Title

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Journal

Journal of Clinical Microbiology, 56(11)

ISSN

0095-1137

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Publication Date

2018-11-01

DOI

10.1128/jcm.00861-18

Peer reviewed

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

MINIREVIEW

Diagnostic Approach to Health Care- and Device-Associated Central Nervous System Infections

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ABSTRACT Health care- and device-associated central nervous system (CNS) infections have a distinct epidemiology, pathophysiology, and microbiology that require a unique diagnostic approach. Most clinical signs, symptoms, and tests used to diagnose community-acquired CNS infections are insensitive and nonspecific in neurosurgical patients due to postsurgical changes, invasive devices, prior antimicrobial exposure, and underlying CNS disease. The lack of a standardized definition of infection or diagnostic pathway has added to this challenge. In this review, we summarize the epidemiology, microbiology, and clinical presentation of these infections, discuss the issues with existing microbiologic tests, and give an overview of the current diagnostic approach.

KEYWORDS central nervous system infections, implanted devices, meningitis, ventriculitis

Health care- and device-associated central nervous system (CNS) infections increase hospital lengths of stay, cost of care, and risk of long-term neurological impairment and death in patients, making early detection and diagnosis imperative (1–4). Yet, early diagnosis is often challenging due to vague presenting signs and symptoms and a lack of standardized definitions or a clear clinical and laboratory distinction between patients with and without infection. This review summarizes the current epidemiology, microbiology, and clinical presentation and proposes a diagnostic approach for these challenging CNS infections.

EPIDEMIOLOGY

The most common type of health care-associated CNS infection is ventriculitis or meningitis, followed by subdural empyema and brain abscess (5), with the major risk factor being recent neurosurgery (6). However, the relative risk varies significantly with the type and location of the neurosurgical procedure, as well as with other factors, including surgical duration, entry into the sinuses, postoperative cerebrospinal fluid (CSF) leak, and the presence of an incisional wound infection or implanted CNS device (7, 8). Generally speaking, the risk of infection is greater with cranial procedures (versus spinal) and when the dura mater is disrupted (Table 1). Among cranial surgeries, the risk of infection is higher (1% to 24.4%) when the portion of the skull removed for the surgery is stored for a prolonged period of time before replacement (i.e., craniectomy with delayed cranioplasty) (9), compared to surgeries in which skull fragments are replaced during the same sterile operation (i.e., craniotomy) (0.3% to 12%) (1, 7, 8, 10, 11). CNS infections are less common after spine surgeries (3% to 7% with hardware; <2% without hardware), since the CNS is generally not violated unless the spinal cord dura mater is punctured inadvertently during the operation (5). For comparison, CNS infection is quite rare after diagnostic lumbar puncture (~1 in 50,000 procedures) (10).

Accepted manuscript posted online 22 August 2018

Citation Martin RM, Zimmermann LL, Huynh M, Polage CR. 2018. Diagnostic approach to health care- and device-associated central nervous system infections. J Clin Microbiol 56:e00861-18. https://doi.org/10.1128/JCM.00861-18.

Editor Colleen Suzanne Kraft, Emory University

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TABLE 1 Rates of infection of common neurosurgical surgeries and devices

Surgery	Rate of infection (%)
Craniectomy	1–24.4
Craniotomy	0.3–12
Spine surgery with hardware	3–7
Spine surgery without hardware	<2
Diagnostic lumbar puncture	~1 in 50,000 procedures
Temporary devices	
Ventriculostomy (i.e., EVD)[a]	2–22 (avg. 8)
Parenchymal ICP monitor	<0.2
Lumbar drain	5
Permanent devices	
Ventricular shunt	8 (pediatric), 4–17 (adults)
Spinal cord medication pumps	<6
Deep brain stimulators	<1

[a]EVD, external ventricular drain.

In terms of timing, two-thirds of health care-associated CNS infections are diagnosed within 2 weeks of surgery, with the remainder being diagnosed months or years later (1, 10).

Device-associated CNS infections are a major subgroup of health care-associated CNS infections that occur when either a temporary or permanent surgically implanted device becomes a source of infection through contamination or colonization by microbes. The most common temporary device is the external ventricular drain (EVD), also known as a ventriculostomy. These silicone catheters are typically placed in emergency departments and intensive care units to monitor intracranial pressure (ICP), treat hydrocephalus, and drain intraventricular hemorrhage after an acute CNS injury. Anatomically, these catheters pass through a surgically created burr hole in the skull and then through the meninges and cerebrum to reach the lateral ventricle of the brain. Externally, they are tunneled briefly under the skin and connected to a pressure transducer and reservoir to form a closed system. As such, these systems are supposed to be sterile, but they can provide a route for CNS infection when microbial contamination occurs during placement, handling, or maintenance. The reported rates of ventriculostomy-associated infection (VAI) range from 2% to 22%, with an average rate of 8% (12). The wide variation in the observed rate of infection is most likely due to differences in EVD utilization and handling at individual facilities and variation in how VAI is defined across studies. Differences in microbiologic culture procedures also contribute to differences in the rate of VAI between institutions (13).

Other temporary CNS devices that can become infected include lumbar drains and intraparenchymal ICP monitors. Lumbar drains are used less often than EVDs but have a similar or slightly lower rate of infection of around 5% (10). On the other hand, intraparenchymal ICP monitors have a much lower risk of infection due to their structure (solid probe versus hollow catheter), tip location (white matter brain tissue versus ventricle), and reduced need for manipulation and handling after placement. In one study, only two clinically relevant CNS infections occurred among 1,130 patients with intraparenchymal ICP monitors; some series describe no infections at all (5, 14).

Permanent CNS devices can be both a source of early infection, when the device or surgical site is contaminated during placement, and late infection long after placement, when an initially sterile device is seeded by microbes. Internal ventricular drains are a major category of permanent devices used to divert CSF from the CNS ventricular system to a remote body cavity as a treatment for chronic hydrocephalus. These "shunts" are named for the proximal source and distal outflow locations: ventriculoperitoneal shunts (VP shunt or VPS) drain into the peritoneal cavity, ventriculoatrial shunts (VA shunt or VAS) drain into the right atrium of the heart, and ventriculopleural shunts (VPL shunt or VPLS) drain into the pleural space. The rates of infection with these devices are around 8% in the pediatric population (5) and 4% to 17% in adults (10).

Most shunt infections occur within the first month after placement (5, 10, 15), but a substantial fraction (up to 10%) present a year or more after the initial shunt placement (15). Infection rates are generally similar between VP, VA, and VPL shunt types (4, 11).

Other permanent CNS devices that can become infected include spinal cord medication pumps and deep brain stimulators. Spinal cord medication pumps have a subcutaneously implanted reservoir that is connected to a catheter that is passed through the lumbar spine into the intrathecal space, allowing the delivery of analgesic and/or antispasmodic medications. These usually become infected when the surgical site or overlying skin is infected or breaks down and contaminates the pump device or "pocket." As such, spinal cord medication pump infections are uncommon and generally occur within the first month after placement, affecting 6% of patients in one study (16). Deep brain stimulators are used to treat medication nonresponsive movement disorders and other conditions. Infection can involve all three components of the device, including the intracranial lead, the connector, and the subcutaneously implanted chest wall pulse generator, but CNS infections are generally rare (<1%) (17).

PATHOPHYSIOLOGY OF INFECTION

Despite improvements in surgical technique, the primary source of health care- and device-associated CNS infection is microbial contamination during the surgery and/or device placement via the breakdown of sterile technique (4, 11, 18). Contamination and colonization occur predominately from skin or mucosal flora, which can occur preoperatively from skin defects (e.g., trauma), intraoperatively through a breach in sterile technique, or postoperatively in the presence of a CSF leak (11). This leads to microbial biofilm formation on devices or devitalized tissue (bone) that protects microorganisms from the host immune response and antimicrobial therapy and serves as a source for CNS infection.

A unique mechanism of infection with CSF shunts is the contamination of the distal end of the shunt in the peritoneal, vascular, or pleural space, which ascends internally through the shunt lumen to involve the CNS (18). This can happen in the setting of a localized abdominal infection, as with ruptured appendicitis, or systemic infection, such as bacteremia. This is also a mechanism of VAI, in which microbes are introduced distally during breaches in the sterile circuit to sample CSF or flush the system.

Antibiotic and silver-impregnated CSF shunts and EVDs have been developed to reduce microbial colonization of these devices, which have cut the rates of infection by half in some studies (4, 19, 20). Synthetic implants have also been developed to replace the bone during cranioplasty procedures, but there is no convincing data to suggest that these are superior to the autologous bone graft material (9).

MICROBIOLOGY

The causative agent(s) of health care- and device-associated CNS infection is driven by the underlying condition of the patient and type of surgery performed. Most are bacterial and monomicrobial, with skin-derived Gram-positive bacteria accounting for 50% to 60% of infections, particularly with EVDs (2, 10, 21). *Staphylococcus epidermidis* and *Staphylococcus aureus* are the predominant Gram-positive pathogens, but *Propionibacterium acnes* (now *Cutibacterium acnes*) is also common if sought, with rare *Corynebacterium jeikeium* infections as well (22).

Gram-negative infections were historically less common, but recent series suggest a shift toward more Gram-negative infections caused by enteric and nonglucose-fermenting Gram-negative rods (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) (10, 21). This shift has been hypothesized to be due to the use of antibiotic prophylaxis targeting Gram-positive bacteria and more prolonged hospitalizations with the expanding complexity of neurosurgical and neurocritical care (8, 23). Antibiotic-resistant organisms are also being recovered more frequently for similar reasons (1), a fact clinicians must consider when initiating therapeutic antibiotics.

Other causes of health care- and device-associated CNS infection are uncommon

and usually associated with additional risk factors. Oral flora bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*, cause infections in patients with skull base fractures and persistent CSF leaks between the CNS and nasal or oral cavities (10). Fungal infections are uncommon (<5%) unless an immunocompromising condition or outbreak is present, with *Candida* spp. being the most common fungal organism (2, 10, 21).

Given these causes, initial empirical treatment usually includes vancomycin for broad Gram-positive coverage, including methicillin-resistant *S. aureus* and an antipseudomonal beta-lactam, such as cefepime, ceftazidime, or meropenem for broad Gram-negative coverage. Antibiotics are subsequently tailored to the identified organism once speciation and antibiotic sensitivities return. In patients with an infected permanent CNS device, the device is usually removed in addition to antibiotic therapy.

CLINICAL SIGNS, SYMPTOMS, AND IMAGING

The conventional clinical signs and symptoms of community-acquired CNS infection are insensitive and unreliable in patients with recent neurosurgery or a CNS device. The classic meningitis triad of fever, neck stiffness, and altered mental status or headache has a sensitivity of just 40% to 50% for health care-associated CNS infections and manifests fully in a minority of cases (24). A large retrospective study highlighted the poor sensitivity of clinical signs and symptoms for VAI, with less than half of patients having headache (48.5%), fever (40.5%), altered mental status (40.6%), nausea or vomiting (39.5%), or photophobia (6.5%) (21). The low sensitivity is presumably due to the routine use of treatments to minimize fever, swelling, and injury in the hospital, the higher rate of localized infections, and infections with indolent/low virulence organisms, which elicit less meningeal inflammation and symptoms. The difficulty interpreting clinical signs and symptoms is compounded by the high frequency of chemical or aseptic meningitis in neurosurgical patients, which accounts for 60% to 75% of postoperative meningitis cases and is clinically indistinguishable from bacterial meningitis (10, 25–27). Clinical signs are even less obvious in patients with infected shunts who commonly present with vague, nonspecific complaints such as malaise, lethargy, or headache without meningeal signs as the only indication of infection (10, 27). VAS patients sometimes present with nephritis as the principal manifestation of shunt infection, presumably caused by kidney injury from glomerular deposition of circulating immune complexes (27).

Imaging studies are also insensitive and nonspecific for infection in neurosurgery patients, with a high rate of false-negative and false-positive findings due to previous surgical manipulation of tissue (28–30).

ROUTINE CSF TESTING

Similar to clinical signs and symptoms, the conventional CSF tests and cutoffs used to define CNS inflammation and predict the etiology of community-acquired meningoencephalitis are less reliable or diagnostically useful in patients with a recent CNS injury, surgery, or device. For example, the traditional threshold of >5 white blood cells/mm^3 for CSF pleocytosis is routinely exceeded in neurosurgical patients without infection and absent in 20% of patients with VAI (25, 26, 31, 32). The interpretation of CSF leukocyte counts is further complicated by differences due to the site of collection, with higher counts collected in CSF from the lumbar spine and shunt valves than in CSF collected directly from the ventricular system (15). CSF protein, glucose, and the CSF/serum glucose ratio alterations are also less discriminatory after CNS trauma, hemorrhage, or surgery (31–33). Hypoglycorrhachia, defined by a CSF/serum glucose ratio of <0.5, is only 80% sensitive and specific for CNS infection in neurosurgical patients (34).

These limitations may be partly overcome by trending CSF parameters over time or normalizing the CSF leukocyte count for hemorrhage and systemic inflammation. An increase in the CSF leukocyte count with serial sampling from an EVD is suggestive of infection (32). An increase in the CSF "cell index" (the CSF leukocyte/erythrocyte ratio

divided by the peripheral blood leukocyte/erythrocyte ratio) to >5 has been proposed as the diagnostic threshold for VAI and may even precede culture positivity but needs to be validated before routine clinical use (31, 35). A major downside to these strategies is the risk that increased access and sampling of the EVD could lead to an increase in contamination and infections.

BIOMARKERS

CSF lactate is probably the most useful biomarker for postneurosurgical CNS bacterial meningitis at the moment, with a better sensitivity and specificity than those of CSF cell count, glucose, protein, and the CSF/blood glucose ratio (34, 36). A recent meta-analysis reported a pooled sensitivity and specificity of 93% and 96%, respectively, for CSF lactate from studies with diagnostic cutoffs ranging from 3.45 to 5.4 mmol/liter (37, 38). However, the sensitivity is probably lower when antibiotics are administered before CSF collection, and CSF lactate values spanned a wide range that extended below the proposed cutoffs in a retrospective study of patients with proven health care-associated meningitis (21, 38). Finally, CSF lactate is elevated in a variety of noninfectious CNS conditions, including recent stroke, seizures, brain hypoxia, and traumatic brain injury, and thus must be interpreted with caution in patients with these and other noninfectious CNS conditions.

Serum C-reactive protein (CRP) is an acute phase reactant with moderate-to-high sensitivity (68% to 100%) and lower specificity (20% to 85%) for community- and health care-associated bacterial meningitis (34, 39). However, its utility is limited in the acutely ill neurosurgical population by the underlying high inflammatory state in many patients, and thus may be a more appropriate test in patients farther removed from surgery or device placement.

The performance of serum procalcitonin is also variable for health care-associated CNS infection with a reported sensitivity and specificity of 67% to 100% and 57% to 100%, respectively, due to the high rate of systemic illness in neurosurgical patients (39, 40). CSF procalcitonin (versus serum) may be more diagnostically useful, especially when combined with CSF lactate measurement, but more research is needed to understand the performance of this approach (41).

MICROBIOLOGIC TESTING

CSF Gram stain and culture are the primary methods of diagnosis for health care- and device-associated CNS infections, but procedural differences between laboratories and the high rate of antibiotic treatment at the time of CSF collection likely contribute to the difficulty confirming and diagnosing these infections. A direct CSF Gram stain is useful when positive but has a lower sensitivity for health care- and device-associated CNS infection than community-associated bacterial meningitis. In a recent study, just 20% of patients with National Healthcare Safety Network (NHSN)-defined health care-associated ventriculitis and meningitis had a positive CSF Gram stain (21, 31).

CSF culture is generally considered the reference standard and most important test for the diagnosis of health care- and device-associated CNS infection but can be negative in 23% to 78% of patients with infections defined by other criteria (15, 21, 32). Prior antibiotic treatment is a common cause of falsely negative CSF Gram stain and culture, with up to 50% of patients having received antibiotics before CSF collection in some studies (21). Interlaboratory differences in the set up and processing of device-collected CSF samples are another major cause of variable culture yield and performance across institutions (13, 33, 42–45). The recommendations regarding the need for CSF centrifugation prior to culture, anaerobic culture, anaerobic transport media, broth culture, duration of broth incubation, and the role, appropriateness, and procedure for CNS device tip cultures are frequently not explicit and differ between standard clinical microbiology references (44, 45). Accordingly, an informal poll of six academic clinical microbiology laboratories while preparing the manuscript suggested that culture procedures and practices vary widely between institutions (unpublished data). Four of the six laboratories did not distinguish between device- and lumbar puncture (LP)-collected

CSF samples or modify their procedure for device-collected CSF samples. Two of these included a thioglycolate broth routinely for all CSF samples but held the broth for different lengths of time; the other two had a strictly aerobic culture procedure with no broth culture and only performed anaerobic culture on the rare occasion when it was requested. The other two laboratories distinguished device- and LP-collected CSF samples but handled their device-collected CSF samples differently; one performed anaerobic plate and broth culture routinely for all device-collected CSF samples, whereas the other used thioglycolate broth alone. Among the four laboratories using thioglycolate broth, the duration of incubation varied from 5 to 14 days. EVD and shunt tip culture practice was similarly variable.

Meanwhile, clinicians and laboratorians have sought ways to enhance the sensitivity and yield of CSF culture with a focus on improving the recovery of slow-growing anaerobes (*P. acnes*) and device/biofilm-related organisms. Several studies have reported an increase in the proportion of positive CSF cultures and clinically significant *Propionibacterium* spp. infections with the addition of anaerobic culture (solid media or broth) and prolonged incubation of broth media (10 to 14 days) (13, 30, 42, 46). Calderaro et al. observed a shorter time-to-positivity and a 79% increase in the detection of aerobic bacteria and yeast with an inoculation of 1 to 3 ml CSF into a Bactec Peds Plus/F blood culture bottle over that with conventional agar culture (43). However, isolated positive cultures from broth media (i.e., thioglycolate broth or blood culture) must be interpreted in the context of the overall clinical likelihood of infection, as they often represent bacterial colonization or contamination (27, 33, 43). Sonication cultures of explanted neurosurgical hardware (e.g., EVD tip) may also increase the yield of cultures and diagnosis of infections when clinical suspicion is high, similar to sonication cultures of orthopedic hardware (47, 48). Conventional blood cultures are generally not helpful in diagnosing most CNS device infections but can be helpful and should be performed in patients with suspicion for ventriculoatrial shunt infection (15, 39). Many of these microbiologic procedural enhancements (e.g., prolonged anaerobic culture for *P. acnes*, culture of explanted neurosurgical device/tip) were recently endorsed in the 2017 Infectious Diseases Society of America (IDSA) clinical practice guidelines, especially when infection is suspected clinically and previous cultures are negative (27).

Nucleic acid-amplification tests (NAATs) have the potential to provide rapid results that are less prone to false negatives after antibiotics than Gram stain or culture (49). However, there are currently no U.S. Food & Drug Administration (FDA)-cleared or approved NAATs for the diagnosis of health care- and device-associated CNS infections; the only NAATs with FDA clearance for CSF (i.e., Xpert EV, Cepheid; FilmArray meningitis/encephalitis [ME] panel, BioFire Diagnostics) target community-associated pathogens not health care-associated pathogens, and the limited data for NAATs in health care-associated CNS infections found that NAATs performed no better than CSF culture (49–51). Thus, more work is needed before NAATs are used to diagnose health care- and device-associated CNS infections in clinical practice.

DIAGNOSTIC APPROACH

In the setting of insensitive and nonspecific clinical signs, symptoms, imaging and laboratory tests, the diagnosis of health care- and device-associated CNS infection is challenging, and a lack of standardized diagnostic criteria has contributed to the problem. In the case of VAI, at least 16 different diagnostic criteria have been reported in the literature; when these definitions are applied to a test cohort, the frequency of infection ranges from 22% to 94% (52). The 2017 Infectious Diseases Society of America (IDSA) clinical practice guidelines for health care-associated ventriculitis and meningitis proposed standard definitions for the contamination, colonization, and infection of ventricular drains (Table 2) (27). However, this classification does not address the most common diagnostic conundrum clinicians face: how to interpret negative CSF cultures when other clinical and laboratory findings are suspicious for infection. Moreover, it is unclear how the colonization classification would be used in practice, since surveillance

TABLE 2 2017 Infectious Diseases Society of America classification of ventricular drain infection[a]

Category	Description
Contamination	An isolated positive CSF[b] 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

[a]See reference 27.
[b]CSF, cerebrospinal fluid.

cultures are no longer recommended without some clinical suspicion for infection (27) and it is unlikely that a clinician would leave multiple positive CSF cultures from a device untreated, even if that means the replacement of the EVD without antibiotic therapy.

Alternatively, the 2018 U.S. Centers for Disease Control and Prevention National Healthcare Safety Network (CDC/NHSN) surveillance definitions for specific types of infections does include a case definition for health care-associated meningitis or ventriculitis in the absence of a positive CSF culture, but this was not intended for clinical diagnosis and has not been validated for clinical use (Fig. 1) (53). Nonetheless, the key take home message from both of these definitions is the need for a comprehensive clinical and laboratory approach for diagnosing these infections, which does not rely on any single clinical sign or test.

In practice, diagnosing health care- and device-associated CNS infections requires a thoughtful approach that considers the patient's clinical signs, symptoms, and overall condition, the proximity in time to the neurosurgical procedure or device placement, and the trends in imaging and laboratory values. We propose a clinical algorithm for the evaluation and management of patients with a suspected health care- or device-associated CNS infection that incorporates these factors to suggest when CSF studies should be performed and the common approach to treatment in the most clinical scenarios (Fig. 2).

In this algorithm, any new headache, persistent or recurrent fever, new or worsening leukocytosis, nausea, lethargy, or change in mental status/neurological deterioration should prompt the consideration of infection in patients with a CNS device. Similarly, new or worsening seizures can be a sign of CNS infection, and abdominal pain can be a sign of infection in patients with a VP shunt (27).

Because clinical signs and symptoms are typically vague and nonspecific, imaging of the brain or spine is also important in evaluating for infection, particularly when a CNS device is present. Computed tomography (CT) can show hydrocephalus or fluid collections suggesting device failure and/or infection. Magnetic resonance imaging (MRI) with gadolinium can show signs of meningeal or ventricular enhancement, as well as focal infection (i.e., subdural empyema or brain abscess). However, it can be difficult to tell if imaging findings are due to the original insult or trauma, surgery, or infection during the early postoperative period.

CSF should only be tested when infection is suspected clinically on the basis of new or worsening signs and symptoms or imaging findings. Serial CSF sampling from an EVD (i.e., daily, every 3 days, weekly, etc.) to screen/monitor for CNS infection in the absence of a change in clinical condition is no longer recommended (27), since it does not lead to earlier detection of infection (54) and has been associated with an increased risk of infection (55, 56). When infection is suspected, a panel of CSF and blood tests should be performed to evaluate the patient's CSF (and device) for infection and to identify the causative organism for treatment (Table 3).

At least one of the following criteria:	
Identified organism from cerebrospinal fluid by a culture or non-culture based microbiological testing performed for purposes of clinical diagnosis or treatment (i.e. not active surveillance**)**	
OR	
The patient has at least two of the following	
>1 year of age	Fever (>38.0C) or headache*
	Meningeal Signs
	Cranial Nerve Deficits
≤1 year of age	Fever (>38.0C), hypothermia (<36.0C) apnea, bradycardia, or irritability*
	Meningeal Signs
	Cranial Nerve Deficits
AND at least one of the following	
All ages	Increase in CSF white cell count, protein or decreased glucose
	Positive CSF Gram stain
	Positive blood culture or non-culture based microbiological testing performed for purposes of clinical diagnosis or treatment (i.e. not active surveillance**)**
	Diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism

FIG 1 CDC/NHSN criteria for the diagnosis of health care-associated meningitis or ventriculitis (53). *, elements in this line alone may not be used to meet the two required elements.

In patients with a CNS device, CSF cultures should include an anaerobic culture component (usually an anaerobic broth) held for a minimum of 10 to 14 days to detect *Propionibacterium* (now *Cutibacterium*) *acnes* (27). The 2017 IDSA guidelines also recommend culturing explanted shunt or drain components (i.e., hardware) in patients with a suspected device infection but not as a routine practice when devices are removed for other reasons (27). Routine testing for fungi (i.e., fungal CSF culture) is not necessary, since most infections are caused by bacteria or *Candida* and routine bacterial culture procedures generally detect *Candida* spp. Fungal cultures may be indicated in patients with an increased risk of non-*Candida* fungal infection, such as immunocompromised patients with clinical suspicion of invasive mold infection, patients with a permanent CNS device in regions with endemic mycoses, or during a fungal outbreak with suspected exposure. β-D-Glucan and galactomannan testing from CSF may also be useful in rare scenarios, but most labs have not validated these tests for CSF; thus, physicians should verify if the lab can test CSF before submitting samples (27).

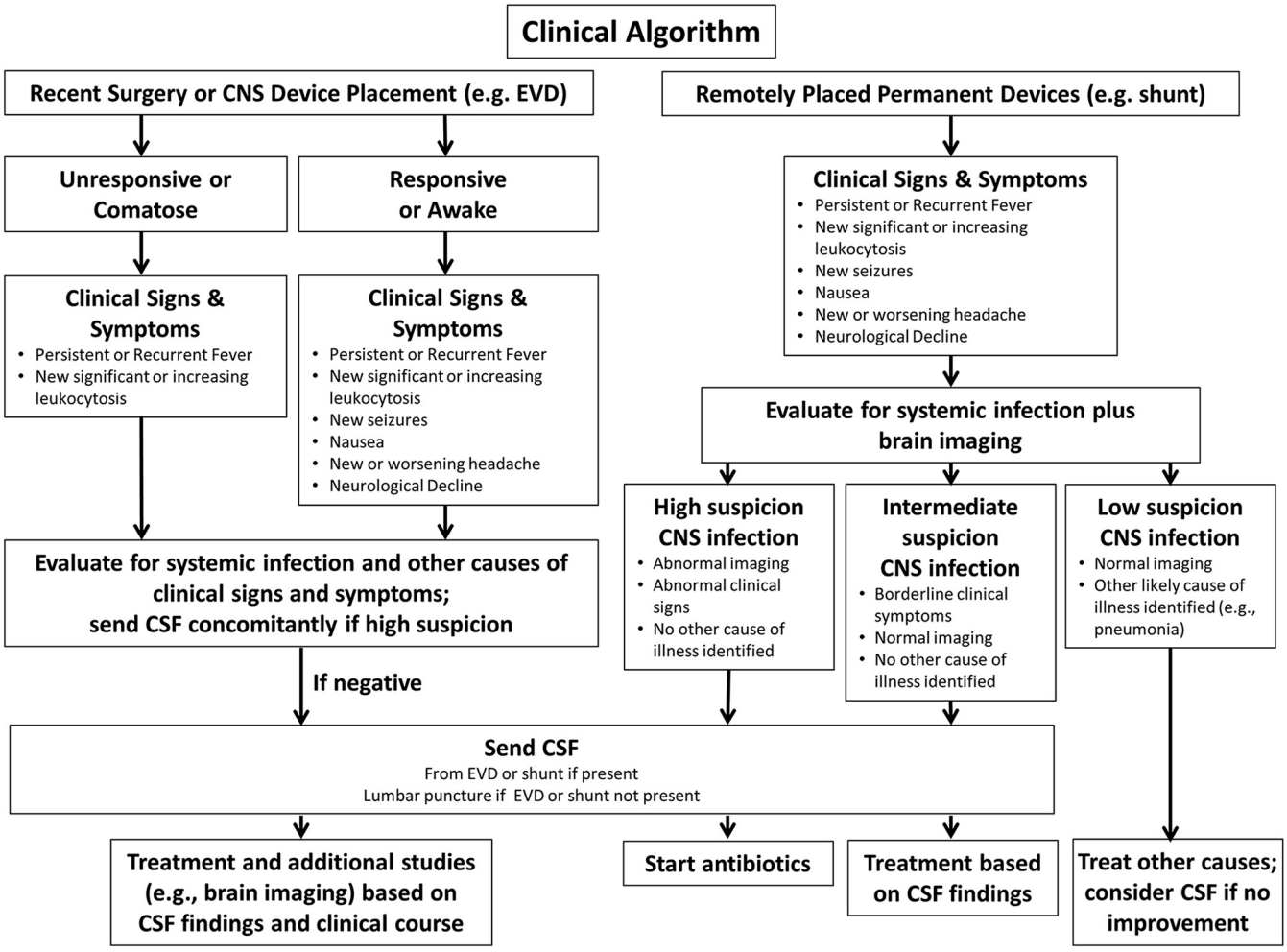


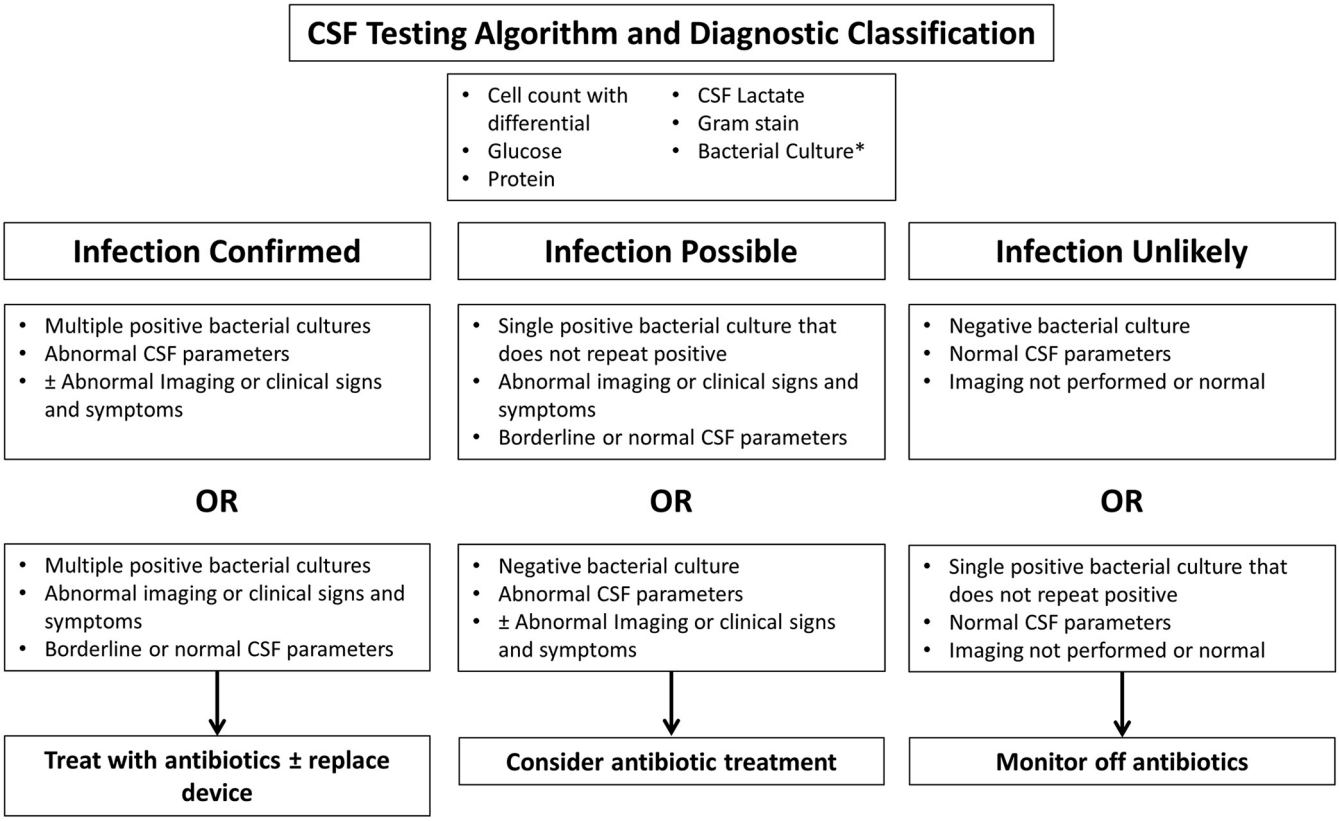
FIG 2 Proposed clinical algorithm for the evaluation of patients with clinically suspected health care- or device-associated central nervous system infection. CNS, central nervous system; CSF, cerebrospinal fluid; EVD, external ventricular device.

CSF tests and cultures should be interpreted in the context of the patient's clinical signs, symptoms, and overall condition. To facilitate this process, we propose a CSF testing algorithm and diagnostic classification to help clinicians interpret results and clinical findings (Fig. 3). In this algorithm, abnormal CSF findings support the diagnosis of infection in patients with negative culture results but otherwise moderate-to-high clinical suspicion; the detection of a typical pathogen by Gram stain or culture confirms an infection. In patients where the clinical picture is less clear and the CSF Gram stain and culture are negative, CSF values may be trended for a few days to assess the

TABLE 3 Routine CSF laboratory tests and parameters for the diagnosis of health care- and device-associated central nervous system infection

Test	Results suggesting CNS[a] infection	Reference
CSF[b] cell index	CSF WBC/RBC[c] ratio divided by blood WBC/RBC ratio of >5	31, 35
CSF glucose/serum glucose	CSF/serum glucose ratio of <0.5	34
CSF lactate	>3.5 mmol/liter	37, 38
CSF Gram stain	Positive Gram stain	
CSF bacterial culture	Positive bacterial culture	

[a]CNS, central nervous system.
[b]CSF, cerebrospinal fluid.
[c]WBC, white blood cell; RBC, red blood cell.



* Include aerobic and anaerobic culture (usually aerobic plates plus anaerobic broth), if a CNS device is present. The anaerobic broth culture should be held for 10-14 days to detect *Cutibacterium acnes.* The first positive bacterial gram stain or culture is usually repeated to verify positive results. If repeat study is positive, infection is confirmed. If repeat study is negative, infection is possible or unlikely depending on the clinical and laboratory context.

FIG 3 Proposed CSF testing algorithm and diagnostic classification. CSF, cerebrospinal fluid.

trajectory of the CSF profile. A down-trending glucose or worsening pleocytosis supports a diagnosis of CNS infection in such cases (27).

Since positive CSF cultures from a temporary drain (i.e., EVD) may be due to contamination, colonization, or infection, a repeat CSF culture should be performed (preferably from a more proximal source) to confirm the prior positive culture result, especially if other CSF results are noninflammatory and clinical signs are questionable (Table 2 and Fig. 3) (27). Other details from positive CSF cultures can offer clues to the significance of the positive result when the clinical picture is mixed. For example, very scant growth of a nonfastidious organism (e.g., *Staphylococcus epidermidis*) on agar plates or from broth only may suggest contamination. Similarly, the detection of multiple organisms may suggest contamination if the clinical picture is not consistent with a polymicrobial infection. On the other hand, positive CSF cultures from permanent hardware, particularly for CSF obtained from a shunt, are usually interpreted as indicative of a true infection, although cultures may be repeated to confirm the infection before removing the hardware. In addition to these scenarios, previously positive or abnormal CSF tests and cultures are often repeated in infected patients to confirm that patients are responding to treatment (i.e., test of cure) or to reevaluate the CSF when clinical improvement is slow or questionable (27).

FUTURE DIRECTIONS

The ongoing challenge of diagnosing health care- and device-associated CNS infections emphasizes the need for more work in this area. The first step is to develop and utilize standardized definitions of infection. We propose clinical and laboratory

testing algorithms in an effort to help with this issue. Second, existing microbiologic tests and culture procedures need to be systematically evaluated using standardized definitions of infection to measure and optimize their analytical performance for clinical diagnosis and then standardized across centers to enable accurate epidemiology and refinement of diagnostic and treatment guidelines. Finally, new tests and approaches are needed to more rapidly and reliably detect the common causes of health care- and device-associated CNS infection, including those involving slow-growing bacteria, such as *P. acnes*. Nucleic acid-amplification tests may help accomplish this, but epidemiologically appropriate NAATs designed for health care- and device-associated CNS infection do not currently exist and will need to be systematically evaluated before they can be implemented for routine clinical use.

ACKNOWLEDGMENTS

C.R.P. reports grants from BioFire and in kind or discounted research materials (test kits) from Cepheid, Alere, and TechLab. C.R.P. is or has been a consultant to BioFire, SlipChip, GenePOC, Blood Source, Seres Therapeutics, Vedanta, Meridian, and Singulex. All other authors report no conflicts of interest.

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