of empiric antimicrobial therapy in conjunction with an attempt at establishing a microbiologic diagnosis (weak, low).

IX. What Is the Optimal Duration of Antimicrobial Therapy in Patients With NVO?

Recommendations

26. We recommend a total duration of 6 weeks of parenteral or highly bioavailable oral antimicrobial therapy for most patients with bacterial NVO (strong, low).
27. We recommend a total duration of 3 months of antimicrobial therapy for most patients with NVO due to *Brucella* species (strong, moderate).

X. What Are the Indications for a Surgical Intervention in Patients With NVO?

Recommendations

28. We recommend surgical intervention in patients with progressive neurologic deficits, progressive deformity, and spinal instability with or without pain despite adequate antimicrobial therapy (strong, low).
29. We suggest surgical debridement with or without stabilization in patients with persistent or recurrent bloodstream infection (without alternative source) or worsening pain despite appropriate medical therapy (weak, low).
30. We advise against surgical debridement and/or stabilization in patients who have worsening bony imaging findings at 4–6 weeks in the setting of improvement in clinical symptoms, physical examination, and inflammatory markers (weak, low).

RECOMMENDATIONS FOR CLINICAL FOLLOW-UP

XI. How Should Failure of Therapy Be Defined in Treated Patients With NVO?

Recommendation

31. We suggest that persistent pain, residual neurologic deficits, elevated markers of systemic inflammation, or radiographic findings alone do not necessarily signify treatment failure in treated NVO patients (weak, low).

XII. What Is the Role of Systemic Inflammatory Markers and MRI in the Follow-up of Treated Patients With NVO?

Recommendations

32. We suggest monitoring systemic inflammatory markers (ESR and or CRP) in patients with NVO after approximately 4 weeks of antimicrobial therapy, in conjunction with a clinical assessment (weak, low).
33. We recommend against routinely ordering follow-up MRI in patients with NVO in whom a favorable clinical and laboratory response to antimicrobial therapy was observed (strong, low).
34. We suggest performing a follow-up MRI to assess evolutionary changes of the epidural and paraspinal soft tissues in patients with NVO who are judged to have a poor clinical response to therapy (weak, low).

XIII. How Do You Approach a Patient With NVO and Suspected Treatment Failure?

Recommendations

35. In patients with NVO and suspected treatment failure, we suggest obtaining markers of systemic inflammation (ESR and CRP). Unchanged or increasing values after 4 weeks of treatment should increase suspicion for treatment failure (weak, low).
36. We recommend obtaining a follow-up MRI with emphasis on evolutionary changes in the paraspinal and epidural soft

tissue findings in patients with NVO and suspected treatment failure (strong, low).

37. In patients with NVO and clinical and radiographic evidence of treatment failure, we suggest obtaining additional tissue samples for microbiologic (bacteria, fungal, and mycobacterial) and histopathologic examination, either by image-guided aspiration biopsy or through surgical sampling (weak, very low).
38. In patients with NVO and clinical and radiographic evidence of treatment failure, we suggest consultation with a spine surgeon and an infectious disease physician (weak, very low).

INTRODUCTION

The incidence of NVO varies by country, age of the population studied, and whether endemic infections are included. In one study from France, the overall incidence of NVO was 2.4 per 100 000. The incidence increased with age to reach 6.5 per 100 000 in patients 50–70 years of age [21]. Although rare, NVO is the most common form of hematogenous osteomyelitis in patients aged >50 years and represents 3%–5% of all cases of osteomyelitis [8]. An increase in the incidence of NVO has been attributed to an increase in susceptible patients such as intravenous drug users, individuals undergoing hemodialysis, and immunocompromised hosts.

The diagnosis of NVO may be difficult and requires many different modalities including serologic, radiographic, and microbiologic diagnostic tests. For the purpose of these guidelines, the term "image-guided aspiration biopsy" epitomizes a needle aspiration, typically from disc space, performed either under computed tomographic (CT) or fluoroscopic guidance. The aspiration biopsy typically incorporates 2 specimens: aspiration fluid and a tissue sample. The management of NVO necessitates a prolonged course of intravenous and or oral antimicrobial therapy as well as surgical debridement in almost 50% of patients [6]. Many questions pertaining to the optimal diagnostic strategies and management of patients with NVO remain unanswered. The primary focus of these guidelines will be to provide evidence-based guidelines, and, if that is not possible, consensus statements that address current controversies in the diagnosis and management of patients with NVO. An exhaustive review of the pathophysiology of NVO is not within the scope of these guidelines. Interested readers are encouraged to review selected references [1, 22, 23]. For the purpose of the guidelines, the following terms will be used: bacterial NVO, brucellar NVO, fungal NVO, or mycobacterial NVO, with bacterial NVO denominating infections due to common bacterial infections (eg, staphylococci, aerobic gram-negatives, streptococci, and anaerobes). The other terms are self-explanatory. In many instances, the panel has made recommendations based on expert opinion only, realizing that the amount of data to support a specific recommendation is limited. The panel acknowledges that there are diverse practice patterns that seem to be equally effective in the management of NVO. However, an essential advantage of this specific therapeutic approach is the strong collaboration between all involved medical and surgical specialists (eg, orthopedic surgeons, radiologists, neurosurgeons, infectious disease specialists, pain specialists). It is anticipated that adoption of these guidelines may help reduce morbidity, mortality, and the costs associated with the management of NVO. The panel acknowledges that not all medical institutions will have the adequate resources to implement all of the recommendations in these guidelines. Proper referral may be needed. The panel elected not to address patients with spinal implant–associated infections, patients with postprocedure infections, and patients with epidural abscess without associated NVO. The management of these entities may differ from the management of patients with NVO. These topics can be addressed in future guidelines. The panel addressed the following 13 clinical questions:

(I) When should the diagnosis of NVO be considered?
(II) What is the appropriate diagnostic evaluation of patients with suspected NVO?
(III) When should an image-guided aspiration biopsy or additional workup be performed in patients with NVO?
(IV) How long should antimicrobial therapy be withheld prior to an image-guided diagnostic aspiration biopsy in patients with suspected NVO?
(V) When is it appropriate to send fungal, mycobacterial, or brucellar cultures or other specialized testing following an image-guided aspiration biopsy in patients with suspected NVO?
(VI) When is it appropriate to send the specimens for pathologic examination following an image-guided aspiration biopsy in patients with suspected NVO?
(VII) What is the preferred next step in patients with nondiagnostic image-guided aspiration biopsy and suspected NVO?
(VIII) When should empiric antimicrobial therapy be started in patients with NVO?
(IX) What is the optimal duration of antimicrobial therapy in patients with NVO?
(X) What are the indications for a surgical intervention in patients with NVO?
(XI) How should failure of therapy be defined in treated patients with NVO?
(XII) What is the role of systemic inflammatory markers and MRI in the follow-up of treated patients with NVO?
(XIII) How do you approach a patient with NVO and suspected treatment failure?

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate healthcare delivery for specific clinical circumstances [24]. Attributes of high-quality guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [24].

METHODOLOGY

Panel Composition

We convened a panel of 11 experts, including specialists in infectious diseases, spine orthopedic surgery, and neuroradiology. The panel included physicians affiliated with an academic institution, and physicians who are mainly clinicians. One is a spine orthopedic surgeon and 1 is a neuroradiologist. Among the 11 panel members, 9 are from the United States, 1 is from Europe, and 1 is from the Middle East.

Literature Review and Analysis

In accordance with the IDSA format, the panel identified 13 clinical questions to address and assigned 3 different groups in charge of drafting responses to the questions identified, divided into the Diagnosis, Management, and Follow-up sections of the guidelines. Panel members thoroughly reviewed the literature pertinent to each of the questions using PubMed/Medline, Cochrane Library, Elton B. Stephens Company, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Google Scholar, the National Guidelines Clearinghouse, ClinicalTrials.gov, references in published articles, pertinent websites, textbooks, and abstracts of original research and review articles in any language on NVO.

The search looked at publications from 1970 to December 2014 to find articles that assessed NVO using the following keywords: vertebral osteomyelitis, pyogenic, infectious, discitis, spondylodiscitis, spinal infection, epidural abscess, diagnostic, therapy, aspiration, antimicrobial therapy, MRI, treatment, empiric antimicrobial therapy, and surgical intervention.

Process Overview

In creating the guidelines, the panel followed the newly created Grading of Recommendations Assessment, Development and Evaluation (GRADE) system recommended by IDSA. This included systematically weighing the quality of the available evidence and grading our recommendations. To evaluate evidence, the panel followed a process consistent with other IDSA guidelines, including a systematic weighing of the quality of the evidence and the grade of recommendation. High-quality evidence does not necessarily lead to strong recommendations; conversely, strong recommendations can arise from low-quality evidence if one can be confident that the desired benefits clearly outweigh the undesirable consequences. The main advantages of the GRADE approaches are the detailed and explicit criteria for grading the quality of evidence and the transparent process for making recommendations [17–20] (Table 1). This system requires that the assigned strength of a recommendation be either "strong" or "weak." The main criterion for assigning a "strong" recommendation is that the potential benefits clearly outweigh the potential risks. The panel chair reviewed all the recommendation grading and then worked with the panel to achieve consensus via regular teleconference and email communications.

Consensus Development Based on Evidence

The panel members met in person twice, during the 2010 and 2012 IDSA annual meetings, and participated in 9 teleconferences. The chair presented a preliminary version of the guidelines in 2012 and sought feedback via email from the panel. All panel members participated in the preparation of the clinical questions and writing for the draft guidelines, which were then collated, revised and disseminated for review to the entire panel. The guidelines were reviewed and endorsed by the European Society for Microbiology and Infectious Diseases, Musculoskeletal Infection Society, American Society of Spine Radiology, and Radiologic Spine Society. We also sought and received extensive feedback from several external reviewers, and the guideline manuscript was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC) and by the IDSA Board of Directors (Steven Schmidt recused himself from Board approval as he was a member of the guideline panel).

Guidelines and Conflicts of Interest

All members of the expert panel complied with the IDSA policy regarding conflicts of interest, which requires disclosure of any financial or other interests that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel were provided a conflicts of interest disclosure statement from IDSA and were asked to identify ties to companies developing products that might be affected by promulgation of the guidelines. The statement requested information regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel was instructed to make decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict, but no limiting conflicts were identified.

Revision Dates

At annual intervals, the panel chair, the liaison advisor, and the chair of the SPGC will determine the need for revisions of the

updated guidelines based on an examination of current literature. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend full revision of the guidelines to the IDSA SPGC and the Board for review and approval.

RECOMMENDATIONS FOR CLINICAL DIAGNOSTICS

I. When Should the Diagnosis of NVO Be Considered?

Recommendations

1. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and fever (strong, low).
2. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and elevated ESR or CRP (strong, low).
3. Clinicians should suspect the diagnosis of NVO in patients with new or worsening back or neck pain and bloodstream infection or infective endocarditis (strong, low).
4. Clinicians may consider the diagnosis of NVO in patients who present with fever and new neurologic symptoms with or without back pain (weak, low).
5. Clinicians may consider the diagnosis of NVO in patients who present with new localized neck or back pain, following a recent episode of *Staphylococcus aureus* bloodstream infection (weak, low).

Evidence Summary

NVO is a serious condition and if the diagnosis is delayed, it may lead to permanent spinal cord injury or septicemia. Because idiopathic back or neck pain are extremely common symptoms, the diagnosis of rare, albeit serious conditions such as infection or malignancy of the spine is often delayed. In one study, the average time to diagnosis was 2–4 months [25]. In another study, 34% of 101 patients with NVO were initially misdiagnosed [26]. The diagnosis can also be delayed in paraplegic patients [27]. Patients who are elderly, immunocompromised, or active intravenous drug abusers (IVDAs), have indwelling central catheters, or have undergone recent instrumentation are most at risk for bacterial NVO [28, 29]. *Mycobacterium tuberculosis* and *Brucella* species should be considered in areas of high endemicity [30]. *Mycobacterium avium* complex NVO should be considered in human immunodeficiency virus-infected patients presenting with back pain in the setting of immune reconstitution following initiation of antiretroviral therapy. The diagnosis of NVO is straightforward when patients present with focal acute back pain and fever. In this circumstance, imaging studies can lead to an accurate and definitive diagnosis. However, fever is only present in up to 45% of patients with bacterial NVO. Fever is rarely present in patients with mycobacterial, brucellar, or fungal NVO and may be masked in patients taking analgesics with antipyretic effects [31–35]. In patients with insidious chronic back pain or in patients with paraplegia, the diagnosis can be overlooked due to other, more common causes of back or neck pain. The pain is typically localized to the infected disc space area and is exacerbated by physical activity or percussion to the affected area. Pain may radiate to the abdomen, hip, leg, scrotum, groin, or perineum [36]. Paravertebral muscle tenderness and spasm, and limitation of spine movement, are the predominant physical examination findings. In a series of 253 patients with bacterial NVO, 43% had epidural or paravertebral extension [6]. Spinal cord or nerve root compression and meningitis may occur. Neurologic signs and symptoms are more commonly encountered in patients with cervical or thoracic involvement.

An elevated ESR or CRP result in patients with back pain, though not specific, has a sensitivity that can range from 94% to 100% [37, 38]. These inflammatory markers are often used to rule out the presence of an infection or a malignancy in patients with protracted back pain. Up to 40% of patients with NVO have a normal white blood cell (WBC) count [37]. Screening for multiple myeloma with an serum protein electrophoresis may be warranted, if the original workup including an image-guided biopsy remains inconclusive.

A history of back pain or radicular symptoms should be elicited in patients with a history of or concomitant *Staphylococcus aureus* bloodstream infection in the previous year [1, 9, 10]. A careful examination and percussion of the spine is warranted [37]. Patients with concomitant back pain and *S. aureus* bloodstream infection should be further investigated with an imaging study to rule out the presence of NVO or paraspinal abscess.

II. What Is the Appropriate Diagnostic Evaluation of Patients With Suspected NVO?

Recommendations

6. We recommend performing a pertinent medical and motor/sensory neurologic examination in patients with suspected NVO (strong, low).
7. We recommend obtaining bacterial (aerobic and anaerobic) blood cultures (2 sets) and baseline ESR and CRP in all patients with suspected NVO (strong, low).
8. We recommend a spine MRI in patients with suspected NVO (strong, low).
9. We suggest a combination spine gallium /Tc99 bone scan, or computed tomography scan or a positron emission tomography scan in patients with suspected NVO when MRI cannot be obtained (eg, implantable cardiac devices, cochlear implants, claustrophobia, or unavailability) (weak, low).
10. We recommend obtaining blood cultures and serologic tests for *Brucella* species in patients with subacute cases of NVO residing in endemic areas for brucellosis (strong, low).

11. We suggest obtaining fungal blood cultures in patients with suspected NVO and at risk for fungal infection (epidemiologic risk or host risk factors) (weak, low).
12. We suggest performing a PPD test or obtaining an interferon-γ release assay in patients with subacute NVO and at risk for *Mycobacterium tuberculosis* NVO (ie, originating or residing in endemic regions or having risk factors) (weak, low).
13. In patients with suspected NVO, evaluation by an infectious disease specialist and a spine surgeon may be considered (weak, low).

Evidence Summary

Medical and neurologic history and examinations should be performed on all patients with suspected NVO, including looking for signs of potential entry sources of hematogenous seeding. Pertinent history should focus on prior use of antimicrobials and prior surgical procedures, as well as history of urinary tract infection, bloodstream infection, skin or soft tissue infection, and intravenous drug use. An appropriate neurologic and medical examination should include an assessment of a motor and sensory function, including assessment for intestinal and urinary incontinence as well as signs and symptoms of infective endocarditis. It takes 3–6 weeks after the onset of symptoms for bone destruction to be evident on plain roentgenography. MRI, when feasible, should be the first diagnostic imaging of choice in patients with suspected NVO [39–41]. MRI of the spine has a sensitivity of 97%, specificity of 93%, and an accuracy of 94% in diagnosing NVO [41, 42]. The inability to distinguish the margins between the disc space and adjacent vertebral marrow on T1-weighted images associated with increased signal intensity from the disc and the adjacent involved marrow on T2-weighted images is the hallmark of bacterial NVO. In tuberculous or brucellar NVO, T1-weighted sequences appear to be more sensitive than T2-weighted sequences in demonstrating the inflammatory processes in the vertebral bodies [43]. Extension of the infectious process to the paravertebral space causing an epidural abscess or a paravertebral abscess is best seen on the gadolinium with diethylenetriaminepentacetate (Gd-DTPA)–enhanced MRI. Gd-DTPA enhancement may be the first sign of an acute inflammatory process and is used to enhance specificity [39]. MRI can also differentiate NVO from more common degenerative, traumatic, or neoplastic diseases. A repeat examination may be warranted within 1–3 weeks if the initial imaging study fails to show typical features of NVO [44].

In patients with implantable devices or severe claustrophobia, in whom MRI cannot be performed, a combination spine gallium/Tc99 bone scan can be performed. Gallium 67 (Ga67) is a group III b transition metal that is analogous to iron. It binds to lactoferrin produced by neutrophils, and siderophores produced by microorganisms. Gallium spine scan is typically combined with a bone scan and has a specificity of >90%. Its sensitivity of 91% makes it a valuable test to rule out NVO in patients with a questionable diagnosis [45, 46]. Indium-tagged WBC scanning lacks sensitivity in the diagnosis of NVO and should not be primarily used in establishing the diagnosis of NVO [47].

CT scanning is useful to assess the degree of bony and soft tissue involvement and is a very useful test to guide the percutaneous needle aspiration biopsy. Adjacent bone edema and narrowing of the disk space are among the earliest and most consistent findings but may be nonspecific. Positron emission tomographic (PET) scanning is highly sensitive for detecting chronic osteomyelitis. A negative PET scan excludes the diagnosis of osteomyelitis, including NVO, as the sensitivity of the test is expected to be very high in view of the high concentration of red marrow in the axial skeleton [48]. Selected third-party payers may limit reimbursement of PET scanning to patients with malignancy. Prior authorization may be warranted in these circumstances.

A minimum of 2 bacterial blood cultures (aerobic and anaerobic) sets should be routinely sent for all patients with suspected NVO [49, 50]. When brucella is suspected, such as in patients with high epidemiologic risk, blood cultures should be incubated for up to 2 weeks and *Brucella* serologic testing should be performed. Outside the United States, the Coombs test is commonly used for the diagnosis of brucellar NVO [51]; in one study, a titer of ≥1:160 was found in all patients with brucellar NVO [40]. Enzyme-linked immunosorbent assay (ELISA) has proven to be superior in complicated cases of brucellosis and might be of value in patients with brucellar NVO [51].

Fungal vertebral osteomyelitis is rare and can occur in patients with certain epidemiologic risks (blastomycosis, coccidioidomycosis, or histoplasmosis) or certain host risk factors such as immunocompromised hosts (*Aspergillus* species), IVDA, indwelling intravenous catheters (*Candida* species, *Aspergillus* species) [52–61]. Fungal serologies, antigen detection assays, and fungal blood cultures may aid in the diagnosis of patients at risk [62–67]. Routine blood cultures may also detect candidemia.

In patients with NVO with suspected tuberculous infection who reside in or have a history of residence in endemic areas, a PPD test or an interferon-γ release assay may be useful. However, false-positive and false-negative results may be encountered with these tests. Hence, in a scenario of high clinical suspicion, we recommend submission of aspiration specimens from an image-guided aspiration biopsy for mycobacterial tissue cultures regardless of the results of these tests. Radiographic findings that should raise suspicion for *Mycobacterium tuberculosis* NVO infection include (1) destruction of 2 or more contiguous vertebrae and their opposed endplates, (2) spread along the anterior longitudinal ligament, (3) disc infection with or

without a paraspinal mass or mixed soft tissue fluid collection, or, less commonly, (4) spondylitis without disc involvement [68]. An interferon-γ release assay has been shown to have a higher sensitivity than PPD, especially in patients with altered immunity [69]. A recent study found a higher sensitivity and specificity of enzyme-linked immunospot assay compared with PPD in the diagnosis of tuberculous NVO (sensitivity, 82.8% vs 58.6% and specificity, 81.3% vs 59.4%, respectively) [70].

III. When Should an Image-Guided Aspiration Biopsy or Additional Workup Be Performed in Patients With NVO?

Recommendations

14. We recommend an image-guided aspiration biopsy in all patients with suspected NVO (based on clinical, laboratory, and imaging studies) when a microbiologic diagnosis for a known associated organism (*S. aureus*, *Staphylococcus lugdunensis*, and *Brucella* species) has not been established by blood cultures or serologic tests (strong, low).
15. We advise against performing an image-guided aspiration biopsy in patients with *S. aureus*, *S. lugdunensis*, or *Brucella* species bloodstream infection suspected of having NVO based on clinical, laboratory, and imaging studies (strong, low).
16. We advise against performing an image-guided aspiration biopsy in patients with suspected subacute NVO (high endemic setting) and strongly positive *Brucella* serology (strong, low).

Evidence Summary

Empiric antimicrobial treatment of NVO should be deferred when possible until a diagnostic image-guided aspiration and/or biopsy of the affected area is obtained. Empiric therapy should not be deferred in life-threatening conditions such as sepsis or impending spinal cord compression. Every effort should be made to identify the offending pathogen prior to initiation of antimicrobial therapy. Image-guided diagnostic aspiration biopsy sampling should be the first invasive diagnostic step in patients suspected of having NVO. The aspiration biopsy may lead to a microbiologic diagnosis and obviate the need for open surgical intervention in 50%–60% of cases or more [5, 71–73]. Pathologic examination of aspiration specimens may help differentiate an infectious from a malignant or degenerative process. The sensitivity of the image-guided biopsy in evaluated studies varied between 30% and 74% [5, 74, 75]. Reported complications of image-guided aspiration biopsy sampling include aortic and vascular injuries, psoas muscle puncture or nerve damage, hematoma formation, and biopsy of incorrect level [76]. Although severe, these complications are exceedingly rare when this procedure is performed by a trained operator.

Image-guided specimens should be processed for pathological examination looking for the presence of acute or chronic inflammation, granuloma formation, and malignancy. In addition to bacterial cultures, mycobacterial, brucellar, and fungal cultures should be obtained in cases of subacute and chronic NVO [52].

The main microbiologic etiology of bacterial NVO is *S. aureus* [9]. Blood cultures can be positive in up to 50% of cases of *S. aureus* NVO. A positive blood culture for *S. aureus* obviates the need for an image-guided aspiration specimen in patients with clinical, laboratory, and radiologic findings suggestive of NVO [1, 10, 77]. In a national study from Denmark of 8739 patients with *S. aureus* bloodstream infection, an incidence of 6% of associated NVO was found in patients aged > 50 years in whom no obvious entry source was identified [77]. *Staphylococcus lugdunensis* has been associated with deep-seated infections and can often behave like *S. aureus* [78, 79]. A persistently positive blood culture for this organism in NVO may obviate the need for an image-guided biopsy. A sustained bloodstream infection with other coagulase-negative staphylococci in patients with suspected NVO receiving chronic hemodialysis or in patients with infected intravascular devices may also obviate the need for image-guided aspiration biopsy [80, 81]. The need for an image-guided aspiration biopsy in patients with suspected NVO and concomitant bloodstream infection with other microorganisms (ie, *Candida* species, Enterobacteriaceae, streptococci, *Pseudomonas* species) is left to the discretion of the treating physicians.

In endemic countries, *Brucella* is a very common cause of NVO. In a recent study from Greece, 11 of 33 patients admitted with spinal infections to a teaching hospital had brucellosis [40, 82]. A false-negative serologic test is unusual in patients with brucellar NVO. In one study, all patients with brucellar NVO had serum antibody titers of ≥1:160 [40]. For serum agglutination and Coombs titers, the cutoff point is ≥1:160. In an endemic setting, patients with suspected brucellar NVO with either positive blood cultures or serology may not require image-guided aspiration biopsy to confirm the diagnosis. In the United States, a low-endemicity country, an ELISA screen is performed initially, followed by a confirmatory agglutination test [52]. In this setting, a false-positive test for *Brucella* serology is more likely and an image-guided aspiration biopsy may be warranted [83]. Given the rarity of this infection in nonendemic areas, an evaluation by a spine surgeon and an infectious disease specialist is advised in the course of management of patients with brucellar NVO [52].

IV. How Long Should Antimicrobial Therapy Be Withheld Prior to an Image-Guided Diagnostic Aspiration Biopsy in Patients With Suspected NVO?

Recommendation

17. In patients with neurologic compromise with or without impending sepsis or hemodynamic instability, we recommend immediate surgical intervention and initiation of empiric antimicrobial therapy (strong, low).

Evidence Summary

Prior exposure to antimicrobial therapy has been associated with a decrease in the microbiologic yield of the image-guided biopsy in patients with NVO [72, 84–86]. In one study, this association was not statistically significant [87]. Holding antimicrobial therapy for a limited period of time prior to an image-guided aspiration biopsy to increase the sensitivity of culture results has been advocated [72, 84–86]. Pending further studies, the panel believes that holding antibiotics when feasible for 1–2 weeks is reasonable [88]. The optimal duration to hold antimicrobials may also be dependent on the half-life of the antimicrobial used and its postantibiotic effect. In patients with neurologic compromise, immediate surgical intervention and use of antimicrobial therapy are often required [89]. Furthermore, the panel believes that clinicians should not withhold antimicrobial therapy prior to image-guided biopsy in patients with impending sepsis or hemodynamic instability.

V. When Is It Appropriate to Send Fungal, Mycobacterial, or Brucellar Cultures or Other Specialized Testing Following an Image-Guided Aspiration Biopsy in Patients With Suspected NVO?

Recommendations

18. We suggest the addition of fungal, mycobacterial, or brucellar cultures on image-guided biopsy and aspiration specimens in patients with suspected NVO if epidemiologic, host risk factors, or characteristic radiologic clues are present (weak, low).
19. We suggest the addition of fungal and mycobacterial cultures, and bacterial nucleic acid amplification testing to appropriately stored specimens if aerobic and anaerobic bacterial cultures reveal no growth in patients with suspected NVO (weak, low).

Evidence Summary

The epidemiology of the causative agents for NVO varies across the geographic locations. In the majority of the world, typical bacterial agents such as *S. aureus*, streptococcal species, enteric bacteria, and other gram-negative rods are the most common pathogens identified in NVO [9]. However, in certain endemic regions, *M. tuberculosis* and *Brucella* species are among the common causative agents of NVO. Mete et al reported 100 cases of NVO in one center in Turkey between 2000 and 2007; 44% had typical bacterial pathogens, 24% had *Brucella* species, and 32% had *M. tuberculosis* [90]. In another study, Sakkas et al describe the epidemiology of NVO in a single center in central Greece over the same time period (2000–2007). Bacterial NVO accounted for 58% of the cases, *Brucella* species for 34%, and *M. tuberculosis* for 9% [91]. Using a national hospital database in France between 2002 and 2003, Grammatico et al reported that typical bacterial pathogens accounted for 58%, tuberculosis for 31%, and *Brucella* species for 0.7% of the cases [21].

There is a significantly higher incidence of human brucellosis in Spain and other countries of the Mediterranean basin, Latin America, the Middle East, parts of Africa, and Western Asia [92]. In a large retrospective study in Spain between 1982 and 2005, 918 patients were identified with brucellar infection, of which 10.4% had NVO [93]. For patients with suspected NVO from highly endemic countries, we recommend that *Brucella* species be considered in the differential diagnosis. In addition to brucellar serology tests and appropriate blood cultures, samples of image-guided aspiration biopsy should be cultured for bacteria when blood cultures and serology tests fail to confirm the diagnosis. When brucellar NVO is suspected, the physician is advised to alert the microbiology laboratory personnel to use extended incubation techniques and to mitigate the risk of laboratory-acquired *Brucella* infection.

Similarly, tuberculous NVO is seen with a greater frequency in parts of the world that have a higher incidence of disease. Tuberculosis is the most common cause of spinal infections worldwide [94–96]. In countries with low tuberculosis incidence, tuberculous NVO (Pott disease) is most commonly encountered in patients coming from areas of higher endemicity. In developed countries with low tuberculosis incidence, tuberculous NVO is seen in older patients (>40 years of age), whereas in countries with higher incidence, Pott disease is more commonly seen in children [94–96].

For patients with suspected NVO from regions of the world that have a higher incidence of tuberculosis, we suggest that Pott disease be considered in the differential diagnosis and that patients should be carefully evaluated for active tuberculosis at other sites. Tissue specimens should be sent for mycobacterial stain and culture. In addition, molecular tests can aid in the diagnosis. Polymerase chain reaction (PCR) was found in one study to have high sensitivity, specificity, and accuracy (95%, 83%, and 92%, respectively) in detecting *M. tuberculosis* from formaldehyde solution–fixed, paraffin-embedded tissue samples from histologically proven tuberculous spondylitis [97]. A comparative study of bacterial and mycobacterial NVO found that tuberculosis more commonly involves 3 or more vertebral bodies, compared with bacterial infections. Although this finding does not exclude bacterial NVO, the clinician should consider screening for *M. tuberculosis* when radiographic pictures are suggestive [98]. MRI of patients with NVO due to *M. tuberculosis* typically have >1 level involvement, larger paravertebral abscesses, heterogeneous magnetic resonance intensity of the involved vertebral bodies, increased rim enhancement with Gd-DTPA, and are more likely to have a thoracic level of involvement compared with patients with bacterial NVO [99, 100]. Although MRI findings of brucellar NVO tend to significantly overlap with the findings of bacterial NVO, patients

with brucellar NVO tend to have multilevel involvement and are less likely to have paravertebral collections [93]. Nontuberculous mycobacteria are rare causes of NVO but have been described in immunocompromised patients including those who have systemic lupus erythematous on receiving steroids, AIDS, interferon receptor defects, carcinoma, and chronic granulomatous disease (CGD) [101]. Intravesicular bacillus Calmette-Guerin (BCG) therapy used to treat carcinoma in situ of the bladder has also been associated with BCG NVO. In patients with intractable back pain, a history of bladder cancer treated with intravesical BCG instillation should be elucidated [102].

Fungal NVO is rare and is most commonly seen in immunocompromised patients. Fungal pathogens account for 0.5%–1.6% of the cases of NVO [95]. Risk factors for these pathogens are significant immunosuppression including steroid use, presence of a long-term indwelling venous catheter, IVDA, neutropenia, and CGD [95].

We suggest for patients with significant impairment of their immunity and clinical and radiographic evidence of NVO to have biopsy material sent for bacterial, mycobacterial, and fungal stains and cultures.

There are no studies to guide a clinician on managing patients with significant clinical or radiographic evidence of NVO and who have sterile blood cultures and an initial nondiagnostic spinal aspiration biopsy result. Studies have shown that microbiologic diagnosis is established in 50%–90% of patients who are aspirated off antibiotics [9, 103, 104]. In one study, the yield was found to increase with open biopsy (93%) compared with needle aspiration biopsy (48%) [103]. Despite the lack of data, we suggest that if a repeat diagnostic aspiration biopsy is performed, material should be sent for (1) Gram stain and aerobic culture, (2) mycobacterial stain and culture (and nucleic acid amplification testing if available), (3) brucellar culture, (4) fungal stain and culture, and (5) pathology. Epidemiologic considerations will need to be made when determining what to test for if specimen is insufficient for all studies.

Molecular diagnostic tools have improved the yield of microbiologic diagnosis via tissue biopsy in several studies [105–108]. These techniques are widely available and currently adopted in routine practice in many centers in Europe. Broad-range PCR might prove to be important in patients who have received prior antimicrobial therapy [105]. Most of these studies used nonstandardized but well-accepted 16S ribosomal RNA PCR techniques. These studies have been especially useful in the diagnosis of brucellar and mycobacterial NVO [97, 106, 107]. Molecular techniques have also been used with fungal infections and have enhanced the sensitivity of conventional methods used in diagnostic mycology. These techniques mainly rely on PCR for the detection of fungal-specific nucleic acids in clinical specimens [108].

VI. When Is It Appropriate to Send the Specimens for Pathologic Examination Following an Image-Guided Aspiration Biopsy in Patients With Suspected NVO?

Recommendation

20. If adequate tissue can be safely obtained, pathology specimens should be sent from all patients to help confirm a diagnosis of NVO and to help guide further diagnostic testing, especially in the setting of negative cultures (strong, low).

Evidence Summary

The differential diagnosis of a patient with back pain and an MRI abnormality includes NVO, neoplasm, acute disc herniation with disc space collapse, and osteoporosis-associated vertebral collapse (vertebral compression fracture). Most patients with bacterial NVO will have inflammatory changes in the disc space with associated end-plate changes of the 2 adjacent vertebral bodies. Exceptions, however are seen, especially in early tuberculous NVO where disease may be limited to the vertebral body only and may be misread as a likely malignancy. Performing an image-guided percutaneous needle biopsy can provide enough tissue for both culture and pathology in many cases that will exclude many of these confounding diagnoses [109]. In addition, the absence of any tissue abnormality suggests that the biopsy performed did not sample the correct area of abnormality. There is limited knowledge on the variables that are associated with accuracy of the image-guided biopsy. Prior use of antimicrobial therapy, tissue or aspiration biopsy volume, the size of the needle used, and sampling errors are among the factors that may affect culture accuracy following an image-guided aspiration biopsy [110]. In a retrospective review of 800 patients undergoing imaging-guided diagnostic bone biopsy, the highest rate of positive cultures was associated with obtaining >2 mL of fluid. The size of the needle used (range, 11–18 gauge) and antibiotic administration before biopsy did not have a significant impact on the yield [110].

In patients with high clinical and radiologic suspicion and a nondiagnostic first image-guided aspiration biopsy, a second or an open biopsy to establish a pathologic and microbiologic diagnosis should be considered. The presence of granulomatous inflammatory changes will prompt the evaluation for tuberculosis. In tuberculous NVO, histological findings may include the presence of caseating necrosis and giant cell formation with or without a positive Ziehl-Neelsen stain for acid-fast bacilli. In the prepurulent phase of granulation tissue, the inflammatory reaction spreading throughout the vessels of the vertebral body can be seen, resulting in bony necrosis. In addition, there may be a pathological fracture with sequestrum formation, compromising the spinal canal. The disc space is usually not involved, but the disc itself lies in a pool of exudates. Paraspinal abscess formation is the hallmark of active tuberculosis. The abscess cavity, surrounded by a wall of

granulation tissue, may be in contact with the dura. In contrast, brucellar NVO is characterized by noncaseating granulomas with negative acid-fast staining and the presence of gram-negative coccobacilli on Gram stain.

Nontuberculous mycobacteria; and fungal infections, including aspergillosis, blastomycosis, and coccidiomycosis, may also cause granulomatous changes without caseation.

VII. What Is the Preferred Next Step in Patients With Nondiagnostic Image-Guided Aspiration Biopsy and Suspected NVO?

Recommendations

21. In the absence of concomitant bloodstream infection, we recommend obtaining a second aspiration biopsy in patients with suspected NVO in whom the original image-guided aspiration biopsy grew a skin contaminant (coagulase-negative staphylococci [except *S. lugdunensis*], *Propionibacterium* species, or diphtheroids) (strong, low).
22. In patients with nondiagnostic first image-guided aspiration biopsy, and suspected NVO, further testing should be done to exclude difficult-to-grow organisms (eg, anaerobes, fungi, *Brucella* species, or mycobacteria) (strong, low).
23. In patients with suspected NVO and a nondiagnostic image-guided aspiration biopsy and laboratory workup, we suggest either repeating an image-guided aspiration biopsy, performing percutaneous endoscopic discectomy and drainage, or proceeding with an open excisional biopsy (weak, low).

Evidence Summary

Identifying the offending pathogen is crucial for appropriate antimicrobial therapy. Performing an image-guided percutaneous needle aspiration biopsy is a relatively safe and inexpensive diagnostic tool [73, 111, 112]. The relevance of a positive culture obtained by this technique is generally to confirm the clinical and/or radiologic suspicion of NVO and to identify the pathogen responsible for the infection. When isolating a common skin contaminant such as *Staphylococcus epidermidis*, *Propionibacterium acnes*, or diphtheroids, efforts should be made to exclude contamination and to try to eliminate the possibility of other pathogens such as tuberculosis, *Brucella*, or fungal pathogens. Further serology and molecular testing might be of help.

In cases where the first image-guided aspiration biopsy is nondiagnostic, appropriate additional testing to exclude brucellar, fungal, or mycobacterial cultures may be obtained [30, 52]. A repeat image-guided aspiration biopsy or a percutaneous PEDD surgical biopsy will improve the sensitivity of the culture results. The decision to perform an image-guided biopsy or a PEDD depends on the yield of an image-guided biopsy in a particular center and its availability [1, 30, 54, 113]. PEDD is an easy technique that presents a sufficient amount of tissue for microbiologic examination obtained directly from the infected disc region, providing higher diagnostic accuracy. Yang et al identified causative bacteria more frequently with PEDD than with image-guided biopsy (18 of 20 [90%] vs 15 of 32 [47%] patients) [114]. Whereas image-guided biopsy has variable rates (36%–91%) for bacteriologic diagnosis in patients with spinal infections [5, 84, 115–118], PEDD is a new simple technique that is proving to have a better diagnostic accuracy [114, 119–121]. If vertebral osteomyelitis is still highly suspected after a nondiagnostic second image-guided aspiration biopsy or PEDD, an open biopsy may be warranted.

When surgical intervention is indicated for decompression because of an epidural abscess or other neurologic complications, excisional biopsy should be done without the need for a preceding image-guided aspiration biopsy.

RECOMMENDATIONS FOR CLINICAL THERAPY

VIII. When Should Empiric Antimicrobial Therapy Be Started in Patients With NVO?

Recommendations

24. In patients with normal and stable neurologic examination and stable hemodynamics, we suggest holding empiric antimicrobial therapy until a microbiologic diagnosis is established (weak, low).
25. In patients with hemodynamic instability, sepsis, septic shock, or progressive or severe neurologic symptoms, we suggest the initiation of empiric antimicrobial therapy in conjunction with an attempt at establishing a microbiologic diagnosis (weak, low).

Evidence Summary

In a single-center retrospective cohort study, the use of prebiopsy empiric antibiotics did not affect the sensitivity of culture results [87]. Given the limitations in study methodology, however, the panel believes that in patients with suspected NVO, prior use of empiric antimicrobial therapy may affect the sensitivity of establishing a microbiologic diagnosis. Most evaluated patients with suspected NVO are hemodynamically stable and have no neurologic symptoms. Attempt at establishing the diagnosis prior to the use of empiric antimicrobial therapy would improve the sensitivity of culture results obtained via either a percutaneous image-guided biopsy or an open biopsy. In clinical circumstances where empiric antimicrobial therapy is deemed appropriate, physicians should use regimens that would include coverage against staphylococci, including methicillin-resistant *S. aureus* (MRSA), streptococci, and gram-negative bacilli. Such regimens might include a combination of vancomycin and a third- or fourth-generation cephalosporin. Alternative regimens, in case of allergy or intolerance, might include a combination of daptomycin and a quinolone. The use of empiric

antifungal and antimycobacterial therapy is not appropriate in most situations. Empiric antimicrobial therapy is dependent on the host, the clinical situation, and the epidemiologic risk, as well as the local historical in vitro susceptibility data. Several empiric antimicrobial regimens were suggested by the panel members. This might include regimens that have coverage against staphylococci, including oxacillin-resistant strains, as well as the coverage of aerobic gram-negative bacilli (Table 2). Selected regimens that were discussed might include vancomycin in combination with ciprofloxacin, vancomycin in combination with cefepime, or vancomycin in combination with a carbapenem. The panel was not in favor of routine use of empiric regimens that include coverage against anaerobes or fungal, brucellar, or mycobacterial organisms.

Table 2. Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis

Microorganism	First Choice[a]	Alternatives[a]	Comments[b]
Staphylococci, oxacillin susceptible	Nafcillin[c] sodium or oxacillin 1.5–2 g IV q4–6 h or continuous infusion or Cefazolin 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h[d] or daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin 500–750 mg PO q24 h and rifampin PO 600 mg daily [122] or clindamycin IV 600–900 mg q8 h	6 wk duration
Staphylococci, oxacillin resistant [123]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin PO 500–750 mg PO q24 h and rifampin PO 600 mg daily [122]	6 wk duration
Enterococcus species, penicillin susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses; or ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15–20 mg/kg IV q12 h (consider loading dose, monitor serum levels) or daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of therapy. Optional for other patients [124, 125]. Vancomycin should be used only in case of penicillin allergy.
Enterococcus species, penicillin resistant[e]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of aminoglycoside. The additional of aminoglycoside is optional for other patients [124, 125].
Pseudomonas aeruginosa	Cefepime 2 g IV q8–12 h or meropenem 1 g IV q8 h or doripenem 500 mg IV q8 h	Ciprofloxacin 750 mg PO q12 h (or 400 mg IV q8 h) or aztreonam 2 g IV q8 h for severe penicillin allergy and quinolone-resistant strains or ceftazidime 2 g IV q8 h	6 wk duration Double coverage may be considered (ie, β-lactam and ciprofloxacin or β-lactam and an aminoglycoside).
Enterobacteriaceae	Cefepime 2 g IV q12 h or ertapenem 1 g IV q24 h	Ciprofloxacin 500–750 mg PO q12 h or 400 mg IV q12 hours	6 wk duration
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Propionibacterium acnes	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Salmonella species	Ciprofloxacin PO 500 mg q12 h or IV 400 mg q12 h	Ceftriaxone 2 g IV q24 h (if nalidixic acid resistant)	6–8 wk duration

Abbreviations: BSI, bloodstream infection; IV, intravenous; PO, take orally; q, every.

[a] Antimicrobial dosage needs to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.

[b] Recommend Infectious Diseases Society of America guidelines for monitoring of antimicrobial toxicity and levels [126].

[c] Flucloxacillin may be used in Europe.

[d] Vancomycin should be restricted to patients with type I or documented delayed allergy to β-lactams.

[e] Daptomycin, linezolid, or Synercid may be used for vancomycin-resistant enterococci.

IX. What Is the Optimal Duration of Antimicrobial Therapy in Patients With NVO?

Recommendations

26. We recommend a total duration of 6 weeks of parenteral or highly bioavailable oral antimicrobial therapy for most patients with bacterial NVO (strong, low).
27. We recommend a total duration of 3 months of antimicrobial therapy for most patients with NVO due to *Brucella* species (strong, moderate).

Evidence Summary

There is a single published randomized clinical trial that showed that 6 weeks of antibiotic treatment is noninferior to 12 weeks in patients with NVO [127]. In this open-label, multicenter, noninferiority randomized trial, 160 of 176 (90.9%) patients in the 6-week group and 159 of 175 (90.9%) of those in the 12-week group were clinically cured. The duration of initial course of antimicrobial therapy has ranged from 4 to 12 weeks in most published cohorts describing the experience of single centers [6, 7, 128]. In an observational study of 91 patients with NVO by Roblot et al comparing the outcomes in patients treated with ≤6 weeks vs ≥6 weeks, the rates of relapse and death were similar in both groups [129]. In this retrospective review, the 2 study groups appeared to have similar characteristics. In a recently published retrospective cohort study of 61 patients with NVO, a switch to an oral antimicrobial therapy was performed in 72% of patients after a median intravenous therapy of 2.7 weeks. In this small cohort, no recurrence was observed. The authors concluded that early switch to an oral regimen may be safe, provided that CRP has decreased and epidural or paravertebral abscesses of significant size have been drained [130]. Prolonged antibiotic treatment has been recommended in most patients with NVO. The rationale behind the prolonged duration mostly stems from the limited bone penetration of most antimicrobials used in patients with NVO, the need for several weeks for bone to revascularize following surgery, and the limited experience derived from trials in pediatric patients with hematogenous long bone osteomyelitis [131–134]. The failure rates of treated patients with NVO in most clinical studies has varied between 10% and 30%. Factors associated with worse outcome have not been well defined but might include multidisc disease, the presence of concomitant epidural abscess, lack of surgical therapy, infection with *S. aureus*, old age, or the presence of significant comorbidities. In an observational nonrandomized study, Daver et al compared the failure rate of patients with staphylococcal osteomyelitis including some with vertebral osteomyelitis treated with an early switch to oral antibiotics (median duration of intravenous treatment was 12 days, followed by 42 days of oral therapy) vs a prolonged parenteral course (median treatment duration, 42 days intravenous followed by 21 days oral). The success rate was 69% in the prolonged intravenous group vs 78% in the early switch group [135]. Selected panel members advocate the use of longer treatment duration for >6 weeks followed by a course of oral therapy for 3 months or longer in patients perceived to be at high risk for failure (ie, MRSA, extensive infection). The use of this strategy should be weighed against the lack of data to support its efficacy and the potential for adverse reactions associated with prolonged use of antimicrobial therapy, including emergence of resistant pathogens and *Clostridium difficile* colitis [6, 128, 133, 136, 137]. Parenteral antimicrobial therapy is the standard mode of treatment for the majority of gram-positive and selected gram-negative microorganisms (Table 2). However, oral antimicrobials with excellent bioavailability, including fluoroquinolones, linezolid, and metronidazole, allow the possibility of an early switch to the oral route without compromising efficacy. This especially applies to the use of quinolones for patients with aerobic gram-negative bacilli. Oral β-lactams should not be prescribed for the initial treatment of NVO given their low bioavailability (Table 3).

The management of brucellar NVO was the subject of a review of 96 patients from a single tertiary referral center from Spain. From this cohort, 65.6% of patients were treated with antimicrobial therapy alone. The 2 most commonly used regimens included a combination of streptomycin for 2–3 weeks and doxycycline for 3 months, or doxycycline and rifampin (both for 3 months). Twenty percent of patients treated in this cohort experienced treatment failure, with no significant difference between patients treated with doxycycline-streptomycin and those treated with doxycycline-rifampin [93].

The management of patients with mycobacterial vertebral osteomyelitis are outlined in other IDSA-sponsored guidelines [138]. The management of patients with fungal NVO is addressed in the referenced IDSA guidelines [62–66].

X. What Are the Indications for Surgical Intervention in Patients With NVO?

Recommendations

28. We recommend surgical intervention in patients with progressive neurologic deficits, progressive deformity, and spinal instability with or without pain despite adequate antimicrobial therapy (strong, low).
29. We suggest surgical debridement with or without stabilization in patients with persistent or recurrent bloodstream infection (without alternative source) or worsening pain despite appropriate medical therapy (weak, low).
30. We advise against surgical debridement and/or stabilization in patients who have worsening bony imaging findings at 4–6 weeks in the setting of improvement in clinical symptoms, physical examination, and inflammatory markers (weak, low).

Table 3. Selected Oral Antibacterial Agents With Excellent Oral Bioavailability Commonly Used to Treat Patients With Native Vertebral Osteomyelitis

Oral Agents	Comments
Metronidazole 500 mg PO tid to qid	Can be used in the intital course of NVO due to *Bacteroides* species and other susceptible anaerobes.
Moxifloxacin 400 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO, but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Linezolid 600 mg PO bid	Can be used in the intital course of NVO due to oxacillin-resistant staphylocci when first-line agents cannot be used.
Levofloxacin 500–750 mg PO once daily	Is not recommended for use in patients with staphylococcal NVO as monotherapy but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms.
Ciprofloxacin 500–750 mg PO bid	Is not recommended for use in patients with staphylococcal NVO but may be used in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms including *Pseudomonas aeruginosa* and *Salmonella* species.
TMX-SMX 1–2 double strength tabs PO bid	Is not recommended for use in patients with staphylococcal NVO but may be recommended as a second-line agent in patients with NVO due to Enterobacteriaceae and other susceptible aerobic gram-negative organisms. May need to monitor sulfamethoxazole levels.
Clindamycin 300–450 mg PO qid	Recommended as second-line choice for sensitive staphylococcal NVO.
Doxycycline and rifampin	Mostly used in patients with brucellar NVO.

Dosages need to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.

Abbreviations: bid, twice daily; NVO, native vertebral osteomyelitis; PO, take orally; qid, 4 times daily; tid, 3 times daily; TMP-SMX, trimethoprim-sulfamethoxazole.

Evidence Summary

The goals of surgical debridement are to debulk infected tissue, to secure an adequate blood supply for tissue healing, and to maintain or restore spinal stability. The indications for surgery have been solely derived from cohorts that identified conditions that are associated with a high risk for recurrence. The indications for surgery may include the presence of neurologic compromise, significant vertebral destruction with instability, large epidural abscess formation, intractable back pain, or failure of medical treatment.

A number of surgical management strategies have been discussed in the literature. None of these approaches have been subjected to randomized clinical trials. These options include an anterior or posterior approach, single vs staged surgery, with or without instrumentation [139].

In a cohort of disc space infection by McHenry et al that included some patients with spinal implant–associated infections, 109 of 253 patients underwent surgical management. The most frequent indications for surgery in this cohort were drainage of abscesses (85 patients); relief of compression of the spinal cord, cauda equina, or nerve roots (48 patients); and spinal stabilization (32 patients). The outcome was favorable in 86 of 109 patients (79%). Of the 48 patients with neurologic impairment who underwent surgical treatment via an anterior or posterior approach, the outcome was favorable for 33 (69%) [6].

Valancius et al reviewed the management strategies in 196 patients with NVO seen in a single institution over a 10-year period, of whom 100 patients required surgical intervention [140]. Forty-six (39.3%) patients had neurologic compromise, 3 (2.5%) of them presented with cauda equina syndrome, and 10 (8.5%) were paraplegic. Four different surgical strategies were used, including posterior debridement with pedicle screw instrumentation (75 patients), and 19 patients were debrided without instrumentation. Seven patients underwent anterior debridement alone. In 16 cases, a combined anterior debridement with posterior pedicle screw instrumentation was performed. Twenty-four patients required repeat surgery; 12 (10%) had mild neurological impairment, and 4 were paraplegic. Twenty-seven patients (23%) had chronic residual pain of varying degrees [140].

RECOMMENDATIONS FOR CLINICAL FOLLOW-UP

XI. How Should Failure of Therapy Be Defined in Treated Patients With NVO?

Recommendation

31. We suggest that persistent pain, residual neurologic deficits, elevated markers of systemic inflammation, or radiographic findings alone do not necessarily signify treatment failure in treated NVO patients (weak, low).

Evidence Summary

Patient outcomes of bacterial NVO have improved dramatically since the preantibiotic era, when the diagnosis carried a mortality rate of approximately 25% [141]. In contemporary cohorts, mortality rates have ranged between 0% and 11% [6, 7, 113, 142, 143]. Frequently, clinicians are faced with NVO patients who exhibit some degree of clinical, laboratory, or radiographic evidence suggesting possible persistent or recurrent infection. There is no consensus in the literature for how one should

define treatment failure in NVO patients. The most specific measure of treatment failure is microbiologically confirmed persistent infection despite receipt of targeted antimicrobial therapy for an appropriate duration [5, 13]. Microbiologically confirmed treatment failure rates occur in 0%–11% of NVO patients in contemporary cohorts [6, 7, 15, 113, 129, 142, 143]. We propose that the definition of treatment failure above be used to standardize future outcome reporting in NVO patients.

Historically, treatment failure was often based upon surrogate markers, such as systemic inflammatory markers, radiographic results, and the clinical status of the patient without an emphasis on microbiologic confirmation. Ascribing treatment failure to NVO patients in the absence of microbiologic evidence may lead to overestimation of treatment failure [14, 15] and predispose patients to potentially unnecessary medical and surgical interventions [14, 15, 144]. Adverse outcomes, such as long-term functional status, neurologic status, and residual pain have been frequently reported as secondary outcomes when assessing the effectiveness of therapy [6, 145–147]. However, these measures may better reflect the extent of infection at the time of diagnosis, the premorbid functional status of the patient, or patient comorbidities rather than the effectiveness of antimicrobial treatment in eradicating infection.

XII. What Is the Role of Systemic Inflammatory Markers and MRI in the Follow-up of Treated Patients With NVO?

Recommendations

32. We suggest monitoring systemic inflammatory markers (ESR and or CRP) in patients with NVO after approximately 4 weeks of antimicrobial therapy, in conjunction with a clinical assessment (weak, low).
33. We recommend against routinely ordering follow-up MRI in patients with NVO in whom a favorable clinical and laboratory response to antimicrobial therapy was observed (strong, low).
34. We suggest performing a follow-up MRI to assess evolutionary changes of the epidural and paraspinal soft tissues in patients with NVO who are judged to have a poor clinical response to therapy (weak, low).

Evidence Summary

Monitoring patients' clinical response to treatment and follow-up values for systemic inflammatory markers may help identify patients at greater risk for treatment failure [148–151]. Paradoxically, values may increase within the first few weeks of diagnosis and treatment despite clinical improvement otherwise [14]. Patients with at least a 25%–33% reduction in systemic inflammatory markers after receipt of approximately 4 weeks of antimicrobial therapy may be at reduced risk of treatment failure [14, 148]. NVO patients with a 50% reduction in ESR after 4 weeks rarely develop treatment failure. In one study, it was found that after 4 weeks of treatment, ESR values >50 mm/hour and CRP values >2.75 mg/dL may confer a significantly higher risk of treatment failure [151]. CRP has been shown to improve more rapidly in patients with spine infection and may correlate more closely with the clinical status of the patient [150]. However, most patients in whom systemic inflammatory markers do not drop significantly or continue to be high during 4- to 8-week follow-up have successful outcomes, highlighting the poor specificity of these markers [14]. Therefore, values should be interpreted in concert with the clinical status of the patient. Patients deemed to have a poor clinical response to therapy (eg, persistent or progressive pain, systemic symptoms of infection) and elevated systemic inflammatory markers may be at highest risk for treatment failure [14, 151].

NVO patients who demonstrate favorable clinical and laboratory response to therapy do not need to undergo follow-up MRI [144, 148, 149, 152–154]. Follow-up imaging performed <4 weeks after the baseline exam may falsely suggest progressive infection despite clinical improvement, particularly when considering vertebral body and disc space findings. This radiographic phenomenon may influence clinicians to perform unnecessary surgical debridement or prolongation of antibiotic therapy. Additionally, radiographic evidence of ongoing inflammation may persist for months to years in patients without clinically relevant implications [144, 148, 149, 152–154].

Appropriately timed and interpreted follow-up MRI may provide prognostic information regarding treatment failure in NVO patients with an unfavorable response to therapy [16, 148]. Improvement in paravertebral and epidural soft tissue on follow-up MRI correlates best with improvement in clinical status and outcomes. Compared to baseline MRI, follow-up exams often demonstrate similar or worsened inflammatory characteristics of the bone and disc structures, despite clinically improved patients and ultimately successful treatment. MRI findings of the soft tissues, such as paravertebral and epidural inflammatory changes and abscesses, may correlate better with clinical status and treatment outcomes. In patients with worsened soft tissue findings on MRI 4–8 weeks after diagnosis, microbiologically confirmed treatment failure rates as high as 44% are reported [144, 148, 149, 152–154].

XIII. How Do You Approach a Patient With NVO and Suspected Treatment Failure?

Recommendations

35. In patients with NVO and suspected treatment failure, we suggest obtaining markers of systemic inflammation (ESR and CRP). Unchanged or increasing values after 4 weeks of treatment should increase suspicion for treatment failure (weak, low).
36. We recommend obtaining a follow-up MRI with emphasis on evolutionary changes in the paraspinal and epidural soft

tissue findings in patients with NVO and suspected treatment failure (strong, low).

37. In patients with NVO and clinical and radiographic evidence of treatment failure, we suggest obtaining additional tissue samples for microbiologic (bacteria, fungal, and mycobacterial) and histopathologic examination, either by image-guided aspiration biopsy or through surgical sampling (weak, very low).
38. In patients with NVO and clinical and radiographic evidence of treatment failure, we suggest consultation with a spine surgeon and an infectious disease physician (weak, very low).

Evidence Summary

The most consistent finding in NVO treatment failure is persistent or recurrent severe back pain [6]. However, many patients with NVO otherwise thought to be cured report persistent pain at the time of last follow-up [6, 146, 147]. Patients with persistent or progressive pain, systemic symptoms of infection, undrained or partially drained large epidural abscess, or persistently elevated systemic inflammatory markers may be at highest risk for treatment failure. Additional clinical findings associated with treatment failure include diabetes mellitus, intravenous drug use, recurrent bloodstream infection, new-onset neurologic deficits, and sinus tract formation [6, 129, 142]. Rarely, patients may demonstrate persistent evidence of systemic infection despite antibiotic therapy, which may suggest failure of medical therapy and the need for surgical intervention [7].

There are limited data to guide the diagnostic approach to NVO patients with suspected treatment failure. Obtaining systemic inflammatory markers and a follow-up MRI may confirm the risk of treatment failure, clarify the presence of abscess in need of drainage, and identify spinal instability that could benefit from surgical correction. Patients with evidence of progressive epidural and/or paraspinal soft tissue infection on follow-up MRI appear to be at a greater risk for treatment failure [148]. The frequency and utility of obtaining follow-up inflammatory laboratory markers (ESR, CRP) while patients are receiving antimicrobial therapy for NVO have not been established.

Therapeutic management of NVO patients with treatment failure should be tailored to the suspected reason for failure. Consultation with a surgeon and infectious disease physician experienced in the treatment of spinal infections may be warranted in patients with suspected or proven treatment failure. NVO patients with established treatment failure have been treated successfully with medical therapy alone or combined medical/surgical therapy. The decision of whether surgical intervention is warranted needs to be individualized, and incorporates similar principles as to whether to perform surgery at the time of NVO diagnosis or not.

In NVO patients with suspected treatment failure in whom surgical debridement is not planned, one should consider image-guided aspiration biopsy to definitively establish the diagnosis of treatment failure and confirm microbiologic etiology. For culture-negative NVO patients with suspected treatment failure, we recommend undertaking additional attempts to isolate an etiologic pathogen. This should include obtaining tissue for histopathology; aerobic and anaerobic bacterial cultures; and fungal, brucellar, and mycobacterial cultures. In select circumstances, serologic assays for uncommon causes of NVO should be considered as well.

RESEARCH GAPS

One of the steps in developing a rational clinical research agenda in NVO is the identification of evidence-based gaps in information. The process of guideline development outlined above serves as a natural means by which such gaps are identified. Clinical questions identified by the NVO guideline authors could shape a research agenda for the diagnosis and management of NVO. Questions are included below.

Diagnostics

1. What are the risk factors associated with the development of NVO?
2. How to develop and validate diagnostic algorithms in patients with suspected NVO?
3. What is the best strategy for patients with a nondiagnostic first aspiration biopsy?
4. What is the optimal timing for withholding antimicrobial therapy prior to image-guided diagnostic aspiration biopsy?
5. What is the optimal size of the needle to be used in image-guided aspiration biopsy and the number of specimens to be submitted in patients with suspected NVO?
6. What is the optimal timing and role of PEDD in patients with suspected NVO?
7. What is the role of [18F]-fluorodeoxyglucose PET scanning in diagnosis of patients with NVO?
8. Is there a role for of novel inflammatory cytokines in the diagnosis of NVO and follow-up of patients with NVO (ie, procalcitonin, IL-6)?
9. What is the optimal role for the use of molecular diagnostic techniques in the diagnosis of NVO?

Management

1. What are the optimal and most cost-effective algorithms of surgical and medical treatment strategies for the management of patients with NVO?
2. What is the optimal duration of parenteral therapy?
3. What are the role, timing, and duration of oral antimicrobial therapy as an alternative or following a course of parenteral therapy?

Follow-up

1. Which factors, including demographics, microbiology, serum inflammatory markers, and imaging studies are useful in predicting the outcome of patients with NVO?
2. How should we manage patients with persistent elevation of inflammatory markers after a course of parenteral antimicrobial therapy?
3. What is the utility of obtaining weekly follow-up inflammatory laboratory markers (ESR, CRP) while patients are receiving antimicrobial therapy for NVO?

Notes

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Potential conflicts of interest. The following list is a reflection of what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process that includes assessment by the SPGC Chair, the SPGC liaison to the development panel, and the Board of Directors liaison to the SPGC and, if necessary, the Conflicts of Interest Task Force of the Board. This assessment of disclosed relationships for possible conflicts of interest will be based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. E. F. B. receives honorarium from UpToDate. S. S. K. is on the speakers' bureaus of Pfizer, AstraZeneca, Gilead, Biologix, and Pasteur Aventis, and is a national Principal Investigator on a clinical trial for Astellas. E. F. H. is a site Principal Investigator for drug development by Medpace. D. R. O. has received research grants from Cubist and Ortho-McNeil. All other authors report no potential conflicts.

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