67 Management of Extracranial Infections

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Recommendations

Level I

There are no Level I recommendations.

Level II

There are a number of Level II recommendations for the majority of infection issues discussed in this chapter.

Level III

There are a large number of recently published major guidelines and their supporting literature giving support for the recommendations given in this chapter.

67.1 Overview

Infections acquired in the intensive care unit (ICU) are a major cause of morbidity and excess mortality. In the Extended Prevalence of Infection in Intensive Care (EPIC II) study, a prospective, point-prevalence study across 1265 ICUs in 75 countries, 51% of patients were considered infected, and 71% were receiving antibiotics (Vincent et al. 2009). The lungs were the most common focus of infections, followed by abdominal and bloodstream infections (BSI), and mortality rates in infected patients were twice those of non-infected (33.1% vs 14.8%). Distinguishing between community-acquired, hospital-acquired, and ICU-acquired infections was not attempted in EPIC II, but data from surveillance studies of ICU-acquired infections show a similar pattern and infection burden. The European Centre for Disease Prevention and Control (ECDC) 2018 report on ICU health care-associated infections (HAI) noted that 8.4% of patients staying in an ICU for more than 2 days presented with at least one ICU-acquired health care-associated infection, 6% pneumonias, 4% bloodstream infections (BSI), and 2% with urinary tract infections (UTIs). Close to all of the episodes of pneumonia and UTI were associated with intubation or indwelling catheters, respectively, and almost half of BSI episodes were catheter related (European Centre for Disease Prevention and Control 2018). Data on nosocomial infections in specific neuro-intensive care units are sparse, but show a similar spectrum and infection density with HAP, VAP, UTIs, and BSI dominating. Post-craniotomy and external drain-related infections constitute a smaller share, with variations

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in frequency depending on the case mix and length of stay in the units (Dettenkofer et al. 1999; Laborde et al. 1993).

Traumatic brain injury patients may be at particular risk for pneumonia. In a study from a large traumatic head injury database, pneumonia occurred in 41% of patients, developing at intermediary and late stages, 5–11 days after injury, and having a significant negative effect on overall outcome (Jürgen et al. 1992). Brain injury has been shown to induce immunosuppression in both animal and humans. It is thought to be the result of dysregulated brain-immune interactions, which may last for weeks and contribute to the infection proneness in brain injury patients of diverse etiologies (Busl 2018). The diagnosis of infection after brain injury is complicated by the high frequency of fever, being a manifestation of both infection and the brain injury per se. Fever was in one study reported in 87% of patients in the first week, correlated to severity of injury (Stocchetti et al. 2002).

A high exposure to antibiotics and long hospital stays put the neuro-intensive care unit patients at risk for *Clostridium difficile* infections (CDIs). CDI illness may range from mild self-limiting diarrhea to fulminant and life-threatening colitis. From 2003 onward, the emergence and spread of more virulent strains (BI/NAP1/027) associated with fluoroquinolone use have led to large outbreaks with more severe disease. After treatment in the intensive care unit, patients with reduced consciousness and neurologic deficits continue to be at risk for nosocomial infections, in particular HAP due to the increased risk of micro and macro aspirations. In the following sections, the prevention and management of the aforementioned infections will be discussed. External drain-related infections and suggestions for general empiric therapy for CNS infections in the TBI patients are discussed separately in Chap. 66.

Tips, Tricks, and Pitfalls

- Nosocomial infections are common in neuro-intensive care units, and pneumonia is by far the most common infection in brain injury patients peaking 5–7 days post-injury.
- Brain injury-induced immunosuppression, a result of dysregulated brain-immune interactions, contributes to the infection proneness in brain injury patients of diverse etiologies.
- Antibiotic treatment should be guided by microbial sampling results, and empiric treatment should be informed by regularly updated local hospital and ICU antibiograms.
- Treatment lengths are being shortened to one week for most ventilator-associated pneumonia (VAP), UTIs, and BSIs except *S. aureus* infections, aimed at reducing the growing concerns of antibiotic resistance pressure and risk of *C. difficile* infections.

67.2 Hospital- and Ventilator-Acquired Pneumonia

67.2.1 Prevention

Hospital-acquired pneumonia (HAP) is by far the most common nosocomial infection in general and neuro-intensive care units (Busl 2018; Vincent et al. 2009). It is defined as pneumonia occurring 48 h after hospital admittance. Ventilator-associated pneumonia (VAP) is a subgroup of HAP and defined as pneumonia occurring 48 h after intubation. The category health care-associated pneumonia (HCAP) has been abandoned, realizing that risk of pneumonia with antibiotic-resistant organisms is more dependent on local resistance patterns and recent antibiotic treatment than on residence in a health-care facility (Kalil et al. 2016). Further discussion will focus on VAP, as it is of particular concern in ICUs.

The risk of VAP is a function of (1) the length of invasive mechanical ventilation because cumulative risk increases with time, (2) the accumulation and leakage of oropharyngeal and gastric

fluids from above the endotracheal tube cuff, and (3) the microbial composition of these fluids, all potentially modifiable. Preventive strategies have therefore focused on preventing intubation choosing noninvasive ventilation whenever possible, and when unavoidable, using weaning and sedation protocols to keep ventilation time as short as possible (Blackwood et al. 2011). Because intubation as such poses an increased risk for VAP, a balance must be struck between too early extubation that may necessitate re-intubation and shortening of ventilation time. A strategy to reduce aspiration of gastric fluids has focused on positioning, keeping the patient in a semi-recumbent (45°) rather than supine position. This has however proven hard to achieve in real-life outside studies, because patients inevitably slide down the bed. Raising the bed to at least 30° is a recommended compromise (Hellyer et al. 2016). Reduction of leakage into the lungs can be achieved by keeping and regularly checking for correct cuff pressure and, increasingly, in patients expected to need more than very short mechanical ventilation, by utilizing endotracheal tubes with a designated suction catheter draining the otherwise inaccessible fluid pool above the cuff but underneath the vocal cords. In different meta-analyses, this strategy has been shown to both reduce length of ventilation and ICU stay and VAP and is recommended in VAP prevention bundle (Hellyer et al. 2016). Decontamination of oral secretions with chlorhexidine has been shown to decrease VAP incidence, however without reduction in mortality. In a recent meta-analysis, there was a signal of increased mortality (Price et al. 2014), and chlorhexidine mouthwash is no longer recommended in VAP prevention bundles. Selective oral decontamination (SOD) and selective digestive decontamination (SDD) with oral administration of broad-spectrum non-absorbable antibiotics have been found to reduce VAP incidence, but studies have mostly been conducted in settings with a low prevalence of resistant microbes (de Smet et al. 2009). Together with increasing concerns of antibiotic usage-driven resistance development, a modest effect on mortality with a high number needed to treat (NTT), and lack of data from countries with higher prevalence of resistance, SOD and SDD have not been widely adopted for the prevention of VAP.

67.2.2 Diagnosis

New lung infiltrate, new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation are the classic clinical criteria for diagnosis. There is insufficient data to support routine use of invasive airways sampling with quantitative cultures thresholds (10^4 colony forming units/mL for BAL) used as a trigger to withhold or stop antibiotics. Clinical criteria alone may however overestimate the incidence of VAP, and antibiotic discontinuation in patients with suspected VAP whose invasive quantitative culture results are below the diagnostic threshold for VAP may decrease unnecessary antibiotic use and reduce antibiotic-related adverse events. There is no evidence that this strategy worsens outcomes (Kalil et al. 2016). Noninvasive or invasive microbial (when performed) sampling should always be used to guide and adjust antibiotic therapy. Although only a minority of VAP episodes are accompanied with bacteremia, blood cultures should be performed as part of diagnostic workup, not the least to confirm or exclude other infectious complications. Biomarkers such as CRP and PCT should *not* be used to overrule a clinical decision to initiate therapy, but can be useful in the re-evaluation of the diagnosis and stopping or shortening of antibiotic therapy.

67.2.3 Antibiotic Treatment

Empiric antibiotic treatment for VAP should consist of antibiotics with activity against both *S. aureus* and *Pseudomonas*, such as piperacillin/tazobactam and carbapenems, with de-escalation to narrower antibiotics when possible according to culture results (Kalil et al. 2016). An alternative carbapenem-sparing "escalation" strategy is preferable if local antibiograms show a low occurrence of *Pseudomonas* and extended-spectrum beta-lactamase (ESBL)-producing

microbes. In an escalation strategy, empiric therapy is commenced with a third-generation cephalosporin and escalated to a carbapenem only if necessitated by culture results *and* poor response to therapy, as cultures do not necessarily discriminate between infections and colonization, leading to many false positives and antibiotic overtreatment. The need for coverage for MRSA or multi-drug-resistant organisms is highly dependent on local resistance patterns. Major guidelines emphasize the need to establish local resistance surveillance preferably both at hospital and ICU levels and regularly communicate antibiogram results to clinicians.

A recent Cochrane analysis did not find evidence for improved outcomes with antibiotic combination therapy (Arthur et al. 2016). Unless necessitated by high local resistance patterns risking under-coverage with monotherapy, combination therapy is neither recommended for empiric nor directed therapy for hard-to-treat organisms such as *Pseudomonas*. A fixed short-course treatment length of 7 days was not inferior to 10–14 days in recent meta-analyses of six RCTs (Pugh et al. 2015) and is now recommended length of treatment (Kalil et al. 2016). Longer courses may reduce relapse rates in VAP due to *Pseudomonas* and other non-fermenting microbes, but the supporting evidence is weak. In "possible" but low probability VAP, stopping antibiotics after 3 days may be possible (Pugh et al. 2015).

67.3 Intravascular Catheter-Related Infections (CRBSI)

Indwelling catheters are a leading cause of bloodstream and health care-associated infections in general, with ICU and chronically ill cancer patients at particular risk. Catheter-related blood stream infections (CRBSI) are associated with increased morbidity and mortality, but tend to be overdiagnosed, leading to unnecessary catheter removals (Raad et al. 2007). The clinical diagnosis is challenging. Fevers and chills in ICU patients are nonspecific, and though catheter insertion site inflammation has a high specificity, the sensitivity for CRBSI is very poor (Safdar and Maki 2002). Probable CRBSI can be diagnosed with positive peripheral blood culture when there is no other apparent source of the bloodstream infection, and findings of *S. aureus*, coagulase-negative staphylococci, and *Candida* species should increase suspicion (Kiehn and Armstrong 1990). A definite diagnosis requires finding the same microorganism from the catheter tip if removed or that blood culture drawn from the catheter becomes positive ≥2 h *before* simultaneously drawn blood culture from a peripheral vein (Rijnders et al. 2001). Unless patients are hemodynamically unstable or otherwise appearing severely ill, catheters need not be removed in suspected CRBSI, but results of blood cultures can be awaited before management decisions. In general, short-term catheters (<14 days) should be removed. Long-term catheters can be managed with catheter retention and antibiotic lock solutions depending on the organism. Isolation of *S. aureus*, gram-negatives, enterococci, and *Candida* generally requires catheter removal if feasible, whereas coagulase-negative staphylococci can be treated with a short 7–10-day antibiotic course or with catheter removal without antibiotic therapy if not longer needed. For more details on the multiple variables determining management, more comprehensive guidelines should be consulted (Mermel et al. 2009).

S. aureus bacteremia carries a risk of metastatic spread by bloodstream seeding, in particular with bacteremia persisting >72 h in spite of therapy. Blood cultures should thus be repeated daily until negative and deep-seated infectious complications, foremost endocarditis and skeletal infections, should be sought when appropriate. If ruled out, a 14-day antibiotic course is sufficient for uncomplicated *S. aureus* bacteremia, but the jury is still out on the safety of even shorter durations. Vancomycin is the preferred empiric antibiotic when MRSA is prevalent and also the safest empiric option for coagulase-negative staphylococci, but beta-lactam antibiotics such as cloxacillin are more potent and preferred for susceptible staphylococci. The need for empiric gram-negative coverage must be decided on a case-by-case basis depending on the host factors and severity of presentation.

67.4 Urinary Tract Infections

Despite figuring prominently on the list of nosocomial infections, notably in the aforementioned EPIC II study (Vincent et al. 2009), the true magnitude of ICU-acquired UTIs is hard to discern. Clinical UTI diagnosis is challenging in the ICU, with a near-universal use of urinary catheters and the resulting unreliability of clinical symptoms of dysuria, pollakisuria, and urinary retention in their presence. Inability of communicating symptoms in sedated and ventilated patients adds to diagnostic uncertainty (Shuman and Chenoweth 2010). The placement of a catheter leads to universal bacterial colonization within few days of insertion, and dipstick tests for leukocytes and protein frequently become positive in the presence of a catheter. The diagnosis thus becomes one of exclusion when no other source of infection can be found. In the ICU patient, this is further complicated by the difficulty of differentiating infectious from noninfectious causes of inflammation, with both being able to cause fever, elevated inflammatory markers, and hemodynamic instability. A more confident diagnosis can be made with a close temporal relation between the placement of the catheter and a presumed infectious episode, the rare UTI episodes which are blood culture positive, or when a CT scan reveals pyelonephritis or obstructions. The most important preventive measures are avoidance of catheterization whenever possible and limiting the duration when catheterization is unavoidable (Lo et al. 2008).

Asymptomatic bacteriuria should not be treated with antibiotics. When UTIs are treated in catheterized patients, the catheter should be replaced if it has been in place for more than 7–14 days, as the formation of a biofilm may impair clearance of infection. There is increasing evidence to support a shorter antibiotic duration of 7 days, also in bacteremic UTIs, at least in patients who are rapidly stabilized (van Nieuwkoop et al. 2017; Yahav et al. 2018). As in the case of VAP, local resistance data should guide antibiotic therapy.

Enterobacteriaceae are by far the most important organisms, and third-generation cephalosporins or penicillins with increased gram-negative spectrum are reasonable options, with the need for added initial coverage for *Pseudomonas* or ESBL-producing microbes with a carbapenem depending on the severity of presentation, host factors, and local antibiograms. Because patients who are at increased risk of developing organ failures and renal failure in particular congregate in the ICU, aminoglycosides, otherwise excellent antibiotics for UTIs, are less attractive.

67.5 *Clostridium difficile* Infections

CDI is a major cause of health care-associated infections (HAI) and the most common cause of antibiotic associated diarrhea, accounting for 10–25% of cases and nearly all cases of pseudomembranous colitis (Bartlett 1994). *C. difficile* is acquired by the fecal-oral route from asymptomatic carriers or patients, via transiently colonized hands of health personnel, or via contaminated surfaces and equipment. Antibiotic disruption of the gut flora promotes transition from colonization to symptomatic disease, and both length of treatment and exposure to multiple antibiotics increase the risk. Certain antibiotics, notably quinolones, have been linked to the spread of more virulent strains like the hypervirulent ribotype 027. However, in clinical practice, any antibiotic can cause CDI and must therefore be prescribed with CDI risk in mind. Broad-spectrum antibiotics are nevertheless recognized to pose the greater risk, and antibiotic stewardship with feedback on appropriate use of narrow-spectrum antibiotics has been shown to significantly reduce CDI incidence (Fowler et al. 2007). Nonmodifiable risk factors are high age, general debility, and serious underlying disease. Chemotherapy and neutropenia also promote CDIs (Guh and Kutty 2018). The entry point for the clinical diagnosis is diarrhea, defined as ≥3 loose stools in 24 h. Diarrhea can be profuse in colitis but may be absent in seriously ill patients with paralytic ileus and toxic

megacolon. Fever, abdominal pain, and leukocyte count >15 × 10^9 cells/L are markers of severe disease, and values >25 × 10^9 cells/L with lactate level ≥5 mmol/L are indicators of need for early surgery. Tests detect either the presence of *C. difficile* in stool (GHD), toxins in stool (toxin EIA), or genes for toxin production (NAATS). Different test combinations are in clinical use, but when testing is restricted to appropriate patients, NAATS alone, or after screening for GHD, is recommended. Repeat testing does not increase sensitivity. If CDI is strongly suspected despite a negative test, sigmoidoscopy may be diagnostic. Tests remain positive long after clinical cure and retesting as treatment control is not indicated. Treatment recommendations have recently been updated by the Infectious Diseases Society of America (IDSA) (McDonald et al. 2018). Ongoing antibiotic therapy should be discontinued if not jeopardizing recovery from other infections and may suffice in mild disease. Vancomycin (125 mg × 4 p.o) or fidaxomicin (200 mg × 2 p.o) for 10 days is recommended over metronidazole, also in non-severe disease. In fulminant cases, and if ileus is present, i.v. metronidazole 500 mg × 3 should be added. In the latter, rectal instillation of vancomycin (500 mg × 4) may also be administered. Recurrences are common, and fecal microbiota transplant (FMT) is highly efficacious and should be considered after more than two recurrences. A novel monoclonal toxin-binding antibody (bezlotoxumab) has recently been approved to reduce risk of recurrences in high-risk patients, and a severely ill neurointensive care unit patient would arguably fit that category. Bezlotoxumab must be given together with conventional CDI therapy as it does not interrupt ongoing infection.

67.6 Specific Pediatric Concerns

With few exceptions (fluoroquinolones, tetracyclines) where age limitations for usage in children are given, most antibiotics can safely be administered respecting weight-based dosage recommendations. There are very limited data for FMT in children.

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