Hospital-Acquired Infections

Section I

Catheter-Related Bloodstream Infections

ANDREW DAVIS ASSAF, ELIZABETH WENQIAN WANG, and ISSAM I. RAAD

INTRODUCTION

In 1929, Werner Forssmann (1) inserted the first reported central venous catheter (CVC) in a human being. Sven-Ivar Seldinger, in 1959, described and performed the Seldinger technique, still widely used today in modified form, that facilitated safe access to the central venous system via a catheter (2). Today, the use of CVCs has expanded in the inpatient and outpatient settings, and particularly in the critically ill patients and patients with invasive cancers; a total of more than 13 million CVCs are inserted annually worldwide, with a gap of more than $26,000 between total cost $33,000 and $75,000 per individual episode of CRBSI in ICU patients, with a gap of more than $26,000 between total cost and reimbursement (7). One study suggested an average of $45,814 per CRBSI with a total annual cost that exceeds $45 million per CRBSI with a total annual cost that exceeds $45 million per patient and an attributable mortality ranging from 12% to 25% (3,6). Therefore, between 48,000 and 100,000 patients may die from CRBSI annually, of which 9,600 to 20,000 occur in the ICU alone. The average cost of treatment ranges between $33,000 and $75,000 per individual episode of CRBSI in ICU patients, with a gap of more than $26,000 between total cost and reimbursement (7). One study suggested an average of $45,814 per CRBSI with a total annual cost that exceeds $18 billion (8). Non-ICU patients, especially the immuno-compromised hosts with CVCs in place, are at significant risk. These infections are often difficult to diagnose, treat, and prevent; this chapter will concentrate on these aspects of CRBSI.

PATHOGENESIS

Diagnosis, treatment, and prevention of CRBSIs are based on our understanding of the pathogenesis of these infections. For short-term, nontunneled, noncuffed, multilumen catheters—which make up 90% of CRBSIs—the skin insertion site is the source of the colonization; organisms migrate along the external surface of the catheter and through the subcutaneous layers and infect the catheter tip (9,10). For long-term catheters—the cuffed, tunneled, silicone catheters, Hickman or Broviac—or implantable devices, the lumen of the hub or belt of the port is the primary source of entry (11,12). Micro-organisms are introduced via the hands of medical personnel while manipulating the hub during, for example, flushing and drawing of blood (11–13). Of note, colonization is universal after insertion of a CVC, can occur as early as 1 day after insertion, and is quantitatively independent of a catheter-related infection (11).

These sources explain the prevalence of Staphylococcus aureus, coagulase-negative Staphylococcus, enterococci, nonenteric hospital-acquired gram-negative bacilli (GNB) (Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Acinetobacter spp., mycobacteria, and Candida spp. as primary organisms of CRBSI (14). Secondary seeding of the CVC, whereby organisms become blood-borne and colonize the catheter, has been suggested (15,16) to the point of recommending treatment of urinary tract infections prior to CVC insertion to prevent a potential CRBSI (17); however, its role in CRBSI has not been corroborated (17). Contamination of the infusate or additives, such as contaminated heparin flush, is a rare cause of colonization and infection of vascular devices (18–20). The contamination of infusate takes place during the manufacture, solution preparation, or handling by health care worker, and leads to a cluster of bloodstream infections (BSIs) with the same—often unusual—organism. The nationwide outbreaks of Enterobacter agglomerans and Enterobacter cloacae in 1971 led to widespread changes and surveillance at industry, hospital, and state and federal levels. Even though TPN has been historically associated with CRBSI mainly due to Candida spp., there is some evidence suggesting that the etiology is mainly polymicrobial (21). Some studies have suggested that a more acidic TPN solution might suppress bacterial growth and skew the etiology toward Candida spp., which is not suppressed by changes in the content pH (22).

The second step in the pathogenesis of CRBSI is the ability of some microbes to form a biofilm of extracellular, polysaccharide-rich slime (23), promoting the adhesiveness of the bacteria to the surface of the CVC. Biofilms form on the external surface of short-term catheters and the internal surface of long-term catheters—that is, those with a dwell time of at least 30 days. This biofilm enables bacteria not only to adhere to the surface of the catheter, but also to resist antibiotics, such that biofilm eradication becomes a difficult task (24). Another factor promoting adherence is the thrombin layer that covers both surfaces of a catheter during its insertion; the rich composition...
of the host’s own blood components enables S. aureus, for example, to adhere to fibrinogen, coagulase-negative Staphylococcus to fibronectin, and Candida spp. to fibrin (25–29).

There has been a correlation of catheter site and risk of infection in the past; however, one study has shown that there is no difference in the risk of CRBSI when comparing the femoral and internal jugular sites (30) and that concept has been enforced in the CDC guidelines (31). Avoiding the use of the femoral is for reasons other than infections such as thrombosis (31). In general, the preferential site for nontunneled CVCs is the subclavian vein (31). In terms of catheter site dressings, the CDC recommends using a sterile gauze or sterile transparent impregnated dressings is acceptable for short-term catheters provided the patient is older than 2 months (31).

**TABLE 88.1.1 Definitions of Catheter-related Bloodstream Infections (CRBSI)**

<table>
<thead>
<tr>
<th>PROBABLE CRBSI</th>
<th>DEFINITE CRBSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical manifestations of infection (fever &gt;38°C, chills/rigors, or hypotension)</td>
<td>• Probable CRBSI criteria outlined above with any of the following:</td>
</tr>
<tr>
<td>• No apparent source of the sepsis/bloodstream infection other than the catheter</td>
<td>• Differential quantitative blood cultures with 5:1 ratio of the same organism isolated from blood drawn simultaneously from the central venous catheter (CVC) and peripheral vein or</td>
</tr>
<tr>
<td>• Common skin organisms (e.g., coagulase-negative staphylococci) isolated from two blood cultures from patients with intravascular device or a known pathogen (Staphylococcus aureus or Candida) isolated from a single blood culture</td>
<td>• Differential positivity time (positive result of culture from a CVC is obtained at least 2 hr earlier than positive result of culture from peripheral blood) or</td>
</tr>
<tr>
<td></td>
<td>• Positive quantitative skin culture whereby the organism isolated from an infected insertion site is identical to that isolated from blood or</td>
</tr>
<tr>
<td></td>
<td>• Isolation of the same organisms from the peripheral blood and from a quantitative or semi-quantitative culture of a catheter segment or tip</td>
</tr>
</tbody>
</table>

**CLINICAL MANIFESTATIONS**

Clinical manifestations of CRBSIs can be divided into two categories: local and systemic. Local manifestations include erythema, edema, tenderness, and purulent discharge. These signs and symptoms are neither sensitive nor specific, and cannot be relied on to identify catheter colonization or CVC-related BSI. On the one hand, they could be completely absent, especially in immunocompromised and neutropenic patients. On the other hand, peripherally inserted central catheters (PICCs) (inserted in the basilic or cephalic veins) are associated with a 26% rate of sterile local exit site inflammation secondary to irritation of small veins (i.e., cephalic vein) by insertion of a large catheter (32); to this must be added the finding that coagulase-negative staphylococci, the most frequent pathogen involved, incites little local or systemic inflammation (33).

The CDC suggests the following definitions:

1. **Exit-site infection:** Purulent drainage from the catheter exit site, or erythema, tenderness, and swelling within 2 cm of the catheter exit site, and colonization of the catheter, if removed, with or without concomitant BSI.
2. **Port-pocket infection:** Erythema, tenderness, induration, and/or necrosis of the skin or subcutaneous tissues either over or around the reservoir of a totally implanted IVD, and colonization of the device if removed, with or without concomitant BSI.
3. **Tunnel infection:** Erythema, tenderness, and induration of the tissues above the catheter and more than 2 cm from the exit site, along the subcutaneous tract of a tunneled catheter and colonization of the catheter if removed, with or without concomitant BSI.

The systemic features of CRBSIs are generally indistinguishable from those of secondary BSIs arising from other foc of infection, and include fever and chills, which may be accompanied by hypotension, hyperventilation, altered mental status, and nonspecific gastrointestinal manifestations such as nausea, vomiting, abdominal pain, and diarrhea. Deep-seated infections such as endocarditis, osteomyelitis, retinitis, and organ abscess may complicate CRBSIs caused by some virulent organisms such as S. aureus, P. aeruginosa, and Candida albicans.

**DIAGNOSIS**

A clinical diagnosis of CRBSI is frequently inaccurate. At this juncture, it is worth noting the difference of CRBSI and CLABSI, as these terms are often used interchangeably but incorrectly. CLABSI is used by CDC’s National Healthcare Safety Network (NHSN) to describe any primary BSI in a patient who had a central line within 48 hours of the development of the BSI, and is not related to an infection at another site, such as pneumonia or osteomyelitis or pneumonia. However, other sources of infection, such as mucositis, that are less identifiable, may have led to the BSI, so the diagnosis of CLABSI is nonspecific and overestimates the true incidence of CRBSI. On the other hand, CRBSI is a subcategory of CLABSI for which specific laboratory testing has been done and identifies the catheter as the source of BSI.

Removal of the CVC has been mandatory to prove the CRBSI. Microbiologic methods requiring removal of the CVC were studied with the semi-quantitative roll-plate catheter cultures, developed by Maki et al. (34) in 1977, and considered the gold standard. However, the majority of the catheters were removed unnecessarily, exposing the patient to the complications related to reinsertion of a new CVC and adding to the cost of care. To prevent that, techniques allowing accurate diagnosis without removing the line have been elaborated; these are reviewed (Table 88.1.2).

**Catheter-Sparing Diagnostic Methods**

**Simultaneous Quantitative Blood Cultures**

This method consists of obtaining paired quantitative blood cultures (QBCs) simultaneously from the CVC and a peripheral vein. The target is to have both samples drawn less than 10
for long-term catheters, respectively (36). This technique also demands a simultaneous blood draw (within 10 minutes) from the line and the peripheral vein with the same amount of blood. One limitation of this study is that its sensitivity could be compromised when antibiotics are given intraluminally at the time of drawing the blood cultures through the catheters (38).

**Acridine Orange Cytospin Leukocyte Technique**

This test involves 1 mL of ethylenediaminetetraacetic acid (EDTA) blood aspirated through the CVC. The sample is added to 10% formalin saline solution for 2 minutes; the sample is then centrifuged, the supernatant decanted, and the cellular deposit homogenized and cytospun. A monolayer is stained with 1 in 10,000 acridine orange and viewed under ultraviolet light; a positive test is indicated by the presence of any bacteria (39). This method is expensive but takes only 30 minutes, with a sensitivity of 87% and specificity of 94% (40). This technique has been tested only by a small group of investigators and is not easy to perform correctly in order to reproduce the Kite method (41). One trial showed that this technique anticipated CRBSI earlier than routine measures (42); it is not recommended by the current guidelines of IDSA.

**Fluorescence In Situ Hybridization on Peptide Nucleic Acid Probes**

Fluorescence in situ hybridization (FISH) using peptide nucleic acid (PNA) probes is a novel technique in detecting several organisms (43). PNA probes are basically similar in structure to DNA or RNA, but have an uncharged backbone which accounts for its superior stability and improved hybridization when compared to DNA or RNA (43). These characteristics of PNA probes improve binding to certain molecules such as rRNA which makes FISH PNA a superior diagnostic test (43). Interestingly, a study comparing acridine orange cytospin leukocyte technique, FISH PNA and DTP found similar results in terms of sensitivity, specificity, positive predictive value, and negative predictive value (91%, 100%, 100%, and 97%, respectively) (44). In another study, even though FISH PNA was a successful diagnostic tool in patients who experience a BSI, positive results from random CVC sampling did not predict clinical progression to CRBSI as this phenomenon was most likely due to CVC colonization (45).

**Diagnostic Methods Requiring Catheter Removal**

**Semi-Quantitative Roll-Plate Catheter Culture**

This method was described by Maki et al. (46) in 1977 and remains the international reference diagnostic method. It consists of rolling a 3- to 5-cm section of the distal tip of the CVC at least four times back and forth over an agar plate surface and incubating overnight. A cutoff of ≥15 CFU defines catheter colonization; if at the same time, a peripheral culture grows the same organism, then a CRBSI is diagnosed. However, this method does not sample the internal lumen of a CVC that is the source of the infection in long-term catheters. Nevertheless, pooled sensitivity and specificity in 14 trials involving short-term catheters were 84% and 85%, respectively (36); this number decreased to 45% and 75%, respectively, with long-term CVCs (i.e., those with more than 30 days of dwell time) (10,47).
Quantitative Catheter Cultures

This type of culture involves flushing or sonication of a catheter segment in broth with the target of retrieving organisms from both surfaces of the line. A threshold of ≥100 CFU (48) correlated best with colonization, although older work (49) used a 1,000 CFU cutoff. CRBSI would be defined by the cutoff of 100 CFU accompanied by a high clinical suspicion and absence of evidence of other sites of infection. As would be expected, the sonication method had a higher sensitivity than the roll-plate method for long-term CVCs (10); however, both sonication and vortexing had the same sensitivity and specificity of the roll-plate method for short-term CVCs (50). Meta-analysis revealed a pooled sensitivity and specificity of 82% and 89% for short-term catheters and 83% and 97% for long-term catheters, respectively (36).

PREVENTIVE STRATEGIES

It should go without saying—but obviously does not—that CVCs should only be used when medically necessary, and should be removed as soon as possible to prevent potential complications. In a large study that included 1,981 ICU months of data, collective antiseptic measures consisting of hand-washing, maximal sterile barriers during insertion, cutaneous antisepsis with CHX, avoidance of femoral site, and removal of CVCs determined to be unnecessary were associated with a significant decrease in CRBSI rate—from 7.7 per 1,000 catheter days to 1.4 per 1,000 catheter days (p < 0.001) over 18 months of follow-up (51). In 1992, Cobb et al. (13), in an attempt to reduce catheter-related infection, conducted a controlled study whereby CVCs or pulmonary artery catheters were changed or exchanged over guidewire every 3 days; the former procedure actually resulted in an increase in the risk of mechanical complications, whereas the latter technique increased the risk of BSI. Table 88.1.3 provides a listing of preventive strategies to decrease the risk of CVC colonization. We review below the novel strategies implemented by the Healthcare Infection Control Practices Advisory Committee (HICPAC) and other professional organizations, including the IDSA, Society for Healthcare Epidemiology of America (SHEA), and American Society of Critical Care Anesthesiologists (ASCCA) aiming at controlling all factors that could lead to colonization of the CVC, and hence decreasing the rate of CRBSI.

### TABLE 88.1.3 Preventive Measures to Decrease the Risk of Colonization of Central Venous Catheters

- Hand hygiene
- Removing unnecessary catheters
- Avoiding femoral site insertion if possible
- Cutaneous antiseptic agents (2% chlorhexidine-based preparation)
- Maximal sterile barrier (hand-washing, sterile gloves, large drape, and sterile gown, mask, and cap)
- Antimicrobial catheter-lock solutions (a combination of an anticoagulant-like heparin or ethylenediaminetetraacetic acid, plus an antimicrobial agent, such as vancomycin, minocycline, or ciprofloxacin)
- Antimicrobial coating of catheter (with minocycline/rifampin or chlorhexidine/silver sulfadiazine)

Cutaneous Antiseptics

The HICPAC/CDC guidelines recommend with level 1A evidence—data derived from multiple randomized clinical trials proving general agreement on its effectiveness—the usage of 2% CHX-based preparation (52). Maki et al. (53) prospectively randomized 68 ICU patients to 10% povidone–iodine, 70% alcohol, or 2% aqueous CHX to disinfect the site before insertion of CVCs and for site care every other day thereafter, and demonstrated that 2% aqueous CHX preparation tended to decrease the rate of CRBSI substantially; using lower concentrations of CHX decreased the effectiveness of this method. Tincture of chlorhexidine gluconate 0.5% is no more effective in preventing CRBSI or CVC colonization than 10% povidone–iodine, as demonstrated by a prospective, randomized study in adults (54). A meta-analysis of eight randomized trials found an overall reduction of 49% in catheter-associated BSIs when a disinfected containing CHX was used (55). A French trial randomly assigned 1,181 ICU patients to CHX-based preparation and 1,168 to povidone–iodine. The CHX preparation was associated with lower incidence of CRBSI, 0.28 versus 1.77 per 1,000 catheter days (95% confidence interval [CI] 0.05 to 0.41, p = 0.0002) (56). Finally, the use of a dilute CHX solution for daily baths has been shown to decrease CRBSI—in a variety of settings (57–63).

Maximal Sterile Barrier

This involves wearing a sterile gown, gloves, and a cap, and using a large drape similar to those used in the operating room during the insertion of catheters as opposed to the regular precautions consisting of sterile gloves and a small drape only. The HICPAC/CDC guidelines recommend this technique while inserting CVCs, PICC lines, and pulmonary artery catheters (52) (category 1A) based on a number of studies (64–66). A prospective study conducted by Raad et al. (64) with long-term, nontunneled silicone CVCs and PICC lines in a cancer patient population demonstrated not only a reduction of CRBSIs (p = 0.03), but also that this practice was cost effective. Mermel et al. (65), in another prospective study with pulmonary artery catheters, found that less stringent barrier precautions were associated with a significantly increased risk of catheter-related infection (relative risk = 2.1, p = 0.03). Of note is that this technique failed to reduce the colonization of CRBSIs associated with arterial catheters (66). It has been shown that dedicated physician education courses can improve compliance with maximal sterile barrier and decrease the incidence of CRBSI (67).

Antimicrobial Catheter-Lock Solutions

Antimicrobial catheter lock involves flushing the catheter lumen and then filling it with 2 to 3 mL of a combination of an anticoagulant plus an antimicrobial agent. The dwell (lock) time varies between clinicians, but 20 to 24 hours is the most preferred. However, this might not be possible if the catheter has to be used (68). This intervention has often been used in long-term CVCs that remain in place longer than 30 days. Henrickson et al. (69) showed that a combination of vancomycin and heparin, with or without ciprofloxacin, was equivalent, but each was superior to heparin alone. Of six studies, four revealed a significant reduction in CRBSI with the above lock solution (70–72), and two demonstrated no
benefit (73,74). However, vancomycin–heparin lock solutions may promote the risk of vancomycin resistance and the risk of superinfection with GNB and Candida is present since the vancomycin spectrum is limited to gram-positive bacteria. A meta-analysis concluded that the use of a vancomycin lock solution in high-risk patient populations being treated with long-term central IV Ds may reduce the risk of BSI with a risk ratio of 0.34 (95% CI, 0.12 to 0.98; p = 0.04) (75).

Minocycline and EDTA (M-EDTA), another lock solution, was reported in a prospective randomized trial to significantly reduce the risk of catheter colonization and infection when compared with heparin in long-term hemodialysis CVCs (76). This solution was superior in an in vitro biofilm model and in an animal model to vancomycin–heparin lock solution (76–78). A clinical study of pediatric cancer populations showed that M-EDTA significantly reduces the risk of catheter infection and colonization when compared to heparin (79).

In a prospective nonrandomized study of tunneled CVCs in a pediatric cancer population, ethanol as a lock solution reduced the risk of relapse of CRBSI and was well tolerated (80). However, symptoms of fatigue, nausea, dizziness, and headache were reported. The study involved filling the catheter lumen with 2.3 mL of a 74% ethanol solution for 20 to 24 hours. The solution was then flushed through to prevent clotting inside the catheter. Each port was alternately blocked for 3 days, allowing the unblocked port to be used. In a study by Raad et al. (81), M-EDTA in 25% ethanol was found to be highly effective in eradicating organisms embedded in biofilm, even after a short exposure of 15 to 60 minutes. Hence, the addition of a low concentration of ethanol (25%) to M-EDTA could expedite its activity and decrease the necessary dwell time. A prolonged dwell time of more than 8 hours is often required for nonalcohol-based antibiotic lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.

A meta-analytic study from 2014 (82), which included 23 studies and 2,896 patients, showed that antimicrobial lock solutions led to a 69% reduction in CLABSI compared with heparin, without significantly causing catheter failure due to noninfectious complications. However, one must keep in mind that all of the trials were done in special population patients, such as hemodialysis and oncology patients, patient receiving TPN, and so forth. As there is some concern for the emergence of bacterial resistance associated with utilization of a sole antibiotic agent and not in combination, some have recommended the use of antibiotic-based catheter-lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.

A meta-analysis of a 2014 (82), which included 23 studies and 2,896 patients, showed that antimicrobial lock solutions led to a 69% reduction in CLABSI compared with heparin, without significantly causing catheter failure due to noninfectious complications. However, one must keep in mind that all of the trials were done in special population patients, such as hemodialysis and oncology patients, patient receiving TPN, and so forth. As there is some concern for the emergence of bacterial resistance associated with utilization of a sole antibiotic agent and not in combination, some have recommended the use of antibiotic-based catheter-lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.

A meta-analysis of a 2014 (82), which included 23 studies and 2,896 patients, showed that antimicrobial lock solutions led to a 69% reduction in CLABSI compared with heparin, without significantly causing catheter failure due to noninfectious complications. However, one must keep in mind that all of the trials were done in special population patients, such as hemodialysis and oncology patients, patient receiving TPN, and so forth. As there is some concern for the emergence of bacterial resistance associated with utilization of a sole antibiotic agent and not in combination, some have recommended the use of antibiotic-based catheter-lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.

A meta-analysis of a 2014 (82), which included 23 studies and 2,896 patients, showed that antimicrobial lock solutions led to a 69% reduction in CLABSI compared with heparin, without significantly causing catheter failure due to noninfectious complications. However, one must keep in mind that all of the trials were done in special population patients, such as hemodialysis and oncology patients, patient receiving TPN, and so forth. As there is some concern for the emergence of bacterial resistance associated with utilization of a sole antibiotic agent and not in combination, some have recommended the use of antibiotic-based catheter-lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.

A meta-analysis of a 2014 (82), which included 23 studies and 2,896 patients, showed that antimicrobial lock solutions led to a 69% reduction in CLABSI compared with heparin, without significantly causing catheter failure due to noninfectious complications. However, one must keep in mind that all of the trials were done in special population patients, such as hemodialysis and oncology patients, patient receiving TPN, and so forth. As there is some concern for the emergence of bacterial resistance associated with utilization of a sole antibiotic agent and not in combination, some have recommended the use of antibiotic-based catheter-lock solutions, which makes their use limited, particularly in critically ill patients or patients requiring TPN.
days achieved with multiple other aseptic measures applied collectively (such as the maximal sterile barrier, CHX cutaneous antisepsis, and hand hygiene).

Two studies by Raad et al. and Jamal and colleagues (99,100) found that minocycline–rifampin impregnated CVVs coated internally and externally with CHX, termed CHX–M/R catheters, were superior to CHX–SSD (chlorhexidine–silver sulfadiazine) or M/R-coated catheters in preventing biofilm formation and catheter colonization particularly when it comes to Pseudomonas and Candida. A novel approach using gendine (CHX and gentian violet)-coated CVVs showed promising results in terms of prevention of biofilm formation with no acute systemic exposure of CHX or gentian violet (101); however, clinical trials involving the use of gendine-coated catheters have yet to be initiated.

When all are said and done, CHX/SSD and M/R catheters both reduce CRBSI when compared to noncoated ones. The HICPAC/CDC recommends the use of either if the medical center continues to have higher than national average CRBSI rates despite successful implementation of provider education, maximal sterile barrier and use of CHX preparation with alcohol for skin antisepsis.

Silver-Impregnated Catheters

Other catheters incorporate silver, platinum, and carbon (SPC) into the polyurethane, allowing topical silver ion release (Vantex CVC with oligan, Edwards Life Sciences, Irvine, CA). One prospective randomized study compared these catheters to the M/R-coated type; the latter was more efficacious in reducing, to a significant degree, CVC colonization with gram-positive and gram-negative bacteria (p = 0.039); however, the CRBSI rates were low and similar between the two groups (102). In another prospective, randomized, controlled, open-label, multicenter clinical trial, the SPC CVVs failed to show any benefit in reducing CRBSI or colonization (103). A meta-analysis study failed to prove any association between reduced rates of colonization or CRBSI and the use of silver-impregnated catheters (104).

MANAGEMENT

The management of CRBSIs involves confirming the source and cause of infection, determining the choice of antimicrobials, determining the duration of therapy, and deciding whether to remove the invasive device. Confirmation of the infection is dependent on the diagnostic measures outlined above. The duration of therapy depends on whether the infection is complicated (i.e., by a septic phlebitis or endocarditis) or uncomplicated.

Coagulase-Negative Staphylococcus

Coagulase-negative staphylococci are the primary organisms involved in CRBSIs because they are the most common skin organisms; however, and for the same reason, they are the most frequent blood contaminants. One study indicated that QBC collected through CVC, with a cutoff point of 15 CFU/mL, could be a useful laboratory criterion, together with positive clinical findings, for differentiating true bacteremia from false-positive contaminated blood cultures, with a sensitivity of 96%, specificity of 94%, positive predictive value of 86%, and negative predictive value of 98% (105); the IDSA guidelines recommend removing the CVC and treating for 5 to 7 days. Otherwise, if the CVC is to be retained, duration of treatment should be 10 to 14 days, and antibiotic lock therapy should be considered (106). Leaving the CVC in place carries a risk of recurrence of 20% (107). Finally, in the absence of endovascular or orthopedic hardware, and with catheter removal, the patient can be monitored off antibiotics while new blood cultures are drawn to confirm the resolution of bacteremia.

Lock solutions used included vancomycin plus heparin. The limited activity of vancomycin against Staphylococcus embedded in biofilms (73,75,108) led investigators to consider other alternatives; minocycline and EDTA, ethanol, or the triple combination (109,110) was used as an alternative. While systemically, vancomycin has been the most frequently used glycopeptide, dalbavancin, a new, long-acting glycopeptide that is dosed weekly, was noted to be superior to vancomycin for adult patients with CRBSIs caused by coagulase-negative Staphylococcus and S. aureus, including methicillin-resistant S. aureus (MRSA) in a phase 2, open-label, randomized, multicenter study; the side effect profile was comparable (111). Linezolid and daptomycin were also used successfully (112,113).

Staphylococcus Aureus

S. aureus CRBSI is associated with high rates of deep-seated infection such as osteomyelitis, septic phlebitis, and endocarditis (114). In addition, Fowler et al. (114) showed that patients whose IVD was not removed were 6.5 times more likely to relapse or die of their infection than were those whose device was removed. IDSA guidelines recommend removing the CVC, as this results in a more rapid response and lower relapse rate but, at the same time, gives the option of keeping it and initiating systemic and lock solutions in the rare and extreme cases of lack of other vascular access, bleeding diathesis, and quality-of-life issues intervene (106). Capdevila et al. (115) used the antibiotic lock technique in addition to standard parenteral therapy for patients with a hemodialysis catheter–related infection. All 40 CRBSIs—including all 12 cases reported to involve S. aureus—were cured and the catheter salvaged. The lock solutions most frequently used in vivo and in vitro are vancomycin plus heparin, or minocycline plus EDTA (71,110). However, the former combination—with or without cefazidine, depending on the organism—was associated with a 60% failure rate in hemodialysis MRSA catheter infections (116). Another study showed that even though systemic antibiotic therapy was not successful in eradicating most CRBSIs without catheter removal, attempted CVC salvage appeared to have not increased the complication rate even in the setting of S. aureus (117). Low-concentration ethanol (25%) is another very appealing component for use in combination lock solutions; Raad and colleagues (81) found that the combination of minocycline–EDTA in 25% ethanol was highly efficacious in eradicating S. aureus in biofilm within 60 minutes of dwell time.

For methicillin-sensitive S. aureus, nafcillin or first-genera
tion cephalosporins are the first-line agents (100). Vancomycin, linezolid, daptomycin, and dalbavancin (111–113) are all appropriate options for MRSA. Duration of therapy usually consists of 10 to 14 days of intravenous therapy if the CVC is removed, with no deep-seated infection present (106). If fever or bacte
ermia persists for more than 72 hours after catheter removal, transesophageal echocardiography should be performed to rule out IE, with the intravenous therapy duration expanded to at
least 4 weeks (106,118). This is especially important as the frequency of IE in S. aureus bacteremia is 25% to 32% (119).

**Enterococcus**

*Enterococcus* is the third most common pathogen seen in CRBSI, accounting for about 10% of nosocomial BSIs (120). The IDSA recommends catheter removal and treatment with systemic antibiotics, beginning with ampicillin as the first-line agent of choice; the organism can be treated with vancomycin if ampicillin-resistant. However, 60% of *Enterococcus faecium* and 2% of *Enterococcus faecalis* are now resistant to vancomycin (120); in such cases, linezolid and daptomycin are the agents of choice.

Antibiotics are recommended for 7 to 14 days in the setting of catheter removal, as well as long-term catheter salvage with systemic antibiotics and lock therapy. A transesophageal echocardiogram (TEE) should be pursued to evaluate for IE if the patient has prolonged bacteremia or fever more than 72 hours after the initiation of appropriate antimicrobial therapy, evidence of septic emboli, a new murmur, or embolic phenomena, all of which are also, in the cases of long-term catheters, indications of salvage therapy failure and the need for removal.

There are data regarding combination therapy for enterococcal CRBSI, namely a cell wall–active antimicrobial and an aminoglycoside. Several retrospective cohort studies found no statistically significant difference in outcomes when treated with combination therapy versus monotherapy (121–123).

**Gram-Negative Bacilli**

GNB bacteremia is rarely due to a CVC; rather, it generally arises from a visceral source of infection such as the genitourinary, pulmonary, or gastrointestinal tracts. However, CRBSIs caused by such organisms as *K. pneumoniae, Enterobacter* spp., *P. aeruginosa* spp., *Acinetobacter* spp., and *Stenotrophomonas maltophilia* have been reported (124,125). Elting and Bodey (124) reported a 13-year experience of 149 episodes of septicaemia caused by *Xanthomonas maltophilia* and *Pseudomonas* spp. in cancer patients where the CVC was the most common source. Hanna et al. (125) demonstrated that catheter removal within 72 hours of the onset of the catheter-related GNB was the only independent protective factor against the relapse of bacteremia (OR, 0.13; 95% CI, 0.02 to 0.75; \( p = 0.02 \)). IDSA guidelines (107) recommend removing nontunneled CVCs and treating for 10 to 14 days with systemic antibiotics. Patients at high risk for colonization or infection with multidrug-resistant gram-negative pathogen (i.e., critically ill, neutropenia) should be covered with either two antibiotics of different classes that provide gram-negative activity or a carbapenem as initial therapy. It is considered appropriate to attempt to salvage the CVC in certain situations (see above) using systemic and lock solution therapies. However, lock therapy for GNB CRBSIs is anecdotal; successful cases were salvaged using gentamicin, amikacin, or ceftazidime (106,118).

**Candida**

Five large prospective studies proved that catheter retention was associated with increased mortality and an increase in the mean duration of candidemia in cases of *Candida* CRBSI (126–130). Hung et al. (128) investigated the predisposing factors and prognostic determinants of candidemia in a Taiwan hospital, and concluded that higher severity scores, nonremoval of the catheter, persistent candidemia, and lack of antifungal therapy adversely affect the outcome. Raad and colleagues (131), in a retrospective study of 404 patients with candidemia and an indwelling CVC, using a multivariate analysis, demonstrated that catheter removal 72 hours or sooner after onset of candidemia improved the response to antifungal therapy exclusively in patients with catheter-related candidemia (\( p = 0.04 \)). IDSA guidelines recommend removing the CVC and treating for 14 days after the last positive blood culture in uncomplicated cases; endophthalmitis merits 6 weeks of therapy (106). Further studies are needed to define the role of antifungal lock solution in these cases. Fluconazole and caspofungin were equivalent to amphotericin B in candidemia, but with a better safety profile (130,131); therefore, fluconazole or caspofungin should be considered in documented cases of catheter-related candidemia. If the rates of fluconazole-resistant *Candida glabrata* and *Candida krusei* in the hospital are high, an echinocandin (caspofungin, micafungin, or anidulafungin) would be the best alternative to amphotericin B.

**PERIPHERALLY INSERTED CENTRAL CATHETERS**

The use of PICCs is very common in cancer patients, patients receiving TPN, and long-term i.v. antibiotics. Their complication rates, including infection and thrombosis, are low in the outpatient setting (0.4 per 1,000 catheter days) (132,133). There has been speculation that perhaps PICCs are less prone to infection compared to CVCs in the critically ill; this has been proved to be untrue.

In a prospective study in which 115 patients had 251 PICCs placed, Safdar and Maki (127) showed that PICCs used in ICU patients are associated with a rate of CRBSI similar to CVCs placed in internal jugular or subclavian veins (2.1 vs. 2 to 5 per 1,000 catheter days). Nolan et al. (134) performed a retrospective cohort study of 200 PICCs and 200 CVCs placed in the medical ICU adults at Mayo Rochester between 2012 and 2013. Overall, thrombotic and infectious complications were rare following PICC and CVC insertion, with no significant difference in complication rates observed. Finally, the meta-analytic study of Chopra and colleagues (135) identified 23 studies that met eligibility criteria for comparing infection risk of PICC versus CVC. Thirteen studies reported CLABSI rates; PICC-related CLABSI occurred as frequently as CLABSI in CVC. The subcategory where PICC showed a significant infection reduction is in outpatients, not in critically ill, hospitalized patients.

**Key Points**

- PICCs are as much a part of modern ICU practice as are mechanical ventilators and antibiotics.
- When CVCs are placed with the appropriate technique, accessed, and cared for, it is possible to use these devices while approximating a zero incidence of infection.
- PICCs are not lower risk for infectious complication when used in critically ill, hospitalized patients.
- As is typically true in the practice of critical care medicine, it is in the details that the battle is won or lost.
Towards understanding the role of fibrinogen in inflammation and infection.

References


Section 2
Respiratory Infections

LISA M. ESOLEN and OLIVIER Y. LEROY

PNEUMONIA

Traditionally, pneumonia has been differentiated as community-acquired or hospital-acquired. For community-acquired pneumonia (CAP), the infection either begins while the patient is an outpatient or becomes apparent within the first 48 hours of admission to an acute care hospital. Conversely, a hospital-acquired pneumonia (HAP) becomes evident more than 48 hours after admission (1). It has become clear, however, that this simplistic dichotomous classification is not sufficient to characterize all patients suffering from pneumonia. First, among HAPs, those occurring during mechanical ventilation (MV) must be differentiated from others because of epidemiologic, prognostic, and therapeutic factors (2,3). Furthermore, numerous outpatients with frequent health care contact and chronic illnesses that utilize dialysis, chemotherapy, or rehabilitation services cannot be simplistically considered as equivalent to all ambulatory patients. Notably, in most nursing homes and rehabilitation hospitals, patients can receive intensive and/or invasive medical care with exposure to different microbial flora and this places them at an altered risk than otherwise healthy outpatients. We now understand that these situations constitute a separate demographic, now defined as a health care–associated pneumonia (HCAP) (3).

Thus, four classes of pneumonia can be distinguished:

1. Community-acquired pneumonia (CAP)
2. Hospital-acquired pneumonia (HAP)
3. Ventilator-associated pneumonia (VAP)
4. Health care–associated pneumonia (HCAP)

We will discuss each of these below, and will also briefly touch on the topics of tracheobronchitis, pleural infections, and pulmonary abscess.

Severe Community-Acquired Pneumonia

Immediate Concerns

CAP is a common infectious disease affecting about 12 per 1,000 adults yearly (4). An intensive care unit (ICU) admission for severe CAP is required for 2% of patients and over 80% of the cases are due to Streptococcus pneumoniae. Despite progress in antibiotic therapy and ICU management, the mortality of pneumococcal pneumonia remains high.

Diagnosis

CAP is suspected on the basis of clinical symptoms: cough, dyspnea, sputum production, pleuritic chest pain, and elevated body temperature; these symptoms can be absent or moderated in older patients. However, these signs are not specific of pneumonia; a chest radiograph or computed tomography (CT) scan revealing a new infiltrate is required to document a pneumonia diagnosis, though false-negative results may be seen during early presentations which are complicated by severe dehydration, neutropenia, or with certain pathogens such as Pneumocystis jiroveci (4).

The chest radiograph might offer insights into the etiologic diagnosis, with S. pneumoniae resulting in a typically lobar pattern, and intracellular pathogens such as mycoplasma typically presenting with an interstitial radiographic pattern. However, these findings are not specific, and caution should be exercised in interpreting radiographs, particularly in critically ill patients. The chest radiograph also allows for staging of severity according to the number of involved lobes, and is helpful to detect complications such as pleural effusions or cavitation. In these situations, CT scan may be advisable for further characterization of the infection, particularly in immunosuppressed patients (e.g., halo or crescent signs in pulmonary aspergillosis of neutropenic patients, cavitation in tuberculosis).

Definition and Decision for ICU Admission

Although there is no gold standard to define severe CAP, criteria do exist that may be used to assess the severity of CAP and define the need for ICU admission.

According to the original American Thoracic Society (ATS) guidelines (5), CAP was considered severe when any one of the following criteria was present:

- Respiratory frequency greater than 30 breaths/min on admission
- Severe respiratory failure (PaO2/FiO2 < 250 mmHg)
- Requirement for MV
- Bilateral or multilobar or extensive (≥50% within 48 hours of admission) involvement of the chest radiograph
- Shock (systolic blood pressure [SBP] < 90 mmHg or diastolic blood pressure < 60 mmHg)
- Requirement for vasopressors for more than 4 hours
- Low urine output (<20 mL/hr or < 80 mL/4 hr) or acute renal failure requiring dialysis

In 1998, Ewig et al. (6) demonstrated that using any one of these factors as the definition of severe CAP had a high sensitivity but a low specificity; a new definition of severe CAP was proposed, which, in 2001, was adopted by the ATS (7). The diagnosis of CAP was considered severe and requiring ICU admission for patients exhibiting either one of two major criteria (the need for MV and septic shock) or two of three minor criteria (SBP 90 mmHg or below, multilobar involvement on chest radiograph, or PaO2/FiO2 less than 250 mmHg) (7). Unfortunately, additional studies suggested that this revised ATS criteria did not discriminate enough to guide decision-making regarding the need for ICU care (8,9).

The British Thoracic Society (BTS) proposed assessing the severity of CAP utilizing three groups of adverse prognostic features: four “core” factors (CURB score: confusion, blood urea nitrogen > 19 mg/dL [7 mmol/L], respiratory rate ≥ 30 breaths/min, and low blood pressure [SBP < 90 mmHg and/or diastolic ≤ 60 mmHg]); two “additional” factors (hypoxemia defined by SpO2 < 92% or PaO2 < 60 mmHg [8 kPa]
and bilateral or multilobar involvement on chest radiograph; and two “pre-existing” factors (age ≥50 years and the presence of coexisting disease) (10). CAP was considered severe in patients having two or more core adverse prognostic features. In patients exhibiting only one of these core factors, the decision, based on clinical judgment, could be assisted by taking into account pre-existing and additional factors (10).

Finally, in 2007, the ATS and Infectious Disease Society of America (IDSA) drafted a consensus guideline (5) which incorporated much of the CURB score, above, along with the additional source, the concentration of the organism, the pathogenicity of the micro-organism such as community-acquired methicillin-resistant, (CA-MRSA) and penicillin-resistant pneumococcal pneumonia and in children (12).

- Blood cultures, drawn before antibiotic therapy, are occasionally positive (6% to 20% of cases).
- Urinary antigen assays. The urinary antigen test is about 80% sensitive for the diagnosis of Legionella pneumophila type 1 with most of the false negatives being due to Legionella species other than L. pneumophila. The urinary antigen assay for S. pneumoniae shows a high sensitivity (82%) and specificity (97%) in bacteremic pneumonia, but is considerably less sensitive and specific in nonbacteremic pneumococcal pneumonia in children (12).

**Polymerase chain reaction (PCR) testing.** Rapid diagnostic testing by PCR now exists for 12 respiratory pathogens including influenza A (12,13), respiratory syncytial virus, parainfluenza, and coronavirus. Available tests can detect pathogens in 30 minutes and can often be done at the point of care. The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal; and aspirates, swabs, or washes) vary by test. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test.

**Serologic testing.** The presence of IgM with a titer greater than or equal to 16 generally indicates a recent infection, but this is rarely observed in the initial phase of infection and is rarely useful. A fourfold rise in convalescent antibody titer requires that samples are drawn 2 weeks apart but can be useful for certain pathogens (e.g., Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamyphila psittaci, Legionella spp., Coxella burnetii, adenovirus).

Minimal diagnostic testing for patients admitted to the ICU with CAP can be done via endotracheal aspiration, blood cultures, L. pneumophila urinary antigen, and thoracentesis, if pleural effusion is present. Despite the potential for microbiologic testing along with the newer rapid modalities, a definitive diagnosis in CAP is obtained, by some reports, in less than 10% of cases (12). More invasive procedures should be reserved for those patients who are critically ill, immunosuppressed, and those with failure of a first-line treatment (7).

### Diagnostic Studies

Evaluation for the etiologic diagnosis is helpful to confirm the infectious origin of the pulmonary findings and direct appropriate antimicrobial therapy (including secondary de-escalation therapy). Numerous methods are available for the microbiologic diagnosis of pneumonia but, importantly, this analysis is influenced by several factors including the specimen source, the concentration of the organism, the pathogenicity of the organism, and the influence of prior antibiotics.

- **Sputum stains and cultures.** These require careful interpretation. A sample should only be considered purulent, and valuable for culture and interpretation, if there are more than 25 polymorphonuclear cells (PMNs) and less than 10 squamous epithelial cells per high power field (HPF). A single predominant organism on a Gram stain is suggestive of a specific etiology. But even with this, the yield on culture for certain pathogens can be low, with 30% to 60% of sputum failing to grow the most common pathogen in CAP, S. pneumoniae, due to its fastidious growth requirements (11). Other stains can be used according to the particular clinical context and may allow for a positive diagnosis: acid-fast stains for Mycobacterium tuberculosis, or various silver stains for cyst wall of Pneumocystis jirovecii.
- **Alternative specimen collection by more invasive sampling methods (endotracheal aspiration, protected tip bronchoscopic brushings, bronchoalveolar lavage [BAL], and transtracheal aspiration).** These methods attempt to bypass the upper airway contamination and are discussed in more detail in the VAP section, but can also be useful in the diagnosis of severe CAP.

---

**Organisms Causing CAP in Hospitalized Patients Requiring ICU Admission.** The epidemiology of CAP patients admitted to the ICU does not appear to be different from other hospitalized individuals with CAP. The most frequent pathogen isolated in ICU-hospitalized CAP patients is S. pneumoniae (Table 88.2.4) (14–16).

Other pathogens responsible for severe CAP, such as H. influenzae or S. aureus, occur with less frequency and sometimes as a secondary bacterial superinfection of an underlying influenza infection. Less-frequent pathogens recovered from patients with underlying chronic lung disease include Pseudomonas aerugi-nosa or, in neutropenic patients, Aspergillus species.

**Drug-resistant Pathogens.** A major emerging challenge in the empiric treatment of CAP is the rise of drug-resistant micro-organisms such as community-acquired methicillin-resistant S. aureus (CA-MRSA) and penicillin-resistant pneumococci (PRP).

For S. pneumoniae, macrolide resistance is above 20% in the United States and greater than 50% in some European and Asian–Pacific countries (17). Decreased susceptibility or resistance to penicillin is observed in 30% to 50% of strains in some studies, and fluoroquinolone resistance has been increasing. While the penicillin resistance is higher for noninvasive
infections, it reached 19% in blood cultures worldwide with risk factors including recent hospitalization, administration of antimicrobials, and immunodeficiency (18,19). The impact of drug resistance on outcome is controversial (20). Some studies have suggested a trend toward higher mortality in patients with pneumococcal pneumonia caused by intermediately resistant strains (21). Fluoroquinolone resistance is increasing, with the prescribing habits of these agents potentially impacting resistance rates (22,23).

Emergence of CA-MRSA with cases of rapidly progressive necrotizing pneumonia, often in previously healthy adults and children, is a new challenge for proper empiric antibiotic choices (24). The further introduction of highly resistant gram-negative pathogens, such as the Enterobacteriaceae with extended-spectrum ß-lactamases (ESBL) and the emergence of Klebsiella pneumoniae with carbapenemase resistance may impact the empiric antimicrobial choices for pneumonia in other clinical settings—ventilator-dependent patients, nosocomially acquired infections—but generally do not impact the etiology of true CAP.

P. aeruginosa are naturally resistant to numerous antibiotics and can elevate to a high-level resistance under treatment. Risk of P. aeruginosa is increased in patients presenting with a previous chronic pulmonary disease such as chronic obstructive pulmonary disorder (COPD) or cystic fibrosis, recent antibiotic therapy, or a stay in the hospital, especially the ICU (11,25).

Specific Etiologies in Immunosuppressed Patients

Immunosuppressed patients have an increased risk of severe CAP; these patients have more frequent bacterial pneumonias, with the typical pathogen dependent upon the underlying immune deficiency.

Human immunodeficiency virus (HIV)-infected patients used to have a 25-fold higher risk of developing bacterial pneumonia as compared to the general population (26). This has largely abated due to the use of more active antiretroviral drugs and, in some studies, shows little difference from the general population (27). P. jiroveci pneumonia (PJP) remains a frequent acquired immunodeficiency syndrome (AIDS)-defining diagnosis, while less frequent causes include cytomegalovirus (CMV) and mycobacteria.

Patients with chemotherapy-induced neutropenia, particularly when severe (<500 neutrophils/µL) and prolonged (>10 days), have an increased risk of invasive pulmonary aspergillosis as well as severe bacterial pneumonia (28,29). In the proper clinical setting, with cavitory or mass-like lesions, this population may require empiric treatment for Aspergillus, usually with a triazole antifungal, such as voriconazole. This risk also exists with targeted monoclonal antibody therapies, which increase the risk of CMV and PJP (30). Patients with solid organ transplant and those receiving antitumor necrosis factor (TNF) monoclonal antibodies both have an increased risk of severe CAP caused by the usual bacterial pathogens, as well as by opportunistic infections such as P. jiroveci and Aspergillus (31,32).

Treatment

Antimicrobial Therapy

Antimicrobial Spectrum. The ideal antibiotic should have a bactericidal activity against the major pathogens responsible for severe CAP. Considerations are given to the severity of clinical presentation, with non-ICU patients being distinguished from ICU patients in terms of empiric therapy. Additionally, special epidemiologic considerations may factor into this decision along with comorbid host conditions that may favor more resistant or unusual pathogens.

Timing of Initial Therapy. The most recent IDSA guideline recommends initial antibiotic administration within 4 hours of admission (25). A reduced mortality (adjusted odds ratio [AOR], 0.85, 95% confidence interval [CI] 0.76 to 0.95) was observed in patients with early therapy in a retrospective study of 18,209 Medicare patients (33). However, other studies contradicted this finding, and suggested that the time to first antibiotic dose was a marker of disease severity rather than an indicator of prognosis (34,35).

Antimicrobial Choices. Drug choice depends on numerous factors, including causative pathogen, pharmacodynamics/pharmacokinetics of the antimicrobial agent, spectrum of activity, adverse events, cost, host factors and, possibly, availability.

The antimicrobial agent must have sufficient diffusion in pulmonary tissues. ß-Lactam antibiotics have a good extracellular diffusion, but are ineffective on intracellular organisms; their concentration in the alveolar lining fluid (ALF) reached 10% to 20% of the serum concentration after a single dose. Macrolides, on the other hand, have a variable intracellular distribution—low for erythromycin and elevated for clarithromycin and azithromycin. Fluoroquinolones have an excellent intracellular and extracellular diffusions with levofloxacin having increased activity against Legionella species as well as enhanced activity against S. pneumoniae (36).

Empiric choices must cover the most common pathogens in severe CAP. While less severe CAP will include S. pneumoniae, other atypicals, such as Mycoplasma, Chlamydia, and respiratory viruses, play a larger role. In severe CAP requiring ICU admission, S. pneumoniae remains common, but S. aureus,

---

**Table 88.2.4 Micro-organisms Causing Severe Community-acquired Pneumonia Requiring Admission to the ICU**

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Yoshimoto (14)</th>
<th>Leroy (15)</th>
<th>Shorr (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aerobic Gram-negative</td>
<td>72%</td>
<td>308%</td>
<td>199%</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
<td>55.6%</td>
<td>45.4%</td>
<td>43.7%</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>2.8%</td>
<td>15.8-24.5%</td>
<td>10.6%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>2.8%</td>
<td>3.2-3.8%</td>
<td>8.9%</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>2.8%</td>
<td>2.8-7.4%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>8.3%</td>
<td>ND</td>
<td>4.9%</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2.8%</td>
<td>17-17.9%</td>
<td>ND</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>11.1%</td>
<td>7.5-8.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Chlamydia spp.</td>
<td>ND</td>
<td>1.9-3.2%</td>
<td>ND</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>2.8%</td>
<td>ND</td>
<td>2.4%</td>
</tr>
<tr>
<td>Other non-gram-positive</td>
<td>1.4%</td>
<td>3.2-3.8%</td>
<td>13%</td>
</tr>
</tbody>
</table>

ND: no data.

*Data presented as number or percentage.*
Legionella, and gram-negative bacilli rise in significance and must be empirically covered. Additionally, there are epidemiologic situations that may contribute to empiric choices. For example, alcoholism raises the concern for oral anaerobes and Klebsiella, COPD, and underlying chronic lung disease for Pseudomonas and Moraxella. Travel history, animal/bird exposures, and intravenous drug abuse may suggest more unusual pathogens, including Coccidioides species, Histoplasma, Hantavirus, or CA-MRSA.

Data suggests that combination regimens which include a macrolide or a quinolone are superior to β-lactam monotherapy for severe CAP (37–39). This is particularly important in cases of bacteremic pneumococcal pneumonia, in which combination therapy was confirmed as superior in an international, multicenter, prospective observational study (38,40,41). Lower mortality was associated with combination therapy for critically ill patients (14-day mortality, 23.4% vs. 55.3%; p = 0.0015), but not for all patients receiving combination versus monotherapy (10.4% vs. 11.5%, p = NS). All combinations using a β-lactam had an enhanced response.

The regularly updated guidelines published by North American and European medical societies recommend the utilization of a β-lactam with a macrolide or a respiratory fluoroquinolone. The 2007 IDSA/ATS guidelines concur, and are presented in Table 88.2.5.

Duration of Therapy. Length of treatment may be modified based on the pathogen, response to treatment, comorbid illness, and complications (42). In general, patients with CAP should be treated a minimum of 5 days, but at least until they are afebrile for 72 hours. Longer durations are needed for necrotizing infections caused by S. aureus—particularly when bacteremic due to endocarditis and/or metastatic infections—P. aeruginosa and Klebsiella, which should probably be treated no less than 2 weeks. Similarly, atypical intracellular pathogens are generally treated for a minimum of 2 weeks.

### Table 88.2.5 Initial Empiric Antibiotic Therapy in Patients Admitted to the ICU for Severe CAP

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Recommended Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pseudomonas or methicillin-resistant Staphylococcus aureus (MRSA) or penicillin allergy</td>
<td>β-Lactam (cefotaxime, ceftriaxone, ampicillin/sublactam) plus azithromycin or a respiratory fluoroquinolone&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients with penicillin allergy</td>
<td>Respiratory fluoroquinolone, with azithromycin</td>
</tr>
<tr>
<td>Suspected Pseudomonas infection</td>
<td>Antipseudomonal β-lactam&lt;sup&gt;a&lt;/sup&gt; plus Ciprofloxacin or levofloxacin&lt;sup&gt;a&lt;/sup&gt; or Aminoglycoside and antipseudomococcal fluoroquinolone&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Suspected community-acquired MRSA</td>
<td>Addition of vancomycin or linezolid</td>
</tr>
</tbody>
</table>


Nonantimicrobial Therapy

Besides antimicrobial therapies, most patients admitted to the ICU for severe CAP need additional treatment. End-organ dysfunction, such as respiratory failure, septic shock, or renal failure, require supportive measures. Similarly, the standard care for acutely ill patients (i.e., nutrition, prevention of ICU-related complications, and treatment of underlying diseases) must be utilized.

Activated Protein C. Severe sepsis is associated with a generalized inflammation and a procoagulant response to infection. Activated protein C is an important endogenous modulator of this response; there are reduced levels of activated protein C in most patients with severe sepsis.

Although drotrecogin-α activated, a recombinant form of human activated protein C (r-aPC), exhibits profibrinolytic, antithrombotic, and anti-inflammatory characteristics, and while large studies suggested that treatment with r-aPC significantly decreased 28-day and hospital discharge mortality rates in patients with severe sepsis, although not in lesser ill patients (43–46), this agent was ultimately found to be inefficacious and has been removed from the market.

Corticosteroids. Confalonieri et al. (47) studied hydrocortisone—200 mg i.v. bolus followed by infusion at a rate of 10 mg/hr for 7 days—randomized against placebo in a cohort of 46 patients. Findings included improvements oxygenation, radiographs, shock and multiorgan dysfunction, length of hospital stay, and mortality. While additional randomized trials are needed to recommend routine use for the treatment of severe CAP, use of hydrocortisone is clearly indicated in patients who do not have normal cortisol responses, and screening for occult adrenal insufficiency in patients who remain hypotensive after fluid resuscitation may be warranted. This is at least controversial (see Chapter 46, Sepsis and Septic Shock).

Expected Clinical Course

Evaluation on Day 3. Clinical response to treatment for severe CAP may not be seen in the first 48 hours. Expectations are that fever and oxygenation will, at least, stabilize even though they may not yet begin to improve. Empiric therapy should be continued during this time, allowing for preliminary culture data to return. Upon reassessment with microbiologic data, de-escalation may be supported or therapy modification may be necessary.

Complications and Failure to Improve. A poor clinical response by day 3 may be a sign of treatment failure. However, in the ICU, other diagnoses such as pulmonary embolism or cardiac failure should be considered in this situation. Treatment failure may be due to a non-infectious cause of the pulmonary issue (concomitant cardiac failure, pulmonary embolism), or to an organism not covered by the first-line antimicrobial therapy, thus necessitating a change or addition to the antimicrobial regimen. Other causes of treatment failure can include infectious complications of the pneumonia despite adequate antimicrobial therapy. These include lung abscess, empyema, endocarditis, or other superinfection.

Prognosis

Mortality in patients with severe CAP requiring admission to the ICU remains high, ranging in various series from 18% to
46% (8,48–54). A meta-analysis of 788 ICU patients found a mean mortality rate of 36.5% (55); in this analysis, Fine and colleagues (55) identified the following 11 factors independently associated with a higher mortality: male gender (OR = 1.3), pleuritic chest pain (OR = 0.5), hypothermia (OR = 5.0), systolic hypotension (OR = 4.8), tachypnea (OR = 2.9), diabetes mellitus (OR = 1.3), neoplastic disease (OR = 2.8), neurologic disease (OR = 4.6), bacteremia (OR = 2.8), leukopenia (OR = 2.5), and multilobar disease (OR = 3.1).

Numerous studies have focused on the prognosis of patients admitted to the ICU for severe CAP (48–50,52–54,56–58). Though inclusion criteria were variable, most independent prognostic factors were similar and demonstrated that, in general, survival in cases of severe CAP depends on the preadmission health status of the patient, the initial severity of illness, and the evolution during the ICU stay (Table 88.2.6). While these findings suggest that there are important nonmodifiable factors which influence mortality, the following points must be underscored:

- The initial empiric antimicrobials must be instituted as soon as possible (<4 hours after hospital admission).
- The empiric antibiotics must be broad enough to cover the most likely pathogens.
- Studies have suggested that empiric initial antimicrobial treatment which utilizes a macrolide or a respiratory fluoroquinolone as a second agent to a β-lactam reduces mortality from CAP (37,59,60). Similar results are seen with bacteremic pneumococcal CAP when combination therapy is prescribed (40,41,61). Of note, however, is the fact that in these retrospective analyses, critically ill patients were often excluded. Rello et al. (38) specifically compared multiple antibiotic combinations and the resultant mortality for patients admitted to the ICU with severe CAP. Their major finding was that the addition of empiric aminoglycosides was suboptimal. Wilson and colleagues (62) compared the two regimens which are concordant with the latest IDSA/ATS guideline (β-lactam + macrolide and β-lactam + respiratory quinolone) and found no significant effect on mortality between these two options, though their findings did suggest an increased length of hospital stay when the quinolone was used instead of the macrolide.

Mortality risk can be assessed by the Pneumonia Severity Index (PSI), which stratifies patients into five classes according to the risk of death within 30 days using a two-step approach (63). First, patients with a low risk (class I) are identified by age younger than 50 years and the absence of comorbidities and vital sign abnormalities. For the remaining patients, a score is determined by adding points assigned to age, comorbid conditions, physical findings, laboratory and radiographic abnormalities (Table 88.2.7). According to the value of this score, patients are classified into class II (≤70 points), III (71 to 90 points), IV (91 to 130 points), or V (>130 points). From class I to class V, mortality rates observed were 0.1%, 0.6%, 2.8%, 8.2%, and 29.2%, respectively. Despite major interest in this finding, the indexing of patients in this manner was to identify patients at low risk for complications, who might be safely treated as outpatients. Consequently, the implications of the PSI for the medical care of patients exhibiting severe CAP, and requiring admission into an ICU, is unclear.

A specific prediction rule for mortality of patients with severe CAP admitted to an ICU was proposed by Leroy et al. (57), emphasizing both initial baseline patient characteristics and the patient’s evolution during the ICU stay. Upon ICU admission, an initial risk score based on the following six independent variables and their respective point value is established: age 40 years or older (+1 point); anticipated death within 5 years (+1 point); nonaspiration pneumonia (+1 point); chest radiograph involvement greater than one lobe (+1 point); acute respiratory failure requiring MV (+1 point);

### TABLE 88.2.6 Independent Prognostic Factors Associated with Mortality of Patients with Severe CAP

<table>
<thead>
<tr>
<th>PREADMISSION HEALTH STATUS</th>
<th>INITIAL SEVERITY OF ILLNESS</th>
<th>EVOLUTION DURING ICU STAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Age &gt;70 yr</td>
<td>Antibiotic administration prior to hospital presentation</td>
<td>Radiographic spread of pneumonia</td>
</tr>
<tr>
<td>+ Immunosuppression</td>
<td>Simplified Acute Physiologic Score (SAPS I) &gt;12 or SAPS II &gt;45</td>
<td>Number of nonpulmonary organs that failed</td>
</tr>
<tr>
<td>+ Comorbidities with anticipated death ≥5 yr</td>
<td>Septic shock</td>
<td>Increase in Logistic Organ Dysfunction score from D1 to D3</td>
</tr>
<tr>
<td></td>
<td>Requirement for mechanical ventilation</td>
<td>Delay in hospital antibiotic administration of more than 4 hr</td>
</tr>
<tr>
<td></td>
<td>Acute renal failure</td>
<td>Ineffective initial antimicrobial therapy</td>
</tr>
<tr>
<td></td>
<td>Bilateral or multilobar pulmonary involvement</td>
<td>Occurrence of nonpneumonia-related complications</td>
</tr>
<tr>
<td></td>
<td>K. pneumonia or P. aeruginosa as etiologic agent</td>
<td>Increase of procalcitonin level in serum from D1 to D3</td>
</tr>
<tr>
<td></td>
<td>Bacteremia</td>
<td>Nonaspiration pneumonia</td>
</tr>
</tbody>
</table>

### TABLE 88.2.7 Criteria and Point Scoring System Used in the Pneumonia Severity Index (Step 2; Classes II–V)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td>Vital signs abnormality</td>
<td>+20</td>
</tr>
<tr>
<td></td>
<td>Female gender</td>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>–10</td>
<td>Altered mental status</td>
<td>+20</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>+10</td>
<td>Respiratory rate &gt;30 breaths/min</td>
<td>+20</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>+20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temperature &lt;35°C or ≥40°C</td>
<td>+15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tachycardia &gt;125 beats/min</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>&lt;30</td>
<td>Laboratory and radiographic data</td>
<td></td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
<td>Neoplastic disease</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>+20</td>
<td>Arterial pH &lt;7.35</td>
<td>+30</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+20</td>
<td>Blood urea nitrogen &gt;30 mg/dL</td>
<td>+20</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
<td>Sodium &lt;130 mmol/L</td>
<td>+20</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
<td>Glucose ≥250 mg/dL</td>
<td>+10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematocrit &lt;30%</td>
<td>+10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCO2 &lt;60 mmHg</td>
<td>+10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleural effusion</td>
<td>+10</td>
</tr>
</tbody>
</table>

and septic shock (+3 points). Summation of these points places patients into one of three classes: class I (0 to 2 points; mortality risk is less than 5%), class II (3 to 5 points; mortality risk is 25%), and class III (6 to 8 points, mortality risk is >50%). Step two is to score three independent variables during the ICU stay. These three variables and their point scores are hospital-acquired, lower respiratory tract superinfections (+1 point); nonspecific CAP-related complications (+2 points); and sepsis-related complications (+4 points). This modified risk score most significantly altered the prognosis for patients initially categorized in the moderate range (class II) risk. The adjusted risk score determined subgroups of patients within this class who exhibited significantly different mortality rates ranging from 2% to 86%. Therefore, this score may help clinicians to reassess severe CAP patients during the ICU stay.

Prevention

Immunization remains the most significant method of prevention (25). Two vaccines are available for preventing pneumococcal disease. Pneumococcal polysaccharide vaccine (PPSV23) and pneumococcal conjugate vaccine (PCV13). Currently, the Advisory Committee on Immunization Practices (ACIP) recommends that all adults 65 years of age or older receive one dose of PCV13 followed by PPSV23 one year later. Adults 19 years of age or older who have functional or anatomic asplenia, CSF leaks, cochlear implants, and immunocompromising conditions (HIV, congenital immunodeficiencies, hematologic malignancies, solid organ transplant, chronic renal disease) should receive PCV13, again followed by PPSV23 no sooner than 8 weeks later. PCV13 alone is also recommended for children 2 years of age or greater who have immunocompromising conditions such as asplenia, sickle cell disease, HIV, or other immunocompromising conditions (64–67).

The ACIP recommends that all persons >6 months of age receive influenza vaccination annually. Persons who are between 2 and 49 years of age may receive either the live-attenuated intranasal vaccine or the inactivated intramuscular injection; the inactivated influenza vaccination should be used in persons 50 and older (68).

Ventilator-associated Pneumonia

VAP is defined as a pneumonia occurring in patients undergoing MV. Although usual guidelines suggest a delay of 48 to 72 hours between the beginning of MV and the occurrence of pneumonia to qualify for this diagnosis (69), some data suggest that a pneumonia acquired earlier than the 48th hour of MV could also be considered a VAP (2,70). VAP represents 80% of pneumonia acquired during hospitalization, and is the most frequent hospital-acquired infection in ICUs.

Immediate Concerns

The major considerations regarding VAP are:
- Prevention
- Acceptable “gold standard” for diagnosis
- Increasing rates of nosocomial drug-resistant pathogens

Incidence

The exact incidence of VAP is difficult to assess, as study populations vary widely because the criteria used to define VAP has evolved, especially from organizations such as the United States Centers for Disease Control (CDC). This leads to overlap between VAP and other hospital-acquired lower respiratory tract infections, such as nosocomial tracheobronchitis, nosocomial or community-acquired aspiration, and even non-infectious respiratory illnesses. With no gold standard for diagnosis, studies show very different incidence rates ranging from 5.6% to 82.4% (Table 88.2.8) (70–78). Nevertheless, the CDC reports a decline in the incidence of VAP over the past several years in the United States, with rates up to 6% (79).

While risk for VAP increases the longer the patient is intubated, the daily hazard rate may decrease over time. In a cohort of 1,014 patients ventilated for 48 hours or more, the overall incidence of VAP was 14.8 cases per 1,000 ventilator days. The daily hazard rate for developing VAP was estimated to be 3% per day at day 5 but only 1.3% by day 15 (80). Overall, the risk of infection is the highest during the first 8 to 10 days of MV and increases with the duration of MV (80,81).

Pathogenesis

Pneumonia is essentially the introduction of pathogenic bacteria into the normally sterile lower respiratory tract, where colonization followed by invasive infection may occur (69,82). Bacteria may reach the lower respiratory tract by four different pathogenic mechanisms: (1) contiguous spread; (2) hematogenous spread; (3) inhalation; and (4) aspiration. The first

### TABLE 88.2.8 Incidence of Ventilator-associated Pneumonia in the ICU

<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients</th>
<th>Characteristics of Patients</th>
<th>Diagnostic Criteria</th>
<th>Incidence of VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres (71)</td>
<td>322</td>
<td>Medicosurgical patients</td>
<td>Clinical and XR</td>
<td>24%</td>
</tr>
<tr>
<td>Chevret (72)</td>
<td>540</td>
<td>Medicosurgical patients</td>
<td>Clinical and XR</td>
<td>12.6%</td>
</tr>
<tr>
<td>Baker (73)</td>
<td>514</td>
<td>Trauma patients</td>
<td>Clinical, XR, and Q bacteriologic cultures</td>
<td>5.6%</td>
</tr>
<tr>
<td>Chastre (74)</td>
<td>56</td>
<td>Patients with ARDS</td>
<td>Clinical, XR, and Q bacteriologic cultures</td>
<td>55%</td>
</tr>
<tr>
<td>Tejada Artigas (75)</td>
<td>103</td>
<td>Trauma patients</td>
<td>Clinical, XR, and Q bacteriologic cultures</td>
<td>22.3%</td>
</tr>
<tr>
<td>Ibrahim (76)</td>
<td>880</td>
<td>Medicosurgical patients</td>
<td>Clinical and XR</td>
<td>15%</td>
</tr>
<tr>
<td>Bouza (77)</td>
<td>356</td>
<td>Heart surgical patients</td>
<td>Clinical, XR, and Q bacteriologic cultures</td>
<td>7.9%</td>
</tr>
<tr>
<td>Hilker (78)</td>
<td>17</td>
<td>Patients with acute stroke</td>
<td>Clinical and XR</td>
<td>82.4%</td>
</tr>
</tbody>
</table>

XR, radiologic; ARDS, acute respiratory distress syndrome; Q, quantitative.
two mechanisms of invasion are infrequent (83). Inhalation refers to the direct inoculation of the respiratory tract by way of an aerosol, such as a contaminated ventilator circuit, a nebulized treatment, or even a contaminated bronchoscope; these would all be considered fairly rare events. The major mode of entry for pathogenic bacteria into the lower respiratory tract is by aspiration of oropharyngeal organisms. Colonization of the oropharyngeal airways by pathogenic micro-organisms occurs during the first week of hospitalization and they are more likely to be gram negative and drug-resistant. The endotracheal tube eliminates the protective barriers between the oropharynx and lower respiratory tract, and leakage around the endotracheal tube cuff of secretions, now colonized with more pathogenic bacteria, allows access to the trachea (69,82).

**Risk Factors**

Patient-related risk factors include male gender, pre-existing pulmonary disease, coma, AIDS, head trauma, age over 60 years, neurosurgical procedures, and multiorgan system failure (84).

The presence of MV alone is associated with a 3- to 21-fold risk of pneumonia (72). The endotracheal tube not only limits the natural elimination of oral secretions contaminated with nosocomial pathogens, but it also impairs ciliary clearance and cough. Furthermore, the MV patient requires other devices, such as nebulizers or humidifiers, which can be an additional, albeit unusual, source of micro-organisms.

Accidental extubation can be distinguished from a more controlled tracheal decannulation as independently elevating the risk for a VAP (85). This may be due to the fact that proper oral care and preparation for the extubation did not occur, and that the patient may be confused or an aspiration risk. GI factors include the use of enteral nutrition administered by a nasogastric, rather than a gastrostomy tube, and the use of H2 blockers and proton pump inhibitors which favor gastric colonization of pathogens due to the elevated pH (80,84).

Other factors that facilitate the inhalation of oropharyngeal secretions include: supine position, patient transportation out of the ICU (86), sedation (87), failed subglottic aspiration of secretions (81), and intracuff pressure less than 20 cm H2O.

**Etiology**

VAP may be caused by a wide spectrum of bacteria, and is often polymicrobial (Table 88.2.9) (88–90). *P. aeruginosa*, *S. aureus*, and gram-negative enteric bacilli are the leading etiologies. However, pathogens may differ according to patient groups, unit types, hospitals, and countries (90). Moreover, the antimicrobial resistance patterns may vary widely with geographic location.

Several studies have tried to identify specific risk factors associated with specific pathogens. The presence of an altered level of consciousness, admission into a medical ICU, and a high Simplified Acute Physiologic Score (SAPS) are independently associated with anaerobes (91). In trauma patients, tracheostomy and prior antimicrobial use with cefepime are associated with *Stenotrophomonas maltophilia* (92). Cytotoxic chemotherapy and use of corticosteroids predispose to pneumonia due to *L. pneumophila* (93). Neurosurgery, acute respiratory distress syndrome (ARDS), head trauma, and large-volume pulmonary aspiration have been associated with *Acinetobacter baumannii* (94). COPD, prior use of antibiotics, and duration of MV longer than 8 days are independently associated *P. aeruginosa* (95). Finally, coma is an independent risk factor for VAP caused by *S. aureus* (96). These risk factors are not sufficient to narrow initial empiric therapy, but are considerations when empiric therapy must be broadened in the critical patient for whom microbiologic studies are pending.

The day of onset of VAP may influence the etiology, making it potentially useful to distinguish early-onset from late-onset VAP. The definitions of early and late-onset VAP may vary, but the IDSA/ATS guidelines define duration of hospitalization fewer than 5 days as early onset, and greater than 5 days as late onset (69,82,97). In early-onset VAP, the main causative pathogens are still community-based and include *S. pneumoniae*, methicillin-susceptible *S. aureus* (MSSA), *H. influenzae*, and susceptible gram-negative enteric bacilli (97). In late-onset VAP, the organisms reflect nosocomial pathogens and include MRSA, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*.

Among these potential nosocomial pathogens, the rate of multidrug-resistant (MDR) pathogens has been increasing. Factors associated with the probability of a drug-resistant pathogen are summarized in Table 88.2.10. Duration of hospitalization (and/or MV) and prior exposure to antimicrobial agents are the major risk factors for VAP due to MDR pathogens (88,89,98–101). Finally, VAP due to fungi such as *Candida* species, *Aspergillus* species, or to viruses such as influenza, parainfluenza, and respiratory syncytial virus is uncommon in immunocompetent patients (69).

### Table 88.2.9 Micro-organisms Causing Ventilator-associated Pneumonia

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Trouillet (88)</th>
<th>Leroy (89)</th>
<th>Rello (90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
<td>135</td>
<td>124</td>
<td>290</td>
</tr>
<tr>
<td>Number of bacteria identified</td>
<td>245</td>
<td>154</td>
<td>321</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>39 (15.9%)</td>
<td>48 (31.1%)</td>
<td>102 (31.7%)</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>22 (9%)</td>
<td>9 (5.8%)</td>
<td>38 (11.8%)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>6 (2.4%)</td>
<td>8 (5.2%)</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>9 (3.7%)</td>
<td>5 (3.2%)</td>
<td>ND</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8 (3.3%)</td>
<td>8 (5.2%)</td>
<td>ND</td>
</tr>
<tr>
<td>Proteus species</td>
<td>7 (2.9%)</td>
<td>5 (3.2%)</td>
<td>ND</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>5 (2.0%)</td>
<td>7 (4.5%)</td>
<td>ND</td>
</tr>
<tr>
<td>Morganella species</td>
<td>4 (1.6%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Serratia species</td>
<td>4 (1.6%)</td>
<td>7 (4.5%)</td>
<td>ND</td>
</tr>
<tr>
<td>Haemophilus species</td>
<td>15 (6.1%)</td>
<td>10 (6.5%)</td>
<td>26 (8.1%)</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>32 (13.1%)</td>
<td>10 (6.5%)</td>
<td>10 (4.0%)</td>
</tr>
<tr>
<td>Methicillin-sensitive <em>S. aureus</em></td>
<td>20 (8.2%)</td>
<td>19 (12.4%)</td>
<td>38 (11.8%)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>3 (1.2%)</td>
<td>9 (5.8%)</td>
<td>25 (7.8%)</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>33 (13.5%)</td>
<td>2 (1.3%)</td>
<td>10 (3.1%)</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>5 (2.0%)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>4 (1.6%)</td>
<td>1 (0.6%)</td>
<td>ND</td>
</tr>
<tr>
<td>Anaerobic pathogens</td>
<td>6 (2.4%)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: no data. *Data are presented as number and (percentage).*
Diagnostic Strategies and Testing

Pneumonia is suspected when a patient exhibits signs and symptoms suggesting both pulmonary involvement and infection. There remains, however, significant interobserver variation in the interpretation of radiographs and clinical determination of pneumonia such that a clear epidemiologic definition is difficult. The CDC, accordingly, removed radiography altogether as a component of the VAP definition used in the NHSN database and currently uses the following criteria to define ventilator-associated events (VAEs), infection-related ventilator-associated complications (IVAC), and possible ventilator-associated pneumonia (PVAP) (102). For a VAE, the patient must have the following:

- A baseline period of stability or improvement on the ventilator defined by at least 2 calendar days of stable or decreasing daily minimum FiO₂ or PEEP values. The daily minimum FiO₂ or PEEP is the LOWEST value during a calendar day that has been maintained for 1 hour.
- After a period of stability, the patient must have at least one of the following indicators of worsening oxygenation:
  - Increase in daily minimum FiO₂ of at least 0.20 (20 points) over the daily minimum FiO₂ from the baseline period, and that increase must be sustained for 2 or more calendar days, or
  - Increase in daily minimum PEEP values of at least 3 cm H₂O over the daily minimum PEEP in the baseline period, sustained for 2 calendar days or longer

In addition to the above criteria, for an IVAC the patient must also have:

- On or after calendar day 3 of MV and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following:
  - Temperature over 38°C or under 36°C, or white blood cell count of at least 12,000 cells/mm³ or no more than 4,000 cells/mm³, and
  - A new antimicrobial agent is started and is continued for at least 4 calendar days.

In addition to the above criteria, for a PVAP the patient must also have:

- Positive culture of endotracheal aspirate or BAL or lung tissue or protected tip brush which meet the quantitative or semi-quantitative thresholds defined in the protocol, or
- Purulent respiratory secretions (>25 neutrophils with <10 squamous cells per low powered field, PLUS the organism is identified in one of the following:
  - Sputum, endotracheal aspirate, BAL, lung tissue, protected tip brush, or

One of the following tests must be positive as defined in the protocol:
- Pleural culture
- Lung histopathology is consistent with infection
- Diagnostic test for Legionella
- Diagnostic test for viral pathogens

The recent ATS/IDSA guidelines propose a “mixed” diagnostic strategy as follows (69):

- The diagnosis of VAP is suspected in the presence of a new or progressive pulmonary infiltrate associated with at least two of the following three infectious signs: fever over 38°C, leukocytosis or leucopenia, and/or purulent secretions. For patients with ARDS, radiographic changes are difficult to analyze, consequently, hemodynamic instability and/or deterioration of blood gases could be considered sufficient to suspect VAP.

As soon as the diagnosis is suspected, lower respiratory tract samples are obtained for microscopy, and quantitative or semi-quantitative cultures and empiric antimicrobial therapy are started unless there is both a low clinical suspicion for VAP and a negative microscopy of the respiratory sample.

On days 2 and 3, the results of cultures should be available, and the clinical response is assessed. According to whether the clinical picture is improving or worsening and the results of cultures, antimicrobial therapy will be stopped, de-escalated, or adjusted, and an investigation for other pathogens, other diagnoses, other sites of infection, or complications is performed.

With the ATS/IDSA definition, all acutely ill, MV patients should have a complete daily investigation including physical examination, an anteroposterior portable chest radiograph, measurement of arterial oxygenation saturation, and determination of necessary laboratory values (complete blood count, serum electrolytes, renal function). When VAP is suspected, each patient should have a complete physical examination to search for another source of infection, arterial blood analysis, and blood cultures collected. In cases of large pleural effusions, a diagnostic thoracentesis is indicated unless there is a contraindication. Samples of lower respiratory tract secretions (endotracheal aspirates or bronchoscopic samples) should be quantitatively cultured (69).

Finally, purulent sputum, even when associated with fever and leukocytosis, may be due only to nosocomial tracheobronchitis (103). An additional, more simplistic, definition would add the presence of a new or progressive radiographic infiltrate associated with at least two of three major clinical findings (104).

In addition to the issues with a consistent clinical definition of VAP, numerous techniques have been proposed to identify causative organism(s) of VAP. Blood cultures are rarely positive and a positive result may reflect an extrapulmonary infection (105). Pleural fluid cultures are helpful if positive, but are rarely needed. Analysis of lower respiratory tract secretions is the most frequently used technique to identify causative organism(s) of VAP. Numerous sampling methods have been described, with the major ones being endotracheal aspiration and bronchoscopic techniques with protected specimen brush (PSB) and/or BAL. These samples may be examined by various stains as described previously under CAP (Gram stains, Giemsa, acid fast stains) and by qualitative, semi-quantitative, and quantitative cultures.
Among all the described microbiologic techniques each have advantages and disadvantages (69, 82). Specifically:

- Microscopy and qualitative culture of expectorated sputum or endotracheal aspirates are associated with a high percentage of false-positive results because of colonization of the upper respiratory tract and/or tracheobronchial tree. However, the initial empiric antimicrobial treatment of VAP could be guided by a reliable tracheal aspirate Gram stain.
- Quantitative cultures with a threshold of 10^6 colony-forming units (CFU)/mL to differentiate colonization from lung infection provide a diagnostic accuracy nearly similar to that of quantitative cultures from samples obtained by bronchoscopic techniques (106, 107). Moreover, when the culture of endotracheal secretions is sterile in a patient with no recent (<72 hours) change in antimicrobial therapy, the diagnosis of a lower respiratory tract infection can be ruled out with a high probability (the negative predictive value is greater than 90%) (108).
- A PSB allows the collection of uncontaminated specimens from the potentially infected pulmonary area. A threshold set at 10^7 CFU/mL is the most adequate for quantitative cultures (109); false-positive results are infrequent (107). False-negative results may be observed when sampling is performed at an early stage of infection, in a technically incorrect (unaffected pulmonary area) manner, in a patient where a new antimicrobial treatment has been initiated, and/or if the specimens are incorrectly processed.
- BAL explores a larger lung area than PSB. Quantitative cultures of BAL fluid, with a threshold set at 10^7 CFU/mL, provided results similar to those obtained by PSB (109). Microscopic examination of the BAL specimen may add critical to rule in certain diagnoses (silver staining for Pneumocystis, for example) (110, 111).

While none of these techniques are without risk of false positives and negatives, an accurate microbiologic diagnosis may reduce VAP mortality (112) and should be attempted.

**Antibiotic Treatment**

**Principles of Initial Empiric Treatment**

Prompt initiation of adequate antimicrobials is the cornerstone of treatment for VAP, as studies have shown that inadequate initial coverage is associated with an increased mortality (98, 113–115). The excess mortality due to inadequate antimicrobial coverage is not reduced if antibiotics are corrected once bacteriologic data is available (114, 115); coverage must be broad initially then de-escalated subsequently. In addition to the proper coverage, Iregui et al. (116) showed that if the antimicrobials were delayed by ≥24 hours, mortality more than doubled (69.7% vs. 28.4%; p < 0.001).

Adequate antibiotic therapy could, therefore, be defined as the administration, at an appropriate dose, of at least one antibiotic with good pulmonary penetration, and bactericidal activity against the major causative pathogens, in a timely manner. One of the more common reasons for inadequate initial coverage is the growing pattern of antimicrobial resistant pathogen(s). Consequently, the presence or absence of risk factors for MDR pathogens (see Table 88.2.10) and the local microbiologic patterns must be considered when choosing empiric treatment.

**Guidelines for Initial Empiric Antibiotic Therapy**

The ATS/IDSA guidelines are based on the time of onset of VAP (early vs. late) and the presence of risk factors for MDR pathogens (69). In patients with no risk factors for MDR pathogens and an early-onset VAP (duration of hospitalization <5 days), limited-spectrum monotherapy targeting community-acquired pathogens has been considered appropriate (Table 88.2.11). Conversely, in patients with late-onset VAP (≥5 days) or exhibiting risk factors for MDR pathogens, broad-spectrum combination therapy with antipseudomonal and MRSA coverage is required (Table 88.2.12).

In addition to considering the underlying host factors that may be associated with a specific microbe, recent antibiotic exposure may be important. A patient who develops a VAP while on treatment for an intra-abdominal infection, perhaps with piperacillin–tazobactam, should raise the possibility of MRSA, or an ESBL or carbapenemase-producing gram-negative. In these cases, local epidemiologic patterns have been shown to improve the choice and appropriateness of broader empiric coverage (117, 118).

The question of quantitative surveillance cultures of endotracheal aspirates in ventilated patients without evidence

---

**Table 88.2.11 Initial Empiric Antibiotic Therapy in Patients with Ventilator-associated Pneumonia**

<table>
<thead>
<tr>
<th>Characteristics of Patient</th>
<th>Recommended Antibiotics and Recommended Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset VAP and no risk factors for multidrug-resistant pathogens</td>
<td>Ceftriaxone (1–2 g/24 hr) or Levofloxacin (750 mg/24 hr), moxifloxacin (400 mg/24 hr), or ciprofloxacin (400 mg/8 hr) or Ampicillin (1–2 g) plus subactam (0.5–1 g)/6 hr or Ertapenem (1 g/24 hr)</td>
</tr>
<tr>
<td>Late-onset VAP or risk factors for multidrug-resistant pathogens</td>
<td>Antipseudomonal cephalosporin: cefepime (1–2 g/6–12 hr) or ceftazidime (2 g/6 hr) or Antipseudomonal carbapenem: imipenem (500 mg/6 hr or 1 g/8 hr) or meropenem (1 g/6 hr) or β-lactam/β-lactamase inhibitor: piperacillin–tazobactam (4.5 g/6 hr) plus Antipseudomonal fluoroquinolone: levofloxacin (750 mg/24 hr) or ciprofloxacin (400 mg/8 hr) or Aminoglycoside: gentamicin (7 mg/kg/24 hr) or tobramycin (7 mg/kg/24 hr) or amikacin (20 mg/kg/24 hr) plus Vancomycin (15 mg/kg/12 hr) or Linezolid (600 mg/12 hr)</td>
</tr>
</tbody>
</table>

*Dosages are based on normal hepatic and renal function.
*Trough levels for gentamicin and tobramycin should be <1 mg/L, and for amikacin should be <4–6 mg/L.
*Trough levels for vancomycin should be <15–20 mg/L.

of VAP has been studied to decide whether they may offer important microbial information on patients should they ultimately develop symptoms of a VAP. The issue is whether this knowledge would allow for more immediate proper antibiotic choice. Michel et al. (119) reported 95% concordance between biweekly endotracheal surveillance cultures and a BAL done at the onset of the VAP. Whether this concordance reflects the true etiology of the pneumonic process or simple concordance with colonization, and whether it results in more appropriate antibiotic use and improved survival would require prospective randomized trials.

**De-escalation Strategy**

Once the results of blood or respiratory tract cultures become available, this strategy recommends the change from a broad-spectrum to a narrow-spectrum antibiotic to which the isolated organism is sensitive (i.e., imipenem to ceftriaxone when the enteric gram-negative bacilli do not exhibit ESBL), as well as removing an antibiotic from an initial combination when the anticipated organism is not recovered (i.e., discontinuation of vancomycin or linezolid when MRSA is not present) (120). Rello and colleagues (121) demonstrated that de-escalation was possible in 31.4% of the 115 patients included in their study.

**Duration of Therapy**

Until recently, the optimal duration of antibiotic therapy for VAP was unknown; lacking prospective controlled studies, experts empirically recommended a 14 to 21 days of treatment (1). A prospective, multicenter, randomized, double-blind trial was performed to determine whether shorter duration (8 vs. 15 days) therapy was equally effective. Patients receiving appropriate antimicrobial treatment during the shorter course (8 days) had similar survival and relapse rates as compared with patients treated for 15 days. For patients suffering from VAP due to nonlactose fermenting gram-negative bacilli (*P. aeruginosa* and *A. baumannii*), although the outcome was similar in the two groups, there was a trend to greater rates of pulmonary infection recurrences (relapses and/or superinfection) in the short duration of treatment group (122). Consequently, ATS/IDSA guidelines suggest shortening the duration of therapy to 7 days, unless the pathogen is *P. aeruginosa* or *A. baumannii*, as long as the patient exhibits a good clinical response (69). Regardless of the specific treatment duration, if aminoglycosides are used in combination with other agents, they may be stopped after no more than 5 to 7 days (69).

Empiric therapy may safely be discontinued after 72 hours if a noninfectious etiology for the pulmonary infiltrates is discovered, or microbiologic data is negative (123,124).

**Specific Antibiotic Regimens**

For VAP caused by *P. aeruginosa*, many recommend combination therapy. The purpose of combination therapy is to achieve antibiotic synergy and prevent the emergence of resistant strains during treatment. However, two meta-analyses on treatment of septic patients, showed that the combination β-lactam plus aminoglycoside compared with β-lactam monotherapy provided no clinical benefit (125), nor did it affect the emergence of antimicrobial resistance (126). However, there were a low number of studies evaluated, and the aminoglycoside dosing was outdated. Therefore, these results are probably insufficient to categorically abandon the practice of short-term aminoglycoside–β-lactam combination therapy for pneumonia caused by *P. aeruginosa*.

Vancomycin remains the accepted standard therapy for treatment of serious infections due to MRSA, with linezolid considered an alternative in some circumstances. Two multicenter studies demonstrated equivalence between linezolid and vancomycin for treatment of HAP due to MRSA; when combining these studies there is a suggestion of lower mortality in the linezolid subgroup, though prospective trials are required (127–129). Nevertheless, linezolid may be preferred to vancomycin in patients with or at risk for renal insufficiency (69).

*A. baumannii* exhibits native resistance to many classes of antimicrobial agents, including carbapenems. Despite the nephrotoxicity of polymyxins, they may be safely used and efficacy has been demonstrated for intravenous colistin in these patients when sensitivity to other antimicrobials is not present (130).

**Local Instillation and Aerosolized Antibiotics**

Although aminoglycosides and polymyxin B have been used by aerosolization to treat VAP due to pathogens that are resistant...
to systemic antimicrobials, there is insufficient data to recommend the use of aerosolized antibiotics routinely for treatment of pneumonia (69).

Response to Therapy

Normal Pattern of Resolution

Improvement usually becomes apparent after 48 to 72 hours of adequate antibiotic therapy. Thus, unless there is clinical deterioration, antimicrobial therapy should not be changed during this period (69).

Clinical response is usually first seen with resolution of fever and improvement in oxygenation. Fever typically resolves in about 72 hours and, in patients without ARDS, a PaO2/FiO2 ratio >250 should occur within that same timeframe. For patients with ARDS, hypoxemia obviously resolves more slowly and cannot be used to indicate appropriateness of VAP treatment (131).

Radiographic studies do not show rapid resolution when the diagnosis of VAP is accurate; in fact, rapid resolution would suggest an alternative diagnosis. Similarly, while leukocytosis should improve with adequate therapy, the improvement may be confounded by other physiologic stressors and cannot be used as a definitive indicator of successful treatment (131,132).

Reasons for Deterioration or Nonresolution

When a patient fails to improve or exhibits rapid deterioration, several causes may be considered (see Table 88.2.12) (69). In these patients, the following may be considered:

- Antimicrobial choice. The antimicrobial spectrum may need to be broadened to cover more resistant or alternate pathogens. Consideration should be given to repeat culturing of the lower respiratory secretions or use of alternative diagnostic tests (i.e., if not already performed, Legionella, rapid viral studies, or search for noninfectious diagnoses).

- Noninfectious process. Consider fever or sepsis due to another site of infection, or occurrence of pulmonary complications such as empyema. If not already done, blood and urine cultures should be performed and a CT scan ought to be considered to evaluate potential thoracic and extrathoracic sites of infection (sinuses, pleural space, abdomen, and pelvis).

- Of note, a high percentage of patients may not respond to treatment quickly. Ioanas et al. (133) observed that the rate of nonresponse could be as high as 62%. The main causes were inappropriate initial antimicrobial treatment (23%), superinfections (14%), another site of infection (27%), and a noninfectious process (16%). In 36% of nonresponding patients, no cause could be identified.

Prognosis

Crude mortality rates associated with VAP vary from 24% to 76% (82). The wide range of rates may be due to differences in VAP definitions, diagnostic criteria and, hence, studied populations. It may also in part reflect the pathogenicity of a wide range of causative organisms.

Furthermore, case-control studies comparing attributable mortality of VAP in patients controlled for ICU admission, admitting diagnosis, duration of MV, and severity of underlying comorbid conditions show VAP attributable mortality ranging up to 25% (134–136).

Risk factors associated with death from VAP include (114–116,137–140):

- Underlying comorbidities (malignancy, immunosuppression, anticipated death within 5 years, American Society of Anesthesiology [ASA] score ≥3)
- Age >64 years
- High APACHE II score, simplify Acute Physiology Score <37
- Multilobar disease
- Platelet count <150,000 cells/μL
- Logistic Organ Dysfunction score <4
- Time of onset of VAP <3 days
- Recent surgery
- Hypotension
- Delay in appropriate antibiotic treatment.

Prevention

Basic infection control techniques such as hand washing, glove use, sterile equipment, and adequate staffing help to limit cross-contamination of resistant organisms through health care workers. In addition, there are specific preventative measures that can greatly decrease risk for a VAP (84,141).

First, the primary intervention to reduce any device-associated hospital-acquired infection (HAI) is to minimize the use of the device. Noninvasive positive pressure ventilation should be maximized and is associated with a relative risk reduction for VAP ranging from 0.67 to 0.87. When intubation and MV are necessary, optimizing sedation and weaning protocols may diminish duration of ventilatory support. Continuous aspiration of subglottic secretions by way of an endotracheal tube with a subglottic port that can be attached to continuous suction (about 90 mmHg) to remove oral secretions is associated with a relative risk reduction VAP of 0.45. Raising the head of the bed by a minimum of 30 degrees and up to 45 degrees reduces VAP incidence. Other aspects of a VAP prevention bundle may include stress ulcer prophylaxis, gastrostomy tube feedings as opposed to use of an orogastric or nasogastric tube, proper ventilator circuitry management, and glycemic control (142).

The CDC published 2004 guidelines on the prevention of VAP (143). In that bundled approach to VAP prevention, only four measures were recommended as per Table 88.2.13.

One last, highly controversial, issue is the use of selective digestive decontamination (SDD) (84,141,144). Topical nonabsorbed antimicrobials (usually combining polymyxin, amingoglycoside, and amphotericin B) with or without the addition of a short-duration systemic broad-spectrum antibiotic are ingested. The theory is that these agents will eradicate potential pathogens (gram-negative aerobic intestinal bacteria, S. aureus, and fungi) but not the anaerobic flora. Impressive

<table>
<thead>
<tr>
<th>TABLE 88.2.13 Measures Recommended by the Centers for Disease Control and Prevention to Reduce the Incidence of VAP (143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Changing the breathing circuits of ventilators only when they malfunction or are visibly contaminated</td>
</tr>
<tr>
<td>- Preferential use of orotracheal rather than nasotracheal tubes</td>
</tr>
<tr>
<td>- Use of noninvasive ventilation</td>
</tr>
<tr>
<td>- Use of an endotracheal tube with a dorsal lumen to allow drainage of respiratory secretions</td>
</tr>
</tbody>
</table>
intravenous antibiotic therapy, chemotherapy, or wound care

for any patient who was hospitalized in an acute care hospital.

HCAP refers to patients who develop pneumonia in the setting of frequent health care contact. Generally, this includes any patient who was hospitalized in an acute care hospital for >2 days within 90 days of the infection; resides in a nursing home or long-term care facility (LTCF); received recent intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of the current infection; or attends a hospital or hemodialysis clinic.

While HCAP refers to pneumonia in several diverse outpatient populations listed above, it is the second most common infection in LTCFs, with an incidence of 0.3 to 4.7 cases per 1,000 resident days (148). Pneumonia is also an independent risk factor for death in this population with mortality that ranges from 5% to 40% (149,150).

It is important to comment on some differences in the elderly and specifically nursing home (LTCF) population with regard to clinical presentation. Notably, fever and respiratory signs may be minimal, while an altered mental status might be the primary symptom (151). Risk factors for pneumonia include decreased functional status, diminished ability to clear airways, underlying comorbidities (such as COPD and heart disease), swallowing disorders, and use of sedatives. Furthermore, the etiology of HCAP in this population suggests a large proportion of gram-negative bacilli and *S. aureus*. However, when using stricter criteria for sputum interpretation (152), *S. pneumoniae* and *H. influenzae* are major pathogens, while gram-negative bacilli account for 0% to 12% of cases (152,153).

The ATS/IDSA (69) guidelines recommend that, in the hospital, these patients be managed like those with HAP (see Tables 88.2.11 and 88.2.12).

### TRACHEOBRONCHITIS

#### Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Acute exacerbation of COPD (COPD-E) is defined by an alteration in the patient’s baseline dyspnea, cough, and/or sputum production (154). The need for ICU or intermediate care unit admission is based on the severity of respiratory failure and/or the presence of associated organ dysfunction (i.e., shock, hemodynamic instability, neurologic disturbances) (154). Therapy in the ICU includes supplemental oxygen, ventilatory support, bronchodilators, corticosteroids, and antibiotics (154); only the latter point will be further discussed here.

The role of bacterial infection in COPD-E remains controversial. As noted by Murphy et al. (155,156), this point is still debated for the following reasons:

- Bacteria routinely colonize the lower respiratory tract of COPD patients.
- Bacteria colonizing the lower respiratory tract vary from one patient to another, as COPD patients are heterogeneous.
- Information provided by sputum culture may not represent conditions in the distal airways.
- Only half of the episodes of acute COPD-E are linked to bacterial causes.
- Animal models are limited by the fact that the most frequently isolated organisms (*S. pneumoniae, H. influenzae, Moraxella catarrhalis*) are exclusively human pathogens.
- Clinical studies on the impact of antibiotic therapy for acute COPD-E suggest that these drugs provide only a small improvement in the most severely ill patients.

Despite this, the ATS/European Respiratory Society Task Force recommends antibiotic treatment in all patients suffering from a severe acute COPD-E requiring ICU admission (154). Two studies support this recommendation. A prospective, randomized, double-blinded, placebo-controlled trial assessing

**Table 88.2.14 Micro-organisms That Cause Hospital-acquired Pneumonia**

<table>
<thead>
<tr>
<th>Micro-organisms</th>
<th>Valles (146)</th>
<th>Spena (147)</th>
<th>Kolleff (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
<td>96</td>
<td>166</td>
<td>835</td>
</tr>
<tr>
<td>Number of bacteria identified</td>
<td>75</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>18 (24%)</td>
<td>7 (11.7%)</td>
<td>18.4%</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>1</td>
<td>5 (8.3%)</td>
<td>2.0%</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>7 (9.3%)</td>
<td>8 (13.3%)</td>
<td>16.1%</td>
</tr>
<tr>
<td><em>Haemophilus species</em></td>
<td>2</td>
<td>2 (3.3%)</td>
<td>5.6%</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>9 (12%)</td>
<td>7 (11.7%)</td>
<td>ND</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>9 (12%)</td>
<td>1 (1.6%)</td>
<td>22.9%</td>
</tr>
<tr>
<td>Methicillin-sensitive <em>S. aureus</em></td>
<td>11 (15%)</td>
<td>3 (6%)</td>
<td>26.2%</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2</td>
<td>16 (26.7%)</td>
<td>3.1%</td>
</tr>
<tr>
<td><em>Enterococcus species</em></td>
<td>ND</td>
<td>ND</td>
<td>13.9%</td>
</tr>
<tr>
<td>Coagulase-negative <em>staphylococcus</em></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Anaerobic pathogens</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><em>Aspergillus species</em></td>
<td>13 (17%)</td>
<td>7 (11.7%)</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, no data.

*Data are presented as number and/or (percentage).*

results have been recently published, though in unblended trials (145). The preventive effects of SDD for VAP are thought to be lower in ICUs with high endemic levels of antibiotic resistance, and, in such cases, SDD may increase the incidence of drug-resistant micro-organisms. Thus, to date, the routine use of SDD in ICUs is not recommended.

### Health Care-associated Pneumonia and Nursing Home Pneumonia

HCAP refers to patients who develop pneumonia in the setting of frequent health care contact. Generally, this includes any patient who was hospitalized in an acute care hospital for >2 days within 90 days of the infection; resides in a nursing home or long-term care facility (LTCF); received recent intravenous antibiotic therapy, chemotherapy, or wound care...
the effects of ofloxacin showed a reduction in mortality, length of hospital stay, and length of MV (157). Similarly, Ferrer et al. (158) observed that inadequate initial antibiotic treatment increased hospital mortality and was associated with failure of noninvasive ventilation. Inadequacy of initial empiric treatment mainly occurred when colonizing pathogens were not the usual community-acquired pathogens (S. pneumoniae, H. influenzae, M. catarrhalis), but were instead nonfermenting (P. aeruginosa) or enteric gram-negative bacilli. Hammond et al. (165) Wang (166)

Current recommendations include treatment with amoxicillin/clavulanate or respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin) (154). If Pseudomonas spp. or Enterobacteriaceae spp. are suspected, combination therapy should be considered with a β-lactam antibiotic and an antipseudomonal fluoroquinolone or an aminoglycoside (154,159).

**Nosocomial Tracheobronchitis**

Few studies have addressed nosocomial tracheobronchitis acquired during MV (160). In a retrospective analysis of 2,128 patients mechanically ventilated more than 48 hours, the incidence of nosocomial tracheobronchitis was 10.6%, without any significant difference between medical (9.9%; 165 of 1,655) and surgical patients (15.3%; 36 of 234) (103). In patients without underlying chronic pulmonary disease, the incidence was similarly 8% (161). The interval between initiation of MV and occurrence of tracheobronchitis averaged approximately 10 days. In medical patients, nosocomial tracheobronchitis was significantly associated with age under 60 years (OR = 1.8), COPD (OR = 1.57), and receiving prior antibiotics within the 2 weeks of ICU admission (OR = 1.52). Major pathogens identified in tracheal aspirate cultures were P. aeruginosa, A. baumannii, and MRSA.

The impact of nosocomial tracheobronchitis on patient outcome is unclear. Two case-control studies compared patients with and without nosocomial tracheobronchitis. In both COPD patients and in those without chronic pulmonary disease, nosocomial tracheobronchitis was associated with longer durations of MV and ICU stay, but no increased mortality (161,162).

Indications for antibiotic treatment in these patients remain unclear. There is, however, increasing evidence that antimicrobial therapy, when targeted against a purulent endotracheal aspirate culture, may reduce duration of MV and the rate of VAP (162–164).

**LUNG ABSCESS**

Lung abscesses may be associated with aspiration pneumonia, poor dental hygiene, alcohol consumption, or chronic lung disease (165). It is relatively uncommon in developed countries, where it occurs mostly in immunosuppressed patients or as a postobstructive complication. Risk factors and underlying diseases are listed in Table 88.2.15 (165,166).

**Bacteriology**

Anaerobes play a more dominant role in cases of parenchymal abscess as compared with pneumonia. Some studies note anaerobes to be the cause in 60% to 80% of cases (167), usually in a polymicrobial setting. Hammond et al. (165) in a study of 34 patients with community-acquired lung abscess, identified 2.3 bacterial species per episode; anaerobes were identified in 75% of cases. Contrary to those findings, a study of 90 patients with lung abscesses in Taiwan observed polymicrobial infection in only 20% of cases, while gram-negative bacilli, notably K. pneumoniae, were identified 47% of the time and anaerobes were isolated in 31% (Table 88.2.16) (166).

**Diagnosis**

Blood cultures and sputum examination are rarely positive (165,166). Methods to obtain a specimen uncontaminated by upper airway bacteria include percutaneous aspiration, transtracheal aspiration, or thoracentesis from empyema fluid. With the exception of thoracentesis when appropriate, the other invasive measures are rarely performed.

**Antimicrobial Therapy**

Lung abscesses are generally treated successfully with prolonged systemic antibiotic therapy. The preferred choice, based on the high frequency of anaerobes, is clindamycin or

**Table 88.2.15 Risk Factors and Underlying Diseases of Adult Patients with Community-acquired Lung Abscess**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hammond (165)</th>
<th>Wang (166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>90</td>
</tr>
<tr>
<td>Smoking</td>
<td>ND</td>
<td>57%</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ND</td>
<td>31%</td>
</tr>
<tr>
<td>Previous aspiration pneumonia</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>38%</td>
<td>14%</td>
</tr>
<tr>
<td>Dental caries</td>
<td>26%</td>
<td>ND</td>
</tr>
<tr>
<td>CNS disease</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>ND</td>
<td>11%</td>
</tr>
<tr>
<td>Steroid use/SLE</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>None</td>
<td>12%</td>
<td>18%</td>
</tr>
</tbody>
</table>

ND, no data; CNS, central nervous system; SLE, systemic lupus erythematosus.

**Table 88.2.16 Pathogens Isolated from Adult Patients with Community-acquired Lung Abscesses**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Hammond (165)</th>
<th>Wang (166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>90</td>
</tr>
<tr>
<td>Number of bacteria identified</td>
<td>79</td>
<td>118</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>59 (75%)</td>
<td>40 (34%)</td>
</tr>
<tr>
<td>Microaerophilic streptococci</td>
<td>7 (20%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Prevotella</td>
<td>17 (50%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>4 (12%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Fusobacterium</td>
<td>4 (12%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Porphyromonas</td>
<td>7 (20%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>3 (9%)</td>
<td>42 (47%)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2 (6%)</td>
<td>30 (33%)</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>12 (35%)</td>
<td>30 (33%)</td>
</tr>
<tr>
<td>Streptococcus milleri</td>
<td>ND</td>
<td>19 (21%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5 (15%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vindans streptococci</td>
<td>7 (20%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (15%)</td>
<td>5 (6%)</td>
</tr>
</tbody>
</table>

ND, no data.

| Other data are presented as number and (percentage).
a β-lactamase inhibitor/aminopenicillin (167,168). Both regimens obtain cure rates between 60% and 70% with a 3-week course of therapy. Surgical resection or an invasive drainage procedure of the diseased lung and abscess are sometimes necessary (169,170).

EMPYEMA (PLEURAL INFECTION)

Pathophysiology

The pleural space is normally sterile. Pleural effusion is favored by an increase in the hydrostatic pressure, a decrease of oncotic pressure, or alterations of pleural permeability. Infection follows contamination of pleural fluid. The formation of an empyema is arbitrarily divided into three phases: (1) an exudative phase with accumulation of pus; (2) a fibropurulent phase with fibrin deposition and localization of pleural exudate; and (3) an organization phase with fibroblast proliferation leading to scar formation and lung entrapment (171).

In up to 50% of cases, empyema is a complication of pneumonia; approximately one-fourth of empyemas are due to a traumatic or iatrogenic injury (surgery, thoracentesis, chest tube placement). In the remaining cases, pleural infection is due to a contiguous infection (i.e., mediastinum, esophagus, subdiaphragmatic areas) extending to the pleura (171).

Bacteriology

The bacterial etiology of empyema depends on the underlying mechanism leading to pleural colonization. With 75% of empyemas developing as a complication of pneumonia or traumatic or iatrogenic injury, most isolated aerobic organisms are Streptococcus species, S. pneumoniae, and S. aureus. The main isolated aerobic gram-negative organisms are Klebsiella species, P. aeruginosa, H. influenzae, and Escherichia coli. These organisms are commonly part of a mixed growth with anaerobes; anaerobic isolates are identified in 12% to 34% of cultures. They can cause empyema without aerobic copathogens in about 15% of cases (171,172).

Treatment

Identification of Pleural Effusion

In patients suffering from empyema, clinical symptoms may include fever, chills, chest pain—particularly with inspiration—and night sweats. Physical examination tends to show diminished breath sounds and, possibly, a friction rub. In patients on MV, these signs may be more difficult to ascertain (171). Chest radiography shows blunting of the costo-diaphragmatic angle when the volume of pleural fluid exceeds 200 mL. The presence of a concomitant pulmonary infiltrate suggests a para-pneumonic effusion which may or may not have evolved to empyema (172). Ultrasonography is useful in unstable or night sweats. Physical examination tends to show diminishment of breath sounds and, possibly, a friction rub. In patients on MV, these signs may be more difficult to ascertain (171). Chest tube drainage is indicated in patients with frankly purulent or turbid/cloudy pleural fluid. Similarly, patients with a pleural fluid pH less than 7.2 and the presence of pathogens identified by Gram stain or culture should receive chest tube drainage (172). Furthermore, when there is not clinical improvement with antimicrobials alone or when the pleural fluid becomes loculated, drainage should be considered.

The use of intrapleural fibrinolytic drugs have not shown consistent benefit. In a randomized, double-blind trial comparing intrapleural streptokinase (250,000 IU twice daily for 3 days) to placebo among 427 studied patients, streptokinase did not reduce mortality, need for drainage surgery, duration...
of hospital stay, and it did not improve radiographic and spirometric outcomes (173). The routine use of fibrinolytic treatment for patients requiring chest tube drainage for empyema or complicated para-pneumonic effusion is not recommended based on a meta-analysis of available data (174).

**Surgical Treatment**

Surgical treatment must be considered in all patients who do not resolve the infection despite antibiotics and chest tube drainage. Different surgical approaches have been described. The choice between video-assisted thoracoscopic surgery (VATS), open thoracic drainage, or thoracotomy with decortication depends on the patient status (age, comorbidity), surgeon preferences, and anatomy of pleural effusion assessed by recent thoracic CT scanning (172).

**SUMMARY**

Pneumonia remains a common and morbid infection in the community in hospitalized and in ventilated patients. Management of severe pneumonia in the ICU may be challenging as the diagnosis can be difficult, and no gold standard exists for the definition of VAP. Preventive strategies for CAP are limited to influenza and pneumococcal vaccinations. However, in the hospitalized critically ill, mechanically ventilated patient, more opportunity exists for aggressive preventative measures focused on oral care and management of oral secretions.

Despite adequate treatment, the death rate remains elevated, ranging from 18% to 46% in CAP, and 24% to 76% in VAP. Adequate antimicrobial therapy is paramount for successful treatment but is increasingly complex. Drug choice depends on numerous factors: pharmacodynamics/pharmacokinetics, spectrum, hospital or health care exposure, dosing schedule, adverse events, costs, and availability. The rise of antimicrobial resistance complicates therapeutic guidelines and empiric therapy needs to be regularly adapted to local resistance patterns.

**Key Points**

- Lower respiratory tract infections in the critical care population are common and include pneumonia, tracheobronchitis, and pleural space infections. Pneumonia carries significant morbidity and mortality depending upon certain host factors, presenting signs and symptoms, and the timing of initial and appropriate antimicrobial therapy.
- Traditionally, pneumonia was simply categorized as either community- or hospital-acquired, but the complexity of interactions between patients and the health care environment has led to further subdivisions which are now: CAP, HCAP, HAP, or VAP.
- The diagnosis of pneumonia depends on various clinical elements including signs of a systemic inflammatory response syndrome, impaired oxygenation, radiographic infiltrates, and microbial testing but, importantly, there is no one simple gold standard for diagnosis.
- Of the major categories of pneumonia, prevention strategies are most clearly defined for VAP, where certain “bundled” interventions are associated with dramatic decreases in incidence.
- Bacterial pathogens that predominate as causes of lower respiratory infections have evolved more resistant antimicrobial patterns, particularly in the hospital environment, making choices of empiric therapy more difficult and reliant on local resistance patterns.

**References**


**ACKNOWLEDGMENT**

The authors thank Serge Alfantandi, MD, MSc, for his contribution to this topic in the previous edition.


Section 3
Urinary Tract Infections
MARC LEONE, GARY DUCLOS, and CLAUDE MARTIN

INTRODUCTION

The intensive care units (ICUs) represent a meeting point between the most seriously ill patients receiving aggressive therapy and the most resistant pathogens, which are selected by the use of broad-spectrum antimicrobial therapy. ICU patients require indwelling devices associated with an increased risk of infection. Most patients who are hospitalized in ICUs receive an indwelling urinary catheter to monitor diuresis; urinary tract infection (UTI) remains a leading cause of nosocomial infections with significant morbidity, mortality, and additional hospital costs (1,2).

Although UTI represents 30% to 40% of nosocomial infections (3), its prevalence in patients admitted to ICU is about 10%, depending on ICU patient’s type (1). In a large European survey, UTI is the third most common cause of infections in ICU (4). Another study suggests that the incidence of urosepsis, which is defined as an inflammation of the upper urinary tract that causes sepsis and bacteremia occurs in approximately 18% of the ICU patient population (5). The aim of this review is to focus on the prevention and management of UTI in patients hospitalized in ICU.

DEFINITIONS

In ICU, UTI is the consequence of the presence of an indwelling catheter (Table 88.3.17). This results in the concept of catheter-associated UTI (CAUTI) (Table 88.3.18), which is defined by Center of Disease Control and prevention (CDC) by the presence of three criteria: presence of an indwelling urinary bladder catheter (IUBC) for more than 2 days; bacteria in the bladder of a patient; and at least one of the following signs or symptoms: fever (>38°C), suprapubic tenderness or costovertebral angle pain or tenderness (6). Bacteriuria was defined as the detection of ≥10^5 organisms/mL of urine with no more than two species of organisms (6). In the ICU, the clinical symptoms can be missing due to the patient’s lack of awareness.

Pathophysiology

With the exception of distal urethra, the urinary tract is normally sterile. The resistance to UTI is influenced by exposure to uropathogenic bacteria, age, hormonal status, and urine flow (7,8). The insertion of an IUBC allows organisms to gain access to the bladder; the device induces an inflammation of the urethra, allowing bacteria to ascend into the bladder in the space between the urethral mucosa and the catheter. CAUTI usually follows formation of biofilm, which consists of adherent micro-organisms, their extracellular products, and host components deposited on both the internal and external catheter surface. The biofilm protects organisms from both antimicrobials and the host immune response.
The isolated pathogens among ICU patients with bacteriuria are essentially *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterococcus* species (1,10,11); polymicrobial infections represent only 5% to 12% (3,10) of cases. In the largest report investigating nosocomial infections in ICU patients, gram-negative bacteria are responsible for 70% of CAUTIs (1).

### Microbiology

The ascending route of infection is predominant in women because of the short urethra and contamination with the anal flora. Intraluminal contamination is less frequent, and is related to reflux of pathogens from the drainage system into the bladder. This contamination occurs in case of failure of closed drainage or contamination of urine in the collection bag.

### Risk Factors

In ICU patients, UTIs are associated with the presence of an IUBC. Among 10,755 patients in a trauma center, risk factors were female gender (59%) and age (>57 years old) (12). Accordingly to prior studies, female gender, length of ICU stay, prior use of antibiotics, severity score at admission, and duration of catheterization were independently associated with an increased risk of catheter-associated bacteriuria (13–15). These results emphasize that preventing or reducing the duration of catheterization is the most important intervention. In a tertiary care hospital, the initial indication for the placement of a urinary catheter was unjustified in 15% of patients and unclear in 28% of patients (14); as a result, the length of stay and cost of care were increased (15). In the medical ICU, an excessively prolonged use of urinary catheter for monitoring urine output resulted in 64% of the total unjustified patient days (16).

### Impact of CAUTIs in ICU

Although adverse consequences of asymptomatic UTIs are described during pregnancy or in nursing home (17,18), the real impact of ICU-acquired CAUTIs on outcome remains unclear. In a general hospital population, Platt et al. (19)
an older medical ICU study, it had been demonstrated that and urinary nitrite production an indicator of bacteriuria. In (29,30). Leukocyte esterase activity is an indicator of pyuria instead of quantitative urine culture in ICU (Table 88.3.21) sticks (leukocyte esterase and nitrite) for screening patients recommended (28)

incidence of symptomatic, catheter-associated UTI and is not routine daily bacteriologic monitoring of the urine from all catheterized patients is not an effective way to decrease the incidence of symptomatic, catheter-associated UTI (5). Accordingly, in a prospective randomized study, 6 out of 60 patients with an IUBC and asymptomatic bacteriuria developed urosepsis (25). Risk factors of developing an urinary tract–related bloodstream infections. The mortality rates of the patients were not influenced by the presence of CAUTI (5). Furthermore, in a prospective randomized study, 6 out of 60 patients with an IUBC and asymptomatic bacteriuria developed urosepsis (25). Risk factors of developing an urinary tract–related bloodstream infection were neutropenia, renal disease, male gender, insulin, and immunosuppressant therapy (26).

Finally, the CAUTIs result in a significant increase in cost. An episode of symptomatic nosocomial CAUTI in hospitalized patients was associated with an additional cost of US$749—1,007/admission (24,25). Among the nosocomial infections, UTIs had the lowest daily antibiotic cost per infected patient (27).

**DIAGNOSTIC TOOLS IN THE ICU**

The diagnosis of urosepsis should be entertained each time a patient has a febrile episode. Because of the prevalence of bacteriuria in patients with urinary catheters, some have advocated daily monitoring of urine in catheterized patients; however, routine daily bacteriologic monitoring of the urine from all catheterized patients is not an effective way to decrease the incidence of symptomatic, catheter-associated UTI and is not recommended (28).

Some clinical trials assess the effectiveness of urinary dipsticks (leukocyte esterase and nitrite) for screening patients instead of quantitative urine culture in ICU (Table 88.3.21) (29,30). Leukocyte esterase activity is an indicator of pyuria and urinary nitrite production an indicator of bacteriuria. In an older medical ICU study, it had been demonstrated that the urinary dipstick strategy was a rapid and cost-effective test with which to screen asymptomatic catheterized patients (29,31,32). This effectiveness was observed only for a positive quantitative urine culture level of 10⁷ organisms/mL; in these cases, the urinary dipstick strategy decreased the cost of nosocomial infection diagnosis and the daily workload in the microbiology laboratory. The authors concluded that the urinary dipsticks were a cost-effective test for screening asymptomatic catheterized patients in a medical ICU (29). During a 2-year period, however, Coman et al. (30) did not show an impact of urinary dipstick on symptomatic CAUTI with fever or hypothermia. The Cochrane review concluded that the effectiveness of urinary dipstick remains unresolved due to the lack of good quality studies (33). The use of dipsticks instead of quantitative urine culture cannot be recommended for symptomatic CAUTIs in ICU patients. Guidelines recommend that asymptomatic bacteriuria or funguria should not be screened for in patients with IUBCs (34). Hence, in symptomatic patients, quantitative urine culture with Gram stain examination is recommended to obtain rapid identification of the pathogen.

**PREVENTION OF UTI IN THE ICU**

Most measures, described below, are useful only in units with a restrictive policy of catheterization (Table 88.3.22).

**Urinary Drainage System**

For preventing infection, the maintenance of a closed, sterile drainage system is recommended (35); this was described for the first time in 1928 (36), and its benefit has been subsequently re-enforced. In a randomized study, a subgroup analysis, which considered patients not receiving an antibiotic treatment, showed a reduction in mortality in the group using the closed system (37). Historically, “open systems” were large, uncapped glass bottles. The drainage catheters were inserted into the glass bottles, often below the level of urine; urine was stagnant, and bacteria could easily grow and ascend through the drainage catheter. The introduction of closed drainage systems was an improvement, dramatically reducing the rate of bacteriuria. However, in the modern era, several studies failed to confirm the benefit of complex closed system compared with simple devices (38,39).

Two studies focused specifically on ICU patients (40,41), comparing a two-chamber drainage system with a complex closed drainage system. In a randomized and prospective trial, 311 patients requiring an IUBC for longer than 48 hours

---

**TABLE 88.3.20 Rates of Sepsis According to Each Site**

<table>
<thead>
<tr>
<th>Study</th>
<th>Lung</th>
<th>Abdomen</th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincent (4) (N = 7,087)</td>
<td>63.5%</td>
<td>19.6%</td>
<td>15.1%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Vincent (21) (N = 1,177)</td>
<td>68%</td>
<td>22%</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>Angus (22) (N = 192,980)</td>
<td>44%</td>
<td>8.6%</td>
<td>17.3%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

**TABLE 88.3.21 Assessing Urinary Reagent Strips in the ICU**

<table>
<thead>
<tr>
<th>Study</th>
<th>Tissot (29)</th>
<th>Mimoz (32)</th>
<th>Legras (31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>31%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td>84%</td>
<td>90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>41%</td>
<td>65%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>31%</td>
<td>46%</td>
<td>61%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96%</td>
<td>81%</td>
<td>91%</td>
</tr>
</tbody>
</table>
were assigned to the two-chamber drainage system group or to a complex closed drainage system group to compare the rates of bacteriuria. Rates of UTIs were 12.1 and 12.8 episodes/1,000 catheter days, respectively \( (p > 0.05) \) (40). The data extracted from the literature do not support the use of complex closed drainage systems in ICU patients in view of the increased cost (42).

For the management of drainage systems, owing to the lack of specific studies in ICU, guidelines may be viewed as recommendations at best. The following are reasonable suggestions: only persons who know the correct technique of aseptic insertion and maintenance of the catheter should handle catheters; hospital personnel should be given periodic in-service training stressing the correct techniques and potential complications of urinary catheterization; hand-washing should be done immediately before and after any manipulation of the catheter site or apparatus; if small volumes of fresh urine are needed for examination, the distal end of the catheter, or preferably the sampling port if present, should be cleansed with a disinfectant, and urine then aspirated with a sterile needle and syringe; larger volumes of urine for special analyses should be obtained aseptically from the drainage bag; unobstructed flow should be maintained; to achieve free flow of urine, (1) the catheter and the collecting tube should be kept from kinking; (2) the collecting bag should be emptied regularly using a separate spigot and nonsterile collecting container should never come in contact; (3) poorly functioning or obstructed catheters should not be irrigated in routine but replaced after reconsidering indication of urinary catheter; (4) collecting bags should always be kept below the level of the bladder; and (5) IUBCs should not be changed at arbitrary fixed intervals (34,43,44).

### Type of Urethral Catheters

There is a vast literature stressing the efficacy of antiseptic impregnated catheters, including silver oxide or silver alloy, and antibiotic-impregnated catheters in hospitalized patients (45–47). In the largest RCT, Pickard et al. showed a nonclinically relevant benefit of using nitrofurazone-impregnated catheters to reduce CAUTI versus silver-coated or standard catheters (47). Diagnosis of CAUTI was supported by microbiologic culture and use of antibiotic, but the difference is probably not clinically relevant (48). A recent Cochrane meta-analysis compared the effectiveness of different indwelling urethral catheters in reducing risk of CAUTI for short-term catheterization (<14 days) (42); silver oxide and silver alloy catheters were not associated with a reduction of CAUTI in short-term catheterized hospitalized adults. Catheters coated with a combination of minocycline and rifampin or nitrofurazone may be beneficial in reducing bacteriuria and symptomatic CAUTI in hospitalized males catheterized less than 2 weeks, but this requires further assessment (42). Comparison of nitrofurazone-coated and silver alloy–coated catheters results in a superiority of antibiotic-coated in reducing bacteriuria and symptomatic CAUTI, but the magnitude of reduction was low and hence may not be clinically relevant (42). However, those catheters are more expensive and are more likely to cause discomfort than standard catheters (42).

In ICU patients, a randomized, prospective, double-blind multicenter trial compared catheters coated with hydrogel and silver salts with classical urinary tract catheters (49). The cumulative incidence of UTIs associated with catheterization was 11.1% overall, 11.9% for the control group, and 10% for the coated catheter group. The odds ratio was 0.82 (95% confidence interval [CI]: 0.30 to 2.20) (49). In a prior blind prospective trial, standard latex IUBCs were switched for a hydrogel latex IUCB with a monolayer of silver metal applied to the inner and outer surfaces of the catheter. The adjusted CAUTI rates during the baseline and intervention periods were 8.1 and 4.9 infections/1,000 device days, respectively \( (p = 0.13) \) (47). With respect to long-term bladder drainage, a Cochrane meta-analysis showed that no eligible trials compared alternative routes of catheter insertion or catheter types (48).

### Meatal Care

Twice daily cleansing with povidone–iodine solution and daily cleansing with soap and water have failed to reduce CAUTIs; thus, at this time, daily meatal care with either of these two regimens cannot be endorsed (34). A randomized, controlled, prospective clinical trial involving 696 hospitalized medical and surgical patients was undertaken to determine the effectiveness of 1% silver sulfadiazine cream applied twice daily to the inner and outer surfaces of the catheter. The adjusted CAUTI rates during the baseline and intervention periods were 8.1 and 4.9 infections/1,000 device days, respectively \( (p = 0.13) \) (47). With respect to long-term bladder drainage, a Cochrane meta-analysis showed that no eligible trials compared alternative routes of catheter insertion or catheter types (48).
catheters should be inserted using aseptic technique and sterile equipment; gloves, drape, and sponges should be used for insertion. However, in a prospective study conducted in the operating room, 156 patients underwent preoperative urethral catheterization, randomly allocated to “sterile” or “clean/non-sterile” technique groups. There was no statistical difference between the two groups with respect to the incidence of UTI, but the cost differs considerably between the two groups (43). A Cochrane meta-analysis of 31 trials showed no evidence that the incidence of CAUTI is affected by the use of aseptic or clean technique for intermittent catheterization in long-term bladder management (50).

Bladder Irrigation and Antiseptic in the Drainage System

The objective of antibiotic irrigation is to clear the bacteria from the urinary tract. A randomized study compared 89 patients receiving a neomycin–polymyxin irrigant administered through closed urinary catheters to 98 patients not given irrigation. Eighteen of 98 (18%) of the patients not given irrigation became infected, as compared with 14 of 89 (16%) of those given irrigation, and the organisms from patients with irrigation were more resistant (51). Another study was conducted in urology patients, evaluating the effect of povidone–iodine bladder irrigation prior to catheter removal on subsequent bacteriuria. Of 264 patients, 138 received irrigation and 126 were controls. Urine cultures were positive in 22% in the control group and 18% in the study group (52). Thus, irrigation methods failed to demonstrate an efficacy in surgical patients and meta-analysis does not show any benefit for long-term catheterization management (53). Experts do not recommend its use in ICU patients (34,44).

In ICU, the addition of antimicrobial agents in the drainage device has not been studied. The largest study investigating the effect of H2O2 insertion in the drainage device of 353 patients compared to 315 control patients failed to show a benefit in treated patients. It is noteworthy that 68% of these patients required an IUBC for hemodynamic monitoring, with antimicrobial therapy prescribed in 75% of patients, suggesting these results can apply to ICU patients (54). Experts recommend not using any kind of irrigation unless obstruction is anticipated, as might occur with bleeding after prostatic or bladder surgery (34,44).

Alternatives to the Urinary Catheter

For selected patients, other methods of urinary drainage such as condom catheter drainage, suprapubic catheterization, and intermittent urethral catheterization should be used as alternatives to an IUBC. While there are few data available in ICU to assess these alternative devices, there is evidence that suprapubic catheterization have advantages over indwelling catheters with respect to bacteriuria, recatheterization, and discomfort after abdominal or pelvic surgery (55–57). The use of condom linked to a collection bag has been evaluated in a study comparing two periods of 6 months, in which 167 patients were included. The occurrence of bacteriuria was significantly decreased for the period using the condoms (26.7% vs. 2.4%) (58). A recent study comparing microbiology reports from cultures collected from external versus indwelling catheters shows no difference in species that colonize, but did not analyze UTI incidence (59). A randomized trial of 75 males older than 40 years compared condom and indwelling catheters. Morbidity risk (bacteriuria, symptomatic UTI, or death) was higher in the catheterized group (hazard ratio = 4.84, 95% CI = 1.46 to 16.02; p = 0.02). Patients reported that condom catheters were more comfortable (p = 0.02) and less painful (p = 0.02) than indwelling catheters (60). The use of intermittent catheterization was also associated with a lower risk of bacteriuria than indwelling urethral catheter; such a procedure has not been systematically investigated in ICU patients (42,61,62).

Miscellaneous Measures

While there is a low risk of bacteremia during the urinary catheterization (63), the administration of prophylactic antimicrobial therapy at the time of catheterization leads to a reduction in bacteriuria and pyuria (64). The efficacy of antibiotic treatment has been assessed as optimal for catheterization lasting less than 14 days in perioperative and nonsurgical patients (64). However, the prophylactic use of antibiotic in ICU can be detrimental for the ecology in increasing the resistance of bacteria. This practice must, therefore, be discouraged in ICU. It is noteworthy that in most ICU studies 75% of patients with an indwelling catheter required antibiotics for different reasons (10).

Care bundles seem efficient to reduce CAUTI in conventional wards. A large survey compared American hospitals applying the “Keystone bladder bundle initiative” (65) with those not applying it (64). The compliant hospitals had better prevention of CAUTI related to improved assessment of initial indication, use of bladder scanner, removal reminder, and/or systematic stop orders (66,67). In the ICU, use of a daily checklist to systematically review invasive devices may increase compliance with recommendations for preventing nosocomial infection, but as of this writing, there is no reduction of CAUTI (68). Emerging work aiming at removing biofilm in order to prevent CAUTI by using low-energy ultrasound (69) or lytic bacteriophages (70) are underway; to date, they are not applicable to the bedside.

In conclusion, few preventive measures have demonstrated efficacy in reducing the rate of UTIs in the ICU. Additionally, the clinical significance of bacteriuria remains uncertain. Consequently, general measures with good adherence to hygiene procedures are more relevant than expensive devices to fight infections.

TREATMENT OF CAUTIS IN THE ICU

The management of CAUTI has not been evaluated in ICU patients. Several nonspecific measures, including hydration, have been advocated in the therapy of UTI. Adequate hydration would appear to be important although there is no evidence that it improves the effectiveness of an appropriate antimicrobial therapy (71). The management of complicated UTIs in the ICU may include mechanical intervention. Consequently, appropriate diagnostic tests and urologic consultation should be included in the algorithm of the management of these patients (Fig. 88.3.1).
Management of Asymptomatic Bacteriuria

Expert opinion holds that asymptomatic catheter-associated bacteriuria does not require treatment or screening in the ICU (34,72). However, antimicrobial treatment may be considered for asymptomatic women with a CAUTI that persists 48 hours after catheter removal (73). In a specific ICU population, 60 patients with an IUBC for longer than 48 hours who developed an asymptomatic positive urine culture were randomized to receive either a 3-day course of antibiotics associated with the replacement of the indwelling urethral catheter 4 hours after first antibiotic administration or no antibiotics and no catheter replacement; six patients, equally distributed in the two groups, developed urosepsis and the profile of bacterial resistance was similar in the two groups. Hence, treating a positive urine culture in an asymptomatic patient with an indwelling urethral catheter does not reduce the occurrence of urosepsis (25).

Management of Symptomatic Urinary Tract Infections

Choice of Antimicrobial Agents

The optimal characteristics of agents to treat UTIs must include activity against the major pathogens involved in these infections, good tissue penetration, and minimal side effects. High urinary levels should be present for an adequate period to eliminate the organisms, since disappearance of bacteriuria is correlated to the sensitivity of the pathogen and to the urine concentration of the antimicrobial agent (74). Inhibitory urinary concentrations are achieved after administration of essentially all commonly used antibiotics. However, an antibiotic achieving active concentrations in the renal tissue is required for infection of the renal tissue; the antibiotic concentration in the serum or plasma can be used as surrogate markers for the antibiotic concentrations in the renal tissue (75). For drugs with concentration-dependent time-kill activity such as the aminoglycosides or the fluoroquinolones, the peak antibiotic concentration is the most important parameter for the in vivo effect. Experimentally, gentamicin and fluoroquinolone treatment are both more effective than β-lactam antibiotics in rapid bacterial killing (Table 88.3.23) (75).

Clinical studies have shown that the renal concentrations of cephalosporins remain higher than the minimal inhibitory concentration for the most common bacteria during the time interval between the administrations of two doses (76–78). In contrast, β-lactam antibiotics with a low pKa and poor lipid solubility penetrate poorly into the prostate, except for some cephalosporins. Good to excellent penetration into the prostatic tissue has been demonstrated with many antimicrobial agents, such as aminoglycosides, fluoroquinolones, sulfonamides, and nitrofurantoin (79).

In ICU patients, the pharmacokinetics of β-lactam and aminoglycosides antibiotics may be profoundly altered due to the dynamic and unpredictable pathophysiologic changes that occur in critical illness (80). Consequently, therapeutic drug monitoring may optimize antibiotic therapy (81) especially in septic shock and when continuous renal replacement therapy (CRRT) is used, to individualize dosing and to ensure optimal antibiotic exposure (82). The side effects of treatment should be minimized at both the individual and the community levels. Many patients develop renal failure, associated with inability to concentrate antimicrobial agents in the urine. Otherwise, antimicrobial treatment should produce a minimal effect on the bacterial flora of the community (83). From this standpoint, there is significant literature demonstrating that the use of fluoroquinolone is associated with the emergence of resistant pathogens (84–87). This implies that an indication for antibacterial therapy should be weighed thoroughly and fluoroquinolones should be used in accordance with sensitivity testing (88). Hence, it is of importance to stress that UTI should not be treated before the results of sensitivity testing, except in patients with pyelonephritis and those with

FIGURE 88.3.1 Suggested algorithm for the management of urinary tract infections related to an indwelling catheter in the ICU. *Discuss the need for antipseudomonal coverage according to the duration of hospitalization, prior medical history, and local ecology. #Discuss if renal failure.
severe sepsis or septic shock who require empirical antimicrobial therapy.

**Cystitis**

As acute uncomplicated cystitis is infrequent in ICU patients, most recommendations focus on the treatment of nonhospitalized women, which makes their relevance in the ICU patients questionable; *E. coli* is the evident target pathogen. The 2010 IDSA guidelines recommend treatment with trimethoprim–sulfamethoxazole for 3 days, nitrofurantoin monohydrate for 3 days, or fosfomycin–trometamol in single dose as standard therapy for acute uncomplicated cystitis (89). Single-dose therapy is less effective in eradicating initial bacteriuria than longer durations, but considering the minimal resistance and low propensity for collateral damage, it is still an appropriate choice (89,90). In contrast, a meta-analysis determined that 3 days of antibiotic therapy is similar to 5 to 10 days in achieving symptomatic cure during uncomplicated UTIs, while the longer treatment is more effective in obtaining bacteriologic cure. Consequently, such durations should be considered for the treatment of women in whom eradication is critical (91). Among fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin are highly efficient in 3-day regimens but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis (89). The rate of adverse events causing antimicrobial withdrawal tends to be lower with norfloxacin and ciprofloxacin than with other quinolones (92).

Antibiotic treatment of UTI depends on the antibiotic being able to inhibit the growth of, or to kill, the bacteria present in the urinary tract; this is related to the concentration of antibiotics at the site of infection. Very high concentrations of antibiotics with renal clearance are obtained in urine. Consequently, even in the presence of pathogens exhibiting *in vitro* resistance, the high concentrations of antibiotics in urine inhibit the growth of pathogens, rendering them effective to treat UTI.

**Prostatitis**

For outpatients, bacterial prostatitis is a common diagnosis and a frequent indication for antibiotics. Although urethral instrumentation and prostatic surgery are known causes of prostatitis, the incidence of prostatitis among ICU patients has never been assessed, and there is only a weak relation between acute and chronic prostatitis.

Acute prostatitis is an acute infection producing local heat, tenderness, and fever, with the presence of IgA and IgG bacteria-specific immunoglobulins in the prostatic secretions. Most patients with chronic prostatitis have no history of positive urine or urethral cultures (93).

In ICU patients, the rate of acute bacterial prostatitis remains unknown; the patient presents septic, but without an evident source of infection. There may be a history of urine retention due to bladder outlet obstruction. Rectal examination, a crucial step in the diagnosis, reveals a warm, swollen, and tender prostate; the prostatic fluid contains leukocytes and the pathogen responsible for the infection. However, massage of the prostate is proscribed to avoid bacteremia. Acute bacterial prostatitis is a serious infection with fever, intense local pain, and general symptoms. Parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin, a third-generation cephalosporin, an aminoglycoside. Oral therapy can be substituted and continued for a total of 2 to 4 weeks after apyrexia is obtained (94). Fluoroquinolones are the drugs of choice to treat acute prostatitis because of their excellent penetration in the tissue and secretions (95,96). The targeted pathogens are *E. coli*, *Proteus* sp., *Klebsiella* sp., *Enterococcus* sp., *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* (97). For acute prostatitis occurring without bacteremia, antimicrobial treatment consists of oral ofloxacin 200 mg twice per day for 28 days (98); ceftriaxone 2 g/d has good prostatic tissue penetration and represents an alternative to ofloxacin (99). Gentamicin 3 mg/kg/d is added in the presence of positive blood cultures. French guidelines suggest that, if possible, bacterial identification be secured before starting a treatment (100). Of importance, urethral instrumentation should be discouraged and if acute retention occurs, suprapubic drainage of urine is required. Treatment of chronic prostatitis is based on the oral administration of ofloxacin 200 mg twice per day, or trimethoprim 160 mg–sulfamethoxazole 800 mg twice per day for at

### TABLE 88.3.23 Antimicrobial Treatment of Urinary Tract Infections. Each Empirical Treatment Must Be Adapted to the Susceptibility Testing Results

<table>
<thead>
<tr>
<th>Source of infection</th>
<th>Pathogens</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute prostatitis (without bacteremia)</td>
<td><em>E. coli</em>, <em>Proteus</em> sp., <em>Klebsiella</em> sp., <em>Enterococcus</em> sp., <em>S. aureus</em>, <em>N. gonorrhoeae</em>, <em>C. trachomatis</em></td>
<td>Ofloxacin 200 mg × 2 (oral)</td>
<td>28 d</td>
</tr>
<tr>
<td>Acute prostatitis (with bacteremia)</td>
<td><em>E. coli</em>, <em>Proteus</em> sp., <em>Klebsiella</em> sp., <em>Enterococcus</em> sp., <em>S. aureus</em>, <em>N. gonorrhoeae</em>, <em>C. trachomatis</em></td>
<td>Ofloxacin 200 mg × 2 (oral) or Ceftriaxone 2 g/d and</td>
<td>28 d</td>
</tr>
<tr>
<td>Chronic bacterial prostatitis</td>
<td><em>E. coli</em>, <em>Proteus</em> sp., <em>Klebsiella</em> sp., <em>Enterococcus</em> sp., <em>S. aureus</em>, <em>N. gonorrhoeae</em>, <em>C. trachomatis</em></td>
<td>Gentamicin 3 to 8 mg/kg/d i.v.</td>
<td>3 d</td>
</tr>
<tr>
<td>Acute pyelonephritis (uncomplicated)</td>
<td><em>Enterobacteriaceae</em>, <em>E. coli</em>, <em>Proteus</em> sp., <em>Enterococcus</em> sp.</td>
<td>Ciprofloxacin 500 mg × 2/day (oral) if oral route not possible. Ceftriaxone 2 g/day i.v.</td>
<td>14 d</td>
</tr>
<tr>
<td>Acute pyelonephritis (complicated)</td>
<td><em>Enterobacteriaceae</em>, <em>E. coli</em>, <em>Proteus</em> sp., <em>Enterococcus</em> sp.</td>
<td>Ciprofloxacin 200 mg × 2/day (oral) or Ceftriaxone 2 g/d i.v. and Gentamicin 3–8 mg/kg/d</td>
<td>14–21 d</td>
</tr>
</tbody>
</table>
are the basis of susceptibility results (89). The targeted bacteria on local resistance data, and the regimen should be tailored on carbapenem. The choice between these agents should be based on spectrum penicillin, with or without an aminoglycoside, or a such as a fluoroquinolone, an aminoglycoside, with or without adequate for the majority of women (89).

Acute Pyelonephritis
The urine of patients with suspicion of complicated pyelonephritis should be cultured and a Gram stain of the spun urine performed. Blood cultures, which are positive in 36% of women not admitted to ICU, are also required (101). There is poor specific data available in the literature on the management of acute pyelonephritis requiring ICU admission. A case series of 68 patients with severe acute pyelonephrosis showed 57% had renal dysfunction, 47% shock status, and 56% required ICU admission; additionally, 75% of the patients had radiologic evidence of urinary tract obstruction requiring drainage. Rate of bacteremia was higher than in cases of uncomplicated pyelonephritis, with 57% positive blood-stream cultures (102). All patients with acute pyelonephritis should have an ultrasound examination or a renal computed tomography scan to evaluate for obstruction and stones.

For uncomplicated acute pyelonephritis, the 2010 IDSA guidelines suggest the following: First, oral ciprofloxacin (500 mg twice daily) for 7 days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is known not to exceed 10%. In addition, oral trimethoprim–sulfamethoxazole (160/800 mg twice daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible. In a comparative study, 255 outpatients were randomized to oral ciprofloxacin, 500 mg twice per day for 7 days followed by placebo for 7 days versus trimethoprim–sulfamethoxazole, 160/800 mg twice per day for 14 days. A 7-day ciprofloxacin regimen was associated with better bacteriologic and clinical cure rates than a 14-day trimethoprim–sulfamethoxazole regimen (103). The second conclusion is that oral β-lactam agents are less effective than other available agents for the treatment of pyelonephritis. Indeed, there is a relatively high prevalence of organisms causing acute pyelonephritis that are resistant to ampicillin, and even for susceptible organisms, there is a significantly increased recurrence rate in patients given ampicillin compared with those given trimethoprim–sulfamethoxazole. If an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside, is recommended. In any event, 10 to 14 days of therapy with β-lactam appears to be adequate for the appropriate of women (89).

Patients with pyelonephritis requiring hospitalization should be initially treated with an i.v. antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside, with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside, or a carbapenem. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results (89). The targeted bacteria are Enterobacter sp., E. coli, Proteus sp., and Enterococcus sp. Ciprofloxacin, 500 mg twice daily, is administered orally for 14 to 21 days as soon as fever decreases; gentamicin, 3 to 8 mg/kg/day intravenously, is added during the first 3 days.

In all cases, plasma peak concentration (30 minutes after end of perfusion) of gentamicin must reach six to eight times the minimal inhibitory concentration (MIC) of treated bacteria to guarantee efficient treatment. Interestingly, oral ciprofloxacin is as effective as the i.v. regimen in the initial empirical management of complicated pyelonephritis (104), and gatifloxacin is as effective as ciprofloxacin (105). If needed, ceftiraxone (2 g/d i.v.) is an alternative choice to ciprofloxacin. Further, the success rates are similar in patients given ceftriaxone or ertapenem (106).

The drainage of urine must be urgently performed using bladder catheterization, percutaneous nephrostomy drainage, or definitive surgery. Antimicrobial treatment is administered after urine and blood specimen collection. The antibiotic selection is based on the result of the Gram stain of the urine and the knowledge of the local ecology. Antimicrobial treatment should be adapted to the susceptibility testing results as soon as possible, and de-escalation be performed in favor of a narrow-spectrum antibiotic.

Specificities of Complicated UTIs in the ICU
Although there is little in the literature on the treatment of UTIs in the ICU, one presumes the need for i.v. antibiotics for these patients because of the possibility of bacteremia or sepsis. The guidelines from the Surviving Sepsis Campaign state that (i) antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained; (ii) initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens and that penetrate the presumed source of sepsis; (iii) monotherapy is as effective as combination therapy with a β-lactam and an aminoglycoside as empiric therapy of patients with severe sepsis or septic shock (107). Hence, empirical antimicrobial therapy should include drugs with good penetration in the urinary tract, and the choice is guided by the susceptibility patterns of micro-organisms in the hospital. For the septic shock patients whose presumed source is urine, we recommend, empirically, a combination of a β-lactam antibiotic with antipseudomonal activity and an aminoglycoside. This broad-spectrum treatment is narrowed as soon as the results of the susceptibility testing are known. The durations of treatment should be tailored to the source of infection.

Management of Candiduria
Candiduria represents from 3% to 15% of catheter-associated UTI in the ICU (10, 23,108). Candida albicans and C. (Torulopsis) glabrata are found in 46% to 60%, and 31% of cases, respectively (108,109). According to the international guidelines, colonized patients without evidence of infection do not require treatment (110,111). But the contributing cause should be addressed such as changing or removing the IUBC and discontinuing inappropriate antibiotic therapy (34). Fluconazole may be the best option for treating candiduria, in case of urologic surgery, for example, but only if the species is C. albicans (110); voriconazole or amphotericin B may be more effective against non-albicans species (111).

Clinician reaction to isolating Candida organisms in urine was assessed in a retrospective review of 133 consecutive patients. The average patient age was 68.8 years old, most (78%) had an IUBC, and many (35%) were in the ICU. In response to culture results, clinicians initiated antifungal therapy in 80 instances (60%); treatment was often based on a single culture result without evidence of infection (66%) and
in the absence of risk of invasive disease. Removal of the IUBC was never attempted and antibiotics were rarely discontinued (1.3%). Fluconazole was the most frequently utilized (52%) agent, followed by amphotericin-B bladder irrigation (32%), and combined fluconazole/amphotericin-B bladder irrigation (15%). Therapy was more frequently initiated in ICU cases (77% vs. 56%; p = 0.02) (112). These results show a worrisome lack of adherence to established guidelines.

A prospective, randomized trial compared fungal eradication rates among 316 hospitalized patients with candiduria treated with fluconazole (200 mg) or placebo daily for 14 days. Candiduria cleared day 14 in 50% of the patients receiving fluconazole and 29% of those receiving placebo, with higher eradication rates among patients completing 14 days of therapy. While fluconazole initially produced high eradication rates, cultures at 2 weeks revealed similar candiduria rates among treated and untreated patients. In 41% of the catheterized subjects, candiduria was resolved as the result of catheter removal only. The outcomes of patients were not provided in the results (113).

Bladder irrigation using amphotericin B has been proposed as an alternative technique to clear Candida from the urine. A comparative and randomized study of 109 elderly patients showed that funguria was eradicated in 96% of the patients treated with amphotericin B, and 73% of those treated with fluconazole (p < 0.05). One month after study enrollment, the mortality rate associated with all causes was greater among patients who were treated with amphotericin B bladder irrigation than among those who received oral fluconazole therapy (41% vs. 22%, respectively; p < 0.05); this finding suggests that irrigation therapy could be associated with poorer survival (114). Reviews suggest that amphotericin B bladder irrigation is as effective as oral fluconazole to treat asymptomatic candiduria. The best method is to use continuous irrigation for more than 5 days. The level of the literature cannot allow drawing definitive conclusions (115).

There has only been one study performed in ICU patients developing candiduria, which reached the same conclusions; unfortunately, methodologic issues restrict the interest of this study. The authors retrospectively compared three means to manage candiduria in ICU patients: successful bladder irrigation with amphotericin B (10/27 patients), failure of bladder irrigation requiring the use of parenteral amphotericin B (n = 17/27), and patients treated with parenteral fluconazole (n = 20). Severity score on the day of admission was significantly lower in the first group than in the two others. However, the mortality rate was 53% and 5% in patients who failed bladder irrigation and in patients receiving fluconazole, respectively (116). These results must be considered with caution because of serious methodologic limitations. However, these data indicate that bladder irrigation of critically ill patients has a negative survival advantage.

**Key Points**

- Preventing or reducing the duration of catheterization is the most important intervention in preventing CAUTIs.
- The initial indication for the placement of an IUBC was unjustified in 15% of patients and unclear in 28% of patients.
- Pathogens among ICU patients with bacteriuria are *E. coli, P. aeruginosa, Enterococcus* species, 70% of cases.
- Polymicrobial infections represent only 5% to 12% of cases.
- Comparison of nitrofurazone-coated and silver alloy-coated catheters results in a superiority of antibiotic-coated in reducing bacteriuria and symptomatic CAUTI, but the magnitude of reduction is low and hence may not be clinically relevant.
- Bacteria in the bladder constitute a reservoir for the development of multiresistant bacterial strains.
- The rate of bacteriuria may be used as a marker of the level of care in the ICU.
- Prevention of UTIs in the ICU is not improved by the use of expensive devices, but can reflect the level of general unit hygiene.
- While management of UTIs in the ICU is poorly described in the literature, it is reasonably clear that there is no need to treat asymptomatic bacteriuria.
- Although infrequent, severe sepsis whose source is urine requires empirical broad-spectrum antimicrobial treatment based upon the local bacterial ecology. Treatment is de-escalated after identification of the pathogen and reporting of the susceptibility testing.

**References**


INTRODUCTION

Acute diarrhea and acute gastroenteritis with vomiting occurring outside the hospital are most often secondary to viral infection. Most cases of health care–associated diarrhea are not etiologically defined, with *Clostridium difficile* being the most important definable cause of illness, identified in 10% to 20% of cases. In the United States, approximately 179 million cases of acute diarrhea occur each year, amounting to 0.6 episodes/person/yr, with approximately 11,255 deaths yearly, of which 83% occur in adults 65 years of age or older (1). The most communicable enteric pathogens are noroviruses and *Shigella* spp. due to their low inoculum requirements, stability in the environment, and because children often harbor the pathogens (2).

Diarrhea is commonly defined as passage of three or more loose stools/d or passage a total stool weight/volume of 250 g/mL of unformed stool/d. The following definitions have been suggested taking into account diarrheal duration:

- **Acute**—up to 14 days
- **Persistent**—14 days or more
- **Chronic**—30 days or more

The cause of the diarrheal illness is divided into three groups: viruses, bacteria, and bacterial toxins and protozoal parasites. Noninfectious causes of diarrhea are characteristically associated with chronic diarrhea.

The severity of diarrhea can be determined functionally:

- **Mild**—requires no change in activities
- **Moderate**—requires a change in activities but does not disable
- **Severe**—disables, usually confining the affected person to bed. It is the severe forms of diarrhea that usually lead to hospitalization

ETIOLOGY OF ACUTE DIARRHEA IN THE UNITED STATES

Diarrhea can be divided into community-acquired, health care–acquired, and traveler’s diarrhea (TD). Community-acquired acute infectious diarrhea is caused by various micro-organisms including bacteria, viruses, and parasites. With widespread use of rotavirus vaccine in the United States, the major viral pathogens seen are a number of noroviruses of which genogroup II, genotype 4 is the most important (3). Noroviruses cause approximately half of all diarrhea for which a cause of illness can be found; noroviruses are usually intense but persist for no more than 60 hours, and do not usually require therapy. For the elderly and infirm, especially after organ and stem cell transplantation, the noroviruses can cause severe and chronic illness and may be fatal (3). Most cases of diarrhea in the community have undefinable causes of illness using currently available diagnostic tests.

The etiology of diarrheal cases presenting to a hospital and hospital-acquired diarrhea is different from the community-based diarrhea. Diarrhea acquired in the hospital is generally not associated with a definable pathogen, although the most important definable pathogen in hospital-acquired diarrhea is *C. difficile*.

EVALUATION OF THE PATIENT WITH SEVERE DIARRHEA

Emergency Department

The first priority in the ED is to evaluate the stability and hydration status of the patient by examining vital signs, mucous membranes, sensorium, and looking for postural hypotension. Rehydration is the mainstay of treatment of gastrointestinal infection; many cases can be treated and maintained using oral rehydration therapy (ORT), although in the United States, most patients with any degree of dehydration are treated with i.v. fluids. Secondly, electrolyte disturbances need to be sought and corrected; electrolyte imbalances may vary depending on the cause and also on other comorbid conditions. The primary concern is to immediately reverse circulatory or organ failure resulting from loss of fluid and salt.

Diagnostic investigations for identifying the causative agent should be done either simultaneously or after stabilization of the patient. Most of the cases requiring hospitalization are due to bacterial causes rather than viral, which tend to be mild. Epidemiologic history and clinical features may provide clues to the diagnosis, for example, prior travel to an economically developing country suggests a bacterial cause of diarrhea. Diarrhea in a person receiving antibacterial or chemotherapeutic drugs suggests *C. difficile* as the etiologic agent. Proctitis in a male with a history of having unprotected receptive anal intercourse suggests sexually transmitted pathogens including *Neisseria gonorrhoeae, Chlamydia trachomatis*, herpes simplex, or *Treponema pallidum*. A diagnostic algorithm is provided to help identify important steps in the workup of patients with acute diarrhea (Fig. 88.4.2).

If the patient with diarrhea is taking a proton pump inhibitor (PPI), they are susceptible to a large number of enteric pathogens (4) as acidic pH of the stomach is one of the important barriers to prevent enteric infection.

The laboratory will help establish the diagnosis. Finding many fecal leukocytes in stool indicates the patient has diffuse colonic inflammation; occult blood in the stool supports an inflammatory type of diarrhea. Other tests for colonic inflammation include studies for the presence of lactoferrin or calprotectin, constituents of polymorphonuclear
leukocytes (5). Gross blood in the stool with mucus may indicate a dysenteric pathogen, such as *Shigella*, *Campylobacter*, *Salmonella*, *Shigatoxin-producing Escherichia coli* (often *E. coli* O157:H7) or *C. difficile*. Stool cultures, parasite examination, or stool toxin test for *C. difficile* may help define the cause of the illness. Some characteristics, when present, requiring aggressive and thorough laboratory workup are fever over 102°F (38.9°C), severe diarrhea, presence of dehydration, presence of dysentery, and coexistence of important immunosuppressive disorder. Physical examination is important and should focus on vital signs—fever, heart rate, and blood pressure including postural hypotension—volume status, abdominal tenderness, and systemic complications. Rectal examination should be performed to assess stool for gross and occult blood; painful hemorrhoids from frequent defecation may be detected. A white blood count may reveal leukocytosis or a shift to the left in neutrophils suggesting a severe inflammatory process of the gut; this finding warrants stool studies, culture if the diarrhea is community acquired and *C. difficile* fecal toxin test if health care–associated. Eosinophilia may be seen in parasitic infection (e.g., strongyloidiasis).

Once disease onset, presentation, and progression of associated symptoms are evaluated, and immediate laboratory work has been performed, it may be useful to categorize the diarrhea into one of two physiologic classifications: noninflammatory and inflammatory (Table 88.4.24). A subcategory of inflammatory is hemorrhagic or dysenteric diarrhea; distinction of the specific type of diarrhea is helpful to focus on appropriate empiric management options.

**TABLE 88.4.24 Classification of Acute Diarrhea Based on Findings of Fecal Markers of Inflammation (Leukocytes or Lactoferrin) or Presence of Gross Fecal Blood**

<table>
<thead>
<tr>
<th>Types of Diarrhea</th>
<th>Possible Causes</th>
<th>Measures to Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninflammatory (negative for fecal inflammatory markers or dysentery)</td>
<td>Toxin-mediated, viral, noninvasive pathogens like <em>Vibrio cholerae</em>, ETEC, EAEC, enteric viruses, protozoal parasites like Giardia or Cryptosporidium</td>
<td>Oral/i.v. fluid replacement and empiric therapy if required</td>
</tr>
<tr>
<td>Inflammatory (clinical colitis or presence of fecal inflammatory markers (e.g., leukocytes, calprotectin, lactoferrin) or presence of dysentery)</td>
<td><em>Shigella</em>, <em>Salmonella</em>, STEC, <em>Entamoeba histolytica</em>, <em>Campylobacter</em>, <em>Clostridium difficile</em></td>
<td>Oral/i.v. fluid therapy based on hydration status and thorough laboratory investigations with specific antibiotic therapy if indicated*</td>
</tr>
</tbody>
</table>

*ETEC, enterotoxigenic *E. coli*; EAEC, enteraggregative *E. coli*; STEC, Shiga toxin–producing *E. coli*.

*Specific therapies are listed in Table 27."
Health Care–acquired Diarrhea

Illness occurring after the 72 hours in the hospital or nursing home can be considered health care–associated. In Fig. 88.4.3, the relative importance of causes of diarrhea in hospitalized patients in one study is provided. Between 10% and 30% of nosocomial diarrhea is due to *C. difficile*; since 10% to 20% of institutionalized patients are colonized with this organism during hospitalization and because most acute diarrhea developing in the hospital is not caused by *C. difficile* the PCR test for fecal toxin often gives a false-positive result (6).

The other important causes of nosocomial diarrhea include antibiotics, chemotherapeutic agents, PPIs, tube feedings, laxatives, other drugs, and various iatrogenic and idiopathic conditions (see Fig. 88.4.3).

It is appropriate, in all hospital-associated diarrheas when a patient is receiving antibacterial treatment, to consider *C. difficile* as the causative agent, and empiric treatment is advisable only in the more severe cases while laboratory tests are pending. Rarely, other pathogens can be found in hospital- and nursing home–associated diarrhea, including rotaviruses.

The International Traveler Returning with Diarrhea

TD may occur when persons travel from industrialized to developing tropical and semitropical areas with reduced levels of personal and food hygiene. TD is the most common travel-related infectious illness, occurring in up to 40% of travelers to regions of Asia, Africa, and Latin America. Among US travelers, the majority of cases of TD occur in individuals returning from Latin America and the Caribbean, but the greatest risk is noted after travel to the Indian subcontinent (7); bacterial enteropathogens cause as much as 80% of TD cases.

The world has been classified into three different risk groups: low, intermediate, and high risk, based on the frequency of TD in the traveling public. The important causes of TD are Enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC), noroviruses, *Campylobacter*, *Shigella*, and *Salmonella*. Less commonly, parasitic agents cause TD and should be suspected in persistent illness; important parasitic pathogens include *Giardia*, *Cryptosporidium*, and *Cyclospora*. Patients with TD should be treated empirically with antibiotics without stool examination.

Immunosuppressed Patient with Diarrhea

An immunosuppressed or immunocompromised patient, including those with congenital or acquired immune deficiency, HIV/AIDS, receipt of immunosuppressive, or cancer chemotherapy drugs, will have increased susceptibility to diarrhea. The etiology of diarrheal diseases in immunocompromised hosts is different from that of other populations in that they are at risk of developing infections from various opportunistic organisms in addition to the routine diarrheal pathogens. The use of various chemotherapy drugs or immunomodulators, such as cyclosporine, mycophenolate mofetil, tacrolimus, or sirolimus may result in drug-induced diarrhea (8); diarrhea in transplant recipients can also be due to graft versus host disease (GVHD). The most commonly identified organisms to consider as causes of diarrhea in this group of patients are *C. difficile* and noroviruses; other causes are *Salmonella*, *Cryptosporidium*, *Isospora*, *Cyclospora*, cytomegalovirus, and *Mycobacterium avium–intracellulare* complex. A thorough and quick evaluation for identifying the causative organism is the key in treating and controlling diarrhea in this patient population. Appropriate rapid diagnostic tests may include direct stool examination for ova, cysts, and parasites; stool test for *C. difficile* toxin; polymerase chain reaction (PCR) for cytomegalovirus or herpesvirus; stool cultures; and blood cultures. If the above tests do not provide a specific diagnosis, endoscopy and mucosal biopsy should be pursued to establish an etiologic diagnosis (9). Abdominal computed tomography (CT) may detect mucosal thickening or other changes of ischemic, hemorrhagic, or inflammatory colitis, and it is the preferred diagnostic study when both intra-abdominal disease and intestinal disease are expected (10).

Patient with Extraintestinal Disease and Diarrhea

Diagnostic evaluation of patients with diarrhea and systemic symptoms and signs will often take the clinician’s focus
away from the gut for the diagnosis. Blood cultures, CT of the abdomen, and serology (for Entamoeba histolytica) may help determine the primary cause of the disease. In cases of sepsis, blood cultures and stool studies may provide the diagnosis; systemic complications are often seen with invasive bacterial and parasitic infections. Systemic complications of enteric infection include hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), Guillain–Barré syndrome, reactive arthritis, iritis, postinfectious irritable bowel syndrome, sepsis, infective endocarditis, and abdominal abscesses or localized abscess elsewhere, or pyogenic arthritis. In immunocompromised patients with diarrhea, systemic complications can occur with any of the etiologic agents. Antimotility drugs should not be used in dysenteric and febrile diarrhea without effective concomitant antibiotics as they can prolong or complicate the disease. Amoebiasis, which is uncommon in the United States, shows an extended spectrum of extraintestinal complications including liver abscess and disseminated infection.

**MANAGEMENT OF ACUTE DIARRHEA**

**Dehydration**

Dehydration is defined as excess loss of body fluids resulting in fluid and electrolyte abnormalities; classifications of dehydration are provided (Table 88.4.25).

<table>
<thead>
<tr>
<th>Dehydration</th>
<th>Symptoms</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dehydration</td>
<td>3–5% loss in body weight</td>
<td>Increased thirst and slightly dry mucous membranes</td>
</tr>
<tr>
<td>Moderate dehydration</td>
<td>6–9% loss in body weight</td>
<td>Loss of skin turgor, dry mucous membranes, tending of skin</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>≥10% loss in body weight</td>
<td>Lethargy, altered consciousness, prolonged skin retraction time, cool extremities, decreased capillary refill</td>
</tr>
</tbody>
</table>

| Oral rehydration solution (ORS) 50 mL/kg over first 2–4 hr |
| ORS 100 mL/kg over first 2–4 hr |
| Immediate i.v. fluid replacement with 20 mL/kg of lactated Ringer solution to restore perfusion and mental status. Continue with 100 mL/kg ORS or i.v. 5% dextrose and 1/2 normal saline at two times the maintenance rate. |

Dehydration can be done depending on severity of the dehydration either by oral or i.v. routes. Where available, oral rehydration salt (ORS) solution can be used in mild or moderate dehydration and for maintenance of hydration after i.v. fluid administration in severe dehydration. Standard or reduced osmolarity (low salt) ORS formulations are preferable where available. In dehydration due to cholera-like profuse watery diarrhea with massive fluid losses, reduced-osmolarity ORS may lead to subclinical reduction of body electrolytes, making standard ORS preferable in this dehydrating form of diarrhea for outpatients (13). In the United States, ORS is not readily available, but Pedialyte or Ricelyte can be used to maintain hydration and treat minor degrees of dehydration for outpatients. For inpatients with cholera-like diarrhea in the United States, i.v. fluids are preferentially used; specific fluid replacement strategies based on severity are presented in Table 88.4.25.

**Dysentery**

Dysentery is defined as passage of bloody stools suggesting bacterial colitis (14). The four major causes of bloody diarrhea in the United States, in descending order of frequency of occurrence, are Shigella, Campylobacter, nontyphoid Salmonella, and Shiga toxin–producing E. coli (15). Single cases of dysentery with high fever should be treated with azithromycin empirically. For nonfebrile or low-grade fever with dysentery in an outbreak with multiple cases, stools studies should be performed to look for the etiology, including Shiga toxin–producing E. coli, before considering therapy. Empiric and specific antibiotic treatments are provided in Tables 88.4.26 and 88.4.27.

**TABLE 88.4.25 Classification of Dehydration in a Patient with Acute Diarrhea (11)**

<table>
<thead>
<tr>
<th>Dehydration</th>
<th>Symptoms</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dehydration</td>
<td>3–5% loss in body weight</td>
<td>Increased thirst and slightly dry mucous membranes</td>
</tr>
<tr>
<td>Moderate dehydration</td>
<td>6–9% loss in body weight</td>
<td>Loss of skin turgor, dry mucous membranes, tending of skin</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>≥10% loss in body weight</td>
<td>Lethargy, altered consciousness, prolonged skin retraction time, cool extremities, decreased capillary refill</td>
</tr>
</tbody>
</table>

| Oral rehydration solution (ORS) 50 mL/kg over first 2–4 hr |
| ORS 100 mL/kg over first 2–4 hr |
| Immediate i.v. fluid replacement with 20 mL/kg of lactated Ringer solution to restore perfusion and mental status. Continue with 100 mL/kg ORS or i.v. 5% dextrose and 1/2 normal saline at two times the maintenance rate. |

**TABLE 88.4.26 Empiric Antimicrobial Therapy of Acute Diarrhea (16–19,20)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile dysentery; fever (temperature &gt; 100.2°F (&gt;38°C)) plus dysentery (passage of grossly bloody stools)</td>
<td>Azithromycin 500 mg PO daily for 3 d</td>
</tr>
<tr>
<td>Moderate to severe traveler’s diarrhea with fever and dysentery</td>
<td>Azithromycin 1,000 mg PO single dose</td>
</tr>
<tr>
<td>Moderate to severe traveler’s diarrhea without fever and dysentery</td>
<td>Rifaximin, 200 mg tid for 3 d; or ciprofloxacin, 500 mg bid for 3 d</td>
</tr>
<tr>
<td>Severe hospital-acquired diarrhea in a patient with comorbidity and prior receipt of antibacterial therapy</td>
<td>Vancomycin, 125 mg every 6 hr orally; or fidaxomicin 200 mg bid for 10–14 d (preferred)</td>
</tr>
<tr>
<td></td>
<td>i.v. metronidazole 500 mg every 8 hr if cannot take oral medications.</td>
</tr>
</tbody>
</table>
**TABLE 88.4.27 Specific Therapy for Pathogen-Specific Diarrhea, Once Etiologic Diagnosis Is Established (1,20,21)**

<table>
<thead>
<tr>
<th>Identified Pathogen</th>
<th>Suggested Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Vancomycin 125 mg qid for 10–14 d; or fidaxomicin 200 mg bid for 10–14 d</td>
</tr>
<tr>
<td>First or second bout</td>
<td></td>
</tr>
<tr>
<td>Recurrent (≥ 3 bouts)</td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em> sp. (treat only for suspected sepsis based on presence of high-risk host)</td>
<td></td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Fluoroquinolones, dosed as in <em>Salmonella</em> above, given for 3 d; or azithromycin 500 mg once daily for 3 d</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Azithromycin 500 mg once a day for 3 d; or erythromycin 500 mg bid for 5 d</td>
</tr>
<tr>
<td><em>Shigatoxin-producing E. coli (STEC)</em></td>
<td>No antimotility drugs, antibiotic treatment not usually given as they may increase the risk of occurrence of hemolytic uremic syndrome</td>
</tr>
<tr>
<td><em>Enterotoxigenic E. coli (ETEC)</em></td>
<td>Rifaximin 200 mg tid for 3 d; or fluoroquinolone in above dose for 1–3 d; or azithromycin 1,000 mg in single dose</td>
</tr>
<tr>
<td><em>Enteropathogenic E. coli (EPEC)</em></td>
<td>Same as ETEC</td>
</tr>
<tr>
<td><em>Enteroinvasive E. coli (EIEC)</em></td>
<td>Same as Shigella, plus perform susceptibility testing to refine treatment</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Same as Shigella</td>
</tr>
<tr>
<td><em>Noncholeraic Vibrio diarrhoea</em></td>
<td>Doxycycline single 300 mg dose</td>
</tr>
<tr>
<td><em>Aeromonas/Plesiomonas shigelloides</em></td>
<td>Ciprofloxacin 750 mg once daily for 3 d, or azithromycin 500 mg once daily for 3 d</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td>Same as Shigella</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td>Metronidazole 750 mg qid for 5 d, plus either diloxanide furoate 500 mg tid for 10 d or paromycin-</td>
</tr>
<tr>
<td></td>
<td>cin 25–35 mg/kg/d divided in 3 d daily for 7 d</td>
</tr>
<tr>
<td><em>Giardia</em></td>
<td>Tinidazole 2 g orally in single dose, nitazoxanide 500 mg twice daily for 3 da, or metronidazole</td>
</tr>
<tr>
<td></td>
<td>250 mg tid for 5–7 d</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>Nitazoxanide 500 mg bid for 3 to 14 d</td>
</tr>
<tr>
<td><em>Cyclospora</em></td>
<td>TMP-SMZ 160 and 800 mg, respectively, bid for 7 d; in immunosuppressed patients, TMP-SMZ treatment is given for 3–4 d followed by 3 times weekly for up to 10 wk</td>
</tr>
<tr>
<td><em>Cystoisospora</em></td>
<td>TMP-SMZ 160 and 800 mg, respectively, qid for 10 d</td>
</tr>
<tr>
<td><em>Microsporidium</em></td>
<td>Albendazole 400 mg bid for 14–28 d or fumagillin, 20 mg bid for 14 d</td>
</tr>
<tr>
<td><em>Cytomegalovirus</em></td>
<td>Ganciclovir 5 mg/kg i.v. every 12 hr for 14 d, or valganciclovir 900 mg twice daily orally for 21 d; maintenance dose of either agent may then be needed</td>
</tr>
<tr>
<td><em>Strongyloides</em></td>
<td>Ivermectin 200 μg/kg orally for 2 d; or albendazole 400 mg twice daily for 7 d</td>
</tr>
<tr>
<td><em>Norovirus</em></td>
<td>Fluid and electrolyte therapy, consider bismuth subsalicylate symptomatic therapy</td>
</tr>
<tr>
<td><em>Rotavirus</em></td>
<td>Fluid and electrolyte therapy</td>
</tr>
</tbody>
</table>

*High-risk patients for *Salmonella enterica* species (nontyphoid *Salmonella*): Any subject who is toxic with fever >102°F (39°C), with age <3 months or ≥65 years, and or with malignancy or AIDS on steroids, with inflammatory bowel disease or renal failure, or undergoing hemodialysis, with hemoglobinopathies such as sickle cell disease. Patients with simple gastrointestinal infections are best not given antibiotic drugs.

**Clostridium difficile Infection and Colitis**

*C. difficile* infection (CDI) was first identified as a causative agent of antibiotic-associated diarrhea in the early 1970s, associated with clindamycin use. The organism is a gram-positive, spore-forming anaerobic bacteria that produces an enterotoxin known as toxin A and a cytotoxin called toxin B; there is a third type of toxin produced, called binary toxin, which is an actin-specific ADP ribosylating toxin that is associated with more severe disease. Toxin A causes necrosis, increased intestinal permeability, and inhibition of protein synthesis. Toxin B is thought to become effective once the gut wall has been damaged. Over the past two decades, an increased virulence of CD strains has evolved, making the disease more severe. The virulence relates to higher levels of toxin production and greater rates of sporulation, which relates to recurrences. The North American PFGE type 1 strain (NAP1) or PCR ribotype 027 strain has been particularly virulent, with higher death and recurrence rates. The incidence of CDI has been rising for the past 20 years; recent surveys in 183 hospitals among 11,282 patients noted 452 patients with one or more health care–associated infection, with gastrointestinal infections seen in 17.1%, and CDI being the most important diagnosis identified in 12.1% of health care–associated infections (22). Since a higher number of hospital associated diarrhea cases do not have CDI plus the fact that *C. difficile* PCR-based diagnostic tests will be positive in colonized patients without diarrhea, *only unformed stool should be tested for C. difficile*, unless the patient has ileus.

Major risk factors for CDI include antimicrobial use, age older than 65 years, severity of existing health condition, use of other drugs such as chemotherapeutic agents and PPIs, renal insufficiency, and gastrointestinal surgery. In CDI, advanced age and comorbidity, plus severity of underlying impairment, predict frequency of infection and outcome (23). Host conditions may influence susceptibility to CDI, such as inflammatory bowel disease (24), IBS (25), and failure to develop serum antibodies to toxin A of *C. difficile*.

When assessing institutionalized individuals, such as nursing home patients with diarrhea, associated risk factors for CDAD should be considered. Some of the risk factors other than antibiotic use and comorbidity are low albumin level (<2.5 g/dL), recent admission to a health care institution,
and use of PPIs (26). In nonhospitalized patients with other predisposing conditions such as cancer, prolonged antibiotic usage—especially with first-generation cephalosporins, fluoroquinolones, or clindamycin—is a recognized risk factor for CDI. The risk is greatest with clindamycin, followed by fluoroquinolones and β-lactam drugs (cephalosporins and penicillins); all antibiotics show a risk for causing CDI except for vancomycin, the major therapeutic drug when given orally.

CDI caused by a spore-forming organism resists curative therapy and recurs in approximately 25% of properly treated cases, often within 7 to 14 days, but occasionally as long as 60 days after completion of therapy. Risk factors for early recurrence of CDI are renal failure; white blood cell counts greater than 15,000 cells/µL with the initial episode, and first episode of community-acquired CDI. Failure to mount a serum antibody response to toxin A during an initial episode of CDI is associated with CD recurrence (27).

Despite the growing incidence of CD and the increased knowledge about CDI, there is no gold standard diagnostic test to diagnose CDI. Diagnosis of CDI is based on both clinical and laboratory findings. The customary way to make the diagnosis is to recover a toxigenic strain of CD through detection one or both of the known CD toxins, A and B, in stool samples by commercial tissue culture cytotoxin assay for toxin B, enzyme immunoassay (EIA) for one or both of the toxins or RT-PCR. Toxigenic culture is a sensitive method of diagnosing CDI, but this test as well as the tissue culture cytotoxin assay takes 3 days to complete, making them impractical for deciding about therapy needs. The EIA is specific testing for toxin but it lacks sensitivity and the PCR while the most sensitive test lacks specificity for CDI as it fails to determine carriers from infected patients. Many groups are going to a two-step diagnostic approach, using very sensitive glutamine dehydrogenase (GDH) screening followed by rejection of patients with negative tests as not having CDI and testing the positive reactions by EIA (28). GDH is an enzyme found in all strains of C. difficile but because it is found in other bacteria, it is not a standalone test.

In a highly probable clinical case with severe disease or fragile clinical picture, it is often advisable to initiate prompt empiric treatment before stool test results are back, or even in the face of negative laboratory tests for the toxins. In these cases, colonoscopy, abdominal CT, or measurement of fecal inflammatory markers could be considered to provide additional evidence of CDI.

### Treatment of Acute Diarrhea

Prompt diagnosis and treatment are important to successful management of CDI (see Tables 88.4.26 and 88.4.27). CDI can be classified into mild, moderate, and severe. Cessation of causative antibiotic use if possible is important and, in very mild cases, it may be enough to result in cure without further treatment. While previous recommendations were made to use oral metronidazole for mild CDI, the drug has serious flaws because it is nearly 100% absorbed, resulting in very low fecal levels (29). Most experts in the field now reserve metronidazole use for i.v. administration when no oral therapy is possible because of ileus or other condition. For therapy of mild to severe cases, oral vancomycin or fidaxomicin is recommended. For first recurrence of CDI, the same drug, oral vancomycin or fidaxomicin, can be used again since resistance development is not a reason for recurrence in infection caused by this spore-forming organism. When two or more recurrences occur, the primary problem is intestinal dysbiosis (decrease in number of species/phyla and evenness of counts of various pathotypes) limiting colonization resistance (30). Fecal microbiota transplantation (FMT) is the most effective treatment in these cases (31). Other approaches, since FMT is not available everywhere, including longer-term oral vancomycin given intermittently or in pulse therapy (20).

### Diarrhea Epidemics in the Hospital

Early identification and controlling the spread of rare hospital epidemics of enteric disease are the keys to successful management. Universal protocols of isolation and personal hygiene measures play an important role. Judicious use of antibiotics in the hospital and prompt discontinuation of possible inciting drugs also can be helpful. Agents showing potential for epidemics in hospitals are C. difficile, Salmonella spp., Shigella, Campylobacter, Vibrio, Aeromonas, Yersinia, noroviruses, and rotavirus. Early therapy of treatable enteric pathogens should occur (see Table 88.4.27). Health care worker and patient education regarding various personal hygiene and isolation procedures could help in stopping the spread within the institution.

### Prevention of Diarrhea in the Hospital

Appropriate use of antibiotics in hospitalized patients, along with the use of the narrowest-spectrum antibiotics possible to treat their infection will preserve gut flora helpful in the prevention of CDI. Additionally, at least in a research setting, Saccharomyces has been used to prevent CDI (32). Other drugs in future study may be effective and reasonable to use to prevent CDI in hospitalized patients (33). Enteric isolation practices for patients with known enteric infection in the hospital will help prevent the spread of diarrhea and lower its incidence, as will effective and widespread hand washing with soap and water. A systematic review and meta-analysis of studies from the developing world and from US and Australian childcare settings estimated that hand-washing with soap reduces the risk for diarrheal diseases in hospitals by 42% to 47% (34); alcohol-based hand cleaners are not effective against strains of C. difficile. Patients with CDI and the health care workers caring for them must use under regular effective hand washing with soap and water, use disposable thermometers for recording temperature, and employ meticulous environmental cleaning with chlorine-based bleach products in clinical settings to prevent spread of infections in the hospital.

Live, oral, human-bovine (Pentavalent/RV5) rotavirus vaccine (RotaTeq) recommended for routine use in infants in the United States since 2006 has had a great impact on the morbidity associated with rotavirus infection in children in the United States (35) in addition to decreasing rates of rotavirus-associated gastroenteritis among adults, since rotavirus vaccine is being used in children (36).
Key Points

- Noroviruses cause approximately half of all diarrhea for which a cause of illness can be found.
- Noroviruses are usually intense but persist for no more than 60 hours, and do not usually require therapy.
- For the elderly and infirm, especially after organ and stem cell transplantation, the noroviruses can cause severe and chronic illness and may be fatal.
- Between 10% and 30% of nosocomial diarrhea is due to C. difficile.
- Since 10% to 20% of institutionalized patients are colonized with this organism during hospitalization and because most acute diarrhea developing in the hospital is not caused by C. difficile, the PCR test for fecal toxin often gives a false-positive result.
- Since a very significant number of hospital associated diarrhea cases do not have CDI plus the fact that C. difficile PCR-based diagnostic tests will be positive in colonized patients without diarrhea, only unformed stool should be tested for CD, unless the patient has ileus.
- Immunosuppressed or immunocompromised patients will have increased susceptibility to diarrhea.
- Antimotility drugs should not be used in dysenteric and febrile diarrhea without effective concomitant antibiotics as they can prolong or complicate the disease.
- Patients with CDI and the health care workers caring for them must employ effective hand-washing with soap and water, disposable thermometers for recording temperature, and meticulous environmental cleaning with chlorine-based bleach products in clinical settings to prevent spread of infections in the hospital.

References