

# 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis\*

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The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee collaborated with partner organizations to convene a panel of 10 experts on healthcare-associated ventriculitis and meningitis. The panel represented pediatric and adult specialists in the field of infectious diseases and represented other organizations whose members care for patients with healthcare-associated ventriculitis and meningitis (American Academy of Neurology, American Association of Neurological Surgeons, and Neurocritical Care Society). The panel reviewed articles based on literature reviews, review articles and book chapters, evaluated the evidence and drafted recommendations. Questions were reviewed and approved by panel members. Subcategories were included for some questions based on specific populations of patients who may develop healthcare-associated ventriculitis and meningitis after the following procedures or situations: cerebrospinal fluid shunts, cerebrospinal fluid drains, implantation of intrathecal infusion pumps, implantation of deep brain stimulation hardware, and general neurosurgery and head trauma. Recommendations were followed by the strength of the recommendation and the quality of the evidence supporting the recommendation. Many recommendations, however, were based on expert opinion because rigorous clinical data are not available. These guidelines represent a practical and useful approach to assist practicing clinicians in the management of these challenging infections.

**Keywords.** ventriculitis; meningitis; cerebrospinal fluid shunts; cerebrospinal fluid drains; central nervous system infections.

## EXECUTIVE SUMMARY

Meningitis may not only be acquired in the community setting, but may be associated with a variety of invasive procedures or head trauma. The latter group has often been classified as nosocomial meningitis because a different spectrum of microorganisms (ie, resistant gram-negative bacilli and staphylococci) is the more likely the etiologic agents, and different pathogenic mechanisms are associated with the development of this disease. Although many of these patients present with clinical symptoms during hospitalization, ventriculitis and meningitis may develop after

hospital discharge or even many years later. We, therefore, prefer the term “healthcare-associated ventriculitis and meningitis” to be more representative of the diverse mechanisms (that include placement of devices) that can lead to these serious illnesses.

Summarized below are recommendations for the evaluation, diagnosis, and management of healthcare-associated ventriculitis and meningitis, specifically addressing the approach to infections associated with cerebrospinal fluid shunts, cerebrospinal fluid drains, intrathecal drug (eg, baclofen) therapy, deep brain stimulation hardware, and neurosurgery and head trauma. These infections may be difficult to diagnose because changes in cerebrospinal fluid parameters are often subtle, making it hard to determine if the abnormalities are related to infection, related to placement of devices, or following neurosurgery. Many of our recommendations are based on expert opinion because rigorous clinical data are not available and the likelihood that clinical trials will be conducted to answer some of these questions is low. Our goal was to develop guidelines that offered a practical and useful approach to assist practicing clinicians in the management of these challenging infections. The panel followed a process used in the development of other IDSA guidelines that

Received 12 December 2016; editorial decision 12 December 2016; accepted 16 December 2016.

\*It is important to realize that 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. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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Clinical Infectious Diseases® 2017;64(6):e34–e65

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DOI: 10.1093/cid/ciw861

included a systematic weighting of the strength of recommendations and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [1–5]. A detailed description of the methods, background, and evidence summaries that support each recommendation can be found in the full text of the guidelines.

**I. What are the Typical Symptoms and Signs in Patients with Healthcare-Associated Ventriculitis and Meningitis?**

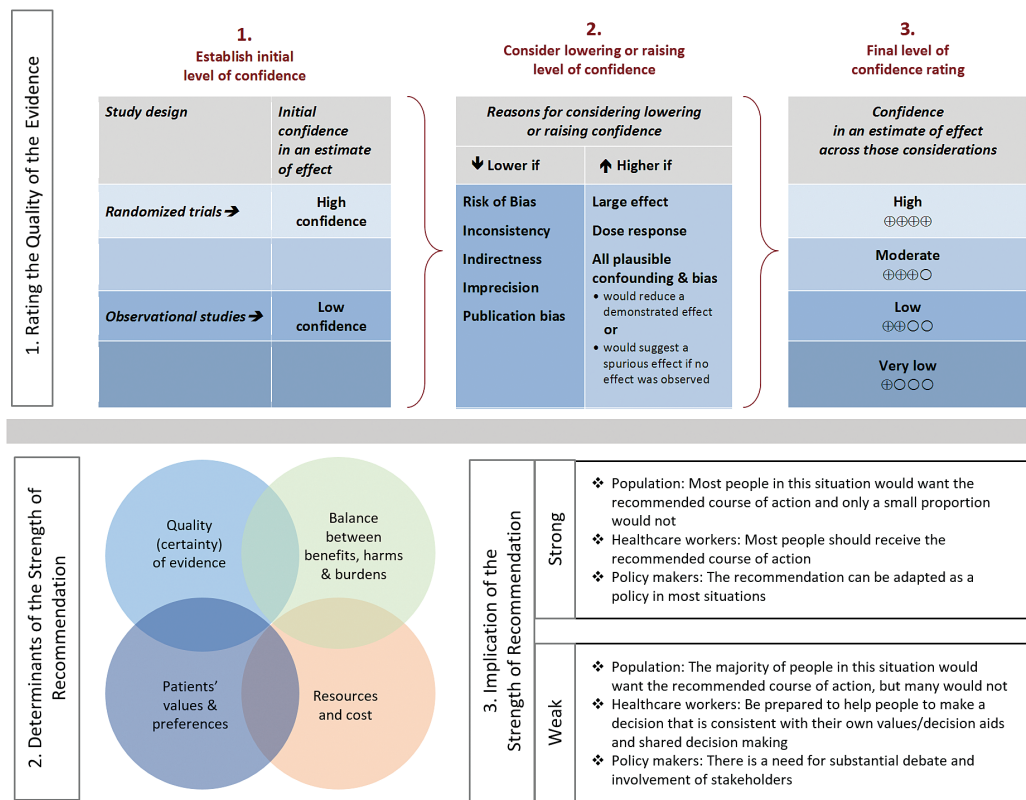
**Cerebrospinal Fluid Shunts and Drains**  
**Recommendations**

1. New headache, nausea, lethargy, and/or change in mental status are suggestive of cerebrospinal fluid (CSF) shunt infection (strong, moderate).
2. Erythema and tenderness over the subcutaneous shunt tubing are suggestive of CSF shunt infection (strong, moderate).
3. Fever, in the absence of another clear source of infection, could be suggestive of CSF shunt infection (weak, low).
4. Symptoms and signs of peritonitis or abdominal tenderness in patients with ventriculoperitoneal shunts, in the absence of another clear etiology, are indicative of CSF shunt infection (strong, moderate).

5. Symptoms and signs of pleuritis in patients with ventriculo-pleural shunts, in the absence of another clear etiology, are indicative of CSF shunt infection (strong, moderate).
6. Demonstration of bacteremia in a patient with a ventriculoatrial shunt, in the absence of another clear source of bacteremia, is evidence of CSF shunt infection (strong, moderate).
7. Demonstration of glomerulonephritis in a patient with a ventriculoatrial shunt is suggestive of CSF shunt infection (weak, low).
8. New or worsening altered mental status in patients with external ventricular drains is suggestive of infection (weak, low).
9. New fever and increased CSF white blood cell count in patients with external ventricular drains could be suggestive of infection (weak, low).

**Neurosurgery or Head Trauma**  
**Recommendations**

10. New headache, fever, evidence of meningeal irritation, seizures, and/or worsening mental status are suggestive of ventriculitis or meningitis in the setting of recent trauma or neurosurgery (strong, moderate).



**Figure 1.** Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (unrestricted use of the figure granted by the US GRADE Network).

11. Fever, in the absence of another clear source of infection, is suggestive of central nervous system (CNS) infection in the setting of recent head trauma or neurosurgery (weak, low).

#### **Intrathecal Infusion Pumps Recommendation**

12. New fever and drainage from the surgical site in patients with intrathecal infusion pumps are suggestive of wound infection (weak, low).

### **II. What are the Typical Cerebrospinal Fluid Findings in Patients with Healthcare-Associated Ventriculitis and Meningitis?**

#### **Cell Count, Glucose, and Protein Recommendations**

13. Abnormalities of CSF cell count, glucose, and/or protein may not be reliable indicators for the presence of infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate).
14. Normal CSF cell count, glucose, and protein may not reliably exclude infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate).
15. A negative CSF Gram stain does not exclude the presence of infection, especially in patients who have received previous antimicrobial therapy (strong, moderate).

#### **Culture Recommendations**

16. CSF cultures are the most important test to establish the diagnosis of healthcare-associated ventriculitis and meningitis (strong, high).
17. If initial CSF cultures are negative in patients with CSF shunts or drains with suspected infection, it is recommended that cultures be held for at least 10 days in an attempt to identify organisms such as *Propionibacterium acnes* (strong, high).
18. If a CSF shunt or drain is removed in patients suspected of having infection, cultures of shunt and drain components are recommended (strong, moderate).
19. If a CSF shunt or drain is removed for indications other than infection, cultures of shunt or drain components are not recommended (strong, moderate).
20. Blood cultures are recommended in patients with suspected ventriculoatrial shunt infections (strong, high).
21. Blood cultures may be considered in patients with ventriculoperitoneal and ventriculopleural shunts (weak, low).
22. Single or multiple positive CSF cultures in patients with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and clinical symptoms suspicious for ventriculitis or meningitis, is indicative of CSF drain infection (strong, high).
23. CSF and blood cultures in selected patients should be obtained before the administration of antimicrobial

therapy; a negative CSF culture in the setting of previous antimicrobial therapy does not exclude healthcare-associated ventriculitis and meningitis (strong, moderate).

#### **Neurosurgery or Head Trauma Recommendations**

24. CSF pleocytosis with a positive culture and symptoms of infection are indicative of a diagnosis of healthcare-associated ventriculitis or meningitis (strong, high).
25. Hypoglycorrhachia and elevated CSF protein concentrations are suggestive of the diagnosis of healthcare-associated ventriculitis or meningitis (weak, low).
26. Growth of an organism that is commonly considered a contaminant (eg, coagulase-negative staphylococcus) in enrichment broth only or on just 1 of multiple cultures in a patient with normal CSF and no fever is not indicative of healthcare-associated ventriculitis or meningitis (strong, low).
27. CSF cultures with multiple organisms from a single sample may be contaminants in patients with no symptoms of infection or CSF pleocytosis (weak, low).
28. CSF cultures that grow *Staphylococcus aureus* or aerobic gram-negative bacilli are indicative of infection (strong, moderate).
29. CSF cultures that grow a fungal pathogen are indicative of infection (strong, moderate).

### **III. What Specific Tests of Cerebrospinal Fluid can be used to Confirm the Patient has Healthcare-Associated Ventriculitis and Meningitis?**

#### **Recommendations**

30. An elevated CSF lactate or an elevated CSF procalcitonin, or the combination of both, may be useful in the diagnosis of healthcare-associated bacterial ventriculitis and meningitis (weak, moderate).
31. An elevated serum procalcitonin may be useful in differentiating between CSF abnormalities due to surgery or intracranial hemorrhage from those due to bacterial infection (weak, low).
32. Nucleic acid amplification tests, such as polymerase chain reaction, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low).
33. Detection of  $\beta$ -D-glucan and galactomannan in CSF may be useful in the diagnosis of fungal ventriculitis and meningitis (strong, moderate).

### **IV. What is the Role of Imaging in Patients with Suspected Healthcare-Associated Ventriculitis and Meningitis?**

#### **Recommendations**

34. Neuroimaging is recommended in patients with suspected healthcare-associated ventriculitis and meningitis (strong, moderate).

35. Magnetic resonance imaging with gadolinium enhancement and diffusion-weighted imaging is recommended for detecting abnormalities in patients with healthcare-associated ventriculitis and meningitis (strong, moderate).
36. In patients with infected ventriculoperitoneal shunts and abdominal symptoms (eg, pain or tenderness), an ultrasound or computed tomography of the abdomen is recommended to detect CSF loculations at the shunt terminus (strong, moderate).

## V. What is the Empiric Antimicrobial Approach for Patients with Suspected Healthcare-Associated Ventriculitis and Meningitis?

### Recommendations

37. Vancomycin plus an anti-pseudomonal beta-lactam (such as cefepime, ceftazidime, or meropenem) is recommended as empiric therapy for healthcare-associated ventriculitis and meningitis; the choice of empiric beta-lactam agent should be based on local in vitro susceptibility patterns (strong, low).
38. In seriously ill adult patients with healthcare-associated ventriculitis and meningitis, the vancomycin trough concentration should be maintained at 15–20 µg/mL in those who receive intermittent bolus administration (strong, low).
39. For patients with healthcare-associated ventriculitis and meningitis who have experienced anaphylaxis to beta-lactam antimicrobial agents and in whom meropenem is contraindicated, aztreonam or ciprofloxacin is recommended for gram-negative coverage (strong, low).
40. For patients with healthcare-associated ventriculitis and meningitis who are colonized or infected elsewhere with a highly antimicrobial-resistant pathogen, adjusting the empiric regimen to treat for this pathogen is recommended (strong, low).
41. If the staphylococcal isolate is susceptible to rifampin, this agent may be considered in combination with other antimicrobial agents for staphylococcal ventriculitis and meningitis (weak, low); rifampin is recommended as part of combination therapy for any patient with intracranial or spinal hardware such as a CSF shunt or drain (strong, low).
42. For treatment of patients with healthcare-associated ventriculitis and meningitis caused by staphylococci in whom beta-lactam agents or vancomycin cannot be used, linezolid (strong, low), daptomycin (strong, low), or trimethoprim-sulfamethoxazole (strong, low) is recommended, with selection of a specific agent based on in vitro susceptibility testing.
43. For treatment of infection caused by *Propionibacterium acnes*, penicillin G is recommended (strong, moderate).
44. For treatment of infection caused by gram-negative bacilli, therapy should be based on in vitro susceptibility testing with agents that achieve good CNS penetration (strong, moderate).
45. For treatment of infection caused by gram-negative bacilli susceptible to third-generation cephalosporins, ceftriaxone or cefotaxime is recommended (strong, moderate).
46. For treatment of infection caused by *Pseudomonas* species, the recommended therapy is cefepime, ceftazidime, or meropenem (strong, moderate); recommended alternative antimicrobial agents are aztreonam or a fluoroquinolone with in vitro activity (strong, moderate).
47. For treatment of infection caused by extended-spectrum beta-lactamase-producing gram-negative bacilli, meropenem should be used if this isolate demonstrates in vitro susceptibility (strong, moderate).
48. For treatment of infection caused by *Acinetobacter* species, meropenem is recommended (strong, moderate); for strains that demonstrate carbapenem resistance, colistimethate sodium or polymyxin B (either agent administered by the intravenous and intraventricular routes) is recommended (strong, moderate).
49. Prolonged infusion of meropenem (each dose administered over 3 hours) may be successful in treating resistant gram-negative organisms (weak, low).
50. For treatment of infection caused by *Candida* species, based on in vitro susceptibility testing, liposomal amphotericin B, often combined with 5-flucytosine, is recommended (strong, moderate); once the patient shows clinical improvement, therapy can be changed to fluconazole if the isolated species is susceptible (weak, low).
51. For treatment of infection caused by *Aspergillus* or *Exserohilum* species, voriconazole is recommended (strong, low).

## VI. Once a Pathogen is Identified, What Specific Antimicrobial Agent(s) Should be Administered?

### Recommendations

41. For treatment of infection caused by methicillin-susceptible *S. aureus*, nafcillin or oxacillin is recommended (strong, moderate). If the patient cannot receive beta-lactam agents, the patient can be desensitized or may receive vancomycin as an alternative agent (weak, moderate).
42. For treatment of infection caused by methicillin-resistant *S. aureus*, vancomycin is recommended as first-line therapy (strong, moderate), with consideration for an alternative antimicrobial agent if the vancomycin minimal inhibitory concentration (MIC) is  $\geq 1$  µg/mL (strong, moderate).
43. For treatment of infection caused by coagulase-negative staphylococci, the recommended therapy should be similar

## VII. What is the Role of Intraventricular Antimicrobial Therapy in Patients with Healthcare-Associated Ventriculitis and Meningitis?

### Recommendations

55. Intraventricular antimicrobial therapy should be considered for patients with healthcare-associated ventriculitis and meningitis in which the infection responds poorly to systemic antimicrobial therapy alone (strong, low).
56. When antimicrobial therapy is administered via a ventricular drain, the drain should be clamped for 15–60 minutes to allow the agent to equilibrate throughout the CSF (strong, low).
57. Dosages and intervals of intraventricular antimicrobial therapy should be adjusted based on CSF antimicrobial concentrations to 10–20 times the MIC of the causative microorganism (strong, low), ventricular size (strong, low), and daily output from the ventricular drain (strong, low).

## VIII. What is the Optimal Duration of Antimicrobial Therapy in Patients with Healthcare-Associated Ventriculitis and Meningitis?

### Recommendations

58. Infections caused by a coagulase-negative staphylococcus or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms or systemic features should be treated for 10 days (strong, low).
59. Infections caused by a coagulase-negative staphylococcus or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features should be treated for 10–14 days (strong, low).
60. Infections caused by *S. aureus* or gram-negative bacilli with or without significant CSF pleocytosis, CSF hypoglycorrhachia, or clinical symptoms or systemic features should be treated for 10–14 days (strong, low); some experts suggest treatment of infection caused by gram-negative bacilli for 21 days (weak, low).
61. In patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy, treatment should be continued for 10–14 after the last positive culture (strong, low).

## IX. What is the Role of Catheter Removal in Patients with Cerebrospinal Fluid Shunts or Drains?

### Recommendations

62. Complete removal of an infected CSF shunt and replacement with an external ventricular drain combined with intravenous antimicrobial therapy is recommended in patients with infected CSF shunts (strong, moderate).
63. Removal of an infected CSF drain is recommended (strong, moderate).
64. Removal of an infected intrathecal infusion pump is recommended (strong, moderate).
65. Removal of infected hardware in patients with deep brain stimulation infections is recommended (strong, moderate).

## X. How are Patients Monitored for Response to Treatment?

### Recommendations

66. Patients with healthcare-associated ventriculitis and meningitis should be monitored for response to treatment based on clinical parameters (strong, low).
67. In patients with healthcare-associated ventriculitis and meningitis and an external drainage device, monitoring of CSF cultures is recommended to ensure that they become negative (strong, low).
68. In patients with no definitive clinical improvement, additional CSF analysis is recommended to ensure that the CSF parameters have improved and the cultures become negative (strong, low).
69. For external CSF drains not being used in the treatment of CSF shunt infection, daily CSF cultures and analysis are not recommended unless clinically indicated (strong, low).

## XI. In Patients with Cerebrospinal Fluid Shunts Who Develop Ventriculitis and Meningitis, When can a New Shunt be Reimplanted?

### Recommendations

70. In patients with infection caused by coagulase-negative staphylococci or *P. acnes*, with no associated CSF abnormalities and with negative CSF cultures for 48 hours after externalization, a new shunt should be reimplanted as soon as the third day after removal (strong, low).
71. In patients with infection caused by a coagulase-negative staphylococcus or *P. acnes*, with associated CSF abnormalities but negative repeat CSF cultures, a new shunt should be reimplanted after 7 days of antimicrobial therapy (strong, low); if repeat cultures are positive, antimicrobial treatment is recommended until CSF cultures remain negative for 7–10 consecutive days before a new shunt is placed (strong, low).
72. In patients with infection caused by *S. aureus* or gram-negative bacilli, a new shunt should be reimplanted 10 days after CSF cultures are negative (strong, low).
73. A period off antimicrobial therapy is not recommended to verify clearing of the infection before shunt reimplantation (strong, low).

## XII. What is the Best Approach to Prevent Infection in Patients Who are Receiving Cerebrospinal Fluid Shunts?

### Recommendations

74. Perioperative prophylactic antimicrobial administration is recommended for patients undergoing CSF shunt or drain insertion (strong, moderate).
75. Perioperative prophylactic antimicrobial administration is recommended for patients undergoing placement of external ventricular drains (strong, moderate).
76. Prolonged antimicrobial prophylaxis for the duration of the external ventricular drain is of uncertain benefit and not recommended (strong, moderate).

77. Use of antimicrobial-impregnated CSF shunts and CSF drains is recommended (strong, moderate).
78. In patients with external ventricular drains, fixed interval exchange is not recommended (strong, moderate).
79. Use of a standardized protocol for insertion of CSF shunts and drains is recommended (strong, moderate).

### **XIII. Is there a Role for Prophylactic Antimicrobial Therapy in Patients Undergoing Neurosurgery or in those with Cerebrospinal Fluid Leak?**

#### **Recommendation**

80. For neurosurgical patients, perioperative antimicrobial agents are recommended to prevent infections of the incision (strong, high).
81. In patients with basilar skull fractures and a CSF leak, prophylactic antimicrobial agents are not recommended (strong, moderate).
82. In patients with basilar skull fractures and a prolonged CSF leakage (>7 days), an attempt to repair the leak is recommended (strong, low).
83. In patients with basilar skull fractures and a CSF leak, pneumococcal vaccination is recommended (strong, moderate).

## **INTRODUCTION**

Meningitis may be acquired in the community setting or may be associated with a variety of invasive procedures or head trauma. The latter group has often been classified as nosocomial meningitis because a different spectrum of microorganisms (eg, resistant gram-negative bacilli and staphylococci) is the more likely etiologic agents and because different pathogenic mechanisms are associated with the development of this disease. Although many of these patients present with clinical symptoms during hospitalization, ventriculitis and meningitis may develop after hospital discharge or even many years later. Therefore, the term “healthcare-associated ventriculitis and meningitis” is more representative of the diverse mechanisms that can lead to this serious illness. The following sections describe specific circumstances associated with healthcare-associated ventriculitis and meningitis.

### **Cerebrospinal Fluid Shunts**

Cerebrospinal fluid (CSF) shunts are considered permanent catheters in which the proximal end of the shunt is in the cerebral ventricle, subdural space, an intracranial cyst, or the lumbar subarachnoid space; the distal end usually terminates in the peritoneal, pleural, or vascular space. Typically, part of the system (as a separate integrated component) is a pressure-regulating valve that is usually placed just outside the skull or as an integral part of the distal tubing [6]. Reservoirs for intermittent percutaneous access can also be added to the system or incorporated into the valve assembly. Additional hardware may include antisiphon valves and various connectors, allowing

interconnection of more than 1 catheter or device. The case incidence of CSF shunt infection (ie, the occurrence of infection in any given patient) has ranged from 5% to 41% in various series, although the incidence is usually in the range of 4%–17% [7–14]. The operative incidence (ie, the occurrence of infection per procedure) has ranged from 2.8% to 14%, although most series have generally reported operative infection rates of less than 4% [15–17]. Factors associated with an increased risk of CSF shunt infection include premature birth (especially when associated with intraventricular hemorrhage), younger age, previous shunt infection, cause of hydrocephalus (more likely after purulent meningitis, hemorrhage, and myelomeningocele), less experienced neurosurgeon, higher number of people traversing the operating theater, exposure to perforated surgical gloves, intraoperative use of the neuroendoscope, longer duration of the shunt procedure, insertion of the catheter below the level of the T7 vertebral body in those with ventriculoatrial shunting, improper patient skin preparation, shaving of skin, exposure of large areas of the patient's skin during the procedure, and shunt revision (risk is especially high in those undergoing 3 or more revisions) [18, 19].

There are 4 mechanisms by which CSF shunts may become infected. The first, and most frequent, mechanism is colonization of the shunt at the time of surgery. This mechanism is suggested by the timing of most shunt infections and by the microorganisms that are isolated. In one study in adults with CSF shunt–associated infections, 62% occurred within the first month after shunt surgery and 72% were thought to be acquired intraoperatively [14]. The second mechanism is retrograde infection from the distal end of the shunt; for example, bowel perforation can lead to distal catheter contamination in patients with ventriculoperitoneal shunts. In addition, certain populations of patients with CSF shunts, such as those with myelomeningocele, may have undergone multiple intraabdominal procedures related to either bowel or bladder continence and may be at greater risk for shunt infection via this route. A third mechanism is through the skin, such as after insertion of a needle into the reservoir or the shunt to culture the CSF or assess patency, after injection of a drug into the ventricular reservoir, or after erosion of the catheter through the skin. The fourth mechanism is hematogenous seeding; patients with ventriculoatrial shunts have a foreign body (ie, the catheter) in the vascular system and are at continued risk of infection from bacteremia (with a retrograde infection). Patients with existing CSF shunts can also develop community-acquired bacterial meningitis unrelated to the shunt, and this may need to be considered in the appropriate clinical circumstance.

### **Cerebrospinal Fluid Drains**

CSF drains are temporary catheters that divert CSF externally [20]. The proximal end is in the cerebral ventricle (ventricular drain), the subdural space, an intracranial cyst, or the lumbar

subarachnoid space (lumbar drain). External ventricular drains are most useful for temporary management in patients with elevated intracranial pressure secondary to acute hydrocephalus caused by intracranial hemorrhage, neoplasm obstruction of the CSF circulation, or trauma. The distal end of the catheter is connected to a collecting system, which has a drip chamber, ports for measuring intracranial pressure, sampling and injection ports (used to obtain CSF and inject medications), and a collection bag. Drains are usually placed via 1 incision and then tunneled a distance subcutaneously before exiting through the skin. In patients with external ventricular drains, the incidence of ventriculitis has ranged from 0% to 22%. In a large metaanalysis of 35 studies that yielded 752 infections from 66706 catheter-days of observation [21], the overall pooled incidence of external ventricular drain–related CSF infection was 11.4 per 1000 catheter-days (95% confidence interval [CI], 9.3–13.5); for high-quality studies, the incidence was 10.6 per 1000 catheter-days (95% CI, 8.3–13). Factors associated with an increased risk of infection are intraventricular or subarachnoid hemorrhage, cranial fracture with CSF leak, catheter irrigation, craniotomy, and duration of catheterization. Although controversy exists regarding the relationship between the duration of catheterization and risk of infection, most studies consider extended catheter duration (usually exceeding 5 days) to be an important risk factor for subsequent infection [20]. However, in the metaanalysis cited above [21], studies in which patients had a mean catheter duration of less than 7 days had a pooled external ventricular drain infection rate of 19.6 per 1000 catheter-days, 12.8 per 1000 catheter-days for drains in place for 7–10 days, and 8 per 1000 catheter-days for drains in place for more than 10 days. Although infection is most likely introduced at the time of placement, retrograde infection is another mechanism of infection of CSF drains. Microorganisms may enter the device by tracking from the exit site alongside the device, gaining access to the fluid column that drains CSF, or they may be introduced from flushing of the tubing to maintain tubular patency.

External lumbar drains, which may be placed to deal with complications of operative or post-traumatic transcutaneous CSF leak or to aid in the diagnosis of normal-pressure hydrocephalus (potentially a lower-risk group), have been associated with meningitis rates of up to 5%. The risk factors associated with these drains include disconnection of the external drainage system and the presence of other infections. In a study involving 233 consecutive patients who underwent placement of an external lumbar drain for normal-pressure hydrocephalus testing, the rate of meningitis was low (0.8%) [22]. The investigators in that study used a strict protocol that called for no surveillance testing of CSF, drainage of CSF for a maximum of 5 days, sterile reconnection after disconnection or fracture of the drain, and permanent removal of the drain after a second disconnection or fracture.

### Intrathecal Infusion Pumps

Administration of drug therapy (eg, baclofen) via intrathecal infusion pumps has been successful for patients with intractable spasticity, most commonly in patients with cerebral palsy but also in patients with spasticity from multiple sclerosis, trauma, hereditary spastic paraplegia, and a variety of other conditions. Intrathecal opiate therapy has been used in the management of intractable pain, usually in patients with malignancy. The catheter is inserted in the lumbar region and passed intrathecally with the tip at the highest spinal cord level at which the drug is to be administered. Initially, the pumps were inserted subcutaneously in the abdomen, but this has been superseded in some centers, particularly those focused on pediatric patients, by placement below the abdominal fascia to decrease the risk of erosion through the skin. Once implanted, the device must be periodically refilled with the desired drug via transcutaneous puncture of the device.

Few studies have evaluated the incidence of meningitis complicating use of intrathecal infusion pumps. Reported infection rates vary from 3.6% for those with subfascial placement of the pump to 20% for those with subcutaneous placement of the pump [23]. Infections are usually more common in pediatric series [24, 25]. Most reported infections are at the incision site; in one series, 3 of 49 patients developed meningitis in concert with an incisional infection, while 4 others had meningitis alone [26]. Another retrospective study identified infectious complications in 38 (18.4%) of 207 children with intrathecal infusion pumps delivering baclofen therapy [27]. Of these 38 patients, 25 had suspected or superficial infections and 13 had deep-seated infections, with 2 patients diagnosed with meningitis. In many reports, it is not possible to distinguish meningitis from local infections related to the infusion pump. The majority of infections occur within the first 2 months of surgery, but infections may occur years after implantation as access for drug refills may be needed every 3–6 months for the service life of the device [26, 28]. The majority of reported infections are caused by *Staphylococcus aureus*, but a variety of other organisms, including multiply drug-resistant gram-negative bacilli, have been recovered.

### Deep Brain Stimulation Hardware

Deep brain stimulation, introduced in 1987 for the treatment of Parkinson's disease, is now being used for other conditions such as dystonia, essential tremor, and obsessive-compulsive disorder [29]. The stimulator consists of an intracranial lead, a connector, and a pulse generator that is implanted in the infraclavicular area [30]. The incidence of infections following implantation of deep brain stimulation hardware varies from 0.62% to 14.3% and can involve all 3 components of the device. The infection of the pulse generator is the most common, with infection usually caused by *S. aureus*, a coagulase-negative staphylococcus, or *Propionibacterium acnes*. These infections

may occur after initial implant or after the battery is exchanged at a subsequent surgery.

Brain stimulation for intractable focal epilepsy involves placement of a combination of cortical and depth electrodes intracranially. These electrodes are used to both sense abnormal electroencephalographic activity and to deliver patterned electrical stimuli to interrupt developing seizures. The electrodes are connected to a controller that is implanted in the skull. In initial trials of this system, involving 256 patients, 2% of patients had a post-operative superficial wound infection; most were treated successfully with antimicrobial therapy, but 1 patient required explantation of the system [31]. The mean follow-up period was 5.4 patient implant years (a total of 1389 patient implant years), during which 20 patients (7.8%) experienced a soft tissue infection at the implant site. Fourteen of these patients underwent removal of the stimulator. The organisms involved and their treatments were not reported.

### Neurosurgery or Head Trauma

Ventriculitis and meningitis can be complications in patients who have undergone neurosurgery or head trauma. Because concern and evaluation of infection in the post-surgical and post-traumatic situations usually occur after a period of hospitalization, this phenomenon is termed “healthcare-associated,” recognizing that there will be individual instances, such as in trauma, in which the contamination that led to infection occurred prior to the patient’s entry into the healthcare system. The diagnosis may be difficult to establish since surgery and trauma can both induce CSF abnormalities that confound the usual diagnostic studies. These patients may also have fever for reasons unrelated to infection (eg, central fever, drug fever, thrombophlebitis, or chemical meningitis after posterior fossa surgery). Also, they are at increased risk of developing infection because of the risk associated with surgery (including surgery after head trauma), direct contamination of the central nervous system (CNS), and the increased risk of meningitis in patients with a CSF leak. In a study of 334 procedures in patients undergoing craniotomy, risk factors associated with post-craniotomy meningitis were use of CSF drain, CSF leak, and perioperative steroid use [32]. Healthcare-associated ventriculitis and meningitis is a problem at medical facilities that perform neurosurgery. In a review of all causes of meningitis at Massachusetts General Hospital between 1962 and 1988, 40% were classified as nosocomial in origin [33]. In another study of confirmed bacterial meningitis in adults who were hospitalized at an acute care teaching hospital in southern Taiwan, 48% of cases were classified as nosocomial infections [34]. In a recent epidemiological study of bacterial meningitis in the United States [35], the incidence of meningitis caused by nosocomial pathogens (eg, gram-negative bacilli and *S. aureus*) approached that caused by *Neisseria meningitidis*.

These guidelines address the management of children and adults with healthcare-associated ventriculitis and meningitis with the objective to provide evidence-based guidelines to manage these infections.

## METHODOLOGY

### Practice Guidelines

“Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances” [36]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [36].

### Panel Composition

The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee (SPGC) collaborated with partner organizations to convene a panel of 10 experts on healthcare-associated ventriculitis and meningitis. The panel represented pediatric and adult specialists in the field of infectious diseases and represented other organizations whose members care for patients with healthcare-associated ventriculitis and meningitis, including the following: American Academy of Neurology, American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), Neurocritical Care Society (NCS), and Society for Healthcare Epidemiology of America (SHEA). The AANS and CNS affirm the educational content and the AAN affirms the value of this document. These guidelines were reviewed and endorsed by NCS and SHEA. These guidelines were also reviewed and approved by the IDSA SPGC and the Board of Directors (BOD).

### Process Overview, Literature Selection, and Consensus Development Based on Evidence

The panel followed a process used by IDSA in the development of other guidelines. The process included a systematic weighting of the quality of the evidence and the grade of the recommendation (Figure 1). [Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology. Available at: <http://www.gradeworking-group.org>—Accessed July 2015].

The panel reviewed articles based on literature reviews (using PubMed and Medline); reviewed articles and book chapters (including references published in reviews and chapters); evaluated the evidence, which included analysis of source literature; and drafted recommendations. Panel members reviewed and approved questions. Subcategories were included for some questions based on specific populations of patients who may develop healthcare-associated ventriculitis and meningitis after the following procedures or situations: cerebrospinal fluid shunt placement, cerebrospinal fluid drain placement,

implantation of intrathecal infusion pumps, implantation of deep brain stimulation hardware, and general neurosurgery and head trauma. Recommendations were followed by the strength of the recommendation and the quality of the evidence supporting the recommendation. Many recommendations, however, were based on expert opinion because rigorous clinical data are not available, and the likelihood that clinical trials will be conducted to answer some of these questions is low. For many of these recommendations, the grade was designated as “strong” and evidence was designated as “low” if there was consensus among the experts around specific recommendations. Drafts were reviewed by panel members, who provided input on the content as well as weighting and grading of the evidence. These guidelines represent a practical and useful approach to assist practicing clinicians in the management of these challenging infections.

### Guideline and Conflicts of Interest

All panel members complied with IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. They were provided IDSA’s conflicts of interest disclosure statement and asked to identify ties to companies that develop products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel decided on a case-by-case basis whether a conflict should limit member participation. Potential conflicts are listed in the Acknowledgments section.

### Future Revision Dates

At annual intervals, the panel chair, SPGC liaison advisor, and SPGC chair will determine the need for guideline revisions by reviewing current literature. If necessary, the entire panel will be reconvened. When appropriate, the panel will recommend revisions to the IDSA SPGC, BOD, and other collaborating organizations for review and approval.

## RECOMMENDATIONS AND EVIDENCE SUMMARIES

### I. What are the Typical Symptoms and Signs in Patients with Healthcare-Associated Ventriculitis and Meningitis?

#### *Cerebrospinal Fluid Shunts and Drains* *Recommendations*

1. New headache, nausea, lethargy, and/or change in mental status are suggestive of CSF shunt infection (strong, moderate).
2. Erythema and tenderness over the subcutaneous shunt tubing are suggestive of CSF shunt infection (strong, moderate).

3. Fever, in the absence of another clear source of infection, could be suggestive of CSF shunt infection (weak, low).
4. Symptoms and signs of peritonitis or abdominal tenderness in patients with ventriculoperitoneal shunts, in the absence of another clear etiology, are indicative of CSF shunt infection (strong, moderate).
5. Symptoms and signs of pleuritis in patients with ventriculopleural shunts, in the absence of another clear etiology, are indicative of CSF shunt infection (strong, moderate).
6. Demonstration of bacteremia in a patient with a ventriculoatrial shunt, in the absence of another clear source of bacteremia, is evidence of CSF shunt infection (strong, moderate).
7. Demonstration of glomerulonephritis in a patient with a ventriculoatrial shunt is suggestive of CSF shunt infection (weak, low).

### Evidence Summary

The clinical features of CSF shunt infection can be quite variable and depend on the pathogenesis of infection, organism virulence, and type of shunt [14, 37–39]. Unlike the organisms that cause community-acquired bacterial meningitis, those that cause CSF catheter-associated ventriculitis, such as coagulase-negative staphylococci and *P. acnes*, are indolent, evoke minimal inflammation, and are primarily pathogenic in the presence of prosthetic material. Frequently, there may only be minimal ventriculitis without meningeal involvement or only mechanical blockage as a result of biofilm formation in or on the catheter [40, 41]. Therefore, the clinical symptoms of meningitis may be absent and the clinical presentation more subtle with a longer duration of symptoms. The most frequent symptoms in patients with CSF shunt infection are headache, nausea, lethargy, and change in mental status (seen in as many as 65% of infected patients). These symptoms occur as a result of shunt malfunction secondary to the infection. Fever is reported in as few as 14% to as many as 92% of cases, so the absence of fever cannot exclude the possibility of infection, although fever is typically present in the majority of patients. Pain, often related to infection at the peritoneal or pleural endings of the shunt, may be absent in as many as 60% of infections [42]. Clinically, individual symptoms are not typically both sensitive and specific [43, 44]. This is not surprising since the most common presenting complaints associated with a request for assessment of a CSF shunt for infection (ie, headache, nausea, vomiting, irritability, and fever) are present in a wide variety of other illnesses. Because the vast majority of shunt infections occur in the first few months after shunt surgery, the positive and negative predictive values of individual symptoms will change depending on when the shunt procedure was performed [45].

Symptoms and signs of a CSF shunt infection may be referable either to the proximal or distal portion of the shunt.

Infection beginning in the proximal portion of the shunt (ie, the catheter within the CSF space) may result in ventriculitis or meningitis and may cause shunt obstruction or decreased function [38, 46]. Rarely, intracranial empyemas and abscesses may occur secondary to an incompletely treated infection or in the presence of hardware not removed as part of the treatment process.

Symptoms of infection referable to the distal portion of the shunt are more specific to terminus location [46]. Infected shunts that terminate in the peritoneal or pleural space may lead to an inflammatory response in the absorbing tissue (ie, peritonitis or pleuritis). In patients with infected ventriculo-peritoneal shunts, symptoms of peritonitis appear as the peritoneal inflammation becomes more severe and as fever, anorexia, and other signs and symptoms of an acute abdomen develop. With low-virulence organisms, localizing signs of peritonitis may be confined to abdominal tenderness and/or guarding. In the peritoneal cavity, host defense mechanisms attempt to limit the infection, often resulting in the encystment of the shunt catheter, fluid buildup within the cyst, and loculation of pockets of fluid within the abdomen. These fluid collections, often termed pseudocysts, can grow quite large because the loculated CSF is not absorbed within the cyst. Partial or complete shunt obstruction may result. However, pseudocyst formation may be the result of noninfectious etiologies (eg, local inflammatory response to the foreign body) that will resolve with reimplantation of the distal part of the catheter.

Infected ventriculoatrial shunts may lead to bacteremia secondary to infected CSF directly entering the bloodstream, an infected thrombus or atrial mural vegetation at the end of the vascular catheter, or true bacterial endocarditis. However, the clinical presentation of an infected vascular shunt is usually nonspecific, with fever and lethargy often seen. One unique complication of a chronic vascular shunt is shunt nephritis [10, 38, 46], which is observed in 4%–14% of patients with infected ventriculoatrial shunts. The majority of isolated bacteria in patients with shunt nephritis are usually coagulase-negative staphylococci and *S. aureus*, although diphtheroids and other pathogens have been isolated. The pathogenesis of shunt nephritis is similar to that of subacute bacterial endocarditis, with deposition of immunoglobulin M and G antigen–antibody complexes in the renal glomeruli. The complement system is activated with subsequent depletion of circulating complement factors C3 and C4. Failure to detect this condition can lead to permanent kidney injury.

However, some shunt infections are insidious and cause few or no symptoms, perhaps only an intermittent low-grade fever or general malaise. The patient may present with an unexplained occlusion of an open-ended peritoneal catheter or failure of peritoneal CSF absorption.

### **Cerebrospinal Fluid Drains Recommendations**

8. New or worsening altered mental status in patients with external ventricular drains is suggestive of infection (weak, low).
9. New fever and increased CSF white blood cell count in patients with external ventricular drains could be suggestive of infection (weak, low).

### **Evidence Summary**

Ventricular drains become infected from organisms that are introduced through the drainage system or through the skin site [47, 48]. Infections are more frequent with external ventricular drains than with CSF shunts and may be caused by hospital flora. The change in mental status that occurs in patients in whom meningitis or ventriculitis develops may be difficult to distinguish from the impaired level of consciousness that is a manifestation of the patient's underlying disease. In patients with CSF drain–related ventriculitis, symptoms and signs are not very useful in determining the underlying reason for drain placement; subarachnoid hemorrhage or tumor can also cause a similar neurologic presentation and these patients are often unresponsive in the intensive care unit and unable to report symptoms. Fever that occurs in these patients may also be from other sources of infection. In one study that compared the clinical and laboratory findings at the time of insertion of the external ventricular drain and at the time of documented infection, increasing CSF pleocytosis (median white blood cell [WBC] count of 175/mm<sup>3</sup>) and fever were the most reliable indicators of infection [49].

### **Neurosurgery or Head Trauma Recommendations**

10. New headache, fever, evidence of meningeal irritation, seizures, and/or worsening mental status are suggestive of ventriculitis or meningitis in the setting of recent trauma or neurosurgery (strong, moderate).
11. Fever, in the absence of another clear source of infection, is suggestive of CNS infection in the setting of recent head trauma or neurosurgery (weak, low).

### **Evidence Summary**

The recognition of infectious meningitis or ventriculitis in patients who have had recent neurosurgery or head trauma can be difficult because patients may not be able to provide any history. Because there are little data on patients in this setting, this recommendation is based largely on studies of patients with bacterial meningitis in the community. The usual symptoms and signs of meningitis can also be due to a recent intracranial bleed or other procedures such as neurosurgery. Fever and altered mental status may be the only signs of infection [50]. Fever and

peripheral leukocytosis are also classic findings in meningitis, but there may be many other causes of these findings in a hospitalized patient [51]. Signs of meningeal irritation, including nuchal rigidity, are seen in only 20%–30% of patients [52, 53]. A history of a device placed into the CSF, a craniotomy or trauma resulting in contamination of the CSF, and the absence of another cause for fevers or seizures makes this diagnosis more likely.

#### **Intrathecal Infusion Pumps Recommendation**

12. New fever and drainage from the surgical site in patients with intrathecal infusion pumps are suggestive of wound infection (weak, low).

#### **Evidence Summary**

The clinical presentation of patients with intrathecal infusion pump infections is not well documented in the literature. One retrospective case series described 45 (8%) infections in 571 baclofen pump surgeries [28]. Clinical features were present for 12 patients with infection caused by gram-negative organisms. The most common presentations were fever and drainage from the surgical site. Other series have reported similar rates of infection [54]. As in patients who have CSF shunts, symptoms can be divided into those indicative of local wound infection (eg, erythema, swelling, and purulent drainage at surgical sites) and those indicative of meningitis. Patients may present with either or both of these classes of symptoms. In one series of 19 infectious complications in 119 patients [23], one-third of patients had meningitic symptoms, and one-half of those occurred in the absence of symptoms at the surgical site, most occurred soon after surgery, implying infection occurring at surgery rather than as a result of a pump refill.

## **II. What are the Typical Cerebrospinal Fluid Findings in Patients with Healthcare-Associated Ventriculitis and Meningitis?**

#### **Cell Count, Glucose, and Protein Recommendations**

13. Abnormalities of CSF cell count, glucose, and/or protein may not be reliable indicators for the presence of infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate).
14. Normal CSF cell count, glucose, and protein may not reliably exclude infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate).
15. A negative CSF Gram stain does not exclude the presence of infection, especially in patients who have received previous antimicrobial therapy (strong, moderate).

#### **Evidence Summary**

The diagnosis of CSF shunt and CSF drain infections is difficult. Nonspecific laboratory parameters (eg, leukocytosis, elevation of

erythrocyte sedimentation rate or C-reactive protein) have not been evaluated in the approach to diagnosis of these infections. In patients with suspected CSF shunt infection (ie, in those in whom evidence of infection is suspected and other sources of infection have been excluded), consultation with a neurosurgeon is necessary to access CSF for analysis. Note that CSF may not need to be obtained if another clear source of infection has been identified. Changes in CSF parameters may be subtle [14], thus making it hard to determine if the abnormalities are related to infection or secondary to the underlying reason for catheter placement or a result of neurosurgery [55, 56]. Although high CSF white blood cell counts correlate with the presence of infection, infection may be present even in patients with normal CSF white blood cell counts. CSF white blood cell counts and lactate concentrations were normal in approximately 20% of episodes in one study of adults with shunt-associated infection [14]. CSF eosinophilia (>8% of the differential count) has been associated with an indolent infection [57]. Using a looser definition of eosinophilia (ie, >1% of the differential count), another analysis noted a correlation of eosinophilia with CSF infection but also with subcutaneous (not transcutaneous) CSF extravasation, blood in the CSF, younger age at shunt insertion, and intraventricular hemorrhage as a cause of the hydrocephalus [58]. However, others have questioned the association between CSF eosinophil count and infection [59]. The cell count may be obscured by recent surgery during which blood spilled into the CSF or may have caused an inflammatory reaction, so-called chemical meningitis [55]. Attention should also be paid to the site of CSF sampling, as the CSF white blood cell count in samples obtained by shunt aspiration or from ventricular fluid tends to be lower than when CSF is obtained after lumbar puncture. Conversely, it should also be considered that in many patients with CSF shunts in the ventricular space, the lumbar cistern may not be in communication with the ventricular space, as is the case in obstructive hydrocephalus.

In one cohort study of 230 consecutive patients with external CSF drains [56], CSF samples were collected daily and prospectively evaluated for the presence of bacteria using Gram stain and culture. In this study, lumbar catheters were placed in 125 patients (54.3%), ventricular catheters in 97 patients (42.2%), and more than 1 type of catheter in 8 patients (3.5%). The CSF was also analyzed for leukocyte count, protein concentration, glucose concentration, and ratio of CSF to blood glucose. External drainage-related bacterial meningitis developed in 22 patients (9.6%). Results from analyses of 1516 CSF samples showed no significant differences between the patients in whom external ventricular drain-related meningitis developed and a control group without external ventricular drain-related meningitis during the first 3 days of infection. Also, there were no significant differences during the 3 days preceding the infection with regard to leukocyte count, protein concentration, glucose concentration, and CSF-to-blood glucose ratio. The predictive

and diagnostic values of the CSF parameters were evaluated using receiver operating characteristic curves. They could not establish a cutoff value with a sensitivity and specificity of at least 60% for any of the CSF parameters.

In a prospective study that included 130 patients at a neurosurgical intensive care unit who received an external ventricular drain [60], daily CSF samples were obtained and examined for cell count and glucose and protein content. Bacteriological cultures were taken 3 times a week. Standard laboratory parameters, such as peripheral leukocyte count, CSF glucose, and CSF protein, were not reliable predictors for incipient ventricular catheter infection. The only parameter that significantly correlated with the occurrence of a positive CSF culture was the CSF cell count ( $P < .05$ ).

One prospective study evaluated the utility of cell index, which is the ratio of leukocytes to erythrocytes in CSF and of leukocytes to erythrocytes in peripheral blood, in predicting ventriculitis [61]. The study was limited to 13 patients with intraventricular hemorrhage who had external ventricular drains; 7 patients developed a culture-confirmed ventriculitis. Diagnosis by cell index was possible up to 3 days prior to conventional diagnosis. The results, however, have not been validated.

The diagnostic accuracy of a Gram stain is a function of the number of microorganisms present, the type of meningeal pathogen, and the receipt of prior antimicrobial therapy [62]. A negative result of a CSF Gram stain does not exclude the likelihood of infection. The CSF Gram stain was positive in 65 (71%) of 91 cases in one study of patients with nosocomial meningitis [63].

### Culture

#### Recommendations

16. CSF cultures are the most important test to establish the diagnosis of healthcare-associated ventriculitis and meningitis (strong, high).
17. If initial CSF cultures are negative in patients with CSF shunts or drains with suspected infection, it is recommended that cultures be held for at least 10 days in an attempt to identify organisms such as *P. acnes* (strong, high).
18. If a CSF shunt or drain is removed in patients suspected of having infection, cultures of shunt and drain components are recommended (strong, moderate).
19. If a CSF shunt or drain is removed for indications other than infection, cultures of shunt or drain components are not recommended (strong, moderate).
20. Blood cultures are recommended in patients with suspected ventriculoatrial shunt infections (strong, high).
21. Blood cultures may be considered in patients with ventriculoperitoneal and ventriculopleural shunts (weak, low).

22. Single or multiple positive CSF cultures in patients with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and clinical symptoms suspicious for ventriculitis or meningitis, is indicative of CSF drain infection (strong, high).
23. CSF and blood cultures in selected patients should be obtained before the administration of antimicrobial therapy; a negative CSF culture in the setting of previous antimicrobial therapy does not exclude healthcare-associated ventriculitis and meningitis (strong, moderate).

### Evidence Summary

CSF cultures from the shunt, reservoir, or drain are the most important tests for establishing the diagnosis of infection. The culture will usually be positive in patients with an infected device even when there is no pleocytosis or alterations in CSF chemistries. Positive cultures in only thioglycolate broth should be interpreted with caution but may be significant in the appropriate clinical circumstance (eg, in patients who have received prior antimicrobial therapy). CSF cultures may require several days to weeks of incubation before they can be called negative, especially for slow-growing organisms such as *P. acnes*, or the results may be negative in patients who have received previous antimicrobial therapy. A negative result of a CSF culture does not exclude the possibility of infection, and cultures should be repeated if initial cultures are negative and infection is considered likely. In a study of 245 children with bacterial meningitis, the sensitivity of the CSF culture decreased from 88% to 70% with any use of antimicrobial therapy ( $P < .001$ ). The sensitivity further decreased to 59% if antimicrobial therapy was administered for >24 hours prior to the lumbar puncture, although patients with CSF shunts were specifically excluded from this study [64]. A similar study in patients with healthcare-associated ventriculitis and meningitis is currently lacking. However, one study of 86 cases of suspected nosocomial meningitis showed that use of broad-range 16S rRNA polymerase chain reaction (PCR) detected bacteria in approximately 50% of culture-negative cases [65]. Most of the patients who were PCR positive and culture negative had received previous antimicrobial therapy.

Occasionally, CSF shunts may be tapped for evaluation of function in patients with no clinical evidence of infection and may be found to be culture positive. In this situation, contamination may be responsible for the positive culture, but true infection must be strongly considered. The shunt should be retapped; a positive culture with the same microorganism is usually indicative of true infection.

Shunt failure in the absence of shunt infection is a common occurrence; shunt components are frequently removed during surgical procedures to revise the failed shunt. In the absence of clinical evidence of a CSF shunt infection,

routine cultures of shunt components, when shunts are removed for other indications, is not recommended. In one study of 174 shunt revisions, 19 patients had positive shunt component cultures without signs of infection (ie, asymptomatic bacteriologic shunt contamination); only 1 patient was treated with antimicrobial therapy [66]. There was no increase in the risk of shunt malfunction in this group when compared to other patients with CSF shunts in the database at their institution.

In patients with ventriculoatrial shunts, blood cultures should be performed because bacteremia is invariably present in patients with infected ventriculoatrial shunts (positive blood cultures in >90% of cases). This contrasts with infections in other types of CSF shunts in which the incidence of negative blood cultures approaches 80% [38]. Blood cultures may be considered in these patients, although positive results should be interpreted cautiously in patients with nonvascular CSF shunts and may represent a contaminant or another source of infection.

In patients with lumbar or ventricular drains, definite infection is defined as a positive CSF culture (obtained from the ventricular or lumbar catheter) associated with CSF pleocytosis [20, 47]. Progressively decreasing CSF glucose and increasing CSF protein accompanied by advancing CSF pleocytosis, in the absence of positive CSF cultures or positive Gram stain, characterizes a suspected infection in the absence of another etiology. A contaminating microorganism is defined as an isolated positive CSF culture and/or positive Gram stain with a normal CSF cell count, CSF glucose, and CSF protein. Lozier et al [20] proposed a classification system for determination of ventriculostomy infection in the presence of ventriculitis. Cases with positive CSF cultures were classified as contaminant, colonization, suspected ventriculostomy-related infection, ventriculostomy-related infection, and ventriculitis. The definition of ventriculitis included “clinical signs of meningitis” such as neck stiffness and photophobia, which are often absent because organisms such as a coagulase-negative staphylococcus and *P. acnes* are indolent and may not cause significant inflammation. In addition, patients with subarachnoid hemorrhage can have symptoms that mimic meningitis. The classification we propose for patients with ventricular drains is a modification, as follows:

- **Contamination:** An *isolated* positive CSF culture or Gram stain, with normal CSF cell count and glucose and protein concentrations and with lack of clinical symptoms suspicious for ventriculitis or meningitis.
- **Colonization:** *Multiple* positive CSF cultures or Gram stain, with normal CSF cell count and glucose and protein concentrations and with lack of clinical symptoms suspicious for ventriculitis or meningitis.

- **Infection:** Single or multiple positive CSF cultures with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and clinical symptoms suspicious for ventriculitis or meningitis.

The Centers for Disease Control and Prevention’s National Healthcare Safety Network (CDC/NHSN) definition of healthcare-associated ventriculitis or meningitis includes at least 1 of the following criteria (CDC/NHSN Surveillance Definitions; January 2015) [67]:

- Organism cultured from CSF
- At least 2 of the following symptoms with no other recognized cause in patients aged >1 year: fever >38°C or headache, meningeal signs, or cranial nerve signs, or at least 2 of the following symptoms with no other recognized cause in patients aged ≤1 year: fever >38°C or hypothermia <36°C, apnea, bradycardia, or irritability and at least 1 of the following:
  - o Increased white cells, elevated protein, and decreased glucose in CSF
  - o Organisms seen on Gram stain of CSF
  - o Organisms cultured from blood
  - o Positive nonculture diagnostic laboratory test from CSF, blood, or urine
  - o Diagnostic single-antibody titer (immunoglobulin M) or 4-fold increase in paired sera (immunoglobulin G) for organism.

However, a nonculture diagnostic laboratory test or antibody titers for specific organisms are not often used in patients with healthcare-associated ventriculitis or meningitis.

#### Neurosurgery or Head Trauma Recommendations

24. CSF pleocytosis with a positive culture and symptoms of infection are indicative of a diagnosis of healthcare-associated ventriculitis or meningitis (strong, high).
25. Hypoglycorrhachia and elevated CSF protein concentrations are suggestive of the diagnosis of healthcare-associated ventriculitis or meningitis (weak, low).
26. Growth of an organism that is commonly considered a contaminant (eg, coagulase-negative staphylococcus) in enrichment broth only or on just 1 of multiple cultures in a patient with normal CSF and no fever is not indicative of healthcare-associated ventriculitis or meningitis (strong, low).
27. CSF cultures with multiple organisms from a single sample may be contaminants in patients with no symptoms of infection or CSF pleocytosis (weak, low).
28. CSF cultures that grow *S. aureus* or aerobic gram-negative bacilli are indicative of infection (strong, moderate).
29. CSF cultures that grow a fungal pathogen are indicative of infection (strong, moderate).

### Evidence Summary

Many criteria have been used to establish the diagnosis of meningitis or ventriculitis in the setting of neurosurgery or head trauma. Because there is no gold standard for defining an infection, the definition has usually included an evaluation of the microorganism that grew in culture, the number of positive cultures, and clinical parameters. However, the CDC/NHSN definition is useful in defining the likelihood of a true infection (see above). Older studies often required only a single positive CSF culture. Others accepted either a CSF pleocytosis or low CSF glucose concentration to diagnose infection. More recently, experts have suggested use of a combination of findings to establish the diagnosis [20]. One study used a combination of a positive CSF culture with CSF pleocytosis (at least 11 WBCs/mm<sup>3</sup> and ≥50% neutrophils) along with clinical symptoms [68]. This definition was later refined to require 2 positive CSF cultures with the same organism on different days [51]. There are also reports of healthcare-associated meningitis in patients with a normal CSF white cell count [50].

CSF changes following neurosurgery, head trauma, or intracranial bleeding may be suggestive of infection. After neurosurgery, the CSF white cell count can be quite high and the glucose concentration may be low. These patients often have headaches, nuchal rigidity, vomiting, and altered mentation. However, if the CSF white blood cells are >7500/mm<sup>3</sup> or if the CSF glucose is <10 mg/dL, infection is more likely. High fever (≥40°C) or prolonged fever (>1 week) was more suggestive of infectious meningitis in one study [55], although a limitation of this study was that there was no single variable that could be used to accurately distinguish between bacterial and aseptic meningitis at the time of presentation.

The most common CSF contaminants are coagulase-negative staphylococci. In a study of pediatric patients who had daily cultures, more than half of the positive cultures were thought to be contaminants, and a coagulase-negative staphylococcus was isolated in more than half of those with positive cultures [47]. It was thought to be a contaminant in 15 positive cultures and a true pathogen in only 3 cultures. However, a coagulase-negative staphylococcus is also one of the more common causes of infection in patients who have had recent surgery or who have external ventricular drains. Clues to this organism being a contaminant included light growth, growth only in enrichment broth, and growth of the organism in a minority of cultures. All patients with predefined “true infections” in this study had fever and a peripheral leukocytosis. However, these results have not been validated in other cohorts.

When cultures are collected from a drainage device (eg, an external ventricular drain or a lumbar drain), the absence of any change in CSF parameters (eg, cell count, glucose, protein) suggests contamination. Ideally, cultures should be collected from the injection site and sampling port of an external ventricular

drain rather than the drainage bag in order to decrease the risk of contamination. Similarly, with a lumbar drain, the sampling port is the preferred site for obtaining CSF.

The majority of reports of healthcare-associated meningitis identified a single pathogen with each episode of meningitis. While sequential infections may be seen in a patient who has a drainage device for a long period of time, it would be unusual to develop an infection with multiple organisms simultaneously unless there was an obvious route of infection from a contaminated source (eg, after head trauma with open fracture). In the absence of a likely source, changes in the CSF, or symptoms of infection, this may represent contamination from the time of CSF collection. If there is a question of whether or not the culture represents contamination, it is reasonable to collect additional CSF to evaluate CSF parameters and repeat cultures in order to determine the significance of the result.

Healthcare-associated fungal ventriculitis and meningitis is much less common than that caused by bacteria; however, it may be seen after surgery or other invasive procedures or trauma. In the post-operative setting, *Candida* species are the most likely pathogen. This organism has been implicated in premature infants and in 5% of cases following neurosurgery [69]. Other fungal pathogens have also been isolated after traumatic head injuries, including *Aspergillus* [70] and *Cryptococcus neoformans* [71]. The underlying host defect may also affect the epidemiology. In a review of oncology patients at Memorial Sloan-Kettering Cancer Center with meningitis between 1993 and 2004 [72], 7% of patients were infected with *C. neoformans* and 1% with *Candida albicans*; 78% of these patients had prior neurosurgery. In a multistate outbreak of fungal meningitis in September 2012 as a result of contaminated methylprednisolone made at a single compounding pharmacy in Massachusetts [73–75], the index patient was infected with *Aspergillus fumigatus*, but most of the subsequent infections were caused by *Exserohilum rostratum*. Of the 749 patients with infections, meningitis was seen in 233 (31%) cases. Another 151 patients (20%) had meningitis and a concurrent spinal or paraspinal infection. In addition, a large number of patients had epidural infections without meningitis [74].

### III. What Specific Tests of Cerebrospinal Fluid can be used to Confirm the Patient has Healthcare-Associated Ventriculitis and Meningitis?

#### Recommendations

30. An elevated CSF lactate or an elevated CSF procalcitonin, or the combination of both, may be useful in the diagnosis of healthcare-associated bacterial ventriculitis and meningitis (weak, moderate).
31. An elevated serum procalcitonin may be useful in differentiating between CSF abnormalities due to surgery or intracranial hemorrhage from those due to bacterial infection (weak, low).

32. Nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low).
33. Detection of  $\beta$ -D-glucan and galactomannan in CSF may be useful in the diagnosis of fungal ventriculitis and meningitis (strong, moderate).

### **Evidence Summary**

#### **Lactate**

An elevated CSF lactate concentration of more than 3.5 to 4.2 mmol/L occurs more frequently in bacterial than in aseptic meningitis. Two large metaanalyses have concluded that elevated CSF lactate concentration is better than the CSF WBC count, glucose, or protein in differentiating bacterial meningitis from aseptic meningitis (sensitivity of 93% and 97% and specificity of 96% and 94%, respectively) [76, 77]. However, the studies in these metaanalyses mostly equated aseptic meningitis with viral meningitis, and few post-surgical or post-trauma patients were included. In patients with healthcare-associated ventriculitis and meningitis, CSF lactate concentrations, using a cutoff of 4 mmol/L, are both sensitive (88%) and highly specific (98%) in making the diagnosis of bacterial meningitis following neurosurgery [78]. The positive predictive value was 96% and the negative predictive value was 94%; this study included patients who had a lumbar puncture performed within 40 days of neurosurgery. However, the evidence is conflicting. In a prospective study of 16 patients with an intraventricular hemorrhage who had an external ventricular drain, the CSF lactate was elevated in all 3 patients with infection. In 11 of 13 patients without infection it was <4 mmol/L, and in 2 patients it was between 4 and 6 mmol/L. One of these patients had a grade 5 subarachnoid hemorrhage and the other had renal insufficiency. In this population, the positive predictive value for infection was 60% and the negative predictive value was 100% [79]. Because subarachnoid hemorrhage and brain injury are known to cause hyperglycolysis, it is not surprising that CSF lactate may be elevated in these patients. Metabolic suppressive therapies (benzodiazepines and opiates) have also been shown to decrease CSF lactate concentrations in this population, and specific elevations in CSF lactate concentrations (mean  $3.2 \pm 0.9$  mmol/L) have been associated with withdrawal of sedation [80, 81]. In a prospective clinical study to evaluate the diagnostic accuracy of CSF lactate as a marker of post-neurosurgical bacterial meningitis [80], increased CSF lactate ( $\geq 4$  mmol/L) demonstrated a better predictive value than CSF hypoglycorrhachia or pleocytosis and had a sensitivity of 97% and specificity of 78%, with a 97% negative predictive value. However, a retrospective review of cases of bacterial meningitis associated with a CSF shunt showed that if a cutoff value of 4 mmol/L for CSF lactate had been used, almost half of the infections would have been missed [14]. In patients who already have a CSF shunt for the management

of hydrocephalus, CSF lactate concentrations were normal in 20% of patients who were diagnosed with a shunt infection.

#### **Procalcitonin**

In patients who presented from the community with meningitis, serum procalcitonin concentrations had the highest specificity for identifying bacterial meningitis when compared to C-reactive protein, blood and CSF leukocyte counts, CSF protein, CSF lactate concentrations, and the CSF-to-serum glucose ratio. The cutoff used in this study was 0.5 ng/mL. The specificity was 100%, but the sensitivity was only 68% [82]. Serum procalcitonin has been studied in patients who had a neurologic disorder that resulted in hydrocephalus and subsequent placement of an external ventricular drain [83]. This included patients with intracranial hemorrhage, infarction, or tumor. In this study, body temperature, CSF white cell count, CSF protein, CSF lactate and CSF-to-serum glucose ratio did not predict infection. All patients with a serum procalcitonin concentration >1 ng/mL had a proven CSF infection. The mean procalcitonin concentration with a positive CSF culture was  $4.7 \pm 1.0$  vs  $0.2 \pm 0.01$  ng/mL ( $P < .0001$ ). The sensitivity and specificity of this cutoff were both 100%. In this study, the CSF lactate in 34 patients with a positive culture compared to those with a negative culture was 42 mmol/L vs 34 mmol/L ( $P = .76$ ) [83]. The CSF lactate in the group with negative cultures was higher than would be expected in patients without bacterial meningitis. This may be due to the large number of patients who had an intracranial hemorrhage. In a more recent observational prospective study of 36 adult patients with severe head trauma and an external ventricular drain [84], patients with negative CSF cultures had a mean serum procalcitonin concentration <2.0 ng/mL, while patients with positive cultures had a mean serum procalcitonin of 4.18 ng/mL. These results suggest that early high serum procalcitonin concentration is a reliable indicator of bacterial CNS infection in patients with external ventricular drains. Another study found the combination of both CSF procalcitonin and CSF lactate concentrations, using cutoff values of 0.075 ng/mL and 3.45 mmol/L, respectively, to have a high diagnostic accuracy (sensitivity of 96% and negative predictive value of 97.6%) in distinguishing between post-neurosurgical bacterial and aseptic meningitis [85]. While these studies are quite supportive, both are small and require further validation.

#### **Nucleic Acid Amplification Tests**

PCR has been evaluated to detect the presence of bacterial DNA in CSF from patients with external ventricular drains and ventriculoperitoneal shunts. In one study that used broad-range 16S rRNA PCR to detect bacteria in 86 specimens of patients with suspected nosocomial meningitis, 42 (49%) were culture negative, but PCR positive [65]. There were no positive culture results in patients with a negative CSF PCR, suggesting that a negative result is predictive of the absence of infection.

However, more studies are needed before routine use of PCR can be recommended in this setting.

In a study of patients with ventricular drainage catheters, adding broad-range real-time PCR (RT-PCR) to culture increased the ability to identify pathogens by 25%; however, the sensitivity of the RT-PCR was only 47.1% (95% CI, 39.8%–64.8%) and the specificity was 93.4% (95% CI, 90.0%–95.8%). The test was most useful for identifying fastidious gram-negative bacilli [86].

#### ***β-D-Glucan and Galactomannan***

If there is a concern for fungal ventriculitis or meningitis, additional studies may be needed because the inability to isolate the organism is not adequate to exclude the diagnosis. These could include CSF galactomannan and CSF (1, 3)-β-D-glucan. *Candida* meningitis may be difficult to diagnose because the sensitivity of CSF cultures is low. CSF *Candida* mannan antigen and anti-mannan antibodies may be useful additional tests in patients with suspected *Candida* meningitis in whom cultures are negative [87]. CSF galactomannan has been evaluated in several studies of patients with CNS infections caused by *Aspergillus* spp. and may be useful in establishing the diagnosis before the culture is positive [74, 88, 89].

In the 2012 outbreak of fungal meningitis that resulted from contaminated methylprednisolone injections [74], laboratory evidence was supportive of a fungal infection in 173 patients (33%) in whom specimens were obtained, including direct detection of fungal DNA in 87 samples (50%), fungal isolation in 33 (19%), and evidence from multiple techniques in 53 (31%). In 5 patients with CSF (1, 3)-β-D-glucan who were evaluated, 3 had elevated CSF (1, 3)-β-D-glucan concentrations (range, 39–2396 pg/mL) and responded to antifungal therapy. Measurement of CSF (1, 3)-β-D-glucan using the manufacturer's cutoff of ≥80 pg/mL was highly sensitive (96%) and specific (95%) for the diagnosis of proven fungal meningitis associated with contaminated methylprednisolone injections [90]. Another study has also demonstrated the usefulness of CSF (1, 3)-β-D-glucan for diagnosing or excluding fungal CNS infection [91].

#### **IV. What is the Role of Imaging in Patients with Suspected Healthcare-Associated Ventriculitis and Meningitis?**

##### ***Recommendations***

34. Neuroimaging is recommended in patients with suspected healthcare-associated ventriculitis and meningitis (strong, moderate).
35. Magnetic resonance imaging with gadolinium enhancement and diffusion-weighted imaging is recommended for detecting abnormalities in patients with healthcare-associated ventriculitis and meningitis (strong, moderate).
36. In patients with infected ventriculoperitoneal shunts and abdominal symptoms (eg, pain or tenderness), an ultrasound or computed tomography (CT) of the abdomen is

recommended to detect CSF loculations at the shunt terminus (strong, moderate).

#### ***Evidence Summary***

Neuroimaging studies, while rarely the definitive study in patients with healthcare-associated ventriculitis and meningitis, are very frequently obtained in the course of patient evaluation. For patients with CSF shunts, and those undergoing craniotomy or suffering from trauma, these studies will be part of the initial evaluation, perhaps even before infection is strongly suspected. In the context of a known infection, findings of potential importance include CSF shunt hardware retained from previous surgical procedures or, rarely, a subdural empyema or brain abscess. Plain radiographs of the shunt system to document retained hardware may also be helpful. Neuroimaging may also be useful in determining the source of infection (eg, local extension from an adjacent infection) and in identifying complications from the infection, including hydrocephalus, vasculitis, or thrombosis of vessels [92, 93]. Noncontrast CT scanning may be useful in evaluating noninfectious complications but is often normal in the setting of uncomplicated meningitis. In the setting of ventriculitis, CT scans will show ependymal enhancement after the administration of intravenous contrast. Magnetic resonance imaging is more sensitive than CT for detecting ventriculitis. Fluid-attenuation inversion recovery and post-contrast T1 weighted images may be most useful. Diffusion weighted imaging may be used to detect pus in the ventricular system (visualized as bright signal) and to differentiate a brain abscess from malignancy [92]. Care must be taken to ensure that the specific devices used for intracranial pressure monitoring and external CSF drainage are cleared for magnetic resonance imaging.

The diagnosis of CSF shunt infection may be more difficult to establish when the distal portion of the ventriculoperitoneal shunt is infected. The shunt tap may be normal with negative cultures if a retrograde infection has not yet developed in the patient. Ventriculoperitoneal shunts with distal occlusion and without an obvious mechanical cause and with no symptoms or signs of infection have been associated with infection. An ultrasound or CT of the abdomen may identify CSF loculations at the shunt terminus in patients with abdominal symptoms or signs. Although some free fluid in the pleural or peritoneal cavities is normal, it should not be confused with the larger volumes and cysts seen with infection at the shunt terminus.

#### **V. What is the Empiric Antimicrobial Approach for Patients with Suspected Healthcare-Associated Ventriculitis and Meningitis?**

##### ***Recommendations***

37. Vancomycin plus an anti-pseudomonal beta-lactam (such as cefepime, ceftazidime, or meropenem) is recommended as empiric therapy for healthcare-associated ventriculitis and meningitis; the choice of empiric beta-lactam agent

should be based on local in vitro susceptibility patterns (strong, low).

38. In seriously ill adult patients with healthcare-associated ventriculitis and meningitis, the vancomycin trough concentration should be maintained at 15–20 µg/mL in those who receive intermittent bolus administration (strong, low).
39. For patients with healthcare-associated ventriculitis and meningitis who have experienced anaphylaxis to beta-lactam antimicrobial agents and in whom meropenem is contraindicated, aztreonam or ciprofloxacin is recommended for gram-negative coverage (strong, low).
40. For patients with healthcare-associated ventriculitis and meningitis who are colonized or infected elsewhere with a highly antimicrobial-resistant pathogen, adjusting the empiric regimen to treat for this pathogen is recommended (strong, low).

#### Evidence Summary

The principles of antimicrobial therapy for patients with healthcare-associated ventriculitis and meningitis are generally the same as those for acute bacterial meningitis [94]: the agent must penetrate the CNS, attain adequate CSF concentrations, and have bactericidal activity against the infecting pathogen. However, some of the microorganisms that cause these infections often form biofilms in those patients with prosthetic devices into which antimicrobial agents do not penetrate well. Therefore, drug therapy may be problematic when the catheter is not removed. When a CSF pleocytosis is present, antimicrobial therapy should be initiated after appropriate cultures are obtained, but before culture results are available, if there is suspicion of infection. The most likely microorganisms associated with CSF shunt and drain infections are coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), *S. aureus*, *P. acnes*, and gram-negative bacilli (including *Escherichia coli*, *Enterobacter* species, *Citrobacter* species, *Serratia* species, and *Pseudomonas aeruginosa*). Empirical therapy with intravenous vancomycin plus cefepime, ceftazidime, or meropenem is appropriate [18]. The serum vancomycin trough concentration should be maintained between 15 and 20 µg/mL in adult patients who receive intermittent bolus administration [94, 95]. The empirical choice to treat a presumptive gram-negative pathogen should be based on the local antimicrobial susceptibility patterns of these pathogens.

In a patient with anaphylaxis to beta-lactam antimicrobial agents and in whom meropenem is contraindicated, empiric therapy against gram-negative pathogens should be either aztreonam or ciprofloxacin. The choice of the specific antimicrobial agents should take into account local in vitro susceptibility patterns as well as the bacteria previously isolated from the patient.

## VI. Once a Pathogen is Identified, what Specific Antimicrobial Agent(s) Should be Administered?

### Recommendations

41. For treatment of infection caused by methicillin-susceptible *S. aureus*, nafcillin or oxacillin is recommended (strong, moderate). If the patient cannot receive beta-lactam agents, the patient can be desensitized or may receive vancomycin as an alternative agent (weak, moderate).
42. For treatment of infection caused by methicillin-resistant *S. aureus*, vancomycin is recommended as first-line therapy (strong, moderate), with consideration for an alternative antimicrobial agent if the vancomycin minimal inhibitory concentration (MIC) is  $\geq 1$  µg/mL (strong, moderate).
43. For treatment of infection caused by coagulase-negative staphylococci, the recommended therapy should be similar to that for *S. aureus* and based on in vitro susceptibility testing (strong, moderate).
44. If the staphylococcal isolate is susceptible to rifampin, this agent may be considered in combination with other antimicrobial agents for staphylococcal ventriculitis and meningitis (weak, low); rifampin is recommended as part of combination therapy for any patient with intracranial or spinal hardware such as a CSF shunt or drain (strong, low).
45. For treatment of patients with healthcare-associated ventriculitis and meningitis caused by staphylococci in whom beta-lactam agents or vancomycin cannot be used, linezolid (strong, low), daptomycin (strong, low), or trimethoprim-sulfamethoxazole (strong, low) is recommended, with selection of a specific agent based on in vitro susceptibility testing.
46. For treatment of infection caused by *P. acnes*, penicillin G is recommended (strong, moderate).
47. For treatment of infection caused by gram-negative bacilli, therapy should be based on in vitro susceptibility testing with agents that achieve good CNS penetration (strong, moderate).
48. For treatment of infection caused by gram-negative bacilli susceptible to third-generation cephalosporins, ceftriaxone or cefotaxime is recommended (strong, moderate).
49. For treatment of infection caused by *Pseudomonas* species, the recommended therapy is cefepime, ceftazidime, or meropenem (strong, moderate); recommended alternative antimicrobial agents are aztreonam or a fluoroquinolone with in vitro activity (strong, moderate).
50. For treatment of infection caused by extended-spectrum beta-lactamase-producing gram-negative bacilli, meropenem should be used if this isolate demonstrates in vitro susceptibility (strong, moderate).
51. For treatment of infection caused by *Acinetobacter* species, meropenem is recommended (strong, moderate); for strains that demonstrate carbapenem resistance, colistimethate sodium or polymyxin B (either agent administered by the

intravenous and intraventricular routes) is recommended (strong, moderate).

52. Prolonged infusion of meropenem (each dose administered over 3 hours) may be successful in treating resistant gram-negative organisms (weak, low).
53. For treatment of infection caused by *Candida* species, based on in vitro susceptibility testing, liposomal amphotericin B, often combined with 5-flucytosine, is recommended (strong, moderate); once the patient shows clinical improvement, therapy can be changed to fluconazole if the isolated species is susceptible (weak, low).
54. For treatment of infection caused by *Aspergillus* or *Exserohilum* species, voriconazole is recommended (strong, low).

### Evidence Summary

Antimicrobial therapy should be modified once a microorganism is isolated and in vitro susceptibility results are available (Table 1), although there are no randomized controlled trials that compared clinically meaningful outcomes (eg, attributable mortality, morbidity, or clinical cure rates) between different antimicrobials, doses, or durations of treatment for healthcare-associated ventriculitis and meningitis. Most studies that evaluated intravenous antimicrobials for meningitis or ventriculitis, including external ventricular drain-related ventriculitis, were pharmacokinetic studies, uncontrolled case series, or case reports reporting clinical and microbiologic cure rates. Recommended dosages of antimicrobial agents in infants and children and in adults with normal renal and hepatic function are shown in Table 2.

Vancomycin should be used if infection is caused by methicillin-resistant *S. aureus* (MRSA). If the patient is infected with MRSA strains that have a vancomycin MIC of  $\geq 1$   $\mu\text{g/mL}$ , linezolid, daptomycin, or trimethoprim-sulfamethoxazole should be considered [96]. If staphylococci are isolated and the organism is methicillin susceptible, therapy should be changed to either nafcillin or oxacillin. The addition of rifampin to an antistaphylococcal agent may augment treatment [97–99], especially if the infected catheter is retained. One patient with an *S. epidermidis* ventriculoperitoneal shunt infection [100] and another with an *Enterococcus faecalis* ventriculoperitoneal shunt infection [101] were cured with shunt removal and intravenous linezolid. Linezolid has been successfully used in a number of other patients with CSF shunt infection [102–104]; however, linezolid is not considered first-line therapy for this infection. Daptomycin, combined with rifampin, has also been successfully used in patients with infections of CSF shunts caused by gram-positive pathogens [105]. In one study of 6 neurosurgical patients with indwelling external CSF shunts and suspected meningitis or ventriculitis [106], a single dose of daptomycin (10 mg/kg) led to an overall CSF penetration of 0.8%. When corrected for protein binding, the overall CSF penetration was 11.5%.

For treatment of healthcare-associated ventriculitis and meningitis caused by gram-negative bacilli, therapy should be based on in vitro susceptibility testing. One retrospective study of meningitis caused by *Enterobacter* spp. in 19 patients showed that clinical cure or improvement occurred in 54% of those treated with a third-generation cephalosporin compared to 83% of patients who were treated with trimethoprim-sulfamethoxazole [107]. Another case series of 13 episodes of *Enterobacter* meningitis treated with various antimicrobial regimens, including an additional 33 episodes from the literature, reported that the development of resistance to beta-lactam agents may be much higher [108]. All patients who received trimethoprim-sulfamethoxazole were cured compared to about 70% of those who received beta-lactam agents. Trimethoprim-sulfamethoxazole or meropenem may be preferred for treatment of organisms that hyperproduce  $\beta$ -lactamase.

For patients with *Acinetobacter* ventriculomeningitis, empiric therapy should be initiated with meropenem. If carbapenem resistance is suspected, a combination of intravenous and intraventricular colistimethate sodium or polymyxin B is recommended [109]. In a recent case series of 40 patients with *Acinetobacter baumannii* meningitis, the mortality was 39%; 55% of them had isolates resistant to carbapenems. Use of either intraventricular or intrathecal colistimethate in those with carbapenem resistance was associated with a cure of their infection [110]. The duration of administration of beta-lactam agents may affect clinical outcomes. When the carbapenems and piperacillin/tazobactam were given as an extended infusion lasting  $\geq 3$  hours or as a continuous infusion rather than with standard short-term infusion, clinical outcomes were improved [111]. Prolonged infusion of meropenem, each dose administered over 3 hours, may also be successful in treating resistant gram-negative infections [112].

The definitive treatment for fungal meningitis depends on the pathogen. An intravenous amphotericin B preparation, often combined with 5-flucytosine, is recommended for *Candida* ventriculitis and meningitis [113]. A lipid formulation of amphotericin B (usually liposomal amphotericin B) is recommended because these formulations achieved higher CNS concentrations than other formulations of amphotericin B in a rabbit model [114]. Consideration can be given to a step-down of therapy to fluconazole after there is clinical improvement and if isolated *Candida* is a susceptible species [113]. Echinocandins should not be used because they do not achieve adequate CSF concentrations. Some agents have shown effectiveness in experimental animal models, but at doses higher than would be used in humans. Treatment should continue until all signs and symptoms of infection have resolved, CSF has normalized, and there is no radiographic evidence of ongoing infection.

The recommended treatment for *Aspergillus* ventriculitis and meningitis is voriconazole [115], with the goal of maintaining a serum trough concentration of 2–5  $\mu\text{g/mL}$ . Posaconazole,

**Table 1. Recommended Antimicrobial Therapy in Patients With Healthcare-Associated Ventriculitis and Meningitis Based on Isolated Pathogen and In Vitro Susceptibility Testing**

Microorganism	Standard Therapy	Alternative Therapies
Staphylococci <sup>a</sup>		
Methicillin sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin resistant	Vancomycin	Daptomycin, trimethoprim-sulfamethoxazole, or linezolid
<i>Propionibacterium acnes</i>	Penicillin G	Third-generation cephalosporin, <sup>b</sup> vancomycin, daptomycin, or linezolid
<i>Streptococcus pneumoniae</i>		
Penicillin MIC ≤0.06 µg/mL	Penicillin G	Third-generation cephalosporin <sup>b</sup>
Penicillin MIC ≥0.12 µg/mL		
Cefotaxime or ceftriaxone MIC <1.0 µg/mL	Third-generation cephalosporin <sup>b</sup>	Cefepime or meropenem
Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL	Vancomycin plus a third-generation cephalosporin <sup>b,c</sup>	Moxifloxacin <sup>d</sup>
<i>Pseudomonas aeruginosa</i>	Cefepime, ceftazidime, or meropenem	Aztreonam or ciprofloxacin
<i>Haemophilus influenzae</i>		
β-lactamase negative	Ampicillin	Third-generation cephalosporin, <sup>b</sup> cefepime, or a fluoroquinolone
β-lactamase positive	Third-generation cephalosporin <sup>b</sup>	Cefepime, aztreonam, or a fluoroquinolone
Extended spectrum β-lactamase-producing gram-negative bacilli	Meropenem	Cefepime or a fluoroquinolone
<i>Acinetobacter baumannii</i>	Meropenem	Colistin (usually formulated as colistimethate sodium) <sup>e</sup> or polymyxin B <sup>e</sup>
Other Enterobacteriaceae <sup>f</sup>	Third-generation cephalosporin <sup>b</sup>	Meropenem, aztreonam, trimethoprim-sulfamethoxazole, or ciprofloxacin
<i>Candida</i> species <sup>g</sup>	Lipid formulation of amphotericin B ± flucytosine	Fluconazole or voriconazole
<i>Aspergillus</i> species	Voriconazole	Lipid formulation of amphotericin B or posaconazole

Abbreviation: MIC, minimal inhibitory concentration.

<sup>a</sup>Add rifampin if organism is susceptible and prosthetic material is also in place.

<sup>b</sup>Cefotaxime or ceftriaxone.

<sup>c</sup>Consider adding rifampin if the MIC to ceftriaxone is >2 µg/mL.

<sup>d</sup>Many authorities would combine moxifloxacin with either vancomycin or a third-generation cephalosporin (cefotaxime or ceftriaxone).

<sup>e</sup>May also need to administer via the intraventricular or intrathecal route.

<sup>f</sup>Choice of agent based in in vitro susceptibility testing. For organisms (eg, Enterobacter, Citrobacter, Serratia) that may hyperproduce β-lactamases, meropenem or trimethoprim-sulfamethoxazole may be preferred.

<sup>g</sup>*Candida krusei* should not be treated with fluconazole. *Candida glabrata* may be treated with fluconazole if it is susceptible; however, many isolates will only be susceptible to high doses or will be resistant.

liposomal amphotericin B, and amphotericin B lipid complex are reasonable alternatives. The duration of therapy for these infections depends largely on the host. If the patient is chronically immunosuppressed, the initial treatment may be followed by oral therapy to prevent relapse. Any immunosuppressive agents that can be safely discontinued should be stopped. In the 2012 outbreak of *E. rostratum* meningitis, voriconazole was also recommended. A 3-month course of treatment appeared to be adequate for patients who had isolated meningitis and who had no symptoms or CSF abnormalities after 3 months [74, 75].

## VII. What is the Role of Intraventricular Antimicrobial Therapy in Patients with Healthcare-Associated Ventriculitis and Meningitis?

### Recommendations

- Intraventricular antimicrobial therapy should be considered for patients with healthcare-associated ventriculitis and meningitis in which the infection responds poorly to systemic antimicrobial therapy alone (strong, low).
- When antimicrobial therapy is administered via a ventricular drain, the drain should be clamped for 15–60

minutes to allow the agent to equilibrate throughout the CSF (strong, low).

- Dosages and intervals of intraventricular antimicrobial therapy should be adjusted based on CSF antimicrobial concentrations to 10–20 times the MIC of the causative microorganism (strong, low), ventricular size (strong, low), and daily output from the ventricular drain (strong, low).

### Evidence Summary

Direct instillation of antimicrobial agents into the lateral ventricle or the lumbar thecal sac (in the case of lumbar shunts) may be necessary in patients with CSF shunt or drain infections that are difficult to eradicate with intravenous antimicrobial therapy alone or when the patient is unable to undergo the surgical components of therapy. This route of administration bypasses the blood–CSF barrier, with controlled delivery of the antimicrobial agent to the site of infection. Intraventricular antimicrobials have the theoretical advantage of achieving high CSF concentrations without high systemic blood concentrations, hence lower potential systemic toxicities [116]. However, the efficacy and safety of this route of

**Table 2. Recommended Dosages of Antimicrobial Agents in Infants and Children and in Adults With Normal Renal and Hepatic Function**

Antimicrobial Agent	Total Daily Dose (Dosing Interval in Hours)	
	Infants and Children	Adults
Amikacin <sup>a</sup>	22.5 mg/kg (8)	15 mg/kg (8)
Amphotericin B lipid complex	5 mg/kg (24)	5 mg/kg (24)
Ampicillin	300–400 mg/kg (6)	12 g (4)
Aztreonam	120 mg/kg (6–8)	6–8 g (6–8)
Cefepime	150 mg/kg (8)	6 g (8)
Cefotaxime	300 mg/kg (6–8)	8–12 g (4–6)
Ceftazidime	200 mg/kg (8)	6 g (8)
Ceftriaxone	100 mg/kg (12–24)	4 g (12)
Ciprofloxacin	30 mg/kg (8–12)	800–1200 mg (8–12)
Daptomycin	Dose not established <sup>b</sup>	6–10 mg/kg (24)
Fluconazole	12 mg/kg (24)	400–800 mg (24)
Gentamicin <sup>a</sup>	7.5 mg/kg (8)	5 mg/kg (8)
Linezolid	Age <12 years: 30 mg/kg (8) <sup>c</sup> Age ≥12 years: 20 mg/kg (12) <sup>c</sup>	1200 mg (12)
Liposomal amphotericin B	3–5 mg/kg (24)	3–5 mg/kg (24) <sup>d</sup>
Meropenem	120 mg/kg (8)	6 g (8)
Moxifloxacin <sup>e</sup>	Dose not established	400 mg (24)
Nafcillin	200 mg/kg (6)	12 g (4)
Oxacillin	200 mg/kg (6)	12 g (4)
Penicillin G	300 000 units/kg (4–6)	24 million units (4)
Posaconazole	—	800 mg (6–12) <sup>f</sup>
Rifampin	20 mg/kg (24) <sup>g</sup>	600 mg (24)
Tobramycin <sup>a</sup>	7.5 mg/kg (8)	5 mg/kg (8)
Trimethoprim-sulfamethoxazole <sup>h</sup>	10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin <sup>i</sup>	60 mg/kg (6)	30–60 mg/kg (8–12)
Voriconazole	16 mg/kg (12) <sup>j,k,l</sup>	8 mg/kg (12) <sup>j,k</sup>

<sup>a</sup>Need to monitor peak and trough serum concentrations.<sup>b</sup>Not approved in pediatrics. Dose is based on trials registered with clinicaltrials.gov (NCT01522105) and (NCT01728376) as follows: 2–6 years, 12 mg/kg (24); 7–11 years, 9 mg/kg (24); and 12–17 years, 7 mg/kg (24).<sup>c</sup>Not to exceed the adult dose.<sup>d</sup>Dose of 5–7.5 mg/kg every 24 hours in patients with *Aspergillus* infection.<sup>e</sup>No data on optimal dose in patients with bacterial meningitis.<sup>f</sup>Dose of 200 mg orally every 6 hours initially, then 400 mg orally every 12 hours. The newer formulations (ie, intravenous and extended-release tablets) of posaconazole appear to have improved pharmacokinetic properties, but there are no available data on their use in treatment of fungal infections of the central nervous system.<sup>g</sup>Maximum dosage of 600 mg.<sup>h</sup>Dosage based on trimethoprim component.<sup>i</sup>Maintain serum trough concentrations of 15–20 µg/mL in adult patients who receive intermittent bolus administration. Some clinicians administer vancomycin with a loading dose of 15 mg/kg, followed by a continuous infusion of 60 mg/kg/day.<sup>j</sup>Load with 6 mg/kg intravenous every 12 hours for 2 doses in adults and 9 mg/kg every 12 hours for 2 doses in children aged 2–12 years.<sup>k</sup>Maintain serum trough concentrations of 2–5 µg/mL.<sup>l</sup>Maximum maintenance dose in children of 350 mg every 12 hours.

administration have not been demonstrated in controlled trials. Intraventricular antimicrobials are not approved by the US Food and Drug Administration and there is insufficient evidence to recommend their general use. However, intraventricular antimicrobial therapy may be considered an option for patients with healthcare-associated ventriculitis and meningitis in which the infection responds poorly to systemic antimicrobial therapy alone. A recent systematic review sponsored by the American Association of Neurological Surgeons/Congress of Neurological Surgeons also noted insufficient evidence to recommend their use in pediatric shunt infections [117]. However, they have been recommended by the Neurosurgery Working Party of the British Society for Antimicrobial

Chemotherapy for the management of neurosurgical patients with postoperative meningitis or external ventricular drain-associated ventriculitis [118]. Reports suggest that intraventricular or intrathecal administration of antimicrobials (eg, polymyxin B, colistimethate sodium, gentamicin, and vancomycin) is not associated with severe or irreversible toxicity [119]. There are also prospective comparative studies that demonstrated that antimicrobials intraventricularly administered show better pharmacodynamics and similar efficacy and safety compared to intravenous antimicrobial agents [120, 121]. Penicillins and cephalosporins should not be given by the intrathecal route because they have been associated with significant neurotoxicity, especially seizures [116].

In several studies on the pharmacokinetics, safety, and efficacy of intraventricular administration of antimicrobial agents [119, 122–126], CSF sterility and normalization of CSF parameters were achieved sooner with intraventricular and intravenous use when compared to intravenous use alone, especially in adults. Combined intravenous and intraventricular use of vancomycin may improve CSF vancomycin concentrations without side effects [127]. However, use of intraventricular antimicrobial agents was not recommended in infants based on data in a recent Cochrane review [128]. One randomized, controlled clinical trial found a 3-times higher relative risk of mortality when infants with gram-negative meningitis were treated with intraventricular gentamicin and intravenous antimicrobials when compared to intravenous therapy alone. However, one half of the infants in the intraventricular gentamicin group had received only 1 dose, raising doubts about the exact cause of death, although it may be related to increased CSF concentrations of interleukin-1 $\beta$ . Antimicrobial agents administered by the intraventricular or intrathecal route should be preservative free. When administered through a ventricular drain, the drain should be clamped for 15–60 minutes to allow the antimicrobial solution to equilibrate in the CSF before opening the drain [129]. In the setting of a CSF shunt that has not been externalized or replaced with an external drainage system, at least one group has recommended administration of intrathecal antimicrobial therapy by a separately implanted shunt reservoir to reduce loss of drug down a shunt system that might occur with direct injection into the CSF shunt [130].

The doses of antimicrobial agents for intraventricular use have been determined empirically, with adjustments of dose and dosing interval based on the ability of the agent to achieve adequate CSF concentrations (Table 3). It is challenging to determine the correct dosing regimen because the CSF concentrations obtained for the same intraventricular dose in pharmacokinetic studies have been highly variable, probably due to the differences among patients in the volume of distribution, ventricular size, or variable CSF clearance as a result of CSF drainage [119, 122–129]. In a consensus guideline, the British Society for Antimicrobial Chemotherapy Working Party on Infections in Neurosurgery recommended that the initial dose of an intraventricular antimicrobial be based on ventricular volume as estimated by neuroimaging [118]. The recommended dose of vancomycin is 5 mg in patients with slit ventricles, 10 mg in patients with normal-sized ventricles, and 15–20 mg in patients with enlarged ventricles. Using the same rationale, the initial dosing of an aminoglycoside can also be tailored to ventricular size. The same working party recommended that the frequency of dosing be based on the daily volume of CSF drainage: once-daily dosing if CSF drainage is >100 mL/day, every other day if the drainage is 50–100 mL/day,

**Table 3. Recommended Dosages of Antimicrobial Agents Administered by the Intraventricular Route**

Antimicrobial Agent	Daily Intraventricular Dose
Amikacin	5–50 mg <sup>a</sup>
Amphotericin B deoxycholate <sup>b</sup>	0.01–0.5 mg in 2 mL of 5% dextrose in water
Colistin (formulated as colistimethate sodium)	10 mg
Daptomycin	2–5 mg <sup>c</sup>
Gentamicin	1–8 mg <sup>d,e,f</sup>
Polymyxin B	5 mg <sup>g</sup>
Quinupristin/dalfopristin	2–5 mg
Tobramycin	5–20 mg
Vancomycin	5–20 mg <sup>e,h</sup>

There are no specific data that define the exact dose of intraventricular antimicrobial agents that should be used in cerebrospinal fluid (CSF) shunt and drain infections. Given the smaller CSF volume in infants (approximately 50 mL) compared to adults (approximately 125–150 mL), doses in infants should probably be decreased at least 60% or more compared to adults.

<sup>a</sup>The usual intraventricular dose is 30 mg daily.

<sup>b</sup>Not usually necessary but may be needed if removal of the device is too risky or the patient has not responded to systemic antifungal therapy.

<sup>c</sup>One study used 10 mg every day for 2 days and then 10 mg every 48 hours. Another study used 5 mg or 10 mg every 72 hours. Data are based on isolated case reports.

<sup>d</sup>Dose is 4–8 mg in adults; 1–2 mg in children.

<sup>e</sup>Dosage recommendations in adults based on ventricle size/volume as follows:

- Slit ventricles: 5 mg vancomycin and 2 mg gentamicin
- Normal size: 10 mg vancomycin and 3 mg gentamicin
- Enlarged ventricles: 15–20 mg vancomycin and 4–5 mg gentamicin.

<sup>f</sup>Recommendations for frequency of administration based on external ventricular drain output over 24 hours as follows:

- <50 mL/24 hours: every third day
- 50–100 mL/24 hours: every second day
- 100–150 mL/24 hours: once daily
- 150–200 mL/24 hours: increase the dosage by 5 mg of vancomycin and 1 mg of gentamicin and give once daily
- 200–250 mL/24 hours: increase the dosage by 10 mg of vancomycin and 2 mg of gentamicin and give once daily.

<sup>g</sup>Dose is 2 mg/day in children.

<sup>h</sup>Most studies used a 10-mg or 20-mg dose.

and every third day if drainage is <50 mL/day. However, these recommendations are based on expert opinion and have not been validated in clinical studies. Additionally, given that the total CSF volume in adults (~125–150 mL) is higher than in infants (~50 mL), intraventricular doses in infants should probably be reduced by 60% or more. Another approach is to base dosing on monitoring of CSF drug concentrations. However, very few studies have evaluated CSF therapeutic drug monitoring and, given the variable CSF clearance of an antimicrobial agent, it is difficult to determine when to obtain CSF to measure peak and trough drug concentrations. A CSF drug concentration obtained 24 hours after administration of the first dose can be presumed to be the trough CSF concentration. The trough CSF concentration divided by the MIC of the agent for the isolated bacterial pathogen is termed the *inhibitory quotient*, which should exceed 10–20 for consistent CSF sterilization [18]. Although not standardized, this approach is reasonable for ensuring that adequate CSF concentrations of these agents are obtained.

Although there are methodological limitations in published studies, intraventricular vancomycin was shown to be safe and efficacious in a systematic review in adults [124]. Intraventricular aminoglycosides were also shown to be effective [122, 126]. In one study, there were no relapses when intraventricular gentamicin was combined with intravenous meropenem in patients with neurosurgical gram-negative bacillary ventriculitis and meningitis [126]. In another study of treatment of 34 consecutive CSF shunt infections in 30 children, high-dose intraventricular antimicrobial therapy sterilized CSF cultures in 100% of 26 children who were treated for 3 days or longer [131]. Intravenous and intraventricular quinupristin/dalfopristin has been used successfully to treat a patient with ventriculostomy-related meningitis caused by vancomycin-resistant *Enterococcus faecium* [132]. Teicoplanin, a glycopeptide antimicrobial agent not currently licensed in the United States, was also found to be successful after intraventricular administration in 7 patients with staphylococcal neurosurgical shunt infections [133]. Intraventricular daptomycin was successfully used in individual case reports in patients with CSF shunt and CSF drain infections caused by methicillin-resistant coagulase-negative staphylococci and resistant enterococci [134–137]. Intraventricular colistin (usually formulated as colistimethate sodium) and polymyxin B have been used in the treatment of gram-negative ventriculitis and meningitis [109, 116, 119, 138–140]; however, these agents should be reserved for patients with infections caused by multidrug-resistant gram-negative bacteria or in those who failed therapy with standard intravenous agents. Intraventricular amphotericin B deoxycholate may be required for *Candida* shunt infections that fail to respond to parenteral therapy and shunt removal.

### VIII. What is the Optimal Duration of Antimicrobial Therapy in Patients with Healthcare-Associated Ventriculitis and Meningitis?

#### Recommendations

58. Infections caused by a coagulase-negative staphylococcus or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms or systemic features should be treated for 10 days (strong, low).
59. Infections caused by a coagulase-negative staphylococcus or *P. acnes* with significant CSF pleocytosis, CSF hypoglycorrachia, or clinical symptoms or systemic features should be treated for 10–14 days (strong, low).
60. Infections caused by *S. aureus* or gram-negative bacilli with or without significant CSF pleocytosis, CSF hypoglycorrachia, or clinical symptoms or systemic features should be treated for 10–14 days (strong, low); some experts suggest treatment of infection caused by gram-negative bacilli for 21 days (weak, low).
61. In patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy, treatment should be continued for 10–14 days after the last positive culture (strong, low).

#### Evidence Summary

The duration of antimicrobial therapy for CSF shunt infections is not completely defined and is dependent on the isolated microorganism, the extent of infection as defined by cultures obtained after externalization, and occasionally CSF findings. There are no controlled trials or studies that compared different durations of antimicrobial therapy for treatment of health-care-associated ventriculitis and meningitis. In a prospective observational study evaluating 70 patients treated at 10 centers [141], treatment duration ranged from 4 to 47 days; reinfection occurred in 26% of patients. Individuals who became reinfected were treated for a mean of 14 days compared to 12.7 days for those who did not experience reinfection. Reinfection rates for therapy durations  $\leq 10$  days, 11–20 days, and  $\geq 21$  days were 28.5%, 23.3%, and 27.7%, respectively (data abstracted from figure 1 in reference). When divided by duration of therapy after the CSF was noted to be free of infection by negative culture, those treated for 7 days or less had a 20% reinfection rate compared to a 28% reinfection rate for those treated for longer than 7 days. It should be noted, however, that treatment for patients in this study was not standardized, with different surgical strategies used for shunt removal and replacement, as well as antimicrobial choices. A second large cohort study of 675 patients followed after first infection noted a mean duration of therapy of 7.5 days in 15% of those who experienced reinfection compared to 9 days of treatment in those who did not experience reinfection (differences not significant) [142].

### IX. What is the Role of Catheter Removal in Patients with Cerebrospinal Fluid Shunts or Drains?

#### Recommendations

62. Complete removal of an infected CSF shunt and replacement with an external ventricular drain combined with intravenous antimicrobial therapy is recommended in patients with infected CSF shunts (strong, moderate).
63. Removal of an infected CSF drain is recommended (strong, moderate).
64. Removal of an infected intrathecal infusion pump is recommended (strong, moderate).
65. Removal of infected hardware in patients with deep brain stimulation infections is recommended (strong, moderate).

#### Evidence Summary

Surgical options for the management of CSF shunt infection include no surgical management (ie, antimicrobial therapy alone), removal of the device and performance of an alternative nonhardware-based procedure for hydrocephalus treatment (when the patient's anatomy allows), removal of the device with immediate replacement, and partial or complete device removal with a period of external drainage followed by subsequent CSF shunt insertion [38, 39, 46, 143]. In children with noncommunicating hydrocephalus and persistent infection, shunt removal

and an endoscopic third ventriculostomy have been advocated [144]. Even if the endoscopic third ventriculostomy fails, the ventriculoperitoneal shunt inserted after failure appears to have better longevity than if it is inserted without first performing the ventriculostomy [145].

Management of shunt infection without removal of shunt hardware has been attempted periodically since shunts were first introduced. In early attempts, intravenous and/or intraventricular antimicrobial agents were used without surgery to avoid the morbidity of additional operations and to maintain CSF diversion during treatment. Success with this approach, however, was low (34%–36%) and carried a high mortality rate [146, 147]. Additionally, instillation of antimicrobial agents into CSF often required a lengthy hospitalization, and the frequency of adverse outcomes was unacceptably high. The ability of many of the organisms to adhere to prostheses and survive antimicrobial therapy likely precluded optimal treatment in situ. However, in one observational study that readdressed the potential for non-operative management using a combination of systemic and intraventricular antimicrobial agents (instilled via a separate ventricular access device), 84% of 43 patients were cured. There was a 92% success rate for infections caused by bacteria other than *S. aureus* [130], suggesting that conservative management may be appropriate for selected patients with CSF shunt infections caused by less virulent organisms such as coagulase-negative staphylococci. Similar results have been achieved in patients with CSF shunt infections caused by *P. acnes* [14]. However, it must be noted that in the only randomized study to include a nonoperative approach to management of infected CSF shunts in 30 children, all of whom received antimicrobial therapy [148], no shunt removal was associated with a 70% recurrence rate.

Combining the removal of shunt hardware with immediate shunt replacement and intravenous and/or intrathecal antimicrobial therapy was also assessed in the above-mentioned randomized trial and a subsequent nonrandomized cohort study [148, 149]. This strategy cured approximately 90% of patients. However, other studies found that this approach cured only approximately 65%–75% of patients with shunt infections [146, 147], with failure and reinfection rates still quite significant with this approach.

The most commonly practiced approach to the surgical treatment of a CSF shunt infection is systemic antimicrobial use with removal of some or all components of the infected shunt followed by insertion of a ventricular drain [141, 150]. The presence of a drainage catheter allows for monitoring of CSF parameters (as needed), including cultures, and administration of intraventricular antimicrobial therapy, if necessary. Ventricular drainage also allows continued treatment of the underlying hydrocephalus and avoids the complications associated with only shunt removal. Once the drainage

cultures become negative, the ventricular drain is removed and a new shunt can be inserted (see Question X for specific recommendations on timing of shunt reimplantation). However, even with this approach, treatment failures still occur in 10%–20% of cases [141, 146, 147, 150, 151]. It is not clear from existing studies whether all or just the externalized portion of the shunt should be removed, although logically, one would expect that complete removal, if possible, would be the better approach. Another option is shunt removal with delayed replacement (to treat the infection with antimicrobial therapy in the absence of any shunt hardware), although this approach leaves the reason for the initial shunt placement untreated.

In patients with intrathecal infusion pumps that deliver baclofen, removal was required in all patients with deep-seated infections [27]. Treatment of deep brain stimulation-associated infections requires surgical removal of the infected components, with follow-up targeted antimicrobial therapy for 2–6 weeks [29, 30].

## X. How are Patients Monitored for Response to Treatment?

### Recommendations

66. Patients with healthcare-associated ventriculitis and meningitis should be monitored for response to treatment based on clinical parameters (strong, low).
67. In patients with healthcare-associated ventriculitis and meningitis and an external drainage device, monitoring of CSF cultures is recommended to ensure that they become negative (strong, low).
68. In patients with no definitive clinical improvement, additional CSF analysis is recommended to ensure that the CSF parameters have improved and the cultures become negative (strong, low).
69. For external CSF drains not being used in the treatment of CSF shunt infection, daily CSF cultures and analysis are not recommended unless clinically indicated (strong, low).

### Evidence Summary

There is no evidence that monitoring of inflammatory markers (ie, peripheral white blood cell count, erythrocyte sedimentation rate, or C-reactive protein) is useful in monitoring response to therapy. In patients with healthcare-associated ventriculitis and meningitis, monitoring of CSF cultures should be performed; typically, cultures should be negative for several days before a new shunt is placed. A retrospective study among pediatric patients examined whether routine CSF bacteriological cultures in patients with external ventricular drains could identify ventriculitis [45]. In all patients in whom infections developed, routine daily cultures of CSF were performed, and these cultures failed to identify the infections before clinical symptoms developed. All 7 patients with infection had fever

(>38.5°C) and peripheral leukocytosis (>11 000/mm<sup>3</sup>) on the day the infection was identified, and 1 had a change in CSF appearance. A prospective study also demonstrated no value of routine analysis of CSF for prediction and diagnosis of external drain-related bacterial meningitis [56]. Another study assessed whether the incidence of ventriculitis changed when CSF sampling frequency was reduced to once every 3 days [152]. In that study, a prospective sample of external ventricular drain-treated patients was compared to a historical comparison group at 2 tertiary hospital intensive care units. The incidence of ventriculitis decreased from 17% to 11% overall and, in those with proven ventriculitis, from 10% to 3% once sampling frequency was reduced.

## **XI. In Patients with Cerebrospinal Fluid Shunts who Develop Ventriculitis and Meningitis, When can a New Shunt be Reimplanted?**

### **Recommendations**

70. In patients with infection caused by coagulase-negative staphylococci or *P. acnes*, with no associated CSF abnormalities and with negative CSF cultures for 48 hours after externalization, a new shunt should be reimplanted as soon as the third day after removal (strong, low).
71. In patients with infection caused by a coagulase-negative staphylococcus or *P. acnes*, with associated CSF abnormalities but negative repeat CSF cultures, a new shunt should be reimplanted after 7 days of antimicrobial therapy (strong, low); if repeat cultures are positive, antimicrobial treatment is recommended until CSF cultures remain negative for 7–10 consecutive days before a new shunt is placed (strong, low).
72. In patients with infection caused by *S. aureus* or gram-negative bacilli, a new shunt should be reimplanted 10 days after CSF cultures are negative (strong, low).
73. A period off antimicrobial therapy is not recommended to verify clearing of the infection before shunt reimplantation (strong, low).

### **Evidence Summary**

Once the infected CSF shunt has been removed, the optimal timing of shunt reimplantation is unclear. Early placement may increase the risk of relapse, but a delay in reimplantation may increase the risk of secondary infection of the external ventricular drain. The timing of reimplantation should be individualized based on the isolated organism, severity of ventriculitis, and improvement of CSF parameters and CSF sterilization in response to antimicrobial therapy. The total duration of antimicrobial therapy (see Question VIII) is difficult to separate from the timing of shunt reimplantation. Some authorities extend antimicrobial therapy for several days after shunt reimplantation, whereas others decide on total duration of therapy based on obtaining negative CSF cultures and do

not extend antimicrobial therapy beyond the time of shunt reimplantation.

In patients with shunt infection caused by coagulase-negative staphylococci and with normal CSF findings, the presence of negative CSF cultures for 48 hours after externalization generally confirms that removal of the hardware affected a cure and that the patient can have a new shunt placed on the third day after removal. If the coagulase-negative staphylococcus was isolated in association with CSF abnormalities (eg, CSF pleocytosis, abnormal chemistries), a true infection was likely present. If repeat cultures are negative, 7 days of antimicrobial therapy are usually recommended before shunt placement. However, if repeat cultures are positive, antimicrobial treatment is continued until CSF cultures remain negative for 7–10 consecutive days before a new shunt is placed. This approach is also recommended for infection caused by *P. acnes* [131]. For shunt infections caused by *S. aureus* or gram-negative bacilli, 10 days of antimicrobial therapy with negative cultures are recommended before shunt placement [18, 153], although some authorities would consider a 21-day course of therapy when gram-negative bacilli are isolated. Some experts also suggest a 3-day period off antimicrobial therapy in order to verify clearing of the infection before shunt reimplantation; this observation period is optional and not routinely recommended. However, these recommendations have not been rigorously studied, and some patients may require a longer duration of antimicrobial therapy before a new CSF shunt is placed. Furthermore, significant variations have been observed in the duration of antimicrobial therapy in patients with CSF shunt infections [141, 150]. Careful follow-up after reimplantation is also critical to ensure that the patient has been cured. Regardless of the manner of treatment, CSF shunt infection can recur. In one study [141], the recurrence rate was 26%, with two-thirds of cases caused by the same microorganism. The recurrence rate in patients with *S. epidermidis* shunt infection was 29%.

In a recent study in children, risk factors identified for reinfection were those with complex shunts (multiple shunts placed or any single shunt with multiple catheters together), an atrial shunt, any complication after the first infection (ie, shunt malfunction, hemorrhage, CSF leak), or intermittent negative cultures defined as positive CSF cultures clearing and then returning over the course of treatment [142].

## **XII. What is the Best Approach to Prevent Infection in Patients Who are Receiving Cerebrospinal Fluid Shunts?**

### **Recommendations**

74. Perioperative prophylactic antimicrobial administration is recommended for patients undergoing CSF shunt or drain insertion (strong, moderate).
75. Perioperative prophylactic antimicrobial administration is recommended for patients undergoing placement of external ventricular drains (strong, moderate).

76. Prolonged antimicrobial prophylaxis for the duration of the external ventricular drain is of uncertain benefit and not recommended (strong, moderate).
77. Use of antimicrobial-impregnated CSF shunts and CSF drains is recommended (strong, moderate).
78. In patients with external ventricular drains, fixed interval exchange is not recommended (strong, moderate).
79. Use of a standardized protocol for insertion of CSF shunts and drains is recommended (strong, moderate).

### Evidence Summary

There have been numerous studies on specific surgical techniques to minimize the possibility of infection in patients undergoing CSF shunt placement; however, there are significant methodological limitations to these studies. Much of what is recommended is based on described risk factors for shunt infection. In one prospective, randomized controlled study of 61 patients undergoing 84 shunt procedures, the shunt infection rate was reduced in those who received antimicrobial-impregnated sutures (4.3% vs 21%;  $P = .038$ ) [154], although there was a high rate of infection in the control group. There is some evidence that double gloving may decrease CSF shunt infection rates [155], and good surgical techniques [156] and adherence to infection control measures are important. There appears to be relatively strong evidence for the use of prophylactic antimicrobial therapy prior to shunt insertion surgery, although the clinical trials supporting this recommendation generally predate the use of antimicrobial-impregnated catheters. The latter have been less well studied to date but appear promising. Studied interventions are detailed in the following sections.

### Antimicrobial Prophylaxis

Evidence supports the use of periprocedural prophylactic antimicrobial administration for patients undergoing CSF shunt insertion and placement of external ventricular drains. Although no randomized studies of periprocedural prophylactic antimicrobial agents for CSF shunt placement have been adequately powered to clearly establish efficacy, several metaanalyses have concluded that this approach decreases infection rates by approximately 50% [157, 158]. A Cochrane database review indicated that the odds ratio for decreased infection was 0.52 (95% CI, 0.36–0.74) [159]. The antimicrobial agent should be given before incision to achieve adequate tissue concentrations and should be continued for as long as 24 hours postoperatively, as studies included in these analyses generally administered therapy for this duration.

With respect to CSF drain infection prevention, one review [20] that cited 10 studies addressed the use of prophylactic antimicrobials [47, 68, 160–167]. One study with 102 ventriculotomies in 70 patients [165] included 44 patients who received antimicrobials and 26 who did not. This study showed a decrease in ventriculitis rates from 27% to 9%. Eight subsequent

studies did not show a difference [20, 47, 160–162, 168], with the caveat that they were underpowered for an event rate of 1%–10%. A recent large review of 35 studies published from 1972 to 2013 noted that about half of these studies describe the use of periprocedural antimicrobial therapy [21], but did not assess the efficacy of this practice. Some studies also showed that use of prophylactic antimicrobials resulted in development of ventriculitis due to resistant organisms [162, 167]. In one study, patients in the prophylactic antimicrobial arm developed ventriculitis caused by MRSA and *Candida* spp. [163]. In another study, rates of gram-negative ventriculitis were higher in patients who received prophylactic antibiotics [160]. However, conflicting reports have been published. In a Brazilian prospective study [169], prophylactic antimicrobials were used in 75% of the patients, and there was no significant difference in ventriculitis when compared to those who did not receive antimicrobials. Another study from the Netherlands also did not show a difference in percentage of patients who developed ventriculitis [170]. The limitations of these studies were that most of them were retrospective, underpowered, used different definitions for ventriculitis, and did not all report adverse effects (eg, adverse reactions to antimicrobials and infections with resistant organisms).

### Prolonged Prophylactic Systemic Antimicrobials for External CSF Drains

Although the use of periprocedural prophylactic antimicrobial agents for placement of external ventricular drains is generally accepted, the use of prophylactic prolonged systemic antimicrobials for the duration of external CSF drainage is more controversial. One study noted that the infection rate was 3.8% in those who received prophylactic antimicrobials for the duration of external ventricular drain placement and 4.0% for those who received only periprocedural antimicrobial therapy [160]. This suggests that prophylactic antimicrobial agents throughout drainage did not significantly decrease the rate of ventriculitis and might select for emergence of resistant organisms. In contrast, another study demonstrated the benefit of prophylactic antimicrobial agents (2.6% CSF infection rate vs 10.6% in those who only received periprocedural antimicrobials;  $P = .001$ ) [163]. It is important to note that the infections in those who received prophylactic antimicrobials were caused by more drug-resistant virulent pathogens and that the mortality rate was higher (66% vs 41%). In a pooled estimate of 9 studies, the CSF infection rate was 8.1% in those who received periprocedural antimicrobials and 5.3% in those who received antimicrobial therapy for the duration of external drainage [20, 168]. This led to a recommendation to maintain prophylactic antimicrobial therapy in all patients while the external ventricular drain is in place, although this is not the practice in all clinical facilities. One randomized study that compared placebo to trimethoprim-sulfamethoxazole did not show a significant difference in the rate of ventriculitis between the 2 groups [171]. A second

randomized study that compared periprocedural antimicrobials only (intravenous ampicillin/sulbactam) to prolonged antimicrobials (ampicillin/sulbactam and aztreonam) revealed that the patients who received prolonged ampicillin/sulbactam and aztreonam had a significantly lower rate of ventriculitis (3 of 115, 3%) than those who received only periprocedural ampicillin/sulbactam (12 of 113, 11%;  $P < .05$ ) [163]. The limitations of this study were that it did not provide a clear definition of ventriculitis and the duration that the external ventricular drain remained in place was not specified for both groups. Another important finding in this study was that infections caused by resistant organisms such as MRSA and *Candida* species were higher in the prolonged antimicrobial arm. The mortality rate in the prolonged antimicrobial arm was 66% (2 of 3) when compared to the periprocedural antimicrobial arm, which had a 41% mortality rate (5 of 12).

In a systematic review that pooled data from 2 randomized studies and 4 observational studies [172], there was a reduced relative risk of 0.45 with use of prophylactic prolonged systemic antimicrobials, although there were significant methodological limitations and heterogeneity in the pooled studies. The definitions of ventriculitis were variable, the type and dose of antimicrobials were different, adverse effects were not well studied, and most of the studies were retrospective and prone to bias. In light of these findings and based on the availability of an efficacious alternative (ie, antimicrobial-impregnated catheters; see below), the use of prophylactic prolonged systemic antimicrobials for prevention of infection in patients with external ventricular drains is not recommended, although prolonged use does remain the practice in some centers. In a recent study in patients with antimicrobial-impregnated external ventricular drains who also received prolonged systemic antimicrobial therapy, the addition of prolonged systemic therapy did not reduce the incidence of catheter-related ventriculitis but was associated with a higher rate of nosocomial infections (bloodstream infections and ventilator-associated pneumonia) and increased cost [173].

#### Antimicrobial-Impregnated Catheters

Antimicrobial-impregnated catheters for CSF shunts and drains have been under development for several decades and, more recently, have been introduced into clinical practice. They are typically impregnated with either minocycline or clindamycin, combined with rifampin. In one randomized study that included 110 patients who underwent placement of CSF shunts impregnated with clindamycin and rifampin, there was a trend toward a decrease in infection rate from 16.6% to 6% ( $P = .084$ ) [174]. However, the study was hampered by a small number of patients and a high infection rate in the control group. Other noncontrolled studies in patients with CSF shunts have led to mixed results, some supporting [175, 176] and others disputing [177, 178] these findings. In a metaanalysis of pooled data from

12 studies that compared antimicrobial-impregnated to non-antimicrobial-impregnated ventriculoperitoneal shunts, there was a statistically significant decrease in infections in patients who had received antimicrobial-impregnated shunts (risk ratio, 0.37;  $P < .0001$ ) [179]. In another systematic literature review of 5613 shunt procedures, use of antimicrobial-impregnated shunt catheters was associated with a decreased risk of shunt infection (3.3% vs 7.2%;  $P < .00001$ ) [180], with significant differences in both children and adults. Use did not appear to be associated with emergence of antimicrobial-resistant infections. Use of antimicrobial-impregnated shunts has not only reduced the incidence of CSF shunt infections but also has resulted in significant hospital cost savings [181]. In a study that compared the effectiveness of antimicrobial-impregnated shunt catheters in treatment of 12 589 consecutive cases from 287 hospital systems in adult and pediatric patients with hydrocephalus [182], antimicrobial-impregnated catheter use was associated with a significant reduction in infection in both adult (2.2% vs 3.6%;  $P = .02$ ) and pediatric (2.6% vs 7.1%;  $P < .01$ ) patients. Reduced infection was demonstrated regardless of hospital size, annual shunt volume, hospital location, or patient risk factors.

Similar results have been noted in patients who received antimicrobial-impregnated external ventricular drains. A randomized study of 306 patients who had placement of external ventricular drains impregnated with minocycline and rifampin showed a decrease in the CSF infection rate from 9.4% to 1.3% compared to those who received uncoated external ventricular drains [183]. The mean duration of external ventricular drain placement in both arms was similar. However, 95% of participants in both arms also received prolonged prophylactic antimicrobials; the antimicrobials were not specified. Pooled data from 5 studies in one metaanalysis showed a statistically significant benefit for antimicrobial-impregnated external ventricular drains (risk ratio, 0.31;  $P = .009$ ) [179].

Sonabend et al [172] conducted a systematic review of studies that used antimicrobial-impregnated external ventricular drains. One randomized, controlled trial [183] and 3 cohort studies [184–186] that assessed the efficacy of antimicrobial-coated external ventricular drains for ventriculitis prevention were included in the metaanalysis. A pooled analysis of these studies showed a relative risk of 0.19 (95% CI, 0.07–0.52) with antimicrobial-coated external ventricular drains. Ventriculitis developed in 2 patients (1.3%) in the intervention group and in 13 patients (9.6%) treated with the standard uncoated external ventricular drains ( $P = .0012$ ). The organism most commonly isolated from CSF samples of control patients was coagulase-negative staphylococcus, whereas CSF cultures from patients in the treated group grew *E. faecalis*, *S. aureus*, and *Enterobacter aerogenes*. The study did not provide a clear definition of colonization or contamination rates vs a definite infection. In another study that compared 47 children treated with a clindamycin and rifampin-coated external ventricular

drain to 44 children who were treated with a standard external ventricular drain [186], CSF cultures were positive in 14 of 44 control patients (31.8%) and in only 1 of 47 patients (2.1%) treated with a coated catheter, demonstrating a statistically significant decrease in ventriculitis with the use of an antimicrobial-coated catheter ( $P < .05$ ). In another study that compared prolonged antimicrobial prophylaxis (ampicillin/sulbactam and ceftriaxone) to antimicrobial-coated external ventricular drains with clindamycin and rifampin [187], the interim data analysis demonstrated that no ventriculitis occurred in either group.

Allergic or systemic complications directly related to the antimicrobial agents in antimicrobial-impregnated catheters have been rare. When used for CSF shunt insertions, antimicrobial-impregnated catheters have not been associated with an increased risk of late CSF shunt infections when compared to historic controls [188].

#### *Elective Fixed Interval Revision*

The greatest risk related to the external ventricular drain is that of secondary infection [20]. A longer duration of drain placement appears to increase the risk. Three studies have shown that the risk of infection does increase with catheter duration [47, 56, 166]. This was also confirmed in another review that demonstrated that longer duration of external ventricular CSF drain placement increased the risk of infection [189], although the risk may plateau over time. Prophylactic catheter exchange has been advocated to reduce this risk. However, prophylactic catheter exchange performed every 5 days does not significantly decrease the likelihood of CSF infection [190, 191]. In one study in 103 patients who required external ventricular drains for more than 5 days [191], the CSF infection rate was 7.8% for the group that underwent catheter exchange every 5 days and 3.8% for the no-change group ( $P = .5$ ). This suggests that a single external ventricular drain can be used for as long as clinically indicated unless a change is necessary because of CSF infection or catheter malfunction. In addition, no significant difference was found in intensive care unit stay, ward stay, or clinical outcome between the 2 groups.

Thus, in addition to use of antimicrobial-impregnated catheters, the infection risk can be lowered by prompt removal of the external ventricular drain when no longer needed, but not with prophylactic catheter exchange at a set interval. While not clearly demonstrated in the medical literature but by extrapolating from studies with other indwelling catheters, it seems likely that attention to maintaining a sterile, closed system with avoidance of injections into the system and surveillance of the draining CSF will also minimize the likelihood of infection.

#### *Combined Interventions*

Many of the studies on prevention of CSF shunt infections detailed above examined single interventions to determine effects on infection rates. However, use of “practice bundles”

may also be valuable in development of standardized protocols for CSF shunt insertion. The Hydrocephalus Clinical Research Network recently undertook an initiative in which centers agreed to develop an 11-step protocol in an effort to reduce CSF shunt infection rates. This was a collaboration of pediatric neurosurgical centers and included all children who received shunts or revisions [192]. The initiative involved 21 surgeons and included 1571 procedures in 1004 children. Overall protocol compliance was about 75%, and another 20% followed 10 of the 11 steps. The network infection rate decreased from 8.8% prior to the protocol to 5.7% while using the protocol ( $P = .0028$ ; relative risk reduction, 36%), indicating that use of a standardized protocol and reduction in variation by adherence to a common protocol are effective at reducing CSF shunt infection rates. Only proper hand-washing technique by all team members emerged as an independent predictor of decreased infection rates. Factors associated with increased infection were use of BioGlide catheters and use of antiseptic cream by any member of the surgical team. However, the nature of the study precluded identification of individual items of the bundle with certainty. Identification of other factors that are associated with infection may lead to addition of new interventions to the protocol in order to further reduce infection rates in the future.

In patients with external ventricular drains, adherence to a checklist for insertion that included hand hygiene, appropriate skin preparation with povidone iodine, allowance of the skin preparation to completely dry before insertion, use of all 5 maximal sterile barriers (sterile gloves, sterile gown, cap, mask, and large sterile drape), and adherence to the policy for external ventricular drain maintenance led to a decline in infection rates from 16 per 1000 external drain catheter days to 4.5 per 1000 catheter days [193]. This infection rate further decreased to 1.3 per 1000 catheter days. Initiation of this protocol eventually resulted in no infections over a 25-month period. However, this study, as with many similar nonrandomized comparisons of care protocols, begins with an awareness of a recent increase in infection rates, making some of the achieved improvement possibly due to regression of the mean.

### **XIII. Is there a Role for Prophylactic Antimicrobial Therapy in Patients Undergoing Neurosurgery or in those with Cerebrospinal Fluid Leak?**

#### *Recommendations*

80. For neurosurgical patients, perioperative antimicrobial agents are recommended to prevent infections of the incision (strong, high).
81. In patients with basilar skull fractures and a CSF leak, prophylactic antimicrobial agents are not recommended (strong, moderate).
82. In patients with basilar skull fractures and a prolonged CSF leakage (>7 days), an attempt to repair the leak is recommended (strong, low).

83. In patients with basilar skull fractures and a CSF leak, pneumococcal vaccination is recommended (strong, moderate).

### Evidence Summary

While perioperative antimicrobial agents have been shown to decrease the risk of cranial wound infections [194–197], they have not been shown to decrease the risk of post-craniotomy meningitis [194, 195] or of meningitis after placement of a CSF shunt [198]. For prophylaxis against cranial wound infections, the first dose of antimicrobials should be given within 1 hour of surgery and should be discontinued within 24 hours after surgery [199].

Patients with traumatic injuries that result in a basilar skull fracture or CSF leak deserve special consideration. The overall infection rate of meningitis has been reported to be 1.4% [200]. However, in those who have depressed cranial fractures (up to 6% of patient with head injuries) [201], the infection rate is as high as 10.6% [202]. In a review of 51 patients with post-traumatic CSF leaks that did not resolve in 24 hours, the risk of meningitis was decreased from 21% to 10% with the use of prophylactic agents [203]. However, in another study of patients with traumatic pneumocephalus, the administration of ceftriaxone did not appear to decrease the risk of bacterial meningitis [204]. A Cochrane systematic review evaluated 208 participants from 4 randomized studies who were considered suitable for inclusion in the metaanalysis [205]. There were no significant differences between antimicrobial prophylaxis groups and control groups in terms of reduction of the frequency of meningitis, all-cause mortality, meningitis-related mortality, and the need for surgical correction in patients with CSF leakage. Leakage of CSF is the major risk factor for the development of meningitis, although most leaks that occur after trauma are unrecognized [200, 206]. Most leaks resolve spontaneously within 7 days, but surgical intervention is indicated if leakage persists.

Since *Streptococcus pneumoniae* is an important pathogen in the setting of head trauma and a CSF leak [207, 208], it is reasonable to try to prevent infections with this organism using pneumococcal vaccination, although clinical studies assessing the efficacy of this approach are lacking. Nevertheless, specific recommendations exist for both adult and pediatric patients with CSF leaks. For unimmunized children aged 6–18 years and adults aged ≥19 years with CSF leak, the 13-valent pneumococcal conjugate vaccine should be administered first followed at least 8 weeks later with the 23-valent pneumococcal polysaccharide vaccine [209, 210]. The Advisory Committee on Immunization Practices recently recommended both the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine, administered in series, with the polysaccharide vaccine given 6–12 months after the conjugate vaccine in all pneumococcal vaccine-naïve adults aged ≥65 years [211].

### Notes

**Acknowledgments.** The expert panel expresses its gratitude for thoughtful reviews of an earlier version by Drs Naomi O'Grady, Richard Whitley, William E. Whitehead, and Ram Yogev. The panel thanks Vita Washington for her guidance and preparation of the manuscript.

**Financial support.** Support for these guidelines was provided by the IDSA.

**Potential conflicts of interest.** The following is a reflection of what has been reported to the IDSA regarding potential conflicts of interest (COI). In order to provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Such relationships as potential conflicts of interest are determined by a review process that includes assessment by the SPGC chair, the SPGC liaison to the development panel, and the BOD liaison to the SPGC, and, if necessary, the COI Task Force of the Board. This assessment of disclosed relationships for possible COI is 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 should be mindful of this when the list of disclosures is reviewed. A. T. received royalties from UpToDate and Elsevier and honoraria from ACP and Merck. A. B. received research support from Cubist. R. H. has received personal fees for speaker bureau participation with Pfizer, Medicine's Company and Biofire; he has served as a consultant for Biomerieux. S. K. served as a consultant for Pfizer; received royalties from UpToDate and Elsevier; and received research grants from Pfizer, Forest Laboratories, Cubist, and Merck. W. M. S. received research grants from the National Institutes of Health, Pfizer, and Wyeth. D. v. d. B. received research grants from the Netherlands Organization for Health Research and Development, Netherlands Scientific Organization, European Research Council, FP-7, Horizon 2020, and Omeros and served as a consultant for GSK. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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