Meningitis and encephalitis management in the ICU

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Purpose of review
Management of patients with meningitis and encephalitis oftentimes requires ICU level of care. This article is an update on management for meningitis and encephalitis with focus on clinical care in the ICU. Information provided is based on a review of recent studies with focus on studies since 2017.

Recent findings
Advances in diagnostic and treatment approach for different pathogens are presented. Nosocomial meningitis now constitutes a major part of brain infections seen in ICUs in the developed world. Advances in ICU care of central nervous system (CNS) infections include application of newer diagnostic methods, improved understanding and delivery of antibiotics to the CNS, infection prevention for nosocomial infections, and application of neuromonitoring where indicated.

Summary
Advances in diagnostics and therapeutic approach to CNS infections are continually made. For intensivists, focus on neuromonitoring and brain resuscitation in critically ill patients with CNS infections may present a path to enhance preservation of brain function and improve outcomes.

Video abstract
http://links.lww.com/COCC/A22.

Keywords
bacterial meningitis, nosocomial meningitis and ventriculitis, viral encephalitis

INTRODUCTION

Central nervous system (CNS) infections are medical emergencies that require immediate diagnosis, initiation of therapy, and oftentimes admission to an ICU. This article focuses on the updated ICU management of infectious meningitis and encephalitis.

DIAGNOSTICS AND INITIAL ANTIMICROBIAL TREATMENT

Community acquired bacterial and viral infections

Common culprits of community-acquired bacterial meningitis in the developed world remain *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*. For diagnosis, blood cultures should be obtained immediately. Empiric antibiotics, ideally started within 1 h of presentation, should be initiated to cover likely organisms [1▪▪]. Antibiotic initiation should not be delayed to obtain cerebrospinal fluid (CSF). Empiric treatment regimens should cover all potential causes that the limited initial diagnostic work-up supports [2▪]. Local patterns of antibiotic resistance need to be considered [3▪▪]. While the debate about utility of steroids is ongoing, adjunctive dexamethasone, if indicated, should be given simultaneously with the first dose of antimicrobials [1▪▪]. Recent European guidelines recommend steroid discontinuation if a patient has bacterial meningitis by an organism other than *Haemophilus influenzae or S. pneumoniae* [1▪▪]. A recent study evaluating delayed outcomes after treatment for bacterial meningitis found that adverse clinical outcomes were associated with the use of adjunctive steroids [4].

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Curr Opin Crit Care 2019, 25:000–000
DOI:10.1097/MCC.0000000000000640

KEY POINTS

- Advances in diagnostic methods have improved early diagnosis of bacterial meningitis.
- Autoimmune encephalitis can develop after a viral encephalitis and should be considered in cases of lack of response to therapy or worsening after initial improvement.
- Nosocomial meningitis represents 40% of bacterial meningitis cases in the developed world.
- While main causative organisms for nosocomial meningitis remain cutaneous Gram-positive organisms, the proportion of Gram-negative infections is increasing.
- Elevated intracranial pressure is prevalent and a common eventual cause of death in patients with meningitis, and might require specific monitoring and treatment.
- Penetration of antimicrobials into the cerebrospinal fluid is highly variable, and dosing regimen should be adjusted to the individual situation.

In addition to conventional CSF analysis, advances using CSF and serum biomarkers to distinguish bacterial meningitis from nonbacterial disease are reported. Community-acquired bacterial meningitis can reliably be diagnosed using CSF lactate (>30 mg/dl) and serum-C-reactive protein (CRP) (>57 mg/dl), and be reliably excluded using CSF absolute neutrophil count and CSF lactate levels [5]. Serum CRP and procalcitonin also exhibit high sensitivity and specificity in differentiating bacterial and viral meningitis [6]. Furthermore, newer assays such as multiplex-PCR assays and DNA-microarray techniques serve to simultaneously detect and identify a greater number of pathogens [7], including rare pathogens such as *Captocytophaga canimorsus* [8].

The differential diagnosis for encephalitides is broad, including infectious and autoimmune causes. Viruses remain the most common culprit, however fungal, protozoan, and immune-related causes should be on the mind of any treating intensivist [9▪▪]. Herpes simplex virus (HSV) encephalitis is the most common identified cause of infectious encephalitis, accounting for 30–40% of cases with identified pathogen [10]. CSF HSV-PCR is the best diagnostic test for HSV encephalitis, but can occasionally produce false negative results when performed early in the course, and should then be repeated after 4 days [11]. If clinical suspicion remains high despite negative testing, treatment should be continued as 0.4% of patients will remain falsely negative [12]. Brain MRI has a high sensitivity and will show abnormalities in 80–100% of cases [13]. Mainstay of treatment is with intravenous acyclovir, but resistance has been reported for both immunocompromised and immunocompetent patients, in which case Foscarnet can serve as alternative [14–16]. During the course of viral management, development of autoimmune encephalitis can occur [17], and appropriate testing should be performed if lack of response to antiviral treatment is seen [11].

Tuberculous and fungal meningitis

Tuberculous (TB) meningitis should be considered in high risk patients or when presenting with complications less typical for other bacterial meningitis, including cranial nerves deficits, hydrocephalus, brain abscesses, or hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting [18▪]. Diagnosis remains difficult with no single test offering sufficient sensitivity, and clinicians being required to exert judgment based on examination, inflammatory CSF markers, imaging studies, and scoring systems [19]. Empiric treatment regimens are largely based on those for pulmonary tuberculosis with a staged combination regimen [18▪].

Fungal CNS infections are highly variable in clinical presentation and can mimic other acute neurological diseases [20]. Prior history of systemic fungal infections, CNS disease, or rapid disease progression should raise the index of suspicion for fungal meningitis. As with other CNS infections, early identification and treatment significantly improve odds for better outcome [21]. If CSF acquisition via lumbar puncture is difficult or impossible, very high (>1 gm/dl) CSF protein and obstructive hydrocephalus should be considered. Empiric amphotericin B will provide broad coverage. For cryptococcal meningitis, the most common fungal meningitis. Updated guidelines by the WHO were published in 2018 including treatment regimens with antifungal agents and management of elevated intracerebral pressure (ICP) with CSF diversion [22].

Nosocomial/postneurosurgical meningitis and ventriculitis

Nosocomial CNS infections are associated with increased mortality, worsening neurological function, and prolonged hospital stay. Nosocomial meningitis now represents 40% of bacterial meningitis cases in the developed world [23]. Reported incidences of nosocomial CNS infections vary widely, with postoperative meningitis occurring in 0.34–25% of cases, and extraventricular drain (EVD) infections in

up to 22% [24]. Accurate estimates of the incidence are difficult, as diagnosis and definition of infection vary, as do institutional infection control and device manufacturers [25,26▪▪]. Importantly, many studies include only culture positive cases in their analysis. This likely results in an overall under-approximation, as at least 11–30% of nosocomial meningitis is estimated to be culture negative [27,28]. A variety of risk factors have been described for the development of postneurosurgical meningitis, including experience in surgical techniques, CSF leaks, concomitant infection at incisional sites, and duration and type of surgery. Tumor surgery, severe head injury and subarachnoid hemorrhage pose the highest risk for postoperative meningitis [23].

The diagnosis of nosocomial meningitis remains challenging. Affected patients are already ill, and fever and headaches are common baseline problems in this population. CSF interpretation is difficult, as cell counts and protein levels are elevated after surgical procedures. Prior antibiotic or steroid use oftentimes further complicates the picture. Paralleling the use of biomarkers in CSF and serum for the diagnosis of community-acquired meningitis, various CSF biomarkers have been studied in the context of nosocomial CNS infections. For CSF lactate, studies have shown cutoff values between 1.9 and 5.4 mmol/l to diagnose bacterial meningitis. Other data are not as conclusive, and no single standard exists, especially when a ventriculostomy is in place [29]. The cell index, assessing CSF cell counts in relation to serum counts, has been reported to have some value in diagnosing nosocomial meningitis [24]. In 2017, the Infectious Disease Society of America published updated guidelines for the diagnosis and management of healthcare-associated ventriculitis and meningitis [26▪▪]. Some experts suggest different, not yet validated, algorithms such as consideration of bacterial meningitis as unlikely with normal CSF glucose, CSF lactate less than 4 mmol/l and negative Gram stain [24]. Another group recently developed a prediction rule to determine the presence of postoperative meningitis. This rule includes six variables (aneurysmal subarachnoid hemorrhage, CRP level, CSF/serum glucose ratio, CSF neutrophil count, CSF leak and CSF lactate level), with an area under the curve of 0.94 for the prediction of CNS infection [27].

For EVD-related infections, the accuracy of the clinical diagnosis remains low [30]. Reported risk factors for EVD-related infections include duration of catheterization, presence of intraventricular hemorrhage, insertion technique, and lack of infection control bundles [25]. While older data indicate repeated CSF sampling as a risk factor for EVD-infection, a recent series did not show this to be a risk factor, but rather reconfirmed previously known risks [31]. In a pooled meta-analysis, the use of antibiotic-impregnated EVD catheters showed reduction of infection rates from Gram-positive organisms with no significant reduction in Gram-negative infections [32]. Silver-impregnated EVDs showed some promise, but recent data did not show an overall reduction of EVD-related infections [33]. Antibiotic use with both conventional and antibiotic-impregnated EVDs has also been studied. Infection rates using conventional EVDs with prolonged antibiotics are similar to using antibiotic-coated EVDs with periprocedural antibiotics. In addition, conventional EVDs with prolonged antibiotics are superior to conventional EVDs with or without periprocedural antibiotics [34]. Recent data also suggest the use of intraventricular antibiotics resulted in significantly lower EVD infection rates (2.7 versus 11.9%) [35].

The main causative organisms for nosocomial meningitis are cutaneous Gram-positive organisms such as coagulase negative Staphylococci, *Staphylococcus aureus*, and *Propionibacterium acnes*, but the proportion of Gram-negative infections is increasing [24], with the percentage of Gram-negative infections now reported as high as 52% [23]. For EVD-related infections, specifically, the proportion of Gram-negative infections has increased with at least 35% being Gram-negative. [32].

Treatment of nosocomial meningitis should include coverage of likely involved pathogens and follow local resistance patterns. Current guidelines recommend treatment with vancomycin, and either an antipseudomonal cephalosporin or carbapenem [26▪▪]. For patients with beta-lactam-allergy, fluoroquinolones or aztreonam are recommended. The duration of treatment for nosocomial meningitis is mostly based on common practice rather than evidence, and usually spans 21 days for Gram-negative, and 10–14 days for Gram-positive meningitis [26▪▪]. If implants or shunts are in place, hardware removal and extended treatment is recommended [26▪▪]. A recent study on the pathogenic role of CSF drainage devices in postoperative neurosurgical patients showed that early device removal and re-implantation avoidance was associated with shorter illness duration [36]. Currently, the Federal Drug Administration has not approved any antibiotics for intrathecal use, and no consensus exists on indications for intrathecal treatment. Intrathecal therapy is considered only for severe ventriculitis, persistently positive CSF cultures despite appropriate intravenous dosing, multidrug-resistant pathogens, intolerance of systemic antibiotic administration, or when device removal is not feasible [37].

Elevated intracranial pressure in patients with central nervous system infections

Guidelines recommend brain imaging prior to performing a lumbar puncture if the patient's age is at least 60, there is a history of CNS disease, seizures, or immunocompromised state, or neurological examination is abnormal [38]. Newer data suggest that lumbar punctures can be performed safely in the large majority of patients with bacterial meningitis, as cerebral herniation is rare [39]. While these data suggest computed tomography (CT) as a screening method for contraindications to lumbar puncture, others point out that CT findings do not reflect elevated ICP [40].

Although elevated ICP is prevalent and a common eventual cause of death in patients with meningitis, data evaluating the significance of ICP monitoring in these diseases are limited. This is likely due to large proportions of patients receiving management in ICUs without subspecialty expertise, where the focus is systemic resuscitation rather than cerebral resuscitation [41]. Older data indicate development of intracranial hypertension in as many as 93% of patients, especially when the Glasgow Coma Scale (GCS) score is 8 or less [42]. In a recent series where all meningitis patients received ICP monitoring, ICP elevations were present in 62% [40]. In patients with cryptococcal meningitis, the prevalence of elevated ICP is estimated at least 50% [43]. As ophthalmoscopy cannot reliably detect acute ICP elevations, newer methods of noninvasive ICP monitoring, such as measurement of optic nerve sheath diameter have become popular [44]. In cryptococcal meningitis, where elevated ICP is particularly common, and repeated lumbar punctures may be necessary, noninvasive ICP monitoring has been described as an alternative to determine need and timing of invasive ICP monitoring [43].

Given that elevated ICP is more prevalent among patients with a lower GCS score, some experts suggest placement of an ICP monitor if the neurological examination deteriorates, pupils are nonreactive, or there is radiographic evidence of herniation [41]. In select cases, continuous ICP monitoring has been linked to improved outcomes. In a series evaluating neurointensive treatment, targeting ICP reduced all-cause mortality at 2 months [45]. However, optimization of ICP alone may not be sufficient. In a recent study comparing ICP targeted therapy to cerebral perfusion pressure (CPP), CPP-targeted therapy was associated with lower 90-day mortality [46]. Another recent study also showed that elevated ICP and the number of episodes when CPP was less than 50 mmHg correlated with functional outcomes [47].

Intracranial pressure management in patients with central nervous system infections

In a large systematic review of osmotic therapies for reduction of cerebral edema and ICP in bacterial meningitis, glycerol was the only agent evaluated, and had no effect on mortality [48]. While there are several case reports of decompressive hemicraniectomy for severely elevated ICP in patients with meningitis [49], decompression is rarely used in infective meningitis, and conclusive data on long-term outcomes are not available. Similarly, there are few structured data on CSF diversion in meningitis. In a series of pneumococcal meningitis, only 3% of survivors required permanent shunting [50]. For cryptococcal meningitis, many patients fare well with serial lumbar punctures (58% in a recent series), and a permanent shunt was more likely to be necessary [51]. In immunocompetent cryptococcal meningitis, shunting was more likely necessary in younger patients and provided significant relief of headaches as well as fungal overload [52]. Outcome after shunting for TB meningitis depends on clinical severity, and HIV-infected patients generally have a worse prognosis [53]. In a study comparing safety and efficacy of endoscopic third ventriculostomy (ETV) versus shunting in TB meningitis, ETV was superior with a lower rate of failure [54].

Use of continuous electroencephalography and other multimodality monitoring

Among neurocritically ill patients, continuous electroencephalography (cEEG) and multimodality monitoring are increasingly used, enabling real-time assessment of brain function in unresponsive or sedated patients [55]. There are few data specific to the use of EEG in meningoencephalitis. cEEG can not only serve to determine control of seizures, but also aid in assessment of progression of disease and prognostication [56]. EEG also aids in identification of CNS side effects of antibiotics, as abnormalities are seen in most patients [57▪]. Cerebral oximetry has been described in select cases of meningitis with ability to predict mortality, though data are limited [58].

Neurological and systemic complications and considerations

The treating intensivist should be aware of neurological complications that might develop during the course of meningoencephalitis: Seizures, vasculitis, cerebral venous sinus thrombosis (CVST), myelitis, cerebritis, and hypothalamic–pituitary dysfunction

[1▪▪]. Seizures occur in at least 25% with community-acquired bacterial meningitis [50,59]. In HSV-encephalitis, seizures occur in as many as 38% of patients [60]. CVST has most commonly been reported after pneumococcal [50] and TB meningitis [61]. It is far less common in meningococcal [62] and cryptococcal meningoencephalitis [63]. Management for CVST requires systemic anticoagulation; however, the risk of anticoagulation should be weighed against other intracerebral or systemic risks.

Regarding general ICU considerations, enhanced contact precautions (such as droplet precautions) may be necessary. Invasive temperature measurement may be indicated in patients with marked tachypnea, diaphoresis, or shivering. Some patients with bacterial meningitis develop distributive shock, and like other diseases, can trigger a pronounced inflammatory response [64]. Initial resuscitation strategies should follow sepsis guidelines [65]. However, the relationship between aggressive early volume resuscitation and cerebral edema is unclear, and as such, hypo-osmolar fluids should be avoided. The results of the recently completed ProCESS, ProMISe, and ARISE studies do not provide adequate data, as less than 2% of the enrolled patients had meningitis [66–71]. Other systemic complications in patients with meningitis include disseminated intravascular coagulation, renal failure, and adult respiratory distress syndrome [50]. Furthermore, patients with altered mental status are at high risk for aspiration, and may require airway control and early enteral feeding via nasogastric tubes. Special attention should also be paid to renal function, as many antibiotics are cleared renally, and any dysfunction requires dose adjustments to avoid toxicity.

Central nervous system penetration of antibiotics

Penetration of antimicrobials into the CSF is highly variable, and dependent on the degree of meningeal inflammation and dosing regimen. Therapeutic drug monitoring (TDM) is available for vancomycin and aminoglycosides, and increasingly for beta-lactams [72]. A recent systematic review on vancomycin CSF levels showed variable penetrance [73]. The CSF protein/serum albumin ratio has been reported to correlate with vancomycin penetration and might be a better estimate of activity in the CSF [74]. Comparing vancomycin CSF penetration in patients with postoperative intracranial infection versus community-acquired meningitis, overall penetrance was similar [75]. Meropenem penetration is also highly variable with reported percentages of 10–55%, with higher dosing and shorter dosing intervals providing higher penetration [76]. Higher dosed meropenem (15 g/day) has achieved CSF levels superior to those with conventional dosing [77]. Continuous infusion of vancomycin and meropenem with concomitant TDM might be another way to titrate to better levels and compensate for individual differences [78]. Linezolid penetrance reached an average of 57% with dosing increases required for critically ill or drug-resistant patients [79]. Another strategy commonly used, but with little substantive data, is addition of intrathecal or intraventricular antibiotics to intravenous dosing. In a meta-analysis studying the role of intraventricular antibiotic administration as an adjunct to intravenous antibiotics in postoperative Gram-negative ventriculomeningitis, intraventricular and intravenous treatment was superior to intravenous-only therapy [80▪].

CONCLUSION AND FUTURE

Published data and guidelines on meningoencephalitis stress the necessity of both early diagnosis and antibiotic administration. Only a few reports however point out the importance of brain resuscitation and brain-focused ICU management. As technology advances, subspecialty management within neuro-ICUs, using multimodality monitoring to target ICP, cerebral perfusion, and metabolism should be considered. Given that cerebral mitochondrial dysfunction is a prominent mechanism in neuronal damage caused by meningitis [81], metabolic monitoring and heightened attention to cerebral resuscitation might be a future direction to advance care and improve outcomes in critically ill patients with CNS infections.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

C.R. and K.M.B. have no relevant conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. ▪▪ van de Beek D, Cabellos C, Dzupova O, *et al.* ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016; 22 Suppl 3:S37–S62.

The article represents the most recently published European guidelines on diagnosis and treatment of bacterial meningitis.

2. Tunkel AR, Hartman BJ, Kaplan SL, *et al.* Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004; 39:1267–1284.

■ These are – while published in 2004 – still the current version of the guidelines endorsed by the American Infectious Disease Society.

3. McGill F, Heyderman RS, Panagiotou S, *et al.* Acute bacterial meningitis in adults. Lancet 2016; 388:3036–3047.

■■ This is a very comprehensive review article written with participation of prominent experts in the field and covering all important aspects of bacterial meningitis in adults to gain a broad understanding.

4. Gallegos C, Tobolowsky F, Nigo M, Hasbun R. Delayed cerebral injury in adults with bacterial meningitis: a novel complication of adjunctive steroids? Crit Care Med 2018; 46:e811–e814.
5. Sanaei Dashti A, Alizadeh S, Karimi A, *et al.* Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: a cross-sectional study. Medicine 2017; 96:e7637.
6. Santotoribio JD, Cuadros-Munoz JF, Garcia-Casares N. Comparison of C reactive protein and procalcitonin levels in cerebrospinal fluid and serum to differentiate bacterial from viral meningitis. Ann Clin Lab Sci 2018; 48:506–510.
7. Hou Y, Zhang X, Hou X, *et al.* Rapid pathogen identification using a novel microarray-based assay with purulent meningitis in cerebrospinal fluid. Sci Rep 2018; 8:15965.
8. Hansen M, Crum-Cianflone NF. *Capnocytophaga canimorsus* meningitis: diagnosis using polymerase chain reaction testing and systematic review of the literature. Infect Dis Ther 2019; 8:119–136.
9. Venkatesan A, Michael BD, Probasco JC, *et al.* Acute encephalitis in immunocompetent adults. Lancet 2019; 393:702–716.

■■ This is a very nice overview article from the Lancet series on acute encephalitis. It provides a valuable broad framework for this heterogenous disease.

10. Boucher A, Herrmann JL, Morand P, *et al.* Epidemiology of infectious encephalitis causes in. Med Mal Infect 2017; 47:221–235.
11. Stahl JP, Azouvi P, Bruneel F, *et al.* Guidelines on the management of infectious encephalitis in adults. Med Mal Infect 2017; 47:179–194.
12. Mendez AA, Bosco A, Abdel-Wahed L, *et al.* A fatal case of herpes simplex encephalitis with two false-negative polymerase chain reactions. Case Rep Neurol 2018; 10:217–222.
13. Bertrand A, Leclercq D, Martinez-Almoyna L, *et al.* MR imaging of adult acute infectious encephalitis. Med Mal Infect 2017; 47:195–205.
14. Schleenvoigt BT, Pletz MW, Deinhardt-Emmer S, Sauerbrei A. Detection of a novel mutation conferring acyclovir resistance and consecutive treatment failure in an HIV-positive patient with recurrent HSV-2 infection. J Glob Antimicrob Resist 2018; 12:20.
15. Sauerbrei A. Acyclovir resistance in herpes simplex virus type I encephalitis: a case report. J Neurovirol 2017; 23:638–639.
16. Karrasch M, Liermann K, Betz BB, *et al.* Rapid acquisition of acyclovir resistance in an immunodeficient patient with herpes simplex encephalitis. J Neurol Sci 2018; 384:89–90.
17. Armangue T, Spatola M, Vlagea A, *et al.* Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol 2018; 17:760–772.
18. Davis A, Meintjes G, Wilkinson RJ. Treatment of tuberculous meningitis and its complications in adults. Curr Treat Options Neurol 2018; 20:5.

■ An updated review on treatment of tuberculous (TB) meningitis – important to stay up to date given rising incidence of TB meningitis.

19. Wang YY, Xie BD. Progress on diagnosis of tuberculous meningitis. Methods Mol Biol 2018; 1754:375–386.
20. Zhou W, Lai J, Huang T, *et al.* Cryptococcal meningitis mimicking cerebral infarction: a case report. Clin Interv Aging 2018; 13:1999–2002.
21. Goralska K, Blaszkowska J, Dzikowiec M. Neuroinfections caused by fungi. Infection 2018; 46:443–459.
22. Migone C, Ford N, Garner P, Eshun-Wilson I. Updating guidance for preventing and treating cryptococcal disease: how evidence and decisions interface. Cochrane Database Syst Rev 2018; 11:ED000130.
23. Kurtaran B, Kuscu F, Ulu A, *et al.* The causes of post-operative meningitis: the comparison of Gram-negative and Gram-positive pathogens. Turk Neurosurg 2017. [Epub ahead of print]
24. Hussein K, Bitterman R, Shofty B, *et al.* Management of postneurosurgical meningitis: narrative review. Clin Microbiol Infect 2017; 23:621–628.
25. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr. Ventriculostomy-related infections: a critical review of the literature. Neurosurgery 2002; 51:170–181; discussion 81–82.
26. Tunkel AR, Hasbun R, Bhimraj A, *et al.* 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis 2017. [Epub ahead of print]

■■ These guidelines are the most recent iteration of definition and treatment for nosocomial meningitis and ventriculitis. The guidelines acknowledge the lack of firm data on many of the recommendations and clearly delineate where data are available and where not and expert opinion thus took place. These guidelines also reframe some of the diagnostic criteria for this very difficult to diagnose entity.

27. Hernandez Ortiz OH, Garcia Garcia HI, Munoz Ramirez F, *et al.* Development of a prediction rule for diagnosing postoperative meningitis: a cross-sectional study. J Neurosurg 2018; 128:262–271.
28. Schade RP, Schinkel J, Roelandse FW, *et al.* Lack of value of routine analysis of cerebrospinal fluid for prediction and diagnosis of external drainage-related bacterial meningitis. J Neurosurg 2006; 104:101–108.
29. Hill E, Bleck TP, Singh K, *et al.* CSF lactate alone is not a reliable indicator of bacterial ventriculitis in patients with ventriculostomies. Clin Neurol Neurosurg 2017; 157:95–98.
30. Berger-Estilita J, Passer M, Giles M, *et al.* Modalities and accuracy of diagnosis of external ventricular drainage-related infections: a prospective multicentre observational cohort study. Acta Neurochir 2018; 160:2039–2047.
31. Thompson DR, Vlachos S, Patel S, *et al.* Recurrent sampling and ventriculostomy-associated infections: a case–control study. Acta Neurochir 2018; 160:1089–1096.
32. Ramanan M, Lipman J, Shorr A, Shankar A. A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections. BMC Infect Dis 2015; 15:3.
33. Nilsson A, Uvelius E, Cederberg D, Kronvall E. Silver-coated ventriculostomy catheters do not reduce rates of clinically diagnosed ventriculitis. World Neurosurg 2018; 117:e411–e416.
34. Albano S, Berman B, Fischberg G, *et al.* Retrospective analysis of ventriculitis in external ventricular drains. Neurol Res Int 2018; 2018:5179356.
35. Fu RZ, Anwar DR, Laban JT, *et al.* Preemptive intrathecal vancomycin therapy reduces external ventricular drain infection: a single centre retrospective case–control study. Br J Neurosurg 2017; 31:16–20.
36. Soavi L, Rosina M, Stefini R, *et al.* Postneurosurgical meningitis: management of cerebrospinal fluid drainage catheters influences the evolution of infection. Surg Neurol Int 2016; 7(Suppl 39):S927–S934.
37. Stenehjem E, Armstrong WS. Central nervous system device infections. Infect Dis Clin North Am 2012; 26:89–110.
38. Glimaker M, Sjolin J. Lumbar puncture is safe in bacterial meningitis: impaired mental status alone does not motivate cranial computed tomography before lumbar puncture. Clin Infect Dis 2019; 68:168.
39. Costerus JM, Brouwer MC, Sprengers MES, *et al.* Cranial computed tomography, lumbar puncture, and clinical deterioration in bacterial meningitis: a nationwide cohort study. Clin Infect Dis 2018; 67:920–926.
40. Larsen L, Poulsen FR, Nielsen TH, *et al.* Use of intracranial pressure monitoring in bacterial meningitis: a 10-year follow up on outcome and intracranial pressure versus head CT scans. Infect Dis 2017; 49:356–364.
41. Tariq A, Aguilar-Salinas P, Hanel RA, *et al.* The role of ICP monitoring in meningitis. Neurosurg Focus 2017; 43:E7.
42. Lindvall P, Ahlm C, Ericsson M, *et al.* Reducing intracranial pressure may increase survival among patients with bacterial meningitis. Clin Infect Dis 2004; 38:384–390.
43. Bollela VR, Frigieri G, Vilar FC, *et al.* Noninvasive intracranial pressure monitoring for HIV-associated cryptococcal meningitis. Braz J Med Biol Res 2017; 50:e6392.
44. Agrawal A, Cheng R, Tang J, Madhok DY. Comparison of two techniques to measure optic nerve sheath diameter in patients at risk for increased intracranial pressure. Crit Care Med 2019; 47:e495–e501.
45. Glimaker M, Johansson B, Halldorsdottir H, *et al.* Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study. PLoS One 2014; 9:e91976.
46. Kumar R, Singhi S, Singhi P, *et al.* Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med 2014; 42:1775–1787.
47. Depreitere B, Bruyninckx D, Guiza F. Monitoring of intracranial pressure in meningitis. Acta Neurochir Suppl 2016; 122:101–104.
48. Wall EC, Ajdukiewicz KM, Bergman H, *et al.* Osmotic therapies added to antibiotics for acute bacterial meningitis. Cochrane Database Syst Rev 2018; 2:CD008806.
49. Hoehne J, Friedrich M, Brawanski A, *et al.* Decompressive craniectomy and early cranioplasty in a 15-year-old boy with *N. meningitidis meningitis*. Surg Neurol Int 2015; 6:58.
50. Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003; 126(Pt 5):1015–1025.
51. Cherian J, Atmar RL, Gopinath SP. Shunting in cryptococcal meningitis. J Neurosurg 2016; 125:177–186.
52. Liu J, Chen ZL, Li M, *et al.* Ventriculoperitoneal shunts in non-HIV cryptococcal meningitis. BMC Neurol 2018; 18:58.
53. Rizvi I, Garg RK, Malhotra HS, *et al.* Ventriculo-peritoneal shunt surgery for tuberculous meningitis: a systematic review. J Neurol Sci 2017; 375:255–263.
54. Aranha A, Choudhary A, Bhaskar S, Gupta LN. A randomized study comparing endoscopic third ventriculostomy versus ventriculoperitoneal shunt in the management of hydrocephalus due to tuberculous meningitis. Asian J Neurosurg 2018; 13:1140–1147.
55. Busl KM, Bleck TP, Varelas PN. Neurocritical care outcomes, research, and technology: a review. JAMA Neurol 2019. [Epub ahead of print]
56. Baten A, Desai M, Melo-Bicchi M, Gutierrez C. Continuous electroencephalogram as a biomarker of disease progression and severity in herpes simplex virus-1 encephalitis. Clin EEG Neurosci 2019; 1550059419835705.

57. Payne LE, Gagnon DJ, Riker RR, *et al.* Cefepime-induced neurotoxicity: a ■ systematic review. Crit Care 2017; 21:276.
Cefepime-induced neurotoxicity is a common phenomenon in practice, however often overlooked or thought of when it already occurred. This review provides a comprehensive overview of available data and reports that are of relevance to any practicing intensivist.
58. Diehl JW, Hullsiek KH, Okirwoth M, *et al.* Cerebral oximetry for detecting high-mortality risk patients with cryptococcal meningitis. Open Forum Infect Dis 2018; 5:ofy105.
59. Wang KW, Chang WN, Chang HW, *et al.* The significance of seizures and other predictive factors during the acute illness for the long-term outcome after bacterial meningitis. Seizure 2005; 14:586–592.
60. Modi S, Mahajan A, Dharaiya D, *et al.* Burden of herpes simplex virus encephalitis in the United States. J Neurol 2017; 264:1204–1208.
61. Bansod A, Garg RK, Rizvi I, *et al.* Magnetic resonance venographic findings in patients with tuberculous meningitis: predictors and outcome. Magn Reson Imaging 2018; 54:8–14.
62. Chirakkara SKP, Bakhsh ARA, Pariyadath AK, Rathinavelu B. Cerebral venous sinus thrombosis in a patient with meningococcal meningitis. Oman Med J 2018; 33:61–64.
63. Senadim S, Alpaydin Baslo S, Tekin Guveli B, *et al.* A rare cause of cerebral venous thrombosis: cryptococcal meningoencephalitis. Neurol Sci 2016; 37:1145–1148.
64. Ribes S, Nessler S, Heide EC, *et al.* The early adaptive immune response in the pathophysiological process of pneumococcal meningitis. J Infect Dis 2017; 215:150–158.
65. Rhodes A, Evans LE, Alhazzani W, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017; 45:486–552.
66. Angus DC, Yealy DM, Kellum JA, Pro CI. Protocol-based care for early septic shock. N Engl J Med 2014; 371:386.
67. Yealy DM, Kellum JA, Huang DT, *et al.* A randomized trial of protocol-based care for early septic shock. ProCess Investigators. N Engl J Med 2014; 370:1683–1693.
68. Peake SL, Delaney A, Bellomo R, Investigators A. Goal-directed resuscitation in septic shock. N Engl J Med 2015; 372:190–191.
69. Peake SL, Delaney A, Bailey M, *et al.* Goal-directed resuscitation for patients with early septic shock. Arise Investigators Anzics Clinical Trials Group. N Engl J Med 2014; 371:1496–1506.
70. Mouncey PR, Osborn TM, Power GS, *et al.* Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015; 372:1301–1311.
71. Mouncey PR, Osborn TM, Power GS, *et al.* Trial of early, goal-directed resuscitation for septic shock. ProMISe Trial Investigators. N Engl J Med 2015; 372:1301–1311.
72. Roberts JA, Paul SK, Akova M, *et al.* DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014; 58:1072–1083.
73. Beach JE, Perrott J, Turgeon RD, Ensom MHH. Penetration of vancomycin into the cerebrospinal fluid: a systematic review. Clin Pharmacokinet 2017; 56:1479–1490.
74. Ishikawa M, Yamazaki S, Suzuki T, *et al.* Correlation between vancomycin penetration into cerebrospinal fluid and protein concentration in cerebrospinal fluid/serum albumin ratio. J Infect Chemother 2019; 25:124–128.
75. Cai Y, Zhou L, Wang H, *et al.* Comparation of vancomycin penetration into cerebrospinal fluid in postoperative intracranial infection and community-acquired meningitis patients. J Clin Pharm Ther 2019; 44:216–219.
76. Zhang Y, Zhang J, Chen Y, *et al.* Evaluation of meropenem penetration into cerebrospinal fluid in patients with meningitis after neurosurgery. World Neurosurg 2017; 98:525–531.
77. Kerz T, von Loewenich FD, Roberts J, *et al.* Cerebrospinal fluid penetration of very high-dose meropenem: a case report. Ann Clin Microbiol Antimicrob 2018; 17:47.
78. Mader MM, Czorlich P, Konig C, *et al.* Intrathecal penetration of meropenem and vancomycin administered by continuous infusion in patients suffering from ventriculitis – a retrospective analysis. Acta Neurochir 2018; 160:2099–2105.
79. Wu X, Tang Y, Zhang X, *et al.* Pharmacokinetics and pharmacodynamics of linezolid in plasma/cerebrospinal fluid in patients with cerebral hemorrhage after lateral ventricular drainage by Monte Carlo simulation. Drug Des Devel Ther 2018; 12:1679–1684.
80. Karvouniaris M, Brotis AG, Tsiamalou P, Fountas KN. The role of intraven- ■ tricular antibiotics in the treatment of nosocomial ventriculitis/meningitis from Gram-negative pathogens: a systematic review and meta-analysis. World Neurosurg 2018; 120:e637–e650.
Intrathecal antibiotics are often reverted to in difficult to treat ventriculitis/meningitis, yet their role is not well defined with many questions remaining about impact on duration of treatment and outcomes. This review summarizes available literature.
81. Munk M, Poulsen FR, Larsen L, *et al.* Cerebral metabolic changes related to oxidative metabolism in a model of bacterial meningitis induced by lipopolysaccharide. Neurocrit Care 2018; 29:496–503.