

Infections in Neurocritical Care

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Abstract Neurointensive care (NICU) patients experience complex infectious disease challenges. Central nervous system (CNS) infections are difficult to diagnose and treat, and post-neurosurgical patients are vulnerable to a unique set of healthcare-acquired infections (HAI) in addition to those typical of critically ill patients. The purpose of this review is to summarize the approach to suspected infection in the NICU and discuss management of several infectious syndromes in the NICU setting.

Keywords Infection · Neurocritical care · Meningitis · ICU · Nosocomial · Ventriculitis

General Principles

The blood–brain barrier presents a challenge to antimicrobial selection and infection treatment. The majority of the capillary space in the brain is covered in tight junctions and gap junctions, preventing large molecules from penetrating into cerebrospinal fluid (CSF). While part of the hypothalamus, the floor of the fourth ventricle, and the roof of the third ventricles do not have tight junctions and allow for limited penetration of large hydrophilic molecules into the CSF space, for the most part, this barrier limits diffusion to small or hydrophobic molecules [1]. As a result, the number of antimicrobials available for infections of the

CNS space is limited and often requires dose adjustment for maximal efficacy (see Table 1) [2]. Although some earlier *in vitro* studies indicated that bacteriocidal drugs would be preferable to bacteriostatic agents in the CSF, *in vivo* experience has not shown this. The issues of penetration beyond the blood–brain barrier and matching spectrum of activity to agents are the most important considerations in treating CNS infections [3].

This makes it critical to identify whether a NICU infection is intra-axial (and thus potentially subject to blood–brain barrier limitations) or extra-axial. Infections that do not involve the CNS space have a wider variety of treatment options than those within the CNS. Mis-identification of a CNS infection as a more superficial infection can lead to under-treatment with ineffective drugs.

Antibiotics that effectively enter the CNS are unfortunately often associated with CNS toxicities. Several antibiotics have been reported to cause encephalopathy either through a direct toxic effect or by causing nonconvulsive seizures that present as altered mental status. The agents most commonly associated with encephalopathy are beta-lactam antibiotics (penicillins, cephalosporins, and carbapenems), quinolones, and metronidazole. Cefepime—a fourth-generation cephalosporin that has excellent CNS penetration—is increasingly used as empiric therapy for serious infections. A syndrome of encephalopathy associated with myoclonus has been well described with this agent. The risk is increased in patients with renal failure, but several cases have been described in patients with normal renal function. Fortunately, the encephalopathy is reversible with discontinuation of the medication. Seizures have been reported with beta-lactams and fluoroquinolones. They bind to γ -aminobutyric acid class A (GABA-A) receptors, impede inhibitory neurotransmission and cause central excitotoxicity. The risk of seizures ranges

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Table 1 CNS properties of selected antimicrobials and antivirals by class. Adapted from Mayo Clinic Antimicrobial Guide [2]

Antibiotic class	Degree of CNS penetration	Dose adjustment required for CNS infections
Aminoglycosides	Poor	Not applicable
Carbapenems	Fair	No
Cephalosporins		Higher-range dosing needed for selected agents
First generation	Poor	
Second generation	Poor	
Third generation	Fair	
Fourth generation	Fair	
Aztreonam	Fair	No
Beta-lactams	Poor to fair	Higher-range dosing needed for selected agents
Penicillin		
Aminopenicillins		
Beta-lactam/beta-lactamase inhibitors		
Quinolones	Fair	No
Tetracyclines		No
Doxycycline	Fair to good	
Minocycline	Fair to good	
Tetracycline	Poor	
Tigecycline	Insufficient data	
Colistin	Poor	Unknown
Daptomycin	Unknown	Unknown
Linezolid	Good	No
Metronidazole	Good	No
Trimethoprim/sulfamethoxazole	Good	No
Vancomycin	Poor to fair	Yes, aim for serum trough of 15–20 mcg/mL to achieve higher levels in the CNS
<i>Antitubercular agents</i>		
Ethambutol	Fair	No
Isoniazid	Good	No
Pyrazinamide	Good	No
Rifamycins	Fair	No
<i>Antifungals</i>		
Amphotericin B (liposomal or conventional)	Poor	No; use in concert with other agents (e.g., flucytosine)
Echinocandins	Poor	Not applicable
Azoles		No
Fluconazole	Good	
Itraconazole	Poor	
Voriconazole	Good	
Posaconazole	Poor	
Flucytosine	Good	No
<i>Antivirals</i>		
Acyclovir	Good	No
Cidofovir	Poor	Not applicable
Foscarnet	Fair	No
Famciclovir	Unknown	Not applicable
Ganciclovir	Unknown	Not applicable
Valacyclovir	Fair	No

CNS Central nervous system

Table 2 CSF interpretation. Adapted from Koski and Loo 2010 [10] and Seehusen et al. 2003 [9]

CSF characteristic	Normal	Bacterial	Viral	Mycobacterial	Fungal
Opening pressure	< 10 mm H ₂ O	200–500 mm H ₂ O	Normal or elevated	Elevated	Elevated (> 250 mm H ₂ O in cryptococcal meningitis)
WBC count	0–5 cells/mm ³	100–20,000 cells/mm ³	5–500 cells/mm ³ cells/uL	5–2000 cells/mm ³	20–2000 cells/mm ³
Differential	N/A	> 80% PMN	Early: neutrophil predominant Late: Lymphocytes	> 80% lymphocytes	> 50% lymphocytes
Protein	15–50 mg/dL	100–500 mg/dL	30–150 mg/dL	> 50 mg/dL	40–150 mg/dL
Glucose*	45–100 mg/dL	< 40 mg/dL	30–70 mg/dL	< 40 mg/dL	30–70 mg/dL
Additional testing of note	N/A	Gram's stain and bacterial cultures, blood cultures	PCR for HSV	Mycobacterial culture and AFB staining	Fungal culture Fungal smear

Normal findings, common findings for untreated infectious syndromes described, as well as a common noninfectious syndrome (subarachnoid hemorrhage) for reference for an infection mimic. * Glucose assumes normal serum glucose

AFB Acid-fast bacilli, CSF cerebrospinal fluid, PMN polymorphonuclear cell, RBC red blood cell, WBC white blood cell

from 0.04% with cephalosporins to as high as 20% with imipenem use in patients who have underlying structural brain lesions (Bhattacharya Current Infectious Disease Reports · December 2014). Aminoglycosides and polymyxins (colistin, polymyxin B) can cause a neuromuscular blockade-like effect. Older age, renal failure, and higher doses are risk factors for beta-lactam-associated neurotoxicity. Risk factors for neurotoxicity with other classes of antimicrobials are generally not well understood, and patients must be closely monitored for side effects [4].

Community-Acquired CNS Infections: Meningitis and Encephalitis

Meningitis and encephalitis are difficult-to-diagnose clinical syndromes. The prototypical manifestations—fever, altered mental status, and occasional focal deficits—are nonspecific and require careful consideration of risk factors, presentation, imaging, and CSF studies. Further, while lumbar puncture is not a technically difficult procedure for an average patient, a rising number of patients with morbid obesity [5] and the increasing use of blood thinners [6] have made obtaining CSF nontrivial for a large subset of patients.

Meningitis and encephalitis are pathologically distinct syndromes but have extensive clinical overlap. In meningitis, the layers surrounding the brain are inflamed, typically causing headache, meningismus, and fever. Encephalitis involves brain parenchyma and presents as altered mental status and cerebral dysfunction, such as

seizures and focal deficits. Though the features of meningitis or encephalitis may predominate in a particular case and affect treatment decisions, infections rarely completely confine themselves to either the parenchyma or the meninges. The term “meningoencephalitis” better captures the clinical overlap often practically encountered [7].

Though characteristic imaging findings and associations exist, the single most important diagnostic tool for CNS infections is CSF analysis. When meningoencephalitis is suspected, blood cultures should be obtained as soon as possible, and empiric antimicrobial therapy should be initiated immediately. If the patient is immunocompromised and has prior CNS disease, focal deficits, or papilledema, imaging should be performed to ensure there is not a contraindication to lumbar puncture. Otherwise, lumbar puncture should be performed expeditiously [8]. Initial testing should include Gram's stain, cell count, differential, glucose, protein, bacterial culture, and testing for herpes simplex virus (HSV) by polymerase chain reaction. Typical patterns [9, 10] of CSF findings are provided in Table 2. Additional testing for fungal, mycobacterial, or other viral causes may be considered in selected patients. We suggest holding 1–2 cubic centimeters of CSF, if possible, to perform additional targeted testing if the initial tests do not provide an etiology for meningitis (see Table 3 for commentary on a selected group of additional tests).

Several noninfectious CNS syndromes can alter the CSF profile and give the appearance of infection. Intracranial bleeding is a cause of centrally mediated fever and will result in pleocytosis and elevated protein in CSF. Similar abnormalities can be seen with malignant,

Table 3 Additional testing on CSF for CNS infection

Test	Utility
Cryptococcal antigen	High in immunosuppressed patients; recommended in suspected cases
Pneumococcal antigen	High; recommended when Gram's stain/culture not available or when antibiotics have been administered prior to culture. Urinary pneumococcal antigen testing is an alternative when CSF examination cannot be performed
Herpes simplex virus (HSV) PCR	High; common, treatable cause of viral meningoencephalitis
West Nile virus (WNV) IgM	High in appropriate clinical setting: viral encephalitis, WNV endemic area, appropriate season
HHV-6 PCR	High in appropriate clinical setting: viral encephalitis in an immunocompromised host
Cytomegalovirus (CMV) PCR	Low; not routinely recommended even in immunocompromised patients
Epstein–Barr virus (EBV) PCR	Low; false positives common, not routinely recommended even in immunocompromised patients

CMV Cytomegalovirus, CNS central nervous system, CSF cerebrospinal fluid, EBV Epstein–Barr virus, HHV Human herpesvirus, HSV herpes simplex virus, PCR polymerase chain reaction, WNV West Nile virus

neuroinflammatory, and vasculitic disorders. In post-ictal patients, protein and lactate may be elevated in the absence of infection. Diagnosing infection in such patients relies on judgment and interpretation of the overall clinical presentation. Often this requires aggressive initial antibiotic therapy for possible meningoencephalitis and rapid de-escalation as alternative possibilities are explored.

Initial empiric therapy varies by age and clinical syndrome. In typical adult patients <50 years old, the most common pathogens are *Neisseria meningitidis* and *Streptococcus pneumoniae*, and thus, recommended empiric therapy is vancomycin plus a third-generation cephalosporin. Susceptibility of *S. pneumoniae* to cephalosporins is unpredictable, hence the empiric addition of vancomycin. Over age 50, the risk of *Listeria monocytogenes* increases and prompts the addition of ampicillin. In patients with suspected or confirmed pneumococcal meningitis, adjunctive dexamethasone is recommended. Dexamethasone is not helpful in other types of bacterial meningitis and should be discontinued if the Gram's stain/cultures identify another pathogen [8]. The only commonly encountered viral meningoencephalitis with effective treatment is HSV, and empiric acyclovir should be administered until HSV infection is ruled out or a clear alternative diagnosis established [7].

The question of prophylaxis of exposed persons, especially healthcare workers, arises after diagnosis of *N. meningitidis*. Despite the anxiety about the possibility of transmission of *N. meningitidis* in the healthcare setting, relatively few individuals actually require chemoprophylaxis. Antimicrobial prophylaxis is recommended only for “close contacts,” i.e., those who spend a prolonged period (>8 h) in close proximity to the patient or had direct contact with oral/airway secretions. Typically, this is limited to household contacts, roommates, and healthcare personnel who participated in invasive procedures such as endotracheal intubation or suctioning without the use of

personal protective equipment. Options for chemoprophylaxis include ciprofloxacin, rifampin, and ceftriaxone. Choice of a specific medication should be based on local resistance patterns and characteristics of the exposed person [11]. Prophylaxis should be administered as soon as possible after exposure; it is not effective if it has been more than 14 days since the exposure (Table 4).

HAI of the CNS Space

Post-neurosurgical infections are relatively rare, with estimated incidences between <1–7%. The low incidence rate makes it difficult to definitively state relative incidence, but the most common organisms appear to be *Staphylococcus aureus* and *Propionibacterium acnes*. Cranial surgeries appear to have a higher risk than spinal procedures, with no clear patient characteristics predicting higher infection risk [12]. Selected post-neurosurgical infections are discussed below.

Shunt and Reservoir Infections

CSF shunts make a communication between the CNS and some other space. The other space may be external (external ventricular drain), peritoneal (ventriculoperitoneal [VP] shunt), or vascular (ventriculoatrial [VA] shunt). In acute care, these primarily relieve increased intracranial pressure. In more chronic settings, shunts are also used to relieve chronic hydrocephalus. Risk factors for shunt infection include trauma, shunt irrigation, hemorrhage, and recent placement [13–15]. Typical organisms involved with infection are with skin flora such as *Staphylococci* and *Propionibacterium* [12, 16], but VP shunts are also prone to gram-negative and anaerobic infections from peritonitis due to distal end contamination. These are challenging to diagnose as they present with nonspecific symptoms of

Table 4 Empiric systemic treatment of selected adult infections in the NICU

Infection	Empiric treatment
Meningitis—Community associated	Dexamethasone 0.15 mg/kg IV every 6 h if pneumococcal meningitis suspected <i>Before or concomitantly with</i> Vancomycin dosed to goal trough 15–20 mcg/mL AND Ceftriaxone 2 g IV every 12 h <i>If over age 50, pregnant or immune compromised</i> Add Ampicillin 2 g IV every 4 h <i>If herpes meningoencephalitis suspected</i> Add Acyclovir 10 mg/kg IV every 8 h
Shunt infection/nosocomial meningitis	Vancomycin dosed to goal trough 15–20 mcg/mL AND one of the following Cefepime 2 g IV every 8 h Ceftazidime 2 g IV every 8 h Meropenem 2 g IV every 8 h
HAP/VAP	Piperacillin/tazobactam 4.5 g IV every 6 h OR Cefepime 2 g IV every 12 h <i>If patient has recent antibiotic exposure, septic shock, organ failure, prolonged hospitalization, or increased local MRSA prevalence</i>
CLABSI	Vancomycin dosed to goal trough 15–20 mcg/mL AND Cefepime 2 g IV every 12 h
CAUTI	Ceftriaxone 2 g IV daily OR Cefotaxime 1 g IV every 8 h OR Cefepime 2 g IV every 12 h

Dosages should be adjusted based on patient renal function, and regimens may need alteration based on patient allergies and intolerances. Pediatric patients may have additional considerations. Duration of therapy should be tailored based on specific information regarding etiologies of infection

CAUTI Catheter-associated urinary tract infection, CLABSI central line associated bloodstream infection, HAP hospital-acquired pneumonia, MRSA methicillin resistant staphylococcus aureus, NICU neurointensive care, VAP Ventilator-associated pneumonia

shunt malfunction such as headache, nausea/vomiting, personality changes, insomnia or somnolence, vision problems, and vomiting. The preferred method of diagnosis of shunt infection is CSF sampling from the shunt itself. Ventricular taps and lumbar punctures may not be representative of organisms associated with inflammation within infected shunts, and negative cultures do not rule out shunt infection. Positive blood cultures, particularly with VA shunts, and neuroimaging findings can support a diagnosis of shunt infection [15, 17, 18].

Treatment of shunt infection is not standardized, but at minimum should include removal of the device, external drainage, and parenteral antibiotics. Current guidelines recommend empiric therapy with a combination of vancomycin plus either a fourth-generation cephalosporin or

carbapenem active against *Pseudomonas* [19] followed by targeted therapy based on culture results.

Shunts should not be replaced until the space is sterile [7, 20]. In cases where the shunt cannot be removed, the addition of rifampin can be considered for staphylococcal infections susceptible to rifampin [21]. This combination is synergistic in staphylococcal infections involving prosthetic material such as endocarditis and osteomyelitis. Although experience in CNS infections is more limited, case series have reported good outcomes with this approach [22, 23]. There are no randomized controlled trials or guidelines at this time to guide duration of antimicrobials, and thus, duration of therapy must be tailored to the individual patient based on concomitant

surgical approaches, time to clearing of CSF, and the type of organisms isolated [24, 25].

Intraventricular antibiotics can be considered in instances where the infection is difficult to eradicate or surgical therapy is not feasible. To date, the only randomized controlled trial examining intraventricular antibiotics compared to intravenous antibiotics alone was in gram-negative meningitis in infants and found a threefold increase in mortality with intraventricular administration [26]. However, the results of that study were not generalizable to adults, as many of the deaths appeared attributable to either delays in antimicrobial administration or technical challenges to catheter placement, which is considerably easier in adults. There has not been a comparable study in adults, and no medication is approved for intraventricular administration by the Food and Drug Administration. Evidence guiding how and when to use interventricular antimicrobials is thus limited. A retrospective study looking at neurosurgical patients with resistant *Acinetobacter baumannii* ventriculitis found that intrathecal colistin along with intravenous colistin was more effective than intravenous colistin alone [27]. With the limited literature about this practice, protocols are not standardized, but experience-based dosing regimens of vancomycin, aminoglycosides, and polymyxins can be found in current guidelines [28]. In the opinion of the authors, intrathecal antibiotics should be considered in conjunction with parenteral therapy in severe infections with resistant organisms, particularly gram negatives, when the CSF does not appear to be clearing rapidly. Once the CNS is sterilized, intrathecal therapy can be discontinued.

Ommaya reservoirs, used for intraventricular antibiotic administration as well as intraventricular chemotherapy, are subject to many of the same infection risks as shunts. The approach to an infected Ommaya reservoir is similar to other shunt infections.

Deep Brain Stimulators

Once used exclusively for Parkinson's disease, deep brain stimulator (DBS) devices are now used for treatment of other movement disorders, pain syndromes, and psychological conditions such as obsessive–compulsive disorder. These devices are relatively new and literature on infections is sparse, but will be of increasing importance in years to come [29]. Device infections can be associated with any component of the DBS, including the intracranial leads, the implanted pulse generator (IPG), or the extracranial lead extender connecting the two. The highest risk period for DBS infections appears to be in the first month after implantation [7].

Infection involving the intracranial portion requires definitive treatment with total hardware removal.

Fortunately, IPG infections appear to be the most common and are the easiest to access. Sillay et al. described an algorithm for managing infections where, so long as there was no evidence of infection of the intracranial lead, multiple drainage sites nor extensive cellulitis, salvage could be attempted via removal of the IPG and lead extenders, antibiotic treatment, and eventual re-implantation. Antibiotics were administered for 2–6 weeks between extraction and implantation. Salvage was successful in 9/14 cases. Notably, in 4/4 failures where culture data were available, the responsible organism was *S. aureus*. Successful salvage was reported in only one case of *S. aureus* IPG infection [21]. A similar study found partial device removal to be successful when infection was limited to the IPG with higher intracranial lead salvage failures reported with *S. aureus* infections [30]. Thus, effective management must involve removal of infected portions of the device, with consideration of total extraction in *S. aureus* infections and in infections involving the intracranial leads.

Post-Craniotomy Infections

Infection following neurosurgery makes up a unique subset of surgical site infections (SSI). Though fortunately rare and often preventable with routine perioperative surgical prophylaxis, those with trauma, repeat surgery, or longer-duration surgery remain at high risk for complications. Typical organisms seen in these infections are skin flora, with a predominance of *Staphylococcal* spp. [31]. Bone flaps performed to access the brain are separated from their blood supply and are at high risk of necrosis and infection in the postoperative period [7].

When the bone flap is infected, optimal treatment involves a combination of surgical debridement, flap removal, and antimicrobials. Duration of therapy is not established, but extends anywhere from 6 weeks to 12 months. Soft tissue reconstruction and cranioplasty should ideally be delayed until infection is adequately cleared [32]. When the bone flap itself becomes infected, discarding the flap is the preferred treatment. A small case series reported some success with sterilizing flaps after gross contamination with betadine, antibiotic irrigation, and/or autoclaving, [33], but these salvage approaches are not routinely recommended.

Several techniques have been employed for cases where immediate cranioplasty is deemed necessary, including placement of titanium mesh or other hardware. Optimal management of infections while hardware is in place is not known, but extended courses of antimicrobials up to 12 months have been reported [34]. Ideally, hardware such as screws and plates should be removed. Grafts may need removal if they are not vascularized, but successful free fascia grafts in the presence of infection have been reported

[35]. If hardware removal is not feasible, chronic antimicrobial suppression targeting likely or cultured organisms may be required.

In other areas, including orthopedic surgery [36] and cardiovascular surgery [37], nasal screening and decolonization for *Staphylococcus aureus* have been a cost-effective tool for reducing SSI. It would be reasonable to apply the same approach to neurosurgical patients. When a Methicillin resistant staphylococcus aureus (MRSA)-colonized individual is identified, they can be decolonized prior to surgery with a combination of chlorhexidine washes daily for five days along with twice daily nasal mupirocin. This combination reduces the bacterial burden prior to surgery and may reduce the rate of staphylococcal SSIs.

Vascular Access Infections

Catheter-related bloodstream infections (CRBSI) are common and often preventable complications seen in all ICU settings. All vascular devices including central venous lines, peripherally inserted central catheters [38], and arterial lines [39] are risk factors for bloodstream infection. CRBSI occurs from either extraluminal or intraluminal bacterial contamination and growth. Typically, extraluminal infections involve migration of skin bacteria along the surface of the catheter with resultant colonization of the catheter. Less commonly, extraluminal contamination can occur when a remote source of infection seeds the extraluminal intravascular portion of the catheter. In either situation, biofilm forms rapidly and the cornerstone of treatment is line removal. The extraluminal route predominates in early line infections and is most often seen in the first several weeks after placement [40].

Intraluminal infection is associated with manipulation of the catheter hub or infusion of contaminated fluids. Long-term lines are at higher risk for this route due to more cumulative manipulation of the hub [40]. Certain infusates, such as total parenteral nutrition [41], are notorious for increasing the risk of CRBSI. Depending on the organism involved, long-term catheters with presumed intraluminal infection sources can be candidates for salvage with antibiotic lock therapy. In this approach, high concentration antibiotics are instilled into the catheter when it is not in use to attempt to sterilize the lumen. Success rates for coagulase-negative staphylococcal infections are reasonably high; *S. aureus*, *Candida* spp., and multidrug-resistant organisms fail lock therapy routinely, and an attempt at salvage is not recommended [42].

In conjunction with either line removal or selected salvage, CRBSI is treated with systemic antimicrobial therapy targeting the organism. The total duration of therapy depends on the time it takes to clear blood cultures. Typically, intravenous antibiotics are administered for

10–14 days beyond clearance of the blood stream, but persistent bacteremia or other risk factors (e.g., endocarditis) may require longer treatment courses [42].

CRBSI is now being recognized as a preventable nosocomial complication in most settings. Use of a “bundle” of practices during catheter insertion including culture of safety, skin antisepsis at the insertion site, full barrier precautions (head to toe draping of the patient and use of sterile gown and gloves, mask and cap by the inserter), and preferential avoidance of femoral access has decreased central line infection rates drastically [43, 44]. Use of chlorhexidine bathing [45] and chlorhexidine dressings [46] may further reduce the risk of infection. Contamination at the time of line accessing can be reduced through nursing education to disinfect the hub or through the use of disinfecting caps [47]. Most importantly, daily reassessment of line need and removal of catheters that are no longer necessary reduces the risk of bloodstream infection [44].

Respiratory Infections

Neurologic illness is recognized as an independent risk factor for developing nosocomial pneumonia and failing therapy in other intensive care settings [48, 49]. It is thus no surprise that nosocomial pneumonia is a leading cause of infection in the NICU [50]. Nosocomial pneumonia occurs when gastrointestinal flora are translocated to the lower respiratory tract. This occurs through microaspiration or gross aspiration of oral and/or gastric flora. Healthcare worker hands or contaminated medical equipment may transfer hospital organisms from one patient to another. The presence of an endotracheal tube bypasses the patient’s first line of defense to aspiration and makes intubated patients more vulnerable to respiratory infections [51]. NICU patients, with higher rates of invasive ventilation and mental obtundation that predisposes to aspiration, are highly vulnerable to nosocomial pneumonia.

Hospital-acquired pneumonia (HAP) is a lower respiratory tract infection that was not incubating at the time of hospital admission and that presents 2 or more days after hospitalization. Ventilator-associated pneumonia (VAP) is defined as pneumonia that presents more than 48 h after endotracheal intubation [52].

Both HAP and VAP management depend, in part, on local resistance patterns and antibiograms. Empiric regimens should cover *S. aureus*, *P. aeruginosa* as well as other gram-negative bacilli. MRSA coverage is necessary only when >10–20% of local isolates are methicillin resistant; otherwise, empiric anti-staphylococcal coverage should target MSSA. Gram-negative and *Pseudomonas* coverage should be likewise selected by based on local susceptibility. Double coverage for gram negatives is not

routinely indicated unless resistance patterns are unpredictable [52].

Empiric therapy should be re-evaluated within 72 h, and de-escalation based on microbiology data initiated. If the patient is stable and cultures are negative, coverage can be narrowed to an agent with good gram-negative coverage based on local data. Treatment should typically be 7 days [52].

The risk of VAP, and to a lesser degree, HAP, can be mitigated by preventing aspiration. Ventilated patients should have the head of bed $>30^\circ$ to avoid aspiration associated with supine positioning. Continuous subglottic suctioning may reduce the risk of VAP in patients who require prolonged mechanical ventilation. Oral decontamination with chlorhexidine reduces the risk of VAP. Other measures, such as selective digestive decontamination, early tracheostomy, and gastric volume monitoring, may be of benefit, but the current evidence is not as clear on the value of these measures [53].

Urinary Tract Infections

Urinary tract infections (UTI) are exceedingly common in neurocritical care, second only to pneumonia [50]. In addition to acutely ventilated and disabled patients seen in every ICU, NICUs have a population of chronically disabled and incontinent patients, such as patients with spinal cord injuries who often have chronic indwelling urinary catheters and thus tend to have a higher rate of catheter-associated urinary tract infection (CAUTI).

CAUTI requires the presence of an indwelling urinary catheter for more than 48 h, a positive urine culture, and signs and symptoms of infection (fever, suprapubic/flank discomfort). NICU patients frequently have fever, and catheter use is higher in NICUs than other kinds of ICUs [54]. Therefore, NICUs tend to have high CAUTI rates. The surveillance definition for CAUTI is nonspecific, and not all patients with CAUTI based on this definition need antimicrobial therapy. Presence of a urinary catheter results in inflammation and pyuria. Hence, presence of pyuria by itself is not indicative of CAUTI and does not help in identifying patients who need treatment. Treatment of asymptomatic bacteriuria and colonization is not beneficial for most patients and subjects them to harm associated with antimicrobial overuse [55]. Ideally, when CAUTI is suspected as a cause of fever, the indwelling catheter should be removed and a urine specimen obtained for culture through a new catheter. It is important to obtain the specimen through the catheter port, not the drainage bag. Empiric treatment for UTI should be initiated if no obvious alternative cause for the fever is present. However, UTI should be treated as a diagnosis of exclusion and other diagnostic possibilities investigated thoroughly. The

diagnosis should be re-evaluated 48–72 h later based on clinical response to therapy, culture results, and any alternative diagnoses made.

Empiric treatment for CAUTI is similar to acute complicated cystitis, typically with a quinolone, third- or fourth-generation cephalosporin. Duration of treatment is 1–2 weeks depending on clinical response and organisms [55]. If the catheter is no longer necessary or intermittent catheterization feasible, the device should be removed to prevent it from acting as a nidus for relapse or reinfection. If continuous catheterization is required, the catheter should be exchanged if this did not occur prior to obtaining the urine culture [56].

Prevention of CAUTI relies mainly on aseptic insertion of catheters and avoiding unnecessary use of urinary catheters. Alternatives to indwelling catheters include condom catheters (in men) and in-and-out catheterization. Antimicrobial prophylaxis and antibiotic-coated catheters have not been shown to be beneficial [55]. Aggressive perineal cares may be counter-productive [57].

Noninfectious Causes of Fever

Fever is very common in the NICU and it is estimated that infection accounts for only 50% of febrile episodes (Rabinstein AA, Sandhu K. Noninfectious fever in the NICU: incidence, causes and predictors. *J Neurol Neurosurg Psychiatry*. 2007; 78(11):1278–1280). Noninfectious causes of fever include drug or alcohol withdrawal, transfusion reactions, drug reactions, thromboembolic events, and central fever.

All of these are diagnoses of exclusion. Therefore, management initially consists of empiric antimicrobial therapy with discontinuation of antimicrobials if an alternative cause of the fever is found. Central fever is more common in the NICU than other types of ICUs. A retrospective review of over 9000 patients admitted to an adult NICU over a 5-year period determined that onset of fever in first 72 h of NICU admission, subarachnoid, intraventricular hemorrhage, or brain tumor were features more likely to be associated with central fever (Hocker SE, Tian L, Li G, Steckelberg JM, Mandrekar JN, Rabinstein AA. Indicators of Central Fever in the Neurologic Intensive Care Unit. *JAMA Neurol*. 2013; 70(12):1499–1504. doi:10.1001/jamaneurol.2013.4354). In patients who meet these criteria, it may be safe to discontinue antimicrobial therapy if cultures are negative at 48–72 h.

Conclusion

NICU patients are at risk of several unique community and healthcare-acquired infections in addition to common HAIs experienced in other settings. The CSF space presents several pharmacologic and diagnostic challenges when

treating infections. Further, the effects of antibiotics on the CNS complicate treatment considerations. A thorough understanding of prevention techniques and special treatment considerations in this patient population is necessary for the neurointensivist.

References

- Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev.* 2010;23:858–83.
- Wilson JW, Estes LL. Mayo clinic. Mayo clinic antimicrobial therapy: quick guide. New York: Mayo Clinic Scientific Press; Informa Healthcare; 2008.
- Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clin Infect Dis.* 2004;38:864–70.
- Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol.* 2011;72:381–93.
- Halpenny D, O'Sullivan K, Burke JP, Torreggiani WC. Does obesity preclude lumbar puncture with a standard spinal needle? The use of computed tomography to measure the skin to lumbar subarachnoid space distance in the general hospital population. *Eur Radiol.* 2013;23:3191–6.
- Domingues R, Bruniera G, Brunale F, Manguera C, Senne C. Lumbar puncture in patients using anticoagulants and antiplatelet agents. *Arq Neuropsiquiatr.* 2016;74:679–86.
- Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;47:303–27.
- Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267–84.
- Seehusen DA, Reeves MM, Fomin DA. Cerebrospinal fluid analysis. *Am Fam Phys.* 2003;68:1103–8.
- Koski R, Van Loo D. Etiology and management of chronic meningitis. *US Pharm.* 2010;35(1):HS-2–HS-8.
- Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1–28.
- McClelland S 3rd, Hall WA. Postoperative central nervous system infection: incidence and associated factors in 2111 neurosurgical procedures. *Clin Infect Dis.* 2007;45:55–9.
- Levitz RE. Herpes simplex encephalitis: a review. *Heart Lung J Acute Crit Care.* 1998;27:209–12.
- Arciniegas DB, Anderson CA. Viral encephalitis: neuropsychiatric and neurobehavioral aspects. *Curr Psychiatr Rep.* 2004;6:372–9.
- 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. doi:10.1093/cid/ciw861.
- Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr. Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery.* 2002;51:170–81 **discussion 81–2**.
- Meredith FT, Phillips HK, Reller LB. Clinical utility of broth cultures of cerebrospinal fluid from patients at risk for shunt infections. *J Clin Microbiol.* 1997;35:3109–11.
- Domingues R, Fink M, Tsanaclis A, et al. Diagnosis of herpes simplex encephalitis by magnetic resonance imaging and polymerase chain reaction assay of cerebrospinal fluid. *J Neurol Sci.* 1998;157:148–53.
- Hart R, Kwentus J, Frazier R, Hormel T. Natural history of Kluver–Bucy syndrome after treated herpes encephalitis. *South Med J.* 1986;79:1376–8.
- VanLandingham KE, Marsteller HB, Ross GW, Hayden FG. Relapse of herpes simplex encephalitis after conventional acyclovir therapy. *JAMA.* 1988;259:1051–3.
- Wilson JW, Estes LL. Mayo clinic antimicrobial therapy quick guide. New York: Oxford University Press; 2011.
- Gombert ME, Landesman SH, Corrado ML, Stein SC, Melvin ET, Cummings M. Vancomycin and rifampin therapy for Staphylococcus epidermidis meningitis associated with CSF shunts: report of three cases. *J Neurosurg.* 1981;55:633–6.
- Conen A, Walti LN, Merlo A, Fluckiger U, Battagay M, Trampuz A. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. *Clin Infect Dis.* 2008;47:73–82.
- Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. *HERPES-CAMBRIDGE-.* 2004;11:57A–64A.
- Landry ML, Greenwold J, Vikram HR. Herpes simplex type-2 meningitis: presentation and lack of standardized therapy. *Am J Med.* 2009;122:688–91.
- McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. *Lancet.* 1980;1:787–91.
- De Bonis P, Lofrese G, Scoppettuolo G, et al. Intraventricular versus intravenous colistin for the treatment of extensively drug resistant *Acinetobacter baumannii* meningitis. *Eur J Neurol.* 2016;23:68–75.
- Johnson R. Aseptic meningitis in adults. In: Ted. W. Post, editor. UpToDate. Waltham, MA: UpToDate; 2016.
- Kupila L, Vuorinen T, Vainionpää R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology.* 2006;66:75–80.
- Mandell G, Bennett J, Dolin R, Tunkel A, Scheld W. Acute meningitis. Principles and practice of infectious disease. 5th ed. Philadelphia: Churchill Livingstone Co.; 2000. p. 959–97.
- Kennedy PG. Viral encephalitis: causes, differential diagnosis, and management. *J Neurol Neurosurg Psychiatry.* 2004;75(Suppl 1):i10–5.
- Brauer E, O'Horo JC. An acute, progressive encephalopathy. *WMJ.* 2012;111:66–7.
- Mir MA. Hantaviruses. *Clin Lab Med.* 2010;30:67–91.
- Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet.* 2015;386:995–1007.
- Hayden FG. Advances in antivirals for non-influenza respiratory virus infections. *Infl Other Respir Viruses.* 2013;7(Suppl 3):36–43.
- Chen AF, Wessel CB, Rao N. Staphylococcus aureus screening and decolonization in orthopaedic surgery and reduction of surgical site infections. *Clin Orthop Relat Res.* 2013;471:2383–99.
- Schweizer M, Perencevich E, McDanel J, et al. Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease Gram positive surgical site infections after cardiac or orthopedic surgery: systematic review and meta-analysis. *BMJ.* 2013;346:f2743.
- Chopra V, O'Horo JC, Rogers MA, Maki DG, Safdar N. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2013;34:908–18.
- O'Horo JC, Maki DG, Krupp AE, Safdar N. Arterial catheters as a source of bloodstream infection: a systematic review and meta-analysis. *Crit Care Med.* 2014;42:1334–9.

40. Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device-related bloodstream infection. I. Pathogenesis and short-term devices. *Clin Infect Dis*. 2002;34:1232–42.
41. Dissanaika S, Shelton M, Warner K, O’Keefe GE. The risk for bloodstream infections is associated with increased parenteral caloric intake in patients receiving parenteral nutrition. *Crit Care*. 2007;11:R114.
42. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
43. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355:2725–32.
44. O’Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52:e162–93.
45. O’Horo JC, Silva GL, Munoz-Price LS, Safdar N. The efficacy of daily bathing with chlorhexidine for reducing healthcare-associated bloodstream infections: a meta-analysis. *Infect Control Hosp Epidemiol*. 2012;33:257–67.
46. Safdar N, O’Horo JC, Ghufran A, et al. Chlorhexidine-impregnated dressing for prevention of catheter-related bloodstream infection: a meta-analysis*. *Crit Care Med*. 2014;42:1703–13.
47. Simmons S, Bryson C, Porter S. “Scrub the hub”: cleaning duration and reduction in bacterial load on central venous catheters. *Crit Care Nurs Q*. 2011;34:31–5.
48. Shorr AF, Cook D, Jiang X, Muscedere J, Heyland D. Canadian Critical Care Trials G. Correlates of clinical failure in ventilator-associated pneumonia: insights from a large, randomized trial. *J Crit Care*. 2008;23:64–73.
49. Cook D. Ventilator associated pneumonia: perspectives on the burden of illness. *Intensive Care Med*. 2000;26(Suppl 1):S31–7.
50. Dettenkofer M, Ebner W, Els T, et al. Surveillance of nosocomial infections in a neurology intensive care unit. *J Neurol*. 2001;248:959–64.
51. Safdar N, Crnich CJ, Maki DG. The pathogenesis of ventilator-associated pneumonia: its relevance to developing effective strategies for prevention. *Respir Care*. 2005;50:725–39 **discussion 39-41**.
52. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–111.
53. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:915–36.
54. Dudeck MA, Horan TC, Peterson KD, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2010, device-associated module. *Am J Infect Control*. 2011;39:798–816.
55. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:625–63.
56. Raz R, Schiller D, Nicolle LE. Chronic indwelling catheter replacement before antimicrobial therapy for symptomatic urinary tract infection. *J Urol*. 2000;164:1254–8.
57. Nicolle LE. Catheter-related urinary tract infection. *Drugs Aging*. 2005;22:627–39.