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Nosocomial Infections in the Intensive Care Unit

■ CATHETER-ASSOCIATED SEPSIS

Catheter-associated sepsis is defined as bloodstream infection due to an organism that has colonized a vascular catheter. Approximately 5% of patients with indwelling vascular catheters (uncoated) will develop bloodstream infection (≈10 infections per 1000 catheter days). The incidence of catheter-associated sepsis increases with the length of time the catheter is in situ, the number of ports, and the number of manipulations. Approximately 25% of catheters become colonized (>15 colony-forming units, CFU) and approximately 20% to 30% of colonized catheters will result in catheter sepsis. *Staphylococcus aureus* and coagulase-negative staphylococci are the most common infecting (and colonizing) organisms, followed by enterococci, gram-negative bacteria, and *Candida* species. Antibiotic-coated catheters significantly reduce catheter colonization and catheter-associated bloodstream infection. Femoral catheters *are not associated* with a higher infection rate. Similarly, neither the type of occlusive dressing nor the frequency of dressing change affects the incidence of catheter-associated sepsis.

Replacement of a colonized catheter over a guidewire is associated with rapid colonization of the replacement catheter. If catheter sepsis is strongly suspected, the catheter must be changed to a *new* site, with withdrawal blood cultures and culture of the catheter tip. In patients with limited venous access or in patients in whom catheter sepsis is less likely, the catheter can be changed over a guidewire; however, withdrawal blood cultures and culture of the catheter tip must be performed and the catheter removed if the cultures are positive.

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The *routine* replacement of central venous catheters is no longer recommended. Central venous catheters should remain in situ until

- Purulent discharge, cellulitis, or erythema develops at the puncture site
- Catheter malfunction
- Any positive blood cultures since the line was inserted
- Septic clinical pattern with no other obvious source of infection

However, it may be prudent to replace a *multilumen catheter* after 10 to 14 days even if the above criteria are not met. All lines that are inserted in emergent situations under conditions that are not strictly aseptic should be removed within 24 hours and replaced at a new site. Patients with colonized catheters (>15 CFU), with negative blood cultures, and no signs of infection should not be treated with antibiotics. All catheters removed from potentially septic patients should be cultured (tip and intracutaneous segment).

■ NOSOCOMIAL SINUSITIS

Nosocomial sinusitis is a common problem in ICU patients. Risk factors include nasotracheal tubes, nasogastric tubes, and patients nursed in a supine position. Almost all patients with nasotracheal tubes will develop opacification of their maxillary sinuses within 3 to 5 days of intubation. Approximately a third of these cases will prove to have infectious sinusitis. It is therefore desirable that patients in whom the length of nasotracheal intubation is expected to exceed 3 days should have all nasal tubes removed and reinserted through the mouth.

Diagnostic Approach

- Computed tomography CT scan of the paranasal sinuses should be performed in patients with a purulent nasal discharge or an offensive nasal discharge, and in patients who have an undiagnosed fever with risk factors for developing sinusitis.
- Plain x-rays are of ***no value*** in diagnosing nosocomial sinusitis.
- Not all patients with radiological sinusitis, i.e., opacification of the sinuses, have infectious sinusitis. Patients who have opacification of the maxillary sinuses should undergo transnasal puncture and aspiration (the nasal mucosa must be thoroughly cleaned before culture, to limit contamination). Only about 30% to 40% of patients with opacification of their maxillary sinuses will have positive cultures with purulent aspirates.

Microbiology of Nosocomial Sinusitis

- Similar spectrum to that of nosocomial pneumonia
- Often polymicrobial
- *Pseudomonas* spp.
- *Acinetobacter* spp.
- *S. aureus*
- *Candida* spp.
- *Hemophilus influenzae*
- Anaerobes

Treatment of Infectious Sinusitis

- Remove all nasal tubes.
- Treat with broad-spectrum antibiotics, tailored to the sinus aspirate Gram stain and culture.
- Local vasoconstrictors and nasal toilet.

■ CANDIDA INFECTIONS IN THE ICU

Candida species are important opportunistic pathogens in the ICU. The Centers for Disease Control National Nosocomial Infection Study reported that 7% of all nosocomial infections were due to candidal species. Patients with candidal infection have been shown to have a longer hospital stay and higher mortality compared to case-matched controls.

It is important to realize that *Candida* species are constituents of the normal flora in about 30% of all healthy people. Antibiotic therapy increases the incidence of enteric colonization by up to 70%. It is probable that *most ICU patients become colonized with* Candida *species soon after admission. Not all patients colonized with* Candida *will become infected with* Candida. Non-neutropenic patients with isolation of *Candida* species from pulmonary samples (tracheal aspirates, bronchoscopic, or blind sampling methods), even in high concentrations, are unlikely to have invasive candidiasis. Indication for initiation of antifungal therapy in these patients should be based on histologic evidence or identification from sterile specimens. Similarly, isolation of *Candida* species from the urine in ICU patients with indwelling catheters usually represents colonization rather than infection. Although candiduria may be observed in up to 80% of patients with systemic candidiasis, most patients with candiduria do not have disseminated infection or upper urinary tract infection. The initial treatment for candiduria consists of the elimination of factors contributing to its occurrence, such as indwelling catheters, immuno-

suppression, or broad-spectrum antibiotics. These options are clearly not possible in most ICU patients. The indwelling catheter should be changed with close observation of the patient. The role of amphotericin B bladder irrigations in these patients is unclear. In patients with pyuria, worsening renal function, and/or systemic signs of infection, it may be prudent to perform blood cultures as well as renal imaging.

The factors predisposing to systemic *Candida* infection include the following:

- Broad-spectrum antibiotics are the single most important risk factor.
- Indwelling intravenous and urinary catheters.
- Parenteral alimentation.
- ICU stay >7 days.
- Perforated viscus.

Clinical features and diagnosis of systemic fungal infections:

- The clinical diagnosis of systemic candidal infection is particularly difficult in the ICU patient. On the one hand, the clinical picture may be indistinguishable from that of a bacteremia with an acute onset of high fever, rigors, tachycardia, and hypotension. Conversely, a low-grade fever or hypothermia may be the only manifestation.
- *Candida* may infect the eyes, causing an endophthalmitis. Funduscopy should therefore be part of the daily examination of the ICU patient.
- Although the respiratory tract is frequently colonized, invasive pulmonary candidiasis is uncommon.
- Approximately 10% of patients will present with a macular rash or discrete skin nodules.
- Other features of systemic candidiasis may include a myocarditis, meningitis, cerebral microabscesses, myositis, endocarditis, osteomyelitis, and arthritis.
- The ante mortem diagnosis of systemic candidiasis is exceedingly difficult, and therefore this diagnosis requires a high index of suspicion (an ante mortem diagnosis of candidal infection is made in only 15% to 40% of patients with systemic candidiasis proven at autopsy).
- Only about 50% of patients with systemic candidiasis at postmortem have ante mortem positive blood cultures.
- Serology has been shown to be of little value in the diagnosis of systemic candidiasis, as have assays for the detection of circulating candidal antigens.

- An association has been demonstrated between the number of sites colonized with *Candida* and the occurrence of invasive candidiasis in high-risk patients.
- A single positive blood culture is highly predictive of candidal infection and should never be considered a contaminant.

Management

- The initial treatment of candidal infections should include removal of all possible foci of infection, including removal of intravascular lines and urinary catheters.
- Candidemia may resolve spontaneously after removal of an intravascular catheter. There is, however, increasing evidence that metastatic foci of infection may develop in patients who do not receive systemic antifungal therapy.
- Drainage is an integral part of the management of patients with intra-abdominal suppuration in whom *Candida* is isolated from a peritoneal culture.
- Amphotericin B has long been the standard treatment for candidemia. However, recent data suggest that fluconazole and amphotericin B may be equally efficacious in the treatment of non-neutropenic patients with candidemia. C. *krusei*, however, is intrinsically resistant to fluconazole.

Drug Therapy

Amphotericin B

- A total dose of 6 to 8 mg/kg is recommended, although some authors have recommended a total dose as high as 2 g. After a 1-mg test dose, amphotericin B is usually given in a daily dose of 0.5 mg/kg over a 2-week period. A daily dose of 1 mg/kg may be given, which is usually well tolerated. Amphotericin B should be given as an infusion in 5% dextrose in water over 8 hours.
- Amphotericin B is associated with reversible nephrotoxicity. Fluid and sodium loading may reduce incidence of nephrotoxicity. The dosage should not be reduced in patients with preexisting renal dysfunction, as only a small fraction of the drug is excreted by the kidney.
- Amphotericin B is associated with a proximal renal tubular acidosis and a profound loss of Na^+, K^+, and Mg^{++} in the urine. These electrolytes must be aggressively replaced.
- Fever, chills, and headaches commonly occur at the initiation of therapy and are probably mediated by the release of tumor necrosis factor and interleukin-1. These side effects can be mini-

mized by infusing the drug slowly and by premedication with antihistamines and nonsteroidal anti-inflammatory agents.

- Liposomal amphotericin B has been demonstrated to be at least as effective as conventional amphotericin B. However, with the liposomal preparation, significantly fewer patients experience infusion-related fever (17% vs. 44%), chills or rigors (18% vs. 54%), and other reactions, including hypotension. Nephrotoxic effects are significantly less frequent among patients treated with liposomal amphotericin B than among those treated with conventional amphotericin B (19% vs. 34%).

Fluconazole

- Loading dose: 800 mg.
- Maintenance dose: 400 mg as a single daily dose. The dose must be adjusted according to the calculated creatinine clearance.

Prophylaxis

- Delaying or preventing oropharyngeal, gut, and skin colonization with *Candida* species may prevent systemic infection.
- Ketoconazole has been shown to reduce the incidence of candidal infections in high-risk surgical patients.
- It is likely that fluconazole may prove to be effective in preventing infection with *Candida* species in high-risk ICU patients. The role of such prophylaxis has yet to be determined.

■ *CLOSTRIDIA DIFFICILE* COLITIS

Clostridia difficile is the agent that causes pseudomembranous colitis and antibiotic-associated diarrhea and has become a common nosocomial pathogen. Approximately 20% of all hospitalized patients become "infected" with *C. difficile*, of whom only about a third develop diarrhea. *Clostridia difficile* is responsible for virtually all cases of pseudomembranous colitis and for up to 20% of cases of antibiotic-associated diarrhea without colitis. The spores of *C. difficile* are easily transmitted by the oral–fecal route from one patient to the next and may become widely disseminated throughout a hospital. Although reported in the preantibiotic era, antibiotics are the most important risk factor leading to colonization and colitis. The normal colonic flora resists colonization by *C. difficile*; however, broad-spectrum antibiotics with activity against enteric bacteria disrupt the normal flora, allowing colonization. Approximately 25% of hospital-

ized adults recently treated with antibiotics will become colonized with *C. difficile*. Once established in the colon, pathogenetic strains of *C. difficile* produce two exotoxins (toxin A and B) that cause diarrhea and colitis.

Antimicrobial Agents That Induce *C. difficile*

Frequent Induction

- Ampicillin and amoxicillin
- Cephalosporins
- Clindamycin

Infrequent Induction

- Tetracyclines
- Sulphanomides
- Erythromycin
- Chloramphenicol
- Trimethoprim
- Quinolones

Rare or no Induction

- Parenteral aminoglycosides
- Metronidazole
- Vancomycin

The majority of hospital patients infected with *C. difficile* are asymptomatic. *Clostridia difficile* infection commonly presents as diarrhea that is mild to moderate, sometimes accompanied by lower abdominal cramping. Symptoms usually begin during or shortly after antibiotic therapy but are occasionally delayed for several weeks. Severe colitis without pseudomembrane formation may occur with profuse, debilitating diarrhea, abdominal pain, and distention. Common systemic manifestations include fever, nausea, anorexia, and malaise. A marked neutrophilia and increased numbers of fecal leukocytes are common. Pseudomembranous colitis is the most dramatic manifestation of *C. difficile* infection; these patients have marked abdominal and systemic signs and symptoms and may develop a fulminant and life-threatening colitis.

Stool assay for toxins A or B are the main clinical tests used to diagnose *C. difficile* infection. The gold standard test is the tissue culture cytotoxicity assay. This test has a high sensitivity (94% to 100%) and specificity (99%). The major disadvantages of this test are its high expense and the time needed to complete the assay (2 to 3 days). There-

fore, this test is no longer routinely performed. Toxin enzyme-linked immunosorbentassay (ELISA) tests are less sensitive (70% to 90%) than the cytotoxicity test but demonstrate excellent specificity (99%) and can be rapidly processed, and they have largely replaced the cytotoxicity assay. It is suggested that two stool specimens be examined for leukocytes and toxin (ELISA test). Should the ELISA be negative and a high index of suspicion for *C. difficile* exist, the following are recommended: (1) sigmoidoscopy, and/or (2) cytotoxicity assay, and/or (3) CT scan of the abdomen looking for thickened colonic wall.

Management

Treatment of asymptomatic carriers is not recommended. Antidiarrheal agents that reduce intestinal peristaltic activity may delay clearance of the organism and are therefore not recommended. The first step in managing patients is to discontinue antibiotic therapy, if possible. Patients with mild diarrhea may not require any other treatment. However, in the ICU, this is often not possible, and therefore specific therapy aimed at eradicating *C. difficile* is necessary. The treatment options for *C. difficile* infection remain limited, although promising agents are currently being assessed. Metronidazole is the first-line drug of choice for those patients requiring specific *anti-C. difficile* treatment; oral metronidazole (250 mg, q6h). Much of the interest in alternative therapies has centered on the difficult management issues posed by patients with multiple symptomatic recurrences of *C. difficile* infection. However, it is now clear that the majority of these episodes are due to reinfections with new *C. difficile* strains and not relapses caused by the original bacterium. Hence, the true efficacy of the alternative regimens remains unclear. Individuals susceptible to *C. difficile* reinfections need to be protected from exposure to *C. difficile* until their bowel flora recovers. While several biotherapeutic approaches to the treatment and prevention of *C. difficile* infection have been described, few controlled data are available. Oral vancomycin (125 mg, q6h) is reserved for patients who cannot tolerate or who do not have a response to metronidazole. Patients who cannot tolerate oral medication can be treated with intravenous metronidazole. In general, sigmoidoscopy should be avoided in severe colitis because of the risk of perforation.

■ ACALCULOUS CHOLECYSTITIS

Acalculous cholecystis, while relatively uncommon, is an important "infection" in critically ill patients. It is often unrecognized and is

therefore potentially life threatening. Only about 10% of cases of acute cholecystitis in the ICU are associated with gallstones, which are usually considered an incidental finding rather than the cause. Critically ill patients have multiple factors that increase their risk for developing this complication.

The diagnosis of acalculous cholecystitis is often exceedingly difficult and requires a high index of suspicion. Pain in the right upper quadrant is the finding that most often leads the clinician to the correct diagnosis, but it may frequently be absent. Nausea, vomiting, and fever are other associated clinical features. The clinical findings and laboratory workup in patients with acalculous cholecystitis are, however, often nonspecific. The most difficult patients are those recovering from abdominal sepsis who deteriorate again, misleadingly suggesting a flare-up of the original infection.

Radiological investigations are required for a presumptive diagnosis. Ultrasound is the most common radiologic investigation used in the diagnosis of acalculous cholecystitis, with a sensitivity and specificity of greater than 80% and 90%, respectively (features include increased wall thickness, intramural lucencies, gallbladder distention, pericholecystic fluid, and intramural sludge). Wall thickness of ≥3 mm is reported to be the most important diagnostic feature on ultrasound examination, with a specificity of 90% and a sensitivity of 100%. In ICU patients, hepatobiliary scintigraphy has a high false-positive rate (>50%), limiting the value of this test. However, a normal scan virtually excludes acalculous cholecystitis. CT scanning has been reported to have a high sensitivity and specificity; however, no prospective studies have been performed comparing ultrasonography with CT scanning in the diagnosis of acalculous cholecystitis.

Management

Once the presumptive diagnosis has been made, the management consists of both medical and interventional therapies. The gallbladder either needs to be drained or removed surgically. Percutaneous cholecystomy is usually the initial procedure of choice, with interval cholecystomy performed when (and if) the patient is considered a suitable surgical candidate. It should be noted that acalculous cholecystitis is primarily a "noninfectious" disease, with bacterial invasion a secondary event (at least a third of patients have sterile bile). However, antibiotics with adequate gram-negative coverage are usually prescribed.

■ VENTILATOR-ASSOCIATED PNEUMONIA (SEE CHAPTER 10)

■ URINARY TRACT INFECTION (SEE CHAPTER 43)

■ NOSOCOMIAL CYTOMEGALOVIRUS (AND HERPESVIRUS) INFECTION IN "NONIMMUNOCOMPROMISED" ICU PATIENTS

Primary cytomegalovirus (CMV) infection usually takes place in childhood, after which the virus remains latent. Depending on the country of residence and social status, between 50% and 100% of the population harbor CMV and are CMV seropositive (immunoglobulin G). In immunocompromised patients, such as those with acquired immune deficiency syndrome and immunosuppressed transplant recipients, the virus becomes reactivated; CMV infections in these patients are an important cause of morbidity and death. CMV may, however, become reactivated during other immunosuppressive illnesses. It is well known that critical illness, particularly sepsis and the systemic inflammatory response, results in perturbations of the immune system. Of particular significance, it has been suggested that tumor necrosis factor may play a role in activating CMV. However, these patients are not classically considered immunocompromised, and CMV infection is not considered a pathogen in these patients. This postulate appears to be incorrect. A number of studies have documented active CMV infections in nonimmunocompromised ICU patients. While the presence of viral antigen and DNA may merely represent carriage of the virus, histologic documentation of CMV pneumonitis has been reported in a number of these patients. CMV pneumonitis should therefore be considered a cause of ventilator-associated pneumonia. Papazian and co-workers reported 18 cases of CMV pneumonitis in 36 (48%) nonimmunocompromised ICU patients with acute respiratory distress syndrome (ARDS) who underwent open lung biopsy. CMV pneumonitis should therefore be considered in patients with nonresolving ARDS and in septic ICU patients who develop ventilator-associated pneumonia. Kutza and colleagues have elegantly demonstrated that the number of CMV-positive peripheral leukocytes increases after about the fifth day of critical illness, peaks at the height of the illness and then declines with recovery. These data suggest that CMV reactivation and CMV infection should be considered in chronic critically ill (~7 to 10 days) ICU patients. It is likely that other herpesviruses may become reactivated in critical illness. Tuxen and colleagues reported the presence

of herpes simplex tracheobronchitis in 14 of 46 (30%) patients with ARDS.

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