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Inflammation and Infection in the ICU

Chapter 40

INFECTION, INFLAMMATION, AND MULTIORGAN INJURY

Inflammation is *not itself considered to be a disease but a salutary operation ... but when* it *cannot accomplish that salutary purpose ...* it *does mischief.*
John Hunter, MD (1728-1793)

The most significant discovery in critical care medicine in the last 20 years is the prominent role played by the inflammatory response in the morbidity and mortality associated with severe sepsis and septic shock. In fact, the tendency for inflammation to "do mischief" that Dr. Hunter described over two centuries ago is probably the leading cause of death in intensive care units. This chapter will describe the relationship between infection, inflammation, and multiorgan failure, and the clinical syndromes that result from this relationship.

INFLAMMATORY INJURY

The inflammatory response is an extremely complicated process that is triggered by a physical, chemical, or infectious insult to the host. The presumed role of the inflammatory response is to protect the host from the damaging effects of the insult, as illustrated in the panel on the left in Figure 40.1. The inflammatory response generates a variety of noxious substances (e.g., proteolytic enzymes, oxygen metabolites) but, under normal conditions, the host is somehow protected from these substances. However, as shown in the panel on the right in Figure 40.1, when the protective devices of the host are lost, the inflammatory response damages the host organism (4). Inflammatory injury, once it starts, becomes

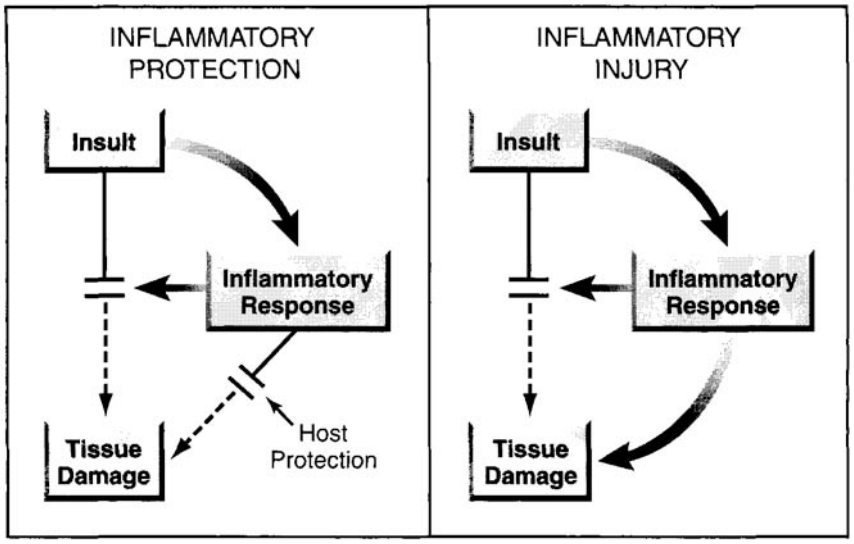

FIGURE 40.1 The dual role of the inflammatory response in protecting and damaging the host organism.

a self-sustaining process, because the tissue damage triggers more inflammation, which produces more tissue damage, and so on. The clinical manifestation of this process is multiorgan dysfunction, which progresses to multi organ failure (5). Therefore, when the host is no longer able to protect itself from the damaging effects of inflammation, the inflammatory response become a toxic insult to the host (5). In this situation, the host is defenseless, and inflammation consumes the organs of the host. This process has been called *malignant inflammation (6).*
The role of infection in this scheme is to serve as one of the insults that triggers the inflammatory response. However, inflammation can be triggered by other insults (e.g., trauma, burns), so inflammatory injury can occur without infection.

Clinical Syndromes
The relationships between infection, inflammation, and organ injury just described is the basis for the following nomenclature and abbreviations (3):
The condition characterized by signs of systemic inflammation (e.g., fever and leukocytosis) is called the *systemic inflammatory response syndrome* (SIRS).
When SIRS is the result of an infection, the condition is called *sepsis.*
When sepsis is accompanied by dysfunction in one or more vital organs, the condition is called *severe sepsis.*

TABLE 40.1 Diagnostic Criteria for the Systemic Inflammatory Response Syndrome (SIRS)

The diagnosis of SIRS requires at least 2 of the following:
1. Temperature >38°C or <36°C
2. Heart rate >90 beats/minute
3. Respiratory rate >20 breaths/minute or Arterial $PC0_2$ <32 mm Hg
4. WBC count >12,000/$mm^3$0r <4000/mm^3 or > 10% immature (band) forms

From Reference 3.

When severe sepsis is accompanied by hypotension that is refractory to volume infusion, the condition is called *septic shock*.
Abnormal function in more than one vital organ is called *multiorgan dysfunction syndrome* (MODS), and failure of more than one organ system is called (surprise!) *multiorgan failure* (MOF).

The major value of this nomenclature is to highlight the distinction between inflammation (SIRS) and infection (sepsis).

Systemic Inflammatory Response Syndrome

The diagnostic criteria for SIRS are shown in Table 40.1. Unfortunately, some of the criteria are very non-specific (e.g., an anxiety attack can produce a heart rate above 90 and a respiratory rate above 20, and would thus qualify to be called SIRS). In one survey, 93% of patients in a surgical leu had SIRS using the criteria in Table 40.1 (7). Infection is identified in only 25 to 50% of patients with SIRS (7,8). Although some patients with SIRS may not be inflamed, these numbers still emphasize the point that infection and inflammation are distinct entities.

Multiorgan Dysfunction and Failure

The organs most often injured by sepsis and inflammation are the lungs, kidneys, cardiovascular system, and central nervous system. The clinical syndromes associated with multiorgan failure are shown in Figure 40.2. The most common of these syndromes is the acute respiratory distress syndrome (ARDS), which is associated with 40% of cases of severe sepsis (9). (This condition is described in Chapter 22.)

Mortality Rate

The mortality rate in multiorgan failure is directly related to the number of organ systems that fail. This relationship is shown in Figure 40.3, which includes studies from the United States (9) and Europe.

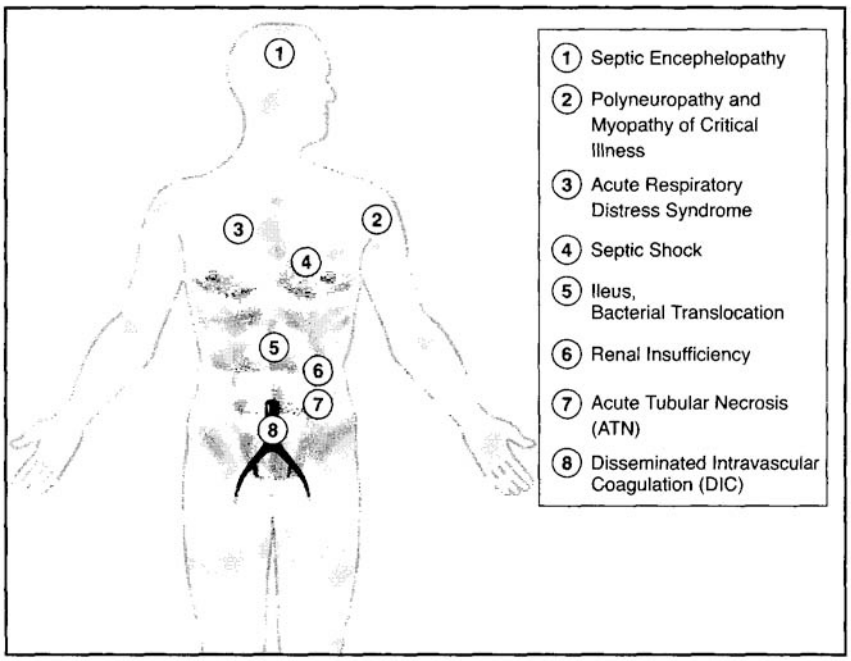

FIGURE 40.2 Components of multiorgan failure. Each of these clinical syndromes is the result of inflammatory injury.

The mortality rate increases steadily as the number of organs fail. This relationship is not surprising, because the chances for survival should diminish as more vital organs fail. In fact, multiorgan failure could be viewed as an expression of the dying process. Death can occur from catastrophic failure of one organ (cardiac arrest), or from a cumulative failure in several organs (multiorgan failure). Why make this point? Because it may not be possible to reverse the dying process, so if multiorgan failure is the dying process, our energies are misplaced because interventions aimed at multiorgan failure will fail (which is the case).

MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

The management of patients with severe sepsis and septic shock is almost a daily exercise in most ICUs because septic shock may be the leading cause of death in ICUs (11). Unfortunately, despite all the efforts expended in this area, the mortality in these conditions has changed little over the years (2,12). The following recommendations represent the latest attempt to create a treatment strategy that will have an impact on the outcome of these conditions (2), but there is no "magic bullet" here.

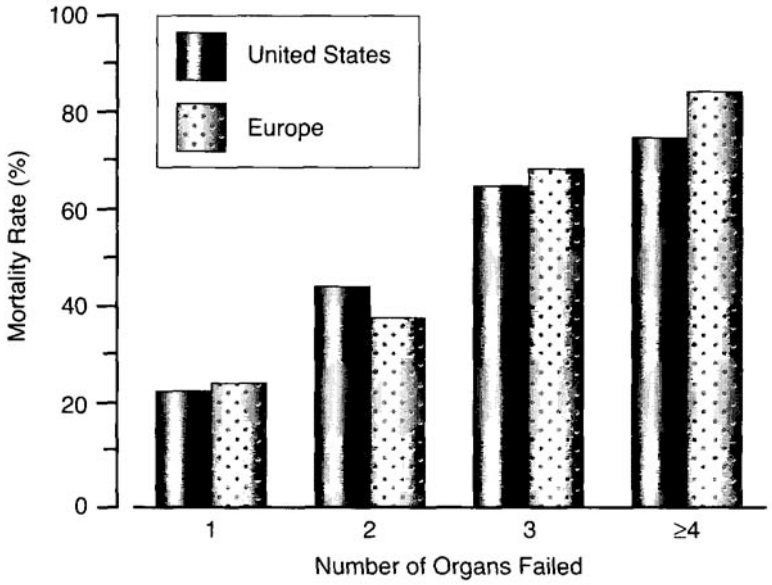

FIGURE 40.3 Relationship between mortality rate and number of organ failures in critically ill patients. (From References 9 and 10).

Tissue Oxygenation Not Impaired in Sepsis

The state of tissue oxygenation in septic shock is described in Chapter 11. To summarize, the prevailing opinion is that the metabolic derangement in severe sepsis and septic shock is not impaired tissue oxygenation, but is a defect in cellular oxygen utilization (13). This condition is called *cytopathic hypoxia* (13), and it explains why tissue levels of oxygen can be increased in patients with severe sepsis (14), as shown in Figure 11.3 (see Chapter 11). If this is the case, then efforts to improve tissue oxygenation in septic shock by improving systemic oxygen delivery are misguided.

The $V0_2$ *in Sepsis*

Also explained in Chapter 11 is the possibility that the increase in oxygen consumption ($V0_2$) in sepsis is not related to aerobic metabolism, but is O_2 consumed in the process of neutrophil activation (the respiratory burst) (5). Although this needs further study, it provides another reason to avoid the use of oxygen transport variables for the management of patients with severe sepsis and septic shock.

Initial Resuscitation
The following goals have been established for the first 6 hours of management for patients with severe sepsis and septic shock (1):

Central venous pressure 8-12 mm Hg.
Mean arterial pressure 265 mm Hg.
Urine output 20.5 mL/kg per hour.
$Sv0_2$ or $Scv0_2$ >=70%

where SvO, and ScvO, are the oxyhemoglobin saturation in central venous (superior vena- cava) blood and mixed venous (pulmonary artery) blood. In ventilator-dependent patients, a higher target central venous pressure of 12-15 mm Hg is recommended.

Fluid Challenge
If there is evidence or suspicion of hypovolemia based on the goals listed above, then fluid challenges can be given as follows:

Infuse 500-1,000 mL of crystalloid fluid or 300-500 mL of colloid fluid over 30 minutes.
Repeat as needed until goals reached or fluid overload imminent.

There is no evidence to favor crystalloid or colloid fluids for volume infusions. Colloid fluids are more likely to expand the plasma volume and less likely to expand the extracellular fluid volume than crystalloid fluids (see Chapter 13). However, because sepsis is often accompanied by hypoalbuminemia (16), initial resuscitation with 5% albumin may be preferred.

Vasopressors
If hypotension persists despite fluid challenges, then vasopressor drug support with either dopamine or norepinephrine should be started.

Dopamine: Usual dose range 5-20 μg/kg/min. (See Table 16.3)
Norepinephrine: Effective dose range in sepsis is 0.2-1.3 μg/kg/min (about 1 to 10 μg/min for a 70 kg patient) (17).

Dopamine is more likely to increase cardiilc output, while norepinephrine produces vasoconstriction with no change in cardiac output (18). Dopamine can promote tissue acidosis in the splanchnic circulation, while norepinephrine does not have this effect (18), and this might be a reason to prefer norepinephrine. However, the choice of vasopressor is largely one of personal preference.
In cases of hypotension that are refractory to dopamine and norepinephrine, vasopressin is a consideration. The recommended infusion rate is 0.01 to 0.04 units per minute (1). Vasopressin is a pure vasoconstrictor that will reduce cardiac output, so it should be used with caution in patients with a history of heart failure. However, if the patient has refractory hypotension, that is not your major worry.

Empiric Antimicrobial Therapy
Intravenous antibiotics are recommended starting within one hour of recognition of severe sepsis or septic shock. Before starting antibiotics, at least 2 sets of blood cultures should be obtained. Remember that the yield from blood cultures is directly dependent on the volume of blood cultured. For an optimal yield from blood cultures, a volume of 20 to 30 mL of blood should be withdrawn from each venipuncture site (20).
Unless the patient has an obvious infection, you will start empiric antibiotic coverage. For recommended empiric antibiotic regimens in serious infections, see Table 43.4 (Chapter 43), and for appropriate starting doses of antibiotics, see Table 41.6 (Chapter 41). A simple regimen to remember is imipenem or meropenem alone (meropenem has a lower risk of seizures) and, **if** there is a risk for methicillinresistant *Staph aureus* (MRSA), add vancomycin or linezolid. (For information on linezohd, which may eventually replace vancomycin, see Chapter 44.)

Corticosteroids
Steroids were anathema for septic shock in the 1980s, but based on the results of 3 more recent studies (21-33), they are now recommended for all patients with septic shock who require vasopressor support (1). The recommended regimen is shown below (1).

Hydrocortisone: 200-300 mg IV daily in 2 or 3 divided doses for 7 days.

The benefit from steroids might be the result of adrenal insufficiency, which can occur in patients with severe sepsis and septic shock (see Chapter 48). In one study (21), the patients who showed improvement on steroids had evidence of adrenal insufficiency.

ANAPHYLAXIS
The inflammatory respunse is also involved in hypersensitivity reactions, and anaphylaxis is the most life-threatening expression of these reactions. Common offenders are antimicrobial agents, anesthetics, radiocontrast dyes, nutrients, and insect venoms (24). Radiocontrast dyes are the most common source of serious anaphylactic reactions, with an incidence of 1 in 1,000 to 14,000 Injections (25). About 10% of these reactions are fatal (25).

Clinical Presentation
Anaphylactic reactions vdry in presentation and severity. Clinical manifestations appear within minutes to a few hours after exposure to the offending agent. Less serious reactions include flushing, erythematous rashes, urticaria, abdominal cramping, and diarrhea. More severe

reactions include angioedema, laryngeal edema, bronchospasm, and hypotension. The most life-threatening reaction is a rapid-onset cardiovascular collapse known as *anaphylactic shock.*

Management

The management of anaphylaxis is dictated by the clinical presentation.

Epinephrine

Epinephrine blocks the release of inflammatory mediators from sensitized cells, and it is the drug of choice for severe anaphylactic reactions. Epinephrine is available in strengths of 1:100 (10 mg/mL), 1:1,000 (1 mg/mL), and 1:10,000 (0.1 mg/mL). The usual dose for anaphylactic reactions is 0.3-0.5 mg (or 0.3-0.5 mL of 1:1,000 solution) by deep IM injection in the thigh. Drug absorption is better with IM injection into the thigh instead of the traditional subcutaneous injection (26). Epinephrine can also be nebulized for laryngeal edema: the inhalant is made up of 0.25 mL 1:100 epinephrine added to 2 mL isotonic saline.

For patients being treated with beta-blocker drugs, the response to epinephrine may be attenuated, and glucagon can be used as a substitute. The glucagon dose is 5-15 μg/min by intravenous infusion.

Second-Line Agents

Histamine blockers have little effect in preventing or treating anaphylaxis, although they can help to relieve pruritis. This lack of efficacy is surprising, considering the presumed importance of histamine in the pathogenesis of anaphylaxis. The histamine H 1 blocker diphenhydramine (25-50 mg PO, 1M, or IV) and the histamine-H 2 blocker ranitidine (50 mg IV or 150 mg PO) should be given together because they are more effective in combination.

Steroids are used primarily to reduce the risk of second-phase symptoms, which appear 1 to 8 hours after the acute episode (24). Prednisone (50 mg PO) and methylprednisolone (125 mg IV) are equivalent in efficacy. These agents can be given every 6 hours for persistent symptoms.

Albuterol (2.5 mL of 0.5% solution via nebulizer) can be used as an adjunct to epinephrine for persistent bronchospasm.

Anaphylactic Shock

Anaphylactic shock is a life-threatening condition that requires prompt intervention using the following measures:

Epinephrine is given intravenously in a dose of 0.3-0.5 mg (3-5 mL of epinephrine 1:10,000). This can be followed by an epinephrine infusion of 2-8 μg/min.

Volume resuscitation is very important because anaphylactic shock can be accompanied by profound hypovolemia due to

massive fluid shifts into the interstitium. Colloid fluids may be preferred to crystalloid fluids because they are less likely to escape into the interstitium.
Persistent hypotension can be managed with dopamine (5-15 μg/kg/min) or norepinephrine (2-8 μg/min).

A FINAL WORD
The most important message in this chapter is the distinction between inflammation and infection, and the importance of inflammation as a source of lethal injury to the host organism. It is clear that antibiotics provide little benefit to patients with severe sepsis and septic shock (because a majority die despite antibiotic therapy), and now you know why. Because the problem in septic shock and multiorgan failure is not infection, it's inflammation.

REFERENCES

Chapter 41

PNEUMONIA IN THE ICU

Everything hinges on the matter of evidence.
Carl Sagan

Pneumonias that are acquired in the ICU can be characterized by one word: *problematic.* The diagnosis of ICU-acquired pneumonias is problematic because there is no "gold standard" method for identifying parenchymal lung infections in ICU patients (other than postmortem examination). As a result, the diagnostic approach to ICU-acquired pneumonia is not standardized, and there are at least 6 different diagnostic methods to choose from (qualitative and quantitative cultures of tracheal aspirates, bronchial brushings with and without bronchoscopy, and bronchoalveolar lavage with .and without a bronchoscopy). Because of the diagnostic uncertainties, treatment of ICU-acquired pneumonias is also problematic. Deciding whether to start antibiotics or which antibiotics to use is often a matter of speculation because it is unclear in many cases if a pneumonia is actually present. As a result of these problems, the approach to ICU-acquired pneumonias is sometimes more fancy than fact.
This chapter will summarize the current knowledge about pneumanias acquired in the ICU, with emphasis on pneumonias acquired by ventilator-dependent patients. The material in this chapter pertains only to patients who are immunocompetent. Special considerations for nosocomial pneumonia in immunocompromised patients are presented in Chapter 43.

GENERAL FEATURES
The following statements summarize some of the general characteristics of pneumonia acquired in the ICU (1)
Pneumonia is considered the most common nosocomial infection in the ICU (see Table 39.3), but the prevalence is overstated

TABLE 41.1 Pathogens Isolated by Bronchoscopy in Ventilator-Associated Pneumonia

Organisms	Frequency
Bacilli	56.5%
Pseudomonas aeruginosa	18.9%
Escherichia coli	9.2%
Hemophilus	7.1%
Enterobacter	3.8%
Proteus	3.8%
Klebsiella	3.2%
Others	10.5%
Cocci	42.1%
Staphylococcus aureus	18.9%
Streptococcus pneumoniae	13.2%
Enterococcus	1.4%
Others	8.6%
Fungi	1.3%

From Chastre J, et al. Comparison of 8 vs 15 days of antibiotic therapy for associated pneumonia in adults. JAMA 2003; 290:2558.

because many cases of presumed pneumonia are not corroborated on postmortem exam (see later).
Over 90% of ICU-acquired pneumonias occur during mechanical ventilation, and 50% of these *ventilator associated pneumonias* occur in the first 4 days after intubation (1).
The predominant pathogens in ICU-acquired pneumonias are *Staphylococcus allreus, Pseudomonas aeruginosa,* and other gram negative aerobic bacilli (see Table 41.1). Viruses, fungi, and anaerobes are uncommon isolates.
Although the mortality rate in ICU-acquired pneumonia is reported at 30% to 50% (1), some studies show no deaths attributed to this condition (2).

Pathogenesis

Aspiration of pathogenic organisms from the oropharynx is believed to be the inciting event in most cases of hospital-acquired (nosocomial) and ICU-acquired pneumonias (3). The organisms that most often colonize the oropharynx in hospitalized patients are enteric gram-negative bacilli and *Staphylococcus aureus* (see Figure 4.5 in Chapter 4), and this explains the predominance of these pathogens in nosocomial pneumonias. The instances of ventilator-associated pneumonia that appear within 4 days after intubation are most likely caused by microbes that have been dragged into the airways during the intubation procedure. Once the oropharynx is colonized, endotracheal tubes and tracheostomy tubes can

TABLE 41.2 Predictive Value of Clinical Criteria in the Diagnosis of Ventilator-Associated Pneumonia

Study	Clinical Criteria	likelihood Ratio for Pneumonia on Autopsy·
Fagon et al.	Radiographic infiltrate + purulent sputum + fever or Leukocytosis	1.03
Timsit et al.	Radiographic infiltrate + 2 of the following: fever, Leukocytosis, or purulent sputum	0.96

'As reported in Reference 4. The likelihood ratio is the likelihood that patients monia will have the clinical findings compared to the likelihood that patients without pneumonia will have the same clinical findings. A likelihood ratio = 1 indicates that the clinical findings are just as likely to be found in the presence and absence of pneumonia.

serve as a nidus for biofilm formation that protects the colonizing pathogens and allows them to proliferate (1). The frequent passage of suction catheters through these tubes can then introduce the pathogens into the airways. Colonization of the oropharynx and stomach with pathogenic organisms in hospitalized patients is described in detail in Chapter 4.

Clinical Features

Bacterial pneumonias typically present with fever, Leukocytosis, purulent sputum production, and a new infiltrate on the chest x-ray. However, these clinical manifestations are nonspecific in ventilator-dependent patients. In ventilator-dependent patients who are suspected of having pneumonia based on clinical findings (the presence of a pulmonary infiltrate plus any combination of fever, Leukocytosis, or purulent sputum production), the actual incidence of pneumonia on postmortem exam is only 30% to 40% (4). The value of clinical findings in the diagnosis of ventilator-associated pneumonia is shown in Table 41.2. This table shows the results of 2 studies that used autopsy evidence of pneumonia to evaluate the premortem diagnosis of ventilator-associated pneumonia based on clinical findings (5,6). In both studies, the clinical criteria for identifying pneumonia were just as likely to occur in the presence and absence of pneumonia. This demonstrates the diagnosis of pneumonia in ventilator-dependent patients is not possible using clinical criteria alone.

Sensitivity of Chest Radiography

The definition of pneumonia proposed by the Centers for Disease Control (CDC) requires the presence of a new infiltrate on chest x-ray (7). A patient who presents with fever and purulent sputum production is considered to have a tracheobronchitis (8). However, it seems unlikely that the chest x-ray is always abnormal in the presence of pneumonia (i.e., has a sensitivity of 100%). For example, pulmonary edema is not evident on a chest x-ray until the extravascular lung water has increased 30 to 50% (9), and this lack of sensitivity for pulmonary edema could also apply to parenchymal infections in the lungs.

The traditional teaching is that pneumonia in a dehydrated patient may become radiographically evident only after rehydration. This seems unlikely because it would mean that dehydration can limit or prevent inflammatory infiltration of vital organs. There are few studies that address this question, but one animal study has shown that dehydration does not influence the x-ray appearance of bacterial pneumonia (10).

Specificity of Chest Radiography

Pneumonia accounts for only 1/3 of all pulmonary infiltrates in ICU patients (11,12), which means that conditions other than pneumonia are the most frequent cause of pulmonary infiltrates in ICU patients. The noninfectious causes of pulmonary infiltrates in the ICU include pulmonary edema, acute respiratory distress syndrome, and atelectasis. An example of how atelectasis can influence the chest x-ray is shown in Figure 41.1. Both images in this figure were obtained within minutes of each other in the same patient. The image on the left shows a marked reduction in lung volume that occurred when the patient changed from the upright to supine position. Note that the volume loss in the supine position produces an area of crowded lung markings at the base of the right lung (dotted triangle). In a patient with fever, this localized atelectasis could be confused with a pneumonia.

Acute Respiratory Distress Syndrome

The most common noninfectious cause of pulmonary infiltrates in ICU patients is the acute respiratory distress syndrome (ARDS) (12). This

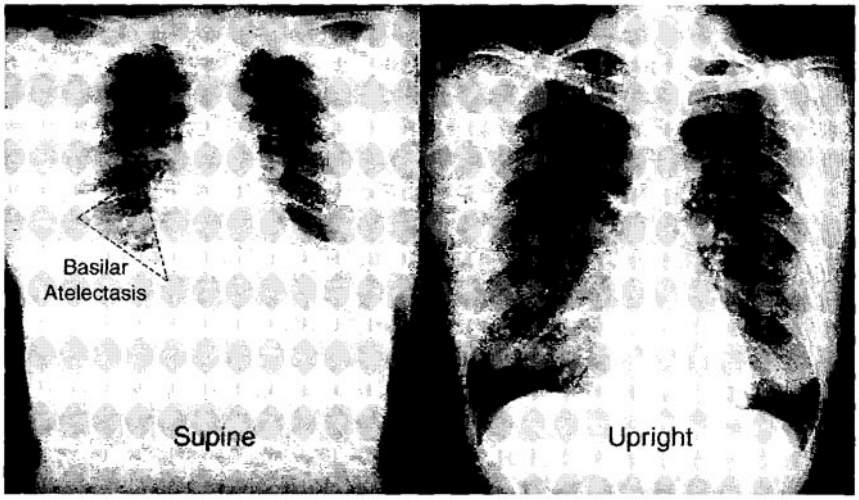

FIGURE 41.1 The effect of body position on the appearance of portable chest x-rays. Both images were obtained within minutes of each other in the same patient. The dotted triangle outlines an area of localized atelectasis that could be misread as a basilar pneumonia. Image on the left digitally enhanced.

condition, which is described in Chapter 22, is an inflammatory disorder of the lungs that produces bilateral infiltrates on chest x-ray. Because it is often accompanied by fever, ARDS can be difficult to distinguish from a multilobar pneumonia. This is illustrated in Figure 41.2. The x-ray image in this figure is from a patient who was admitted to the ICU with fever and respiratory insufficiency. The patient was initially treated for a severe community-acquired pneumonia, but subsequent evaluation revealed *Escherichia coli* in cultures of blood and urine, while cultures taken from the lower respiratory tract (by bronchoscopy) were sterile. The final diagnosis in this case was ARDS secondary to gram-negative septicemia from a urinary tract infection. In addition to masquerading as pneumonia, ARDS can also co-exist with pneumonia. About 10% of cases of ARDS are the result of a pneumonia, and about 50% of patients with ARDS will develop a pneumonia at some time during their ICU stay (13). The methods used to identify infection in ARDS and other ventilator-dependent patients are described in the next section.

Summary

In summary, the usual clinical criteria for pneumonia (fever, Leukocytosis, purulent sputum, and a new infiltrate on chest x-ray) should not be used as evidence of pneumonia in ICU patients, but instead are indications to proceed with the diagnostic evaluation described next to document infection and identify the responsible pathogen.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of suspected pneumonia includes cultures of blood, pleural fluid, and a variety of specimens collected from the respiratory tract. Blood cultures have limited value in the diagnosis of ICUacquired pneumonia because organisms are isolated from blood in only 25% of ICU patients with suspected pneumonia (1), and these organisms can originate from extrapulmonary sites (14). Cultures of specimens obtained from the respiratory tract are usually required to confirm or exclude the presence of pneumonia.

Tracheal Aspirates

The standard practice for the evaluation of pneumonia in ventilator-dependent patients is to aspirate secretions through an endotracheal or tracheostomy tube and perform qualitative cultures on the aspirates. These cultures have a high sensitivity (usually >90%) but a very low specificity (15 to 40%) for the diagnosis of pneumonia (15). This means that a negative culture of a tracheal aspirate can be used to exclude the diagnosis of pneumonia, but a positive culture cannot be used to confirm the presence of pneumonia. The poor predictive value of positive cultures is due to contamination of tracheal aspirates with secretions from the mouth and upper airways. The diagnostic accuracy of tracheal aspirates can be improved by screening the specimens with microscopic visualization to include only specimens originating from the lower airways, and then performing quantitative cultures on the screened specimens. This is explained in the following sections.

Microscopic Analysis

The cells identified in Figure 41.3 can help to determine if aspirated secretions originate in the upper or lower airways, and also if there is evidence of infection. Each type of cell can be identified and interpreted as follows.

The squamous epithelial cells that line the oral cavity are large and flattened with abundant cytoplasm and a small nucleus (see Fig. 41.3). The presence of more than 25 squamous epithelial cells per low-power field (x 100) indicates that the specimen is contaminated with mouth secretions (16). If there is evidence of contamination, the specimen should be discarded.

Lung macro phages are large, oval-shaped cells with a granular cytoplasm and a small, eccentric nucleus (Fig. 41.3). The size of the nucleus

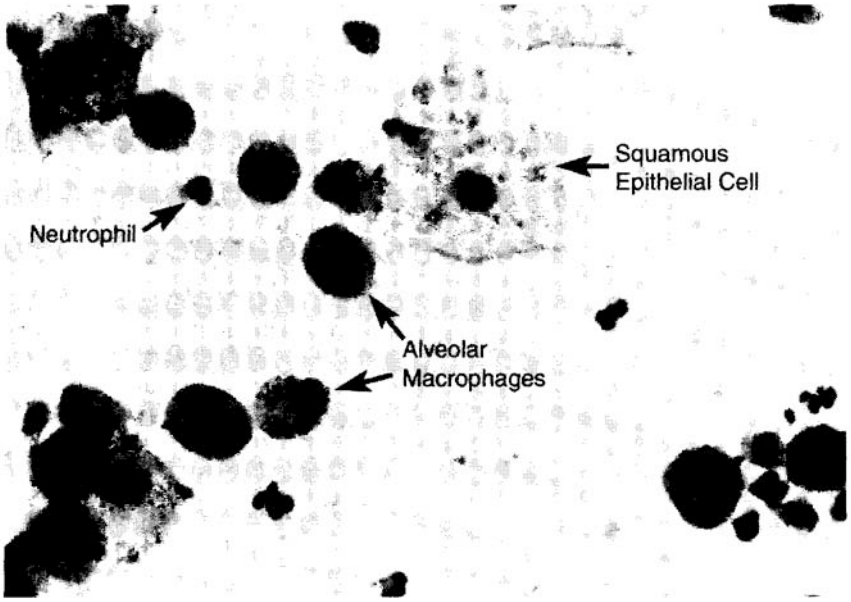

FIGURE 41.3 Microscopic appearance (magnification ×400) of bronchial brushings from a ventilator-dependent patient. The paucity of squamous epithelial cells and the presence of alveolar macrophages both confirm that the specimen is from the distal airways.

in a macrophage is roughly the same size as a neutrophil. Although ffiacrophages can inhabit the airways (17), the predominant home of the macrophage is the distal airspaces. Therefore, the presence of macrophages, regardless of the number, indicates that the specimen is from the lower respiratory tract.

The presence of neutrophils in respiratory secretions is not evidence of infection because neutrophils can make up 20% of the cells recovered from a routine mouthwash (17). The neutrophils should be present in abundance to indicate infection. More than 25 neutrophils per lowpower field (x 100) can be used as evidence of infection (18). When an infection is evident, a search for macrophages and squamous epithelial cells will help to determine if the infection is in the upper airways (tracheobronchitis) or the lower airways (pneumonia). When a tracheal aspirate shows evidence of lower airways infection (i.e., abundant neutrophils and macrophages with few epithelial cells), the specimen is suitable for culture.

Quantitative Cultures

Quantitative cultures of tracheal aspirates produce fewer false-positive results than qualitative cultures. To perform quantitative cultures, the tracheal aspirate should be collected in a sterile trap without adding saline or lidocaine (the latter can inhibit microbial growth). When a volume of at least 1 mL is collected, the specimen is sent to the laboratory

TABLE 41.3 Quantitative Cultures for the Diagnosis of Pneumonia in Ventilator-Dependent Patients

	TA	PSB	BAL
Diagnostic Threshold (CFU/mL)	10^5 to 10^6	10^3	10^4 to 10^5
Sensitivity (mean)	76%	66%	73%
Specificity (mean)	75%	90%	82%
Relative Performance	Most Sensitive	Most Specific	Most Accurate

Abbreviations: *TA* = tracheal aspirates, *PSB* = protected specimen *BAL* = bronchoalveolar
From References (1,15,21).

(make sure you specify that you want *quantitative* cultures) where it is vortexed (agitated) in isotonic saline. A sample is then collected with a 0.01mL loop and the sample is placed on a culture plate for incubation. For quantitative cultures, growth on the plate is reported as follows: 10 colonies is reported as 10^3 colony-forming units per mL (CFU /mL), 100 colonies is 10^4 CFU/mL, 1,000 colonies is 10^5 CFU/mL, and more than 1,000 colonies is 10^6 CFU / mL (this technique might vary in different laboratories, but the principle is the same).

For quantitative cultures of tracheal aspirates, the threshold growth for the diagnosis of pneumonia is 10^5 to 10^6 CFU / per mL (the lower threshold is sometimes used for patients who are on antibiotic therapy when the cultures are performed). Studies using these thresholds have shown a (mean) sensitivity and specificity of 76% and 75%, respectively, for the diagnosis of pneumonia (see Table 41.3) (1,15). Comparing these results to the sensitivity and specificity of qualitative cultures mentioned earlier (i.e., sensitivity >90% and specificity <=40%) shows that quantitative cultures of tracheal aspirates are less sensitive but much more specific than qualitative cultures for the diagnosis of pneumonia.

Protected Specimen Brush

Aspiration of secretions through a bronchoscope produces a high rate of false-positive cultures because the bronchoscope picks up contaminants as it is passes through the upper respiratory tract (19). To eliminate this problem, a specialized brush called a *protected specimen brush* (PSB) was developed to collect uncontaminated secretions from the distal airways. The brush sits in the inner lumen of a catheter-over-catheter device that has a gelatin plug at the distal end. When the device is advanced through the bronchoscope, the gelatin plug protects the brush from contamination with upper airways secretions. When the bronchoscope is advanced into the area of lung infiltration, the entire catheter device is advanced out of the bronchoscope and into the lower airways (see Fig. 41.4). The inner catheter is advanced until it knocks off the gelatin plug (which dissolves without harming the patient), and the brush is then advanced into the distal airways to collect the specimen. After vigorous brushing, the brush is retracted into the inner cannula, the inner cannula is retracted

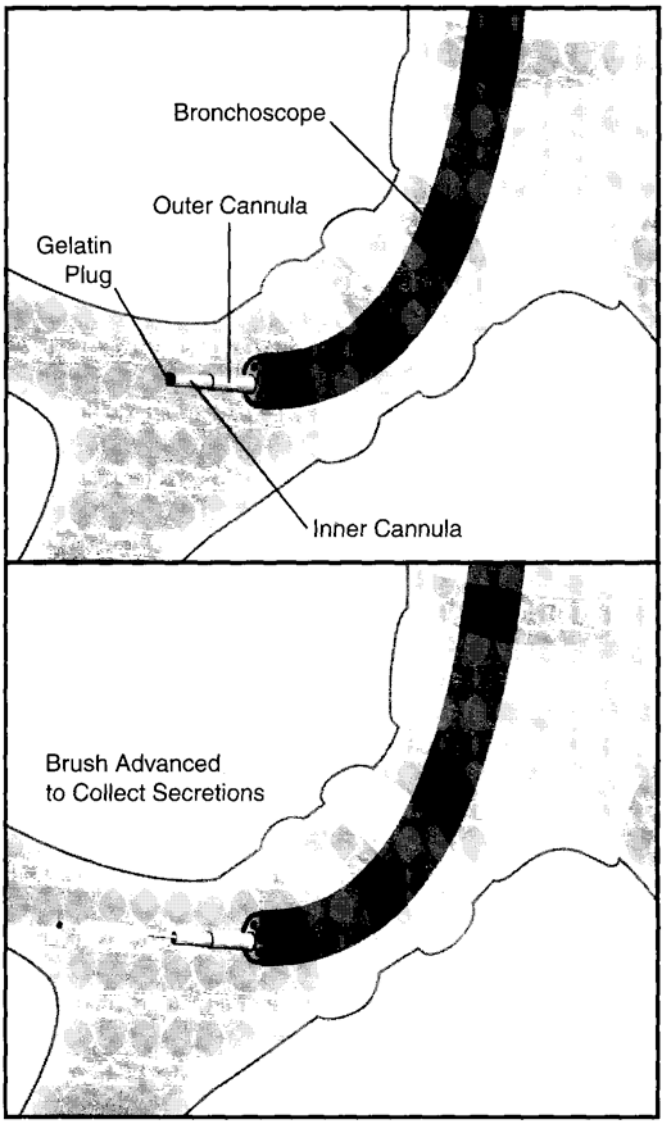

FIGURE 41.4 The protected specimen brush (PSB) technique for obtaining uncontaminated secretions from the lower airways.

into the outer cannula, and the entire device is retracted through the bronchoscope.

Quantitative Cultures

Using sterile technique, the brush is severed from its wire and is placed in 1 mL of transport medium. In the microbiology lab, the brush is vortexed in the transport medium to disperse microorganisms. The specimen is

then processed in the same fashion as described for tracheal aspirates. Growth of 10^3 CFU *j* mL is the threshold for the presence of infection (pneumonia) 0). The reported sensitivity and specificity of PSB cultures are shown in Table 41.30). A positive culture result has a relatively low sensitivity (66%) but a high specificity (90%) for the diagnosis of pneumonia. This means that a negative PSB culture does not exclude the presence of pneumonia, but a positive PSB culture confirms the presence of pneumonia with 90% certainty.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) is performed by wedging the bronchoscope in a distal airway and performing a lavage with sterile isotonic saline. A minimum lavage volume of 120 mL is recommended for adequate sampling of the lavaged lung segment (9), and this is achieved by performing a series of 6 lavages using 20 mL for each lavage. The same syringe is used to introduce the fluid and aspirate the lavage specimen (only 25% or less of the volume instilled will be returned via aspiration).

Quantitative Cultures

The first lavage is usually discarded, and the remainder of the lavage fluid is pooled and sent to the microbiology lab, where it is centrifuged and processed in the same manner as described for tracheal aspirates. The threshold for a positive BAL culture is 10^4 to 10^5 CFU/mL (the lower threshold is for patients who are on antibiotic therapy when the procedure is performed) (1). The reported sensitivity and specificity of BAL cultures are shown in Table 41.3 (1,20). Neither the sensitivity nor the specificity exceeds both of the diagnostic methods in Table 41.3, but when sensitivity and specificity are considered together, BAL cultures have the highest overall accuracy for the diagnosis of pneumonia.

Intracellular Organisms

Inspection of BAL specimens for intracellular organisms can help in guiding initial antibiotic therapy until culture results are available. When intracellular organisms are present in more than 3% of the cells in the lavage fluid, the likelihood of pneumonia is over 90% (21). Unfortunately, this is not done on a routine Gram stain, but requires special processing and staining in the microbiology lab (see references 21 and 22 for the methodology).

BAL without Bronchoscopy

The limited availability of bronchoscopy on a 24-hour basis has led to the introduction of a non-bronchoscopic technique for BAL where specialized catheters are inserted through a tracheal tube and advanced blindly until wedged in the lower airways. A variety of catheters and techniques have been used (for examples of two techniques, see references 23 and 24), and the method has proven safe and effective when performed by respiratory therapists (23). In general, cultures obtained by nonbronchoscopic

and bronchoscopic BAL have shown equivalent sensitivities and specificities for the diagnosis of pneumonia (1,25), and there is evidence that nonbronchoscopic BAL is better tolerated than bronchoscopic BAL (24). However, there is concern about adopting nonbronchoscopic procedures to diagnose pneumonia because of the lack of standardization of the techniques in clinical studies (26).

Which Diagnostic Method is Best?

There is little agreement on which method should be preferred for the diagnosis of pneumonia. The following statements include some pertinent observations.

The diagnostic yield from all culture methods is adversely affected by ongoing antibiotic therapy (1). Therefore, when possible, cultures should be obtained before antibiotics are started.

Tracheal aspirates should be screened by microscopic examination, and the specimens should be discarded if there is evidence of contamination with secretions from the mouth and upper airways.

Quantitative cultures of tracheal aspirates are preferred to qualitative cultures because they have a higher specificity, and thus are more likely to identify a pneumonia and the responsible pathogen(s).

Treatment based on cultures of tracheal aspirates will result in excessive use of antibiotics because cultures of tracheal aspirates are most likely to produce false-positive results (1,27).

Most studies show that the mortality in ventilator-associated pneumonia is not influenced by the diagnostic method. In other words, there is no survival benefit with the more invasive methods (protected specimen brushings and bronchoalveolar lavage) compared to the relatively simple method of aspirating secretions through an endotracheal or tracheostomy tube.

Based on the absence of a survival benefit with the invasive diagnostic methods, many prefer tracheal aspirates for the diagnostic approach to pneumonia, even though this practice will result in excessive use of antibiotics (1). Tracheal aspirates should, however, be screened by microscopic inspection and cultured using quantitative techniques. Qualitative cultures of tracheal aspirates are useful only when there is no growth, which can be used to exclude the presence of pneumonia.

Parapneumonic Effusions

Pleural effusions are present in up to 50% of bacterial pneumonias (28), and these *parapneumonic* effusions should be evaluated in the following situations (1): when the pleural effusion is large, when the patient appears toxic, and when the patient is not improving on antibiotic therapy. If the effusion is loculated (i.e., it does not move with change in body position), computed tomography or bedside ultrasound can be

TABLE 41.4 Management of Parapneumonic Effusions

	Immediate Drainage?	
Clinical Finding	Yes	No
Air-fluid level	X	
Hydropneumothorax	X	
Grossly purulent fluid	X	
Pleural fluid pH:		
<7.0	X	
>7.2		X
Pleural fluid glucose:		
<40 mg/dL	X	
>40 mg/dL		X

used to mark the location and depth of the fluid. In addition to Cram stain and culture, the Pleural fluid glucose concentration and pH should be measured. Classification of the fluid as a transudate or exudate (by Pleural fluid protein and LDH levels) is unnecessary because this does not reliably identify infection.

Indications for Drainage

The indications for immediate drainage of para pneumonic effusions are listed in Table 41.4. The radiographic criteria for drainage include the presence of an air-fluid level in the effusion, or a hydropneumothorax (both are signs of a bronchopleural fistula). Chemical criteria for drainage include a pleural fluid glucose concentration below 40 *mg*/ dL (2.4 *μ*mol/L) or a pleural fluid pH below 7.0 (28). If a patient with a para pneumonic effusion improves clinically on antibiotics, there is little need for further evaluation or drainage of the effusion.

EARLY ANTIMICROBIAL THERAPY

There is a definite tendency to begin antibiotics at the earliest hint of a pneumonia in the ICU. According to one study, antibiotic treatment for pneumonia accounts for half of all antibiotic use in the ICU, but 60% of antibiotic use for pneumonias involve suspected pneumonias that are not confirmed by bacteriologic studies (29). The rush to antibiotics in cases of suspected pneumonia is fueled by studies showing that the mortality in ventilator-associated pneumonia is increased when there is a delay in starting appropriate antibiotic therapy "(30). However, there are also studies showing that ventilator-associated pneumonia does not increase mortality (2,31,32), so the survival benefit of the rush to antibiotics is not firmly established. (See the last section of this chapter for a comment on this situation).

Suggested Strategy

One early antibiotic strategy that is appealing is to administer antibiotics immediately (i.e., when pneumonia is first suspected) for patients who are immunocompromised, or have evidence of severe sepsis (i.e., multiorgan dysfunction) or septic shock. Otherwise, hold antibiotics until you collect specimens from the respiratory tract for Gram stain and culture. Then begin antibiotic therapy based on the appearance of the Gram stain, or using recommended empiric regimens (described next) but *stop* the antibiotics in 2 to 3 days if the cultures do not confirm the presence of pneumonia (33). There will be a tendency to continue antibiotics despite sterile cultures in patients with progressive respiratory insufficiency, but these patients are likely to have ARDS and not pneumonia. If respiratory tract cultures are obtained when patients are not receiving antibiotics, continuing antibiotics in the face of sterile cultures is rarely justified.

Empiric Antibiotic Therapy

The choice of empiric antibiotics should be dictated by the likelihood that the patient is colonized with *Staphylococcus aureus* and gram-negative enteric pathogens (the pathogens listed in Table 41.1). The characteristics of patients who are likely and unlikely to be colonized with these pathogens are shown in Table 41.5, along with the recommended empiric antibiotic regimens for each type of patient. The recommended starting doses for each antibiotic are shown in Table 41.6.

Colonization Unlikely

The typical patients who are not colonized by S. *aurellS* and gram-negative pathogens have been admitted recently (within 5 days) from home, have no debilitating chronic illness (including renal failure that requires dialysis), and have no other hospital admissions in the past 3 months. Patients like this can be treated with a single antibiotic like ceftriaxone or a f1uoroquinolone (levofloxacin or moxifloxacin), as shown in Table 41.5. This treatment is primarily directed at pneumococci, including penicillinresistant strains, and is similar to the treatment of community-acquired pneumonia (34).

Colonization Likely

Colonization with S. *aureus* and gram-negative enteric pathogens is likely when a patient has been in the hospital for 5 days or longer, or when the patient is a nursing home resident, has a chronic debilitating illness, or has had other hospital admissions within the past few months. The empiric antibiotic regimen for these patients, which is shown in Table 41.5, is designed to cover staphylococci and gram-negative enteric pathogens, and is particularly designed for *Pseudomonas aeroginosa* and methicillin-resistant S. *aureus* (MRSA). There is no coverage for fungi, and coverage for anaerobes is not a priority because anaerobes are not considered to be important pathogens in ventilator-associated pneumonia (35). Specific choices of antibiotics will be guided by the profile of nosocomial pathogens and resistance patterns in individual ICUs.

TABLE 41.5 Empiric Treatment for Ventilator-Associated Pneumonia Based on Likelihood of Colonization with Pathogens in Table 41.1[t]

Colonization Unlikely	Colonization Likely
Type of Patient: • Admitted less than 5 days ago and • Admitted from home, and • No other admissions in past 3 months, and • Not a dialysis patient. *Empiric Antibiotics:* • Ceftriaxone, or • A fluoroquinolone (levofloxacin, moxifloxacin, or ciprofloxacin)	*Type of Patient:* • Admitted more than 5 days ago,or • Admitted from a nursing home, or • Other admissions in the past 3 months, or • A dialysis patient. *Empiric Antibiotics:* • Pipericillin/tazobactam, or • Imipenem or meropenem, or • Ceftazidime or cefepime plus • Ciprofloxacin or levofloxacin*, or • An aminoglycoside* plus • Vancomycin or linezolid*

*Benefit is questionable (see text).
*When colonization with methicillin-resistant S. *aureus* is known or likely.
tFrom the American Thoracic Society and Infectious Disease Society of Guidelines for the.management of adults with hospital-acquired, ventilator-healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171 :388-

Double Coverage for Pseudomonas?

The empiric regimen for patients likely to be colonized with gram-negative pathogens includes a second antibiotic for gram-negative coverage (a f1uoroquinolone or aminoglycoside), which is designed to provide double coverage for pneumonias caused by *Pseudomonas aeruginosa.* This recommendation is questionable and is based on one study that showed improved survival in patients with *Pseudomonas* bacteremia (many of whom did not have pneumonia) when double antibiotic coverage was used instead of monotherapy (36). However, another study shows no difference in survival when double coverage for *Pseudomonas* is compared to single drug therapy in patients with serious gram-negative infections (37). Furthermore, empiric double coverage for *Pseudomonas* pneumonia is not justified based on the following reasoning: 0) pneumonia is expected in only about 30% of ICU patients with suspected pneumonia, (2) in the patients with pneumonia, *Pseudomonas* is expected in only 20% of cases, and (3) in the patients with *Pseudomonas* pneumonia, bacteremia is expected in only about 25% of cases. If these estimates are combined, then *Pseudomonas* bacteremia (the only condition with evidence of benefit from double coverage) is expected in only 1.5% of ICU patients with suspected pneumonia.

TABLE 41.6 Recommended Starting Doses for Empiric Antibiotics[t]

Antibiotic	Intravenous Dosage*
Beta-Lactam/Beta-lactamase Inhibitor	
Pipericillin/tazobactam	4.5 grams every 6 hours
Carbepenems	
Imipenem	1 gram every 8 hours
Meropenem	1 gram every 8 hours
Antipseudomonal cephalosporins	
Cefepime	1-2 grams every 8-12 hours
Ceftazidime	2 grams every 8 hours
Antipseudomonal quinolones	
Levofloxacin	750 mg once daily
Ciprofloxacin	400 mg every 8 hours
Aminoglycosides	
Gentamicin	7 mg/kg daily
Tobramycin	7 mg/kg daily
Amikacin	20 mg/kg daily
Antistaphylococcal agents	
Vancomycin	15 mg/kg every 12 hours
Linezolid	600 mg/kg every 12 hours

"For patients with normal renal and hepatic

tFrom the American Thoracic Society and Infectious Disease Society of Guidelines for the management of adults with hospital-acquired, ventilator-healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171 :388-416.

Recommendation

For patients likely to be colonized with S. *aureus* and gram-negative pathogens, empiric antibiotic therapy for most patients will be adequate using imipenem or imipenem plus vancomycin. Imipenem has a very broad spectrum of activity, and is active against staphylococci (methicillinsensitive strains), and gram-negative enteric pathogens, including *Pseudomonas aeruginosa.* The addition of vancomycin is necessary only if methicillin-resistant *Staphylococcus aureus* is a concern. Linezolid is gaining popularity as an alternative to vancomycin because of increasing vancomycin failures for treating MRSA pneumonias (1). The second antipseudomonal antibiotic should not be necessary unless the Cram stain of respiratory secretions shows a preponderance of gram-negative bacilli and the patient is immunocompromised (see Chapter 43 for the management of immunocompromised patients in the ICU).

Duration of Antibiotic Therapy

Empiric antibiotics regimens will be adjusted according to the results of quantitative cultures. For pneumonias documented by culture, the

traditional duration of antibiotic therapy has been 14 to 21 days (1). However, one large study (including 50 ICUs) has shown that 8 days of antibiotic therapy for ventilator-associated pneumonia is associated with the same mortality and risk of recurrent infection as 15 days of therapy (38), and the popular opinion at present is that one week of antibiotic therapy is adequate for most patients with ventilator-associated pneumonia.

Antibiotic Prophylaxis

Efforts to prevent nosocomial pneumonia continue to be neglected despite evidence that some measures are effective. One of the effective measures involves the topical application of an antimicrobial paste to the oral mucosa to prevent colonization of the oropharynx with pathogenic organisms (39). The preparation most often used is a methylcellulose paste (Orabase, Squibb Pharmaceuticals) containing 2% polymyxin, 2% tobramycin, and 2% amphotericin B, which is applied to the inside of the mouth with a gloved finger every 6 hours (39). As shown in Figure 4.6 (Chapter 4), this regimen of oral decontamination decreases the incidence of ventilator associated pneumonia by about 2/3 (39). Results like this should not be ignored in the approach to pneumonia in the ICU.

A FINAL WORD

Reports that mortality is not increased by ventilator-associated pneumonia (2,31,32) deserve much more attention in discussions of how to manage pneumonia in the ICU. For example, if mortality is not increased by ventilator-associated pneumonias, then mortality rate should not be used as an end-point for evaluating diagnostic or therapeutic approaches to these pneumonias (as it often is). It also means that ICU-acquired pneumonia is overhyped as a life-threatening condition that requires immediate and aggressive therapy. Because there is no gold-standard method for identifying ICU-acquired pneumonia other than post-mortem examination (1), it is possible that studies showing a lack of impact on survival included many false-positive diagnoses of pneumonia. However, this observation is still relevant because these studies used methods that we all use to diagnose pneumonia and to justify antibiotic therapy. If what we think is pneumonia has no impact on survival, then the problems mentioned earlier still apply. For now, this is just another problem in a long list of problems associated wi.th. pneumonia in the ICU.

REFERENCES

Chapter 42

SEPSIS FROM THE ABDOMEN AND PELVIS

One of the recurring themes in this book is the importance of the gastro-intestinal (GI) tract as a source of infection in critically ill patients. This chapter focuses on that theme, and describes the infectious risks at both ends of the GI tract, including the neighboring biliary tree. The last section of this chapter describes nosocomial infections in the urinary tract, with emphasis on infections associated with indwelling urethral catheters.

ACALCULOUS CHOLECYSTITIS

Aca1culous cholecystitis is a condition that could be described as an ileus of the gallbladder. Although an uncommon condition, it can be fatal if not recognized and treated promptly.

Pathogenesis

There are a number of conditions that predispose to aca1culous cholecystitis. Most cases occur in association with multiple trauma and abdominal (nonbiliary) surgery. A number of mechanisms may be involved in the pathogenesis of aca1culous cholecystitis, including ischemia (e.g., multiple trauma, shock), stasis (e.g., parenteral nutrition), and reflux of pancreatic secretions (e.g., opioid analgesics). In patients with immunodeficiency virus (HIV) infection, opportunistic pathogens like cytomegalovirus are often found

on histologic examination of the gallbladder, but it is unclear if these organisms are the cause or the consequence of the cholecystitis (3).

Clinical Features

The clinical manifestations of aca1culous cholecystitis include fever, nausea and vomiting, abdominal pain, and right upper quadrant tenderness

TABLE 42.1 Routine Clinical Evaluation in 143 Patients with Intra-Abdominal Abscesses

Clinical Finding	Frequency (%)
Physical Examination:	
Localized abdominal tenderness	36
Palpable abdominal mass	7
Chest Films:	
Pleural effusion	33
Basilar atelectasis	12
Abdominal Films:	
Extraluminal air or air-fluid level	13
Mechanical bowel obstruction'	4

From Fry D. Noninvasive imaging tests in the diagnosis and treatment of intra-abscesses in the postoperative patient. Surg Clin North Am 1994; 74:693-709.

(Table 42.1). Abdominal findings can be minimal or absent, and fever may be the only presenting manifestation. Elevations in serum bilirubin, alkaline phosphatase, and amylase can occur but are variable 0,2).

Diagnosis

An ultrasound of the right upper quadrant often provides diagnostic information. Gallbladder sludge and distention of the gallbladder are common findings but can be nonspecific. More specific findings include a gallbladder wall thickness of at least 3.5 mm and submucosal edema 0,2). If ultrasound visualization is hampered, computed tomography (CT) scanning can provide useful information (1).

Management

Prompt intervention is necessary to prevent progressive distention and rupture of the gallbladder. The latter complication has been reported in 40% of cases when diagnosis and treatment is delayed for 48 hours or longer after the onset of symptoms 0). The treatment of choice is cholecystectomy. In patients who are too moribund for surgery, percutaneous cholecystostomy is a suitable alternative. Empiric antibiotics are often recommended, but the value of this practice is unproven.

Colonization of the GI Tract

The GI tract can become a source of sepsis when overgrowth of pathogenic organisms occurs as a result of a change in the normal environment of the bowel lumen. This occurs in the upper GI tract when patients are given acid-suppressing drugs, and occurs in the lower GI tract when patients are given antibiotics. The following is a look at this colonization as a source of sepsis.

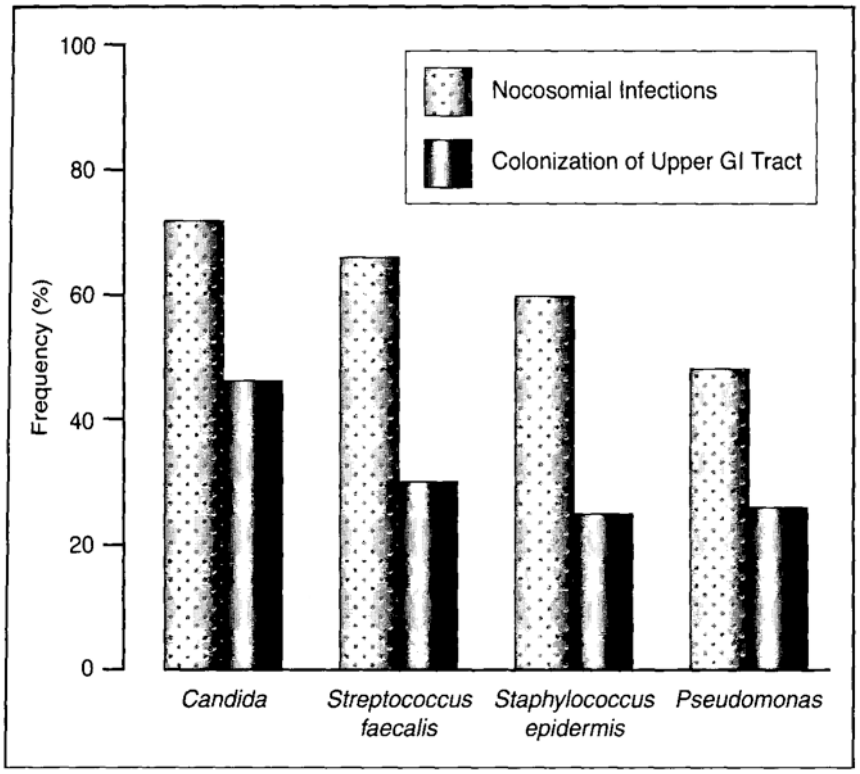

FIGURE 42.1 Correlation between the organisms that most often colonize the upper GI tract and the organisms most often isolated in nosocomial infections in critically ill patients. (Data from Marshall JC, Christou NV, Meakins JL, et al. The gastrointestinal tract: the "undrained abscess" of multiple organ failure. Ann Surg 1993;218:111–119.)

Gastric Colonization

Gastric acid suppression and subsequent colonization of the upper GI tract is discussed in Chapter 4 (see Fig. 4.1 for a demonstration of the bactericidal actions of low pH). The pathogens that commonly colonize the stomach are the same pathogens that are commonly involved in nosocomial infections (4). This correlation is shown in Figure 42.1. Although it does not prove a causal relationship between gastric colonization and nosocomial infections, it does show that the upper GI tract serves as a reservoir for pathogens that are commonly involved in nosocomial sepsis.

Preventive Measures

There are two practices that will reduce colonization of the upper GI tract, and both have proven to reduce the incidence of nosocomial infections. The first practice is to avoid the use of drugs that suppress gastric

acidity (i.e., histamine H2 antagonists and proton pump inhibitors). Prophylaxis for stress ulcer bleeding is not necessary if the patient is eating or receiving enteral tube feedings. If prophylaxis is desired, consider using sucralfate, a cytoprotective agent that does not increase the pH of gastric secretions. The relative advantages and disadvantages of using sucralfate instead of acid-inhibiting drugs are discussed in Chapter 4, and shown in Figure 4.4.

The second practice that impedes colonization is the use of nonabsorbable antibiotics placed in the mouth and stomach. This practice is described in Chapter 4, and the results are shown in Figures 4.6 and 4.7. Despite the obvious benefits for reducing nosocomial infections, this practice is not popular in the United States (see Chapter 4 for more on this topic). However, the success of decontamination practices in reducing nosocomial infections is evidence that the GI tract is indeed an important source of nosocomial sepsis.

Clostridium Difficile Colitis

Colonization with pathogenic organisms can also occur in the lower regions of the GI tract. The most troublesome intruder is *Clostridium difficile,* a spore-forming gram-positive anaerobic bacillus that is not a prominent bowel inhabitant in healthy subjects, but proliferates when the normal microflora of the lower GI tract is altered by antibiotic therapy (5,6). *Clostridium difficile* is not an invasive organism, but it elaborates cytotoxins that incite inflammation in the bowel mucosa. Severe cases of mucosal inflammation are accompanied by raised plaque-like lesions on the mucosal surface called pseudomembranes. These lesions are responsible for the term *pseudomembranous colitis,* which is used to describe advanced cases of C. *difficile* enterocolitis.

Epidemiology

Although C. *difficile* is found in fewer than 5% of healthy adults in the community, it can be seen in as many as 40% of hospitalized patients (7). More than half of the patients who harbor C. *difficile* in their stool are asymptomatic (8). The organism is found primarily in patients receiving ongoing or recent (within 2 weeks) antibiotic therapy and in patients who are in close proximity to other patients who harbor the organism. C. *difficile* is readily transmitted from patient to patient by contact with contaminated objects (e.g., toilet facilities) and by the hands of hospital personnel (8). Strict adherence to the use of disposable gloves can significantly reduce the nosocomial transmission of C. *difficile (9).*

Clinical Manifestations

The most common manifestations of symptomatic C. *difficile* infection are fever, abdominal pain, and watery diarrhea. Bloody diarrhea is seen in 5% to 10% of cases. Rarely, the enterocolitis can progress to toxic megacolon, which presents with abdominal distention, ileus, and clinical shock. This latter complication can be fatal and requires emergent subtotal colectomy (O).

Laboratory Tests

The diagnosis of C. *difficile* enterocolitis requires laboratory tests for the presence of the appropriate toxins in stool. Stool cultures for C. *difficile* are unreliable because they do not distinguish toxigenic from nontoxigenic strains of the organism. Most laboratories use an ELISA (enzyme-linked immunosorbent assay) method to detect the cytotoxins. The sensitivity of this test is about 85% for one stool specimen and up to 95% for 2 stool specimens (5,6,11). Therefore, the cytotoxin assay will miss 15% of cases of C. *difficile* enterocolitis if one stool specimen is tested, but only misses 5% of cases if two stool specimens are tested. The specificity of this test is up to 98% (6), so false-positive results are uncommon.

Computed Tomography

Computed tomography (CT) of the abdomen can reveal findings like those shown in Figure 42.2 (2). There is marked thickening in the wall of the colon, which appears as a low density region between the mucosa and serosa. The small bowel is not similarly affected. These findings are characteristic of an inflammatory process involving the large bowel (an enterocolitis), but they are not specific for C. *difficile* enterocolitis.

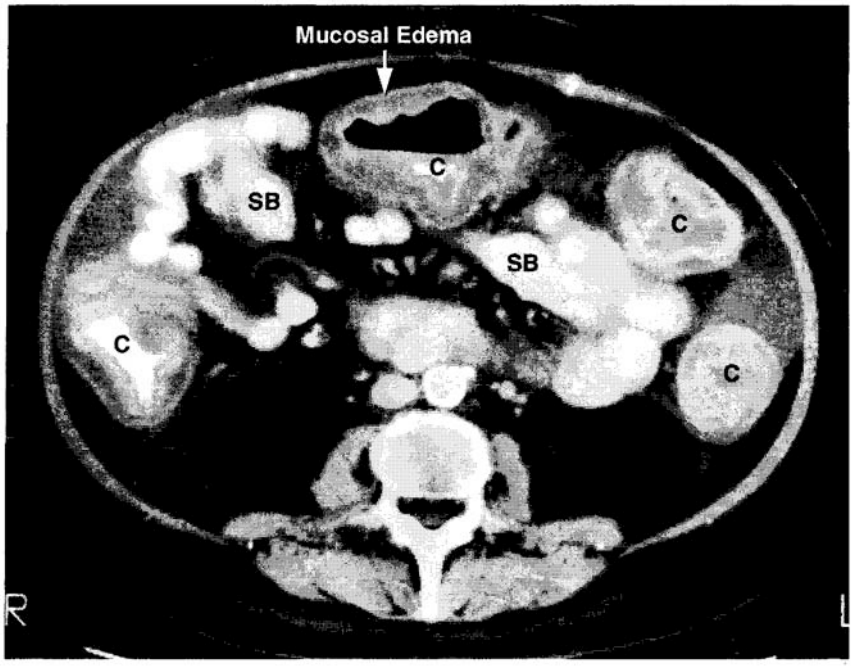

FIGURE 42.2 Contrast-enhanced CT scan of a patient with *C. difficile* enterocolitis. There is marked thickening of the wall of the colon (*C*), but not the small bowel (*SB*). (From Braley SE, Groner TR, Fernandez MU, Moulton JS. Overview of diagnostic imaging in sepsis. New Horiz 1993;1:214–230.) Image digitally enhanced.

Lower GI Endoscopy
Direct visualization of the lower GI mucosa is usually reserved for the few cases where the suspicion of C. *difficile* enterocolitis is high but the toxin assays are negative. The presence of pseudomembranes on the mucosal surface confirms the diagnosis of C. *difficile* enterocolitis. Colonoscopy is preferred to proctosigmoidoscopy for optimal results.

Treatment
The first step in treatment is to discontinue the offending antibiotic(s) if possible, and observe for improvement. Antibiotic therapy to eradicate C. *difficile* is recommended only if the diarrhea is severe and associated with signs of systemic inflammation (fever, leukocytosis, etc.), or if it is not possible to discontinue the offending antibiotic(s) (13). The recommended antibiotic regimens are shown below (5,6,13,14).

Oral or intravenous metronidazole (500 mg three times daily) is the treatment of choice, and should be continued for 10 days. The oral route is preferred, and the intravenous route should be reserved for patients who are unable to receive oral medications. Both routes are equally effective.

Oral vancomycin 025 mg four times daily) is as effective as metronidazole, but is used as a second-line agent because of the efforts to curtail vancomycin use and limit the spread of vancomycin-resistant enterococci. Vancomycin is preferred for pregnant or lactating females, but is otherwise reserved for cases where metronidazole is ineffective or is not tolerated. Vancomycin is not effective when given intravenously.

Antiperistaltic agents are contraindicated (5,14) because reduced peristalsis can prolong exposure to the cytotoxins.

The expected response is loss of fever by 24 hours and resolution of diarrhea in 4 to 5 days (5). Most patients show a favorable response, and in the few who do not respond by 3 to 5 days, a switch from metronidazole to vancomycin is indicated. Although rarely necessary, surgical intervention is required when C. *difficile* colitis is associated with progressive sepsis and multiorgan failure, or signs of peritonitis, despite antibiotic therapy **(O)**. The procedure of choice is subtotal colectomy.
Relapses following antibiotic treatment occur in about 25% of cases (5,6,11). Most relapses are evident within 3 weeks after antibiotic therapy is completed. Repeat therapy using the same antibiotic is successful in about 75% of relapses, and another relapse is expected in about 25% of cases (4). As many as 5% of patients experience more than 6 relapses (5).

Probiotic Therapy
Antibiotic therapy for C. *difficile* enterocolitis can itself promote persistence of the organism, and this could explain the high relapse rate. Oral administration of *Saccharomyces boulardii* (lyophilized yeast preparation)

or *Lactobacillus* spp. can be used as primary prophylaxis of C. *difficile* enterocolitis, or can be started along with antibiotics and continued to prevent relapses of symptomatic disease. This approach has proven successful in reducing the incidence of C. *difficile* enterocolitis (15,16), but it has not gained favor in the United States.

ABDOMINAL ABSCESS

Abdominal abscesses are an important consideration in septic patients who have sustained blunt abdominal trauma or are recovering from abdominal surgery (17,18).

Clinical Features

Abdominal abscesses are difficult to detect on routine clinical evaluation, as demonstrated in Table 42.1. Note that localized abdominal tenderness is present in only one third of cases, and a palpable abdominal mass is present in fewer than 10% of cases. Note also that routine abdominal films provide valuable information in fewer than 15% of patients.

Computed Tomography

Computed tomography (CT) of the abdomen is the most reliable diagnostic method of detection for intra-abdominal abscesses, with a sensitivity and specificity of 90% or higher 07,18). However, CT imaging in the early postoperative period can be misleading because collections of blood or irrigant solutions in the peritoneal cavity can be misread as an abscess. CT scans are most reliable when performed after the first postoperative week (when peritoneal fluid collections have resorbed) (8). The appearance of an abscess on an abdominal CT scan is demonstrated in Figure 42.3.

Management

Immediate drainage is mandatory for all intra-abdominal abscesses (9). Precise localization with CT scanning allows many abscesses to be drained percutaneously with radiographically-directed drainage catheters. Empiric antibiotic therapy should be started while awaiting the results of abscess fluid cultures. Single drug therapy with ampicillin-sulbactam (Unasyn) or imipenem is as effective as multiple-drug regimens (20).

URINARY TRACT INFECTIONS

Urinary tract infection (UTI) accounts for 30% of all ICU-acquired infections, and 95% of UTIs occur in patients with indwelling urethral catheters (21). The following description is limited to UTIs in the catheterized patient.

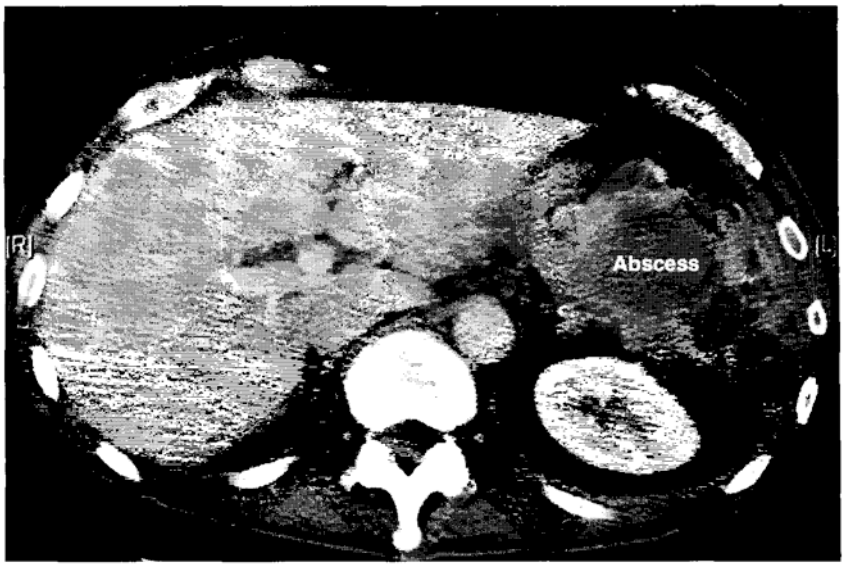

FIGURE 42.3 Abdominal CT scan showing a multiloculated abscess in the left upper quadrant in a post-splenectomy patient. (CT image courtesy of the Loyola University Medical Education Network, www.lumen.luc.edu/lumen)

Pathogenesis

The presence of a bladder drainage catheter in the urethra creates a 4 to 7% risk of developing a UTI *per day* (22). Bacterial migration along the catheter is the presumed mechanism for this risk, but there is more to the puzzle. The question that needs to be answered is why bacteria that migrate up the urethra and into the bladder are not washed out of the bladder by the urine flow. The flushing action of urine is a defense mechanism that protects the bladder from retrograde invasion by skin pathogens. This protective action explains why direct injection of bacteria into the bladder will not produce a UTI in a healthy subject (23).

Bacterial Adherence

The answer to the question posed in the last paragraph is linked to observations regarding bacterial adherence to the bladder epithelium. The epithelial cells of the bladder are normally coated with *Lactobacillus* organisms, as shown in Figure 42.4. These organisms are not pathogenic for man, and their presence on the surface of the epithelial cells prevents organisms that are pathogenic from attaching to the bladder wall. Loss of this protective coating and subsequent colonization of the bladder mucosa with gram-negative pathogens is the critical event that eventually leads to infection in the lower urinary tract (24). This is the same phenomenon that occurs in the oral mucosa in patients who develop nosocomial pneumonias, as described in Chapter 4. The events that link urethral catheterization to bacterial adherence in the bladder are unknown.

FIGURE 42.4 Photomicrograph showing *Lactobacillus* organisms blanketing a bladder epithelial cell. (From Sobel JD. Pathogenesis of urinary tract infections: host defenses. Infect Dis Clin North Am 1987;1:751–772.)

Microbiology

The common pathogens isolated from urine in medical ICU patients in the United States are listed in Table 42.2. Two surveys are included (21,25) to demonstrate that gram-negative aerobic bacilli are common isolates, but *Candida albicans* has emerged as a prominent isolate. Almost half (46%) of the cases of candiduria are asymptomatic (21) and therefore might not represent infection.

Diagnostic Criteria

The diagnosis of urinary tract infection based on urine cultures alone is misleading in patients with indwelling urethral catheters because half of these patients will have positive urine cultures after 5 days and virtually all patients will have positive urine cultures after 30 days of urethral catheterization (26). The criteria for the diagnosis of urinary tract infection in catheterized patients are shown in Table 42.3. These criteria are from a recent consensus conference on the definition of nosocomial infections (26), and they incorporate criteria proposed by the Centers for Disease Control in 1988 (27). Note that the diagnosis of UTI requires a symptom or sign of infection (fever, etc). Unfortunately, only fever and suprapubic tenderness apply to catheterized patients because indwelling urethral catheters eliminate the discriminating value of urgency,

TABLE 42.2 Pathogens Isolated from the Urine of Medical ICU Patients

	Incidence (% total isolates)	
Microorganism	1990-1992	1992-1997
Escherichia coli	31%	14%
Enterococci	15%	14%
Pseudomonas aeruginosa	13%	10%
Klebsiella pneumoniae	8%	6%
Proteus	7%	2%
Staphylococci	6%	6%
Candida albicans	5%	21%

"From Reference 25.
tFrom Reference 21.

frequency, and dysuria. Approximately 50% of elderly patients will also develop a change in mental status in association with UTIs (28). Severe cases of urosepsis can be accompanied by multiorgan dysfunction that progresses to multiorgan failure (29).

Urine Cultures

The threshold for significant bacteriuria in catheterized patients is 10^5 colony forming units per mL (cfu/mL). However, colony counts as low as 10^2 du/mL can represent infection if growth is sustained in more than one urine sample (collected on different days) (30).

Urine Microscopy

Urine microscopy is diagnostic only if an unspun urine specimen shows organisms on Gram stain or at least 3 leukocytes per high-powered field. The common practice of examining spun urine sediments has little value in identifying infection in catheterized patients.

Empiric Antimicrobial Therapy

Empiric antibiotic therapy pending culture results is recommended for patients with suspected UTI who are immunocompromised, have evidence of multiorgan dysfunction, or have a prosthetic or damaged heart valve. The urine Gram stain, if positive, can be used to guide antibiotic selection. The following are some suggestions.

Gram-Negative Bacilli

According to the susceptibility graphs in Chapter 44 (Figs. 44.1 and 44.2), imipenem should suffice for empiric coverage of gram-negative bacilli, and amikacin could be used for patients who have a prosthetic or damaged heart valve, or are seriously ill (i.e., are hemodynamically unstable or have evidence of multiorgan failure).

TABLE 42.3 Criteria for the Diagnosis of Upper Tract UTI in Patients with Indwelling Urethral Catheters·

I. The presence of one of the following:

• Body temperature >38°C

• Urgency or frequency or dysuria

• Suprapubic tenderness

AND

II. Urine culture growing >=10^5 CFU/mL of no more than 2 organisms.

OR

III. One of the following is present:

• Positive urine dipstick for leukocyte esterase or nitrates

• >=3 WBCs per high-power field using unspun urine

• Organisms present on Gram stain of unspun urine

• 2 urine cultures with >=10^2 CFU/mL of the same organism

·Upper tract UTI includes infection involving the kidneys, ureters, bladder, sue surrounding the retroperitoneal or perinephric space.
From Calandra T, Cohen J. The international sepsis forum consensus nitions of infection in the intensive care unit. Crit Care Med 2005: 33:1538.

Gram-Positive Cocci

A preponderance of gram positive cocci on the urine Gram's stain suggests that enterococcus is the responsible pathogen because staphylococci are uncommon offenders in nosocomial UTIs. If the patient is not seriously ill, enterococcal UTI can be treated effectively with ciprofloxacin. If the patient is seriously ill or has a prosthetic or damaged heart valve, ampicillin or vancomycin plus gentamicin is the preferred regimen. Ampicillin resistance is reported in 10 to 15% of nosocomial enterococcal infections (31), so vancomycin may be preferred. If vancomycin-resistant enterococci are a concern, linezolid can be used as a substitute for vancomycin (see the very end of Chapter 44 for a description of linezolid).

Candiduria

The presence of *Candida* in the urine often represents colonization, but candiduria can also be a sign of disseminated candidiasis (the candiduria in this case is the result, not the cause, of the disseminated candidiasis). Disseminated candidiasis can be an elusive diagnosis because blood cultures are sterile in more than 50% of cases (32), and candiduria may be the only sign of disseminated disease. The following recommendations are from recent guidelines published by the Infectious Disease Society of America (33). Asymptomatic candiduria in immunocompetent patients does not require antifungal therapy. However, the urinary catheter

should be removed if possible because this can eradicate candiduria in 40% of cases (34).
Candiduria should be treated in symptomatic patients (i.e., fever or suprapubic tenderness), and patients with neutropenia or a renal allograft, because candiduria can be a sign of disseminated candidiasis in these patients.
Persistent candiduria in immunocompromised patients should prompt further investigation with ultrasonography or CT images of the kidney.

Antifungal Therapy
Bladder irrigation with amphotericin B is not recommended because local recurrence is common (33). For non-neutropenic patients with symptomatic candiduria, fluconazole (200 to 400 mg daily) for 7 to 14 days can be effective (33). For patients with renal insufficiency or for infection with species other than *Candida albicans,* the new antifungal agent capsofungin (50 mg daily) is a reasonable choice (see Chapter 44 for a description of capsofungin). For all other patients, amphotericin B (0.3 to 1 mg/kg daily) for 1 to 7 days can be effective (33).

A FINAL WORD
The unifying feature in infections that involve, or originate from, the gastrointestinal, urinary, and respiratory tracts (see also Chapter 41) is the initial colonization with pathogenic organisms that first takes place. This colonization seems to involve a change in the ability of microorganisms to adhere to epithelial surfaces. In healthy subjects, the epithelial surfaces in the mouth, GI tract, and urinary tract are covered by harmless commensal organisms, but in patients who develop an acute or chronic illness, these surfaces are covered with pathogenic organisms, and this serves as a prelude to nosocomial infections. This repopulation is not just a matter of "territorial imperative" (where one population forces another population to leave), but seems to involve the ability of microorganisms to adhere to the epithelial cells. If this is the case, then we need to study the mechanisms whereby microorganisms adhere to epithelial surfaces in health and disease if we are to effectively deal with the threat of nosocomial infections.

REFERENCES

Chapter 43

THE IMMUNOCOMPROMISED PATIENT

When you do battle, overcome your opponent by calculation.
Sun *Tzu (The Art of War)*

The care of critically ill patients is a labor-intensive, time-consuming, and mentally exhausting experience, and each of these aspects of patient care in the ICU reaches its zenith in the care of patients with impaired immune function. This chapter will focus on two patient populations who suffer the consequences of immune suppression: those infected with the human immunodeficiency virus (HIV), and those who develop myelosuppression from cancer chemotherapy. The care of immunocompromised patients like these is a topic of monumental size, and the material in this chapter represents only the tip of the iceberg .

THE HIV-INFECTED PATIENT

The introduction of *highly active antiretroviral therapy* (HAART) in 1996 has changed the character and outlook of patients with HIV infection who are admitted to the ICU. This is demonstrated in Figure 43.1 0). Prior to HAART, most HIV-related admissions to the ICU were for *Pneumocystis* carinii pneumonia, and about 50% of the patients survived to hospital discharge 0,2). Since the introduction of HAART, the prevalence of pneumocystis pneumonia has decreased considerably, and bacterial pathogens have emerged as the most common etiologic agents in HIV-related pneumonia 0,2). Survival has also improved to the point where three of every four patients admitted to the ICU with an HIV related disorder can now leave the hospital.

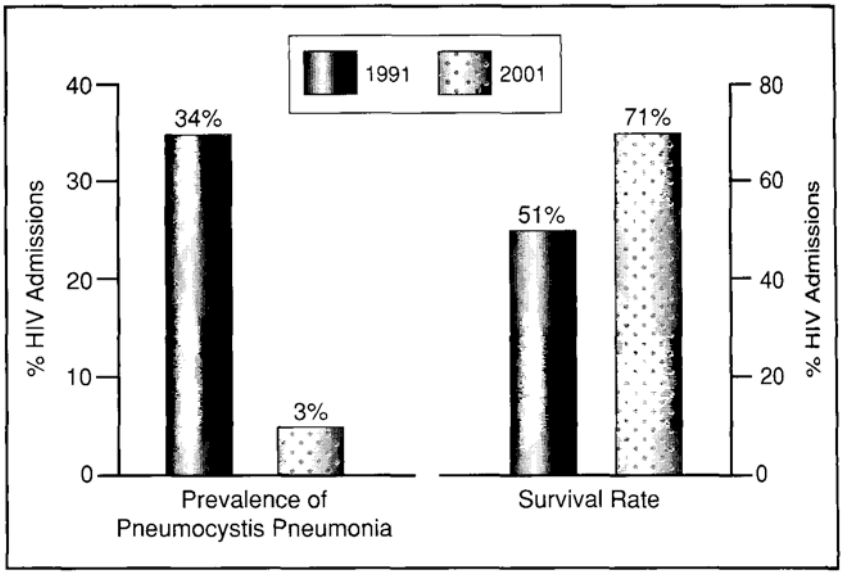

FIGURE 43.1 The change in character of HIV-related ICU admissions after the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s. (Data from Reference 1)

Pneumonia

Pneumonia continues to be the most common cause of HIV-related ICU admissions. The wide spectrum of etiologic agents in HIV-related pneumonias is evident in Table 43.1 (2-5). Bacterial pneumonias are most common, while nonbacterial pneumonias occur more often in the advanced stages of HIV infection (e.g., when CD4-lymphocyte counts are below 200/mL). The shaded box in Table 43.1 highlights the observation that

TABLE 43.1 Causes of Pneumonia in HIV Patients·

Bacterial Pneumonia	Nonbacterial Pneumonia
Streptococcus pneumoniae (15-20%)	*Pneumocystis carinii* (3-15%)
Hemophitus influenza (5-15%)	Fungi (5-10%)
Staphylococcus aureus (3-5%)	*Mycobacterium tuberculosis and*
Pseudomonas aeruginosa (3-6%)	*Mycobacterium avium* complex (5%)
Other Gram-negative bacilli (3-5%)	
Atypical organisms (1-4%)t	

-From References 1-3. The parentheses show the reported· incidence for

tIncludes *Chlamydia pneumoniae, Legionella spp,* and *Mycoplasma pneumoniae.*

there is often no pathogen identified in HIV patients with suspected pneumonia (3,5).

Bacterial Pneumonia

The most common bacterial isolates in HIV-related pneumonias are encapsulated organisms like *Streptococcus pneumoniae* (pneumococci), *Haemophilus influenza,* and *Staphylococcus aureus* (3,4). Pneumococcal pneumonia is the most common bacterial pneumonia, and is associated with bacteremia much more frequently than in non-HI V-infected patients. The clinical presentation and treatment of pneumococcal pneumonia is the same as in non-HIV-infected patients. There is a high rate of recurrence (10-15%) within 6 months (3), so vaccination against pneumococcal infection is particularly important in HIV-infected patients (see later).

The other organism that is prevalent in HIV-related pneumonias is *Haemophilus influenza.* The incidence of *Haemophilus influenza* pneumonia is about 100-fold higher in HIV-infected patients than in the general population (3). This organism can be difficult to isolate because its growth is easily suppressed by ongoing or recent antibiotic treatment (3). The antibiotics that are effective against H. *influenza* include second- and third-generation cephalosporins (e.g., ceftriaxone), azithromycin, and fluoroquinolones.

Pneumocystis Pneumonia

Pneumocystis carinii (renamed *Pneumocystis jurovecii* when it infects humans), is a protozoa-like organism (reclassified as a fungus in 1988) that proliferates in patients who are immunosuppressed. Although declining in frequency, pneumocystis pneumonia is still considered the most common opportunistic infection in HIV-infected patients (6), and it is almost always seen in advanced stages of the disease (e.g., when CD4+ lymphocyte counts are less than 200/mL).

Patients with pneumocystis pneumonia typically present with fever, non-productive cough, and hypoxemia that is out of proportion to the appearance of the chest x-ray. The initial chest x-ray can be normal in 40% of patients (7), but as the disease progresses, bilateral infiltrates like those in Figure 43.2 begin to appear. In advanced cases of pneumocystis pneumonia, the bilateral infiltrates coalesce to produce a chest x-ray like the one in Figure 43.3. The radiographic features of severe pneumocystis pneumonia are similar to those of the acute respiratory distress syndrome (ARDS) (see Fig. 22.3).

The diagnosis of pneumocystis pneumonia requires visualization of the organism in specimens obtained from the respiratory tract. The most popular method of detection is the use of monoclonal antibodies directed at pneumocystis antigens (direct fluorescent antibody method), which will detect both trophic and cystic forms of the organism (6). Sputum induction with hypertonic saline has a diagnostic yield of 50 to 90% (3,6), although this varies with the prevalence of HIV infection (and thus the experience of cytopathologists) in individual medical centers. The highest diagnostic yield is provided by bronchoalveolar lavage, which demonstrates the organism in over 90% of cases (3). The treatment of pneumocystis pneumonia is described later in the chapter.

Tuberculosis

As many as 10% of HIV-infected patients who are purified protein j derivative (PPD) positive will develop active tuberculosis (TB) each year! (3). The radiographic features of pulmonary TB are determined by the CD4+ lymphocyte count in blood. When the CD4+ cell count is above 200/mL, the chest x-ray often shows upper lobe cavitary disease, similar in appearance to active TB in non-HIV-infected patients. However when the CD4+ cell count is below 200/mL, active TB can be accompanied by non-cavitary infiltrates in the mid-lung fields (3), and this radiographic appearance can be confused with a bacterial pneumonia.

Diagnostic Approaches to Pneumonia

The clinical presentation of HIV-related pneumonia is often nonspecific, and does not allow identification of the responsible pathogen (3,6,7). In particular, the pattern of infiltration on the chest radiograph is not pathogen specific. As mentioned earlier, pneumocystis pneumonia can present with a clear chest x-ray or a non-specific radiographic pattern such as the one in

Figure 43.2, and the typical appearance of advanced pneumocystis pneumonia in Figure 43.3 can also be seen in atypical pneumonias and ARDS. Identification of the etiologic agent requires blood cultures and an evaluation (with histologic examination and cultures) of sputum and bronchoscopic specimens from the lower respiratory tract.

Bronchoscopy
Bronchoscopy is a valuable diagnostic tool in HIV-related pneumonias because specimens obtained from the lower respiratory tract (by bronchial brushing or bronchoalveolar lavage) will identify over 90% of cases of pneumocystis pneumonia and pulmonary TB (3). In addition, quantitative bacterial cultures of bronchial brushings and bronchoalveolar lavage specimens can identify the responsible pathogen(s) in 70 to 80% of bacterial pneumonias (see Table 41.3). The use of bronchoscopy to diagnose bacterial pneumonias is described in Chapter 41. The ability to isolate bacterial pathogens in sputum or bronchoscopic specimens is markedly reduced in patients who are receiving antibiotic treatment. (The ability to identify *Pneumocystis carinii* is not affected by a few days of appropriate

antibiotic coverage). Therefore, sputum and bronchoscopic specimens should be collected prior to starting antibiotic therapy, if possible.

An Organized Approach
The initial approach to the HIV-infected patient with pneumonia can be guided by the CD4+ lymphocyte count in blood. If the CD4+ cell count is above 200/mL, then the patient should be evaluated for a bacterial pneumonia as described in Chapter 41. If the CD4+ count is below 200/mL, then the management can proceed as follows:

Place the patient in respiratory isolation (because pulmonary .
TB can have a nonspecific radiographic appearance at reduced CD4+ cell counts). .

Collect sputum for Gram's stain, Ziehl-Neelson stain (for tubercle . bacilli) and direct fluorescent antibody stains (for *Pneumocystis carinii*). Induce sputum production with nebulized hypertonic saline if necessary. Make sure sputum is screened for microscopic evidence that the specimen originates from the lower airways (see Figure 41.3). Obtain appropriate cultures (bacterial and TB) when indicated.

If the microscopic examination of sputum is unrevealing, perform bronchoalveolar lavage to identify *Pneumocystis carinii* and tubercle bacilli, and to obtain TB cultures and quantitative bacterial cultures.

If bronchoscopy is not immediately available, begin empiric antibiotic treatment for pneumocystis pneumonia and/or bacterial pneumonia based on clinical judgment (e.g., empiric coverage for pneumocystis pneumonia is usually given to patients with respiratory failure or diffuse infiltrates on chest x-ray). Pneumocystis can be demonstrated in the lower respiratory tract for days after starting appropriate antibiotic coverage, so bronchoscopy should be attempted, if possible, in the first few days of empiric antibiotic treatment.

Treatment for pulmonary TB is started only if there is evidence of infection on Ziehl-Neelson stains for tubercle bacilli. If there is no evidence of pulmonary TB on two or three sputum samples, respiratory isolation can be discontinued.

Despite its diagnostic value, bronchoscopy is performed on fewer than 50% of patients with the diagnosis of pneumocystis pneumonia (8). Most of these patients are given empiric antibiotic treatment for pneumocystis pneumonia with no attempt to identify the organism. This practice should be discouraged because it mandates three weeks of (possibly unnecessary) antibiotic therapy and the antimicrobial agents are often poorly tolerated (see next).

Treatment for Pneumocystis Pneumonia
Trimethoprim-sulfamethoxazole (TMP-SMX) is the antibiotic of choice for pneumocystis pneumonia. The recommended dose is 20 mg/kg of

TMP and 100 mg/kg of SMX daily, administered in three or four divided doses. Although TMP-SMX can be given orally, intravenous therapy is advised for patients with respiratory failure. A favorable clinical response may not be apparent for 5 to 7 days (9), and there may be an initial period of deterioration. Radiographic improvement lags behind the clinical improvement (9), so the chest x-ray should not be used to evaluate the response to therapy. If a favorable response is not evident after 5 to 7 days, the treatment is considered a failure. If there is improvement in 5 to 7 days, treatment is continued for a total of 3 weeks (3,10).
Adverse reactions to TMP-SMX develop in 30 to 50% of HIV-infected patients. These reactions usually appear during the second week of treatment, and they are often severe enough to warrant discontinuing the drug. The most common side effects are neutropenia (45 to 50%), fever (45 to 50%), skin rash (35 to 40%), elevated hepatic transaminase enzymes (30 to 35%), hyperkalemia (30%), and thrombocytopenia (10 to 15%). A case of fatal pancreatitis has also been linked to TMP-SMX (4). Only 35 to 45% of patients who receive TMP-SMX are able to complete the full course of therapy. The high incidence of adverse reactions to TMP-SMX is specific for HIV infection. In other groups of patients, adverse reactions to TMP-SMX develop in only 10% of the patients.

Pentamidine isothionate is the preferred second-line agent when TMP-SMX fails or is not tolerated. The recommended dose is 4 mg/kg given intravenously as a single daily dose. Intramuscular injection is not recommended because of the risk for sterile abscesses. The response time and duration of therapy are the same as for TMP-SMX. Treatment failures occur in one-third of patients (0).
Adverse reactions are also common with intravenous pentamidine 00,15-17). These side effects include neutropenia (5 to 30%), hyperglycemia and hypoglycemia (10 to 30%), prolonged Q- T interval (3 to 35%), torsade de pointes (up to 20%), renal insufficiency (3 to 5%), and pancreatitis (up to 1 %). Almost half of the patients who receive intravenous pentamidine are unable to complete therapy because of adverse reactions 00,15).
In patients who are unable to complete therapy with either TMPSMX or pentamidine, a variety of other agents (e.g., clindamycin and primaquine) are available. In this situation, leave the decision to an infectious disease specialist.

STEROIDS. A brief course of steroid therapy is standard for cases of pneumocystis pneumonia that result in respiratory failure. When started at the time of antimicrobial therapy, steroid therapy is associated with improved outcomes in pneumocystis pneumonia (8). Most clinical trials used oral prednisone, but intravenous methylprednisolone (40 mg every 6 hours for at least 7 days) has also been recommended (0). Delay of treatment for 72 hours after the start of antimicrobial therapy negates any possible benefit from steroids (8). The response to steroids seems to vary in different clinical reports, and favorable responses can be short-lived (9).

Pneumocystis and Pneumothorax
Pneumothorax is an uncommon (5% of cases) but serious complication of pneumocystis pneumonia (20). When it occurs during mechanical

ventilation, as illustrated in Figure 43.4, it is usually a sign of extensive underlying tissue destruction in the lungs, and few patients survive (20). To reduce the risk of this serious complication, it seems wise to adopt the strategy known as "limited-volume" ventilation for patients with pneumocystis pneumonia. This method is designed to limit the inflation volumes during mechanical ventilation, and it is used to prevent lung injury from overdistention in patients with acute respiratory distress syndrome. A description of this method is in Chapter 22 (see Table 22.4).

Cryptococcal Meningitis

Cryptococcal meningitis is the most common life-threatening fungal infection in HIV-infected patients (21,22). It is expected in 10% of patients with HIV infection, and usually appears in the advanced stages of immunosuppression (i.e., when CD4 lymphocyte counts fall below 50/mm^3).

Clinical Features

The most common manifestations are fever and headache, each reported in approximately 85% of cases (21). Other findings include meningeal

signs (35 to 40%), altered mental status 00 to 15%), and seizures (less than 10%) (21). Cryptococcal infections at other sites (e.g., pneumonia and skin rash) are seen in 20% of cases (22).

Diagnosis
The diagnosis of cryptococcal meningitis requires lumbar puncture. Standard measurements in cerebrospinal fluid (CSF), such as glucose, protein, and leukocyte count, can be normal in up to 50% of cases (21). The organism can be demonstrated on india ink stains of CSF in 75% of cases (which is higher than the yield from india ink stains in non-HIVinfected patients) (21). CSF cultures and cryptococcal antigen titers are positive in over 90% of cases (21).

Treatment
The recommended treatment for cryptococcal meningitis in HIV-infected patients is shown below (23).
Start with amphotericin B (0.7-1 mg/kg/ day) and flucytosine (100 mg/kg/day) for the first 2 weeks.
After 2 weeks, switch to oral fluconazole (400 mg/ day) and continue for a minimum of 10 weeks. Thereafter, the dose of fluconazole is reduced (200 mg/ day) and treatment is continued indefinitely.
Chapter 44 contains a description of these antifungal agents. The mortality in this disorder is about 30% despite antifungal therapy (21).

Toxoplasmic Encephalitis
Toxoplasma gondii encephalitis is the most common neurologic disorder in HI V-infected patients. Clinical evidence of toxoplasmic encephalitis is reported in 5 to 15% of HIV-infected patients, and autopsy evidence of the disease is present in up to 30% of patients (21).

Clinical Features
Toxoplasmic encephalitis is characterized by focal brain lesions. Hemi-paresis and other focal neurologic deficits are seen in 60% of cases, and seizures are reported in 15 to 30% of patients (21). Other manifestations include fever (5 to 55%), confusion (60 to 65%), and choreiform movements (considered by some to be pathognomonic of toxoplasmic encephalitis) (21). Although extra neural disease is not common, disseminated toxoplasmosis with septic shock has been reported (24).

Diagnosis
Computerized tomography (CT) usually reveals solitary or multiple hypo-dense, contrast-enhancing lesions in the basal ganglia and frontoparietal regions of the cerebral hemispheres (21). An example of such a lesion is shown in Figure 43.5. Note the hypodense core and the contrast enhancement at the outer edges of the lesion. Because of the radiographic

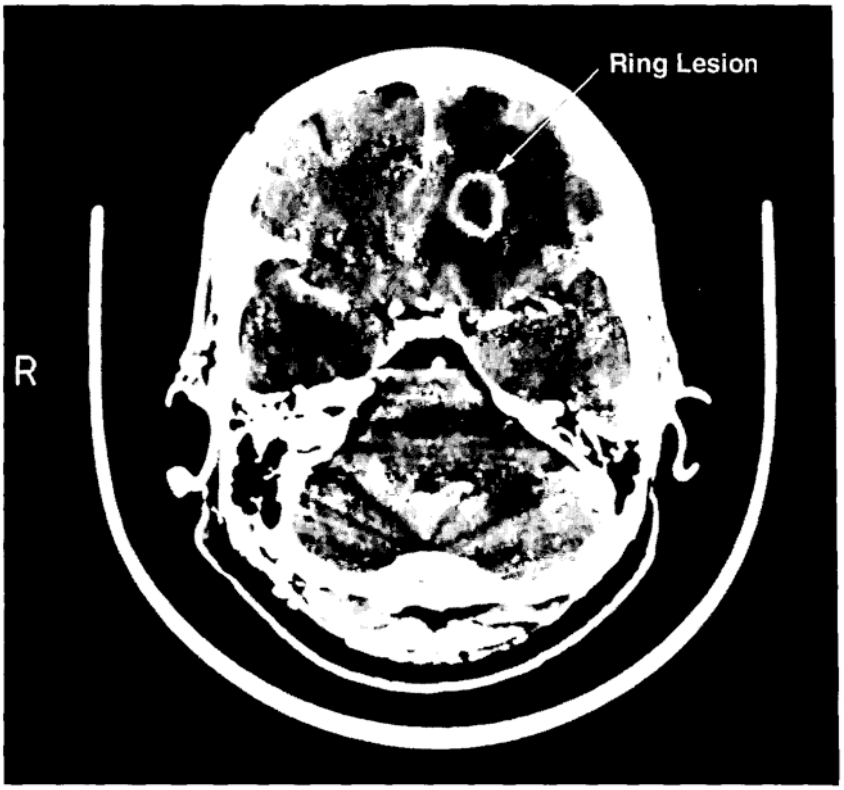

FIGURE 43.5 CT image showing a ring-enhancing lesion in a patient with toxoplasmic encephalitis. The hypodense area surrounding the lesion is evidence of cerebral edema.

appearance, these lesions are sometimes called "ring-enhancing lesions" or "ring lesions." These lesions are not pathognomonic of toxoplasma encephalitis: similar lesions can be found in cases of lymphoma. CT scans can be unrevealing in the early stages of the disease. Magnetic resonance imaging (MRI) is more sensitive than CT scans and can reveal lesions when CT scans are negative (25). Lumbar puncture usually reveals abnormal findings, but these are nonspecific.

The diagnosis of toxoplasma encephalitis can be made with certainty when the organism is identified in excisional brain biopsies using immunoperoxidase staining. (Needle biopsies have a lower diagnostic yield). However, the common practice is to bypass the brain biopsy and rely instead on a presumptive diagnosis of toxoplasmosis based on the presence of characteristic lesions in the brain plus with serologic evidence of recent toxoplasma infection. Over 90% of patients with toxoplasma encephalitis will have anti-toxoplasma antibodies (IgG) in their blood, so a positive antibody titer is a sensitive marker of toxoplasma infection. Unfortunately, 20% of the general population also have these antibodies

in their blood (26), so a positive antibody titer lacks specificity for toxoplasma encephalitis.

Treatment

The preferred treatment for toxoplasma encephalitis is a combination of pyrimethamine (200 mg loading dose, then 75 mg daily) and clindamycin (600 mg every 6 hours). Because pyrimethamine is a folate antagonist, folinic acid 00 mg) is given with each dose of pyrimethamine to reduce the incidence of bone marrow suppression. All agents are given orally. Approximately 70% of cases show a favorable response to this regimen, and improvement is usually evident within the first week of therapy (27). The condition is considered uniformly fatal without appropriate therapy.

Drug-Related Problems

The drugs currently used for antiretroviral therapy have certain adverse effects and drug interactions that deserve mention.

Lactic Acidosis

Nucleoside reverse transcriptase inhibitors can be associated with a lactic acidosis caused by inhibition of mitochondrial enzymes involved in the electron transport chain. This problem is most often associated with danosine and stavudine (28,29). The lactic acidosis can be severe, and a mortality of 77% has been reported (29). Case reports suggest a beneficial response to riboflavin (50 mg daily), thiamine 000 mg daily) and L-carnitine (50 mg/kg) (28), and all three can be given as treatment. The offending drug should, of course, be discontinued.

Drug Interactions

Antiretroviral drugs are sometimes given to patients in the ICU. These drugs have a multitude of potential drug interactions, and the ones most likely to be seen in the ICU are included in Table 43.2. Most of these

TABLE 43.2 Drug Interactions with Antiretroviral Drugs·

Drug	Antiretroviral	Effect
Amiodarone	Ritonavir, Other Pis	Bradycardia, hypotension
Diltiazem	Aprenavir, Atazanavir	Hypotension
Meperidine	Ritonavir	Increased normeperidine
Methadone	Pis, NRTIs, NNRTIs	Opiate withdrawal
Midazolam	Pis, NNRTIs	Enhanced sedation

*From Reference 27.

PI = protease inhibitor, *NRTI* = nucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor.

interactions are significant enough to recommend avoiding the drug combinations instead of reducing the drug dose.

THE NEUTROPENIC PATIENT

The risk of infection with neutropenia (neutrophil count less than 500/mm^3) depends on the cause, severity, and duration of the neutropenia. Most cases of neutropenia that are complicated by serious infections are persistent (last longer than 10 days) and are caused by bone marrow suppression from chemotherapy (30). Neutropenia from other causes (e.g., viral infections) is rarely associated with an increased risk of infection, particularly if the neutropenia lasts less than 10 days (30). The reason for this discrepancy is not clear, but the propensity for infections in chemotherapy-induced neutropenia may be due to additional immune suppression from the primary disease that requires the chemotherapy (i.e., cancer or organ transplantation).

Febrile Neutropenia

The following statements highlight some of the important observations in patients with neutropenia and fever (30).

About two-thirds of patients with fever and neutropenia will not have an apparent infection on the initial evaluation.

Gram-positive organisms, especially coagulase-negative staphylococci, are the most frequent causes of bacterial infections in febrile neutropenia.

Bacteremia is relatively uncommon, and occurs in only 10 to 15% of patients with neutropenia and fever.

The most likely sites of infection in neutropenic patients are the lungs, urinary tract (in patients with indwelling drainage catheters), central venous catheters, and skin (for transplant patients with surgical wounds). Whether or not there is evidence of infection at these sites, blood cultures should be obtained routinely, prior to starting empiric or directed antibiotic therapy.

Pulmonary Infiltrates

The infectious and noninfectious causes of pulmonary infiltrates in neutropenic patients with fever is shown in Figure 43.6 (31). In this study, fungal pneumonia is the most common lung infection, while bacterial and viral pneumonias are uncommon. The most common cause of fungal pneumonia in this study was *Aspergillus fumigatus,* and the remaining isolates included *Fusarium, Histoplasma capsulatum,* and *Candida glabrata.* The bacterial isolates included staphylococci (coagulase positive and negative) and gram-negative enteric organisms, including *Pseudomonas aeruginosa.* The only virus isolated in this study was cytomegalovirus.

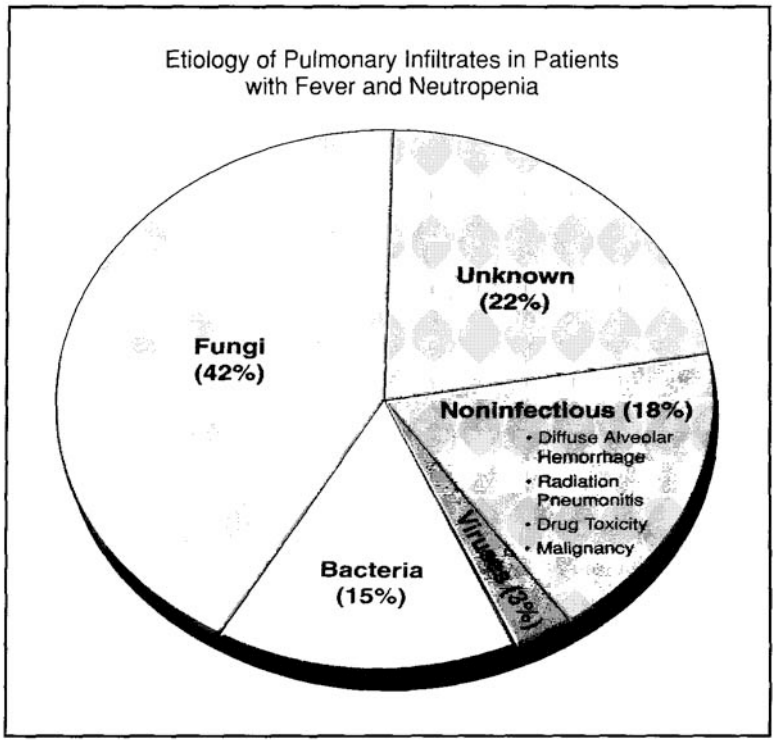

FIGURE 43.6 Pie chart showing the infectious and noninfectious causes of pulmonary infiltrates in neutropenic patients with fever. (Results from Piekert T, et al. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. Mayo Clin Proc 2005;80:1414.)

The pie graph in Figure 43.6 also demonstrates that a **considerable proportion of neutropenic patients with suspected fever have no evidence of infection**. Forty percent of the patients in this study had no evidence of infection, and 22% had no identifiable cause for the infiltrates. The noninfectious causes of pulmonary infiltrates are listed in the figure. The most common noninfectious pulmonary disorder is diffuse alveolar hemorrhage.

The prevalence of fungal pneumonias in neutropenic patients highlights the value of bronchoscopy in the diagnostic evaluation of pneumonia in these patients. Sputum is notoriously unreliable for the diagnosis of fungal pneumonia, and demonstration of the organisms deep within the lungs is required. Bronchoscopy can establish the diagnosis of fungal pneumonia with bronchial brushings, bronchoalveolar lavage, or transbronchiallung biopsy (the latter technique is not appropriate for ventilator-dependent patients or patients with thrombocytopenia). In one study that provided the data in Figure 43.6, the results of bronchoscopy resulted in a change in therapy in 50% of the patients. Bronchoscopy

also provided the diagnosis in the patient whose chest x-ray is shown in Figure 43.2.

Empiric Antibiotics

Prompt initiation of antibiotic therapy is recommended for all neutropenic patients with fever. This recommendation is based on the observation that patients with gram-negative septicemia due to *Pseudomonas aeru-1ginosa* can deteriorate rapidly without appropriate antibiotic coverage (30). However, pseudomonas bacteremia is not common in neutropenic patients (except following kidney transplantation) (30), so the rush to antibiotics may not be justified in most patients. Regardless of timing, empiric antibiotics are recommended for all patients with neutropenia and fever (32). The choice of antibiotics is determined by the likelihood that the patient has a serious infection, as described next.

Low Risk Patients

The criteria for identifying patients who are unlikely to have a serious infection are shown in Table 43.3. The typical patient who meets these criteria has no evidence of infection, does not appear to be ill, and has neutropenia that is expected to resolve in about one week. The recommended antibiotics for such patients are shown in Table 43.4. The intravenous regimen uses one of three antibiotics: ceftazidime, cefepime, or a carbepenem (imipenem or meropenem). These antibiotics provide broad spectrum coverage, but are selected for their activity against *Pseudomonas aeruginosa.* I prefer imipenem because it is active against all possible gram-positive and gram-negative pathogens with the exception of methicillin-resistant *Staph aureus.*

TABLE 43.3 Criteria For a Low Risk of Serious Infection*

History and Physical Exam	X-Ray and Laboratory Tests
• Malignancy in remission.	• No infiltrate on chest x-ray.
• Neutropenia present <7 days and expected to *resolve* within 10 days.	• Neutrophil count *>=100/mm3.*
• Does not appear ill.	• Monocyte count *>=100/mm3.*
• Peak temperature <39^0 C.	• Lab tests of hepatic and renal function close to normal.
• No comorbid conditions. t	
• No abdominal pain or neurologic abnormalities.	
• No apparent catheter-site infection.	

'From Hughes WT, et al. 2002 guidelines for the use of antimicrobial agents in neutrope-
nic patients with cancer. Clin Infect Dis 2002; 34:730.
tIncludes shock, hypoxia, pneumonia or other deep organ infection, vomiting or diarrhea.

TABLE 43.4 Risk-Based Empiric Antibiotic Therapy·

Low Risk of Serious Infection	High Risk of Serious Infection
Oral Therapy	Vancomycin not Needed
• Ciprofloxacin + amoxicillin clavulenate	• Basic Regiment or • Aminoglycoside + Basic Regiment
IV Therapy	Vancomycin Needed
• Basic Regiment	• Vancomycin + Basic Regiment +/-Aminoglycoside

'For the recommended starting doses of each antibiotic, see Table 41.6.
From Hughes WT, et al. 2002 guidelines for the use of antimicrobial agents in patients with cancer, Clin Infect Dis 2002;34:730.

tBasic Regimen = ceftazidine or cefepime or a carbepenem.

High Risk Patients

For patients who do not satisfy the criteria in Table 43.3, the recommended antibiotic regimens are determined by the perceived need for vancomycin. The vancomycin requirement is determined by the likelihood of infection with methicillin-resistant strains of *Staph aureus* (MRSA). The patient who is at risk for MRSA infections will satisfy one or more of the following conditions: (1) Has a prior history of colonization or infection with MRSA, (2) is a resident of a nursing home, (3) has a chronic debilitating illness and has received multiple antibiotics in the past year, or (4) is in an ICU where MRSA is prevalent.

All patients in the high risk category will receive one of the drugs in the basic regimen (ceftazidime, cefepime, or a carbepenem). Vancomycin is then added if it is considered necessary. The addition of an aminoglycoside is a consideration in patients who appear seriously **ill** (e.g., those with septic shock), or if pseudomonas infection is suspected.

Evaluate Response to Therapy

A favorable response is expected within 5 days of starting antibiotics (32). **If** the fever has resolved and there is no evidence of infection at 3 to 5 days, continued antibiotic therapy for a total of 7 days is still recommended, even when the neutropenia is resolving (32). This practice seems ill-advised, particularly when the bone marrow is recovering and the neutropenia is resolving. The more significant problem is what to do when the fever persists for longer than 5 days on empiric antibiotics and there is no evidence of infection. This situation is considered in the next section.

Persistent Fever

Continued fever after 1 week of empiric antibiotic therapy has several possible explanations (e.g., the fever may be due to a noninfectious process), and one of these is a disseminated fungal infection. Up to

one-third of neutropenic patients with persistent fever have a disseminated fungal infection, and most cases involve *Aspergillus* and *Candida* species (32). Because of this possibility, intravenous amphotericin (0.5 mg/kg daily) is an appropriate consideration for persistent fever in this setting. The amphotericin trial should probably not exceed 2 weeks (32).

AN OUNCE OF PREVENTION

The Centers for Disease Control and Prevention recommends that pneumococcal polyvalent vaccine should be given to all adults who are immunosuppressed as a result of HIV infection, malignancy (particularly hematologic), chemotherapy, and chronic steroid use (for a complete list of all candidates for vaccination, see reference 33). The vaccine can be administered just prior to discharge from the ICU. Patients who have received the vaccine within the past 5 years do not need revaccination until 5 years have elapsed from the time of initial vaccination. Revaccination is not a universal recommendation, but is advised for patients who are immunosuppressed (33).

Unfortunately, the efficacy of the pneumococcal vaccine is limited in patients who are immunosuppressed. This is not surprising because vaccines require an immune response to confer immunity.

A FINALWORD

One of the harsh realities in critical care medicine is the realization that antibiotics have had little impact on survival rates in serious, life-threatening infections. This can be explained by the notion that body's immune system and other defenses are the principal deterrents of infection, while antibiotics provide only supplemental aid. Patients who develop serious infections might do so because they have impaired defenses against infection. If this is the case, then antibiotics are expected to have limited efficacy.

The importance of host defenses in the pathogenesis of infection is demonstrated by the colonization of the oropharynx with gram-negative pathogens that occurs in patients who are acutely or chronically ill (see Chapter 4). In this case, a defect in the host's normal defenses allows pathogenic bacteria to adhere to the oral mucosa and proliferate, and this colonization serves as a prelude to nosocomial pneumonia. When a pneumonia does develop, systemic antibiotics might provide some temporary relief, but their impact on the final outcome will be limited as long as the colonization in the mouth is allowed to continue.

The problem of impaired host defenses against infection reaches its pinnacle in the immunocompromised patient, which means that juggling antibiotics to eradicate infections will be particularly futile in this patient population. As Sun Tzu indicates in the opening quote, a more calculated approach than antibiotic therapy is needed to do battle with invading microbes in the immune-impaired patient.

References

Chapter 44

ANTIMICROBIAL THERAPY

The danger with germ-killing drugs is that they may kill the patient as well as the germ.
J.B.S. Haldane

Antibiotic therapy is a way of life in intensive care units. The antibiotics used most often in the ICU are included in the list shown later. Each of these will be presented in alphabetical order as listed.

Aminoglycosides
Antifungal agents
Cephalosporins
Fluoroquinolones
Imipenem

Penicillins
Vancomycin

AMINOGLYCOSIDES

The amino glycosides are a group of antibiotics derived from cultures of *Streptomyces* (hence the name streptomycin for the first amino glycoside). There are eight drugs in this class, but only three are clinically relevant: gentamicin, tobramycin, and amikacin (introduced in 1966, 1975, and 1981, respectively). These drugs were once the darlings of the infectious disease world because of their activity in serious gram-negative infections, but their popularity has waned because of renal toxicity.

Activity and Clinical Uses

The amino glycosides are among the most active antibiotics against aerobic gram-negative bacilli (see Fig. 44.1), including *Pseudomonas aeruginosa* (see Fig. 44.2). Amikacin is the most active of the three amino glycosides, probably because it has been in clinical use for a shorter period of time

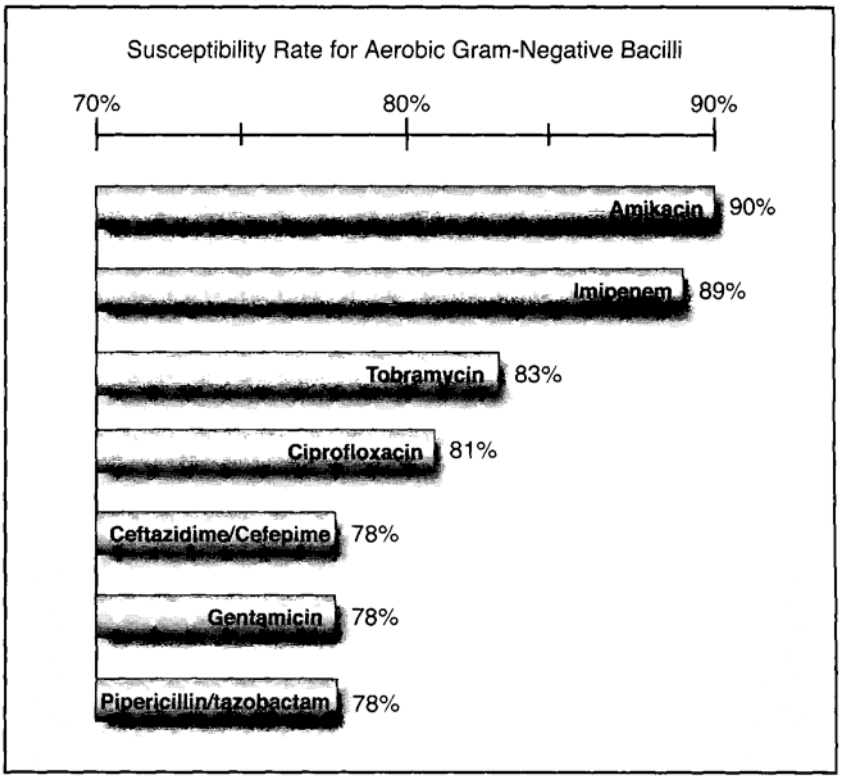

FIGURE 44.1 Susceptibility of gram-negative bacilli to commonly used antibiotics. Data from 35,790 cultures obtained from ICU patients during the years 1994–2000. (From Reference 2).

(giving microbes less time to develop resistance). Amino glycosides can be used to treat any serious infection caused by gram-negative bacilli, but their use is generally reserved for infections involving *Pseudomonas* species. They are the favored drugs for *Pseudomonas* bacteremia, particularly in immunocompromised patients. Amino glycosides are also used in empiric antibiotic regimens for neutropenic patients with fever (see Table 43.4).

Dosing

Amino glycoside dosing is based on body weight, and is influenced by changes in renal function. A dosage chart for the amino glycosides is shown in Table 44.1.

Dosing by Body Weight

The choice between actual body weight and ideal body weight for amino glycoside dosing is determined by the weight of the patient. The total

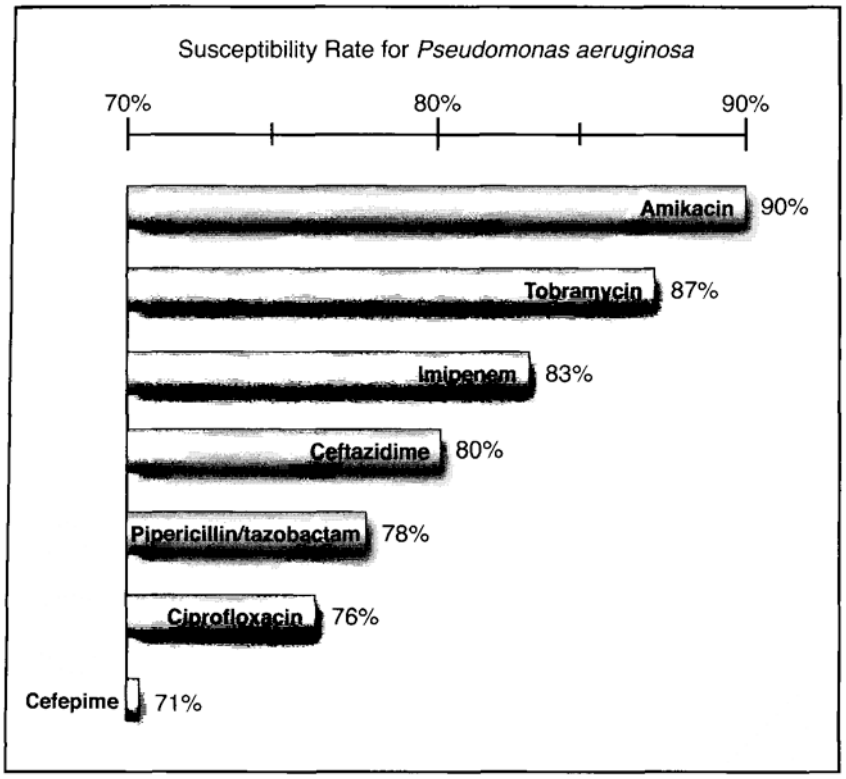

FIGURE 44.2 Susceptibility of *Pseudomonas aeruginosa* to commonly used antibiotics. Data from 8,244 cultures obtained from ICU patients during the years 1994–2000. (From Reference 2).

body distribution of aminoglycosides includes only a small fraction in adipose tissue, so ideal body weight would be appropriate to prevent overdosing in obese patients. However, dosing based on ideal body weight will result in overdosing patients who are underweight, so actual body weight is more appropriate for aminoglycoside dosing in underweight patients. To simplify this situation, you can compare the ideal and actual body weight of each patient, and use the lower of the two weights to determine the aminoglycoside dose. (Formulas for determining ideal body weight in men and women are in Appendix 2).

Once-Daily Dosing

The bactericidal effect of the aminoglycosides is concentration dependent, so higher drug concentrations in the body will produce more bacterial killing (1). This is the rationale for the popularity of administering amino glycosides in one daily dose (which produces higher drug concentrations in tissues than divided-dose regimens). The once-daily regimen has not proven more effective than the divided-dose regimens.

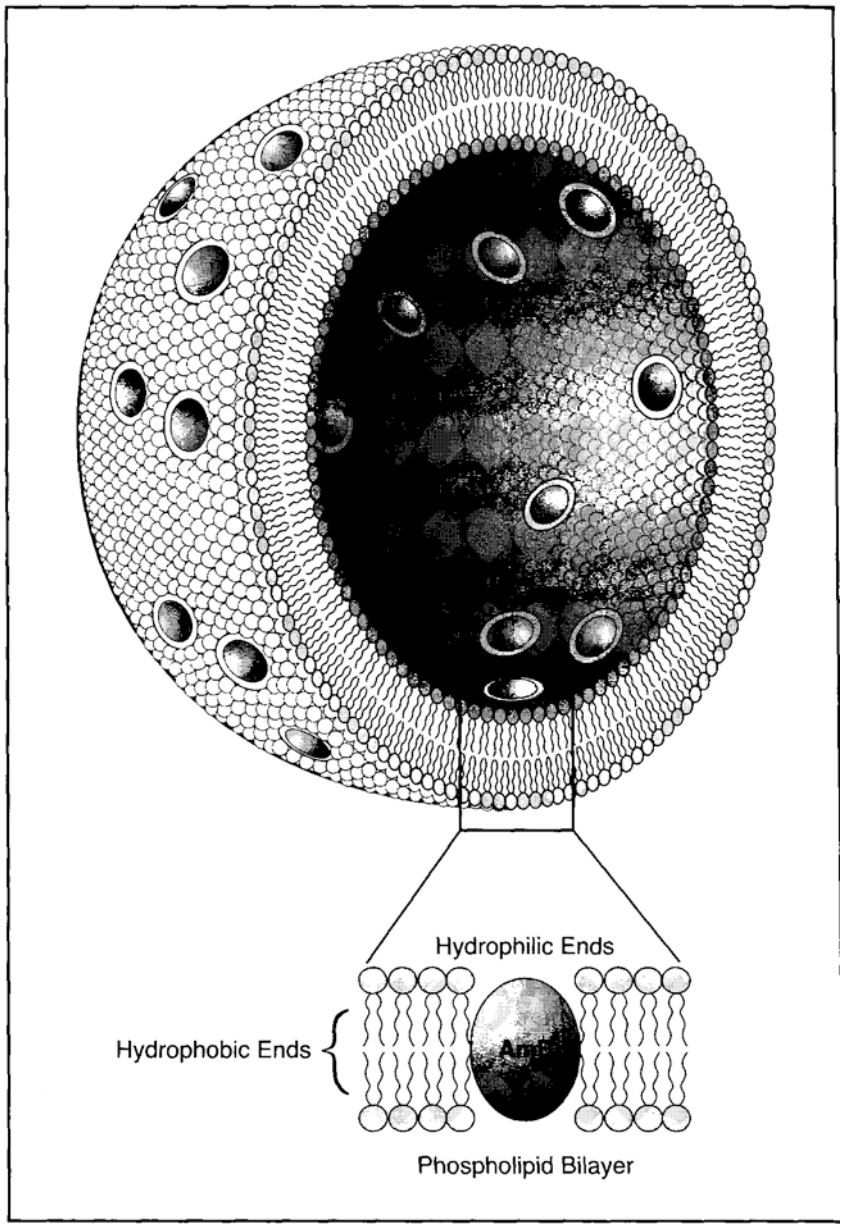

FIGURE 44.3 Schematic view of a liposome shown in cross-section to show the phospholipid bilayer and the amphotericin B (AmB) situated in the bilayer. Scale is in nanometers (nm).

TABLE 44.1 Amlnoglycoside Dosing by Creatinine Clearance*

Cr Cl (mL/min)	Dose (mg/kg) Gentamicin / Tobramycin	Amlkacin	Dosing Interval
>=80	5	15	24 hrs
70	4	12	
60	4	12	to
50	3.5	7.5	
40	2.5	7.5	48 hrs
30	2.5	4	to
20	4	7.5	72 hrs
10	3	4	to
HD	2	5	96 hrs

Abbreviations: Cr Cl = creatinine clearance, HD = hemodialysis.

"Adapted from Turnidge J. Pharmacodynamics and dosing of amino Clin N Am 2003: 17:503-528.

However, once-daily dosing is still preferred because it is equivalent to divided-dose regimens in efficacy and toxicity (1), but is less time-consuming and less costly.

Dosing by Renal *Function*

The aminoglycosides are cleared by filtration in the kidneys, and dose adjustments are necessary when renal clearance is impaired. The dosing adjustments for creatinine clearance are shown in Table 44.1. Note that the reduction in aminoglycoside dose can involve a decrease in the strength of the drug injection, and increase in the dosing interval, or both. The formula for estimating creatinine clearance based on body weight is included in Table 31.2.

Adverse Effects

Nephrotoxicity

Aminoglycosides are referred to as *obligate nephrotoxins* because renal impairment will eventually develop in all patients if treatment is COIltinued 0). These drugs are capable of provoking oxidative injury in cells lining the proximal tubules, and the risk of renal injury is the same with each of the aminoglycosides. The earliest signs of injury include cylindrical casts in the urine, proteinuria, and inability to concentrate urine (3). The urinary changes appear in the first week of drug treatment, and the serum creatinine begins to rise 5 to 7 days after the start of therapy. The nephrotoxicity is enhanced by hypovolemia, advanced age, preexisting renal impairment, hypokalemia, hypomagnesemia, and

concurrent therapy with selected drugs (i.e., loop diuretics, cyclosporin, cisplatin, and vancomycin) (1,3). The renal impairment can progress to acute renal failure, but this is usually reversible.

Other Adverse Effects

Other adverse effects, which include ototoxicity and neuromuscular blockade, are rarely a problem. The ototoxicity can produce irreversible hearing loss and vestibular damage, but these are almost never apparent to the patient (1). Aminoglycosides can block acetylcholine release from presynaptic nerve terminals, but this is never clinically apparent with therapeutic dosing (4). There is a small risk that aminoglycosides will aggravate the neuromuscular blockade a.,sociated with myasthenia gravis and nondepolarizing muscle relaxants (1,5), and it is wise to avoid aminoglycosides in these conditions.

Comment

Because of the substantial risk of renal damage, you should avoid using aminoglycosides whenever possible. A number ofless harmful but equally effective antibiotics are available for treating gram-negative infections. Aminoglycosides should be reserved for immunocompromised or hemo-dynamically unstable patients with gram-negative bacteremia, particularly when *Pseudomonas* species are involved.

ANTIFUNGAL AGENTS

Amphotericin B

Amphotericin B (AmB) is a naturally occurring antibiotic that is fungicidal for most of the pathogenic fungi in humans (6). It is the most effective antifungal agent in clinical use, but is also the most toxic antifungal agent as well. The adverse effects of AmB include an infusion-related inflammatory response, and nephrotoxicity.

Clinical Uses

AmB is the drug of choice for all life-threatening fungal infections, and for empiric antimicrobial therapy in neutropenic patients with persistent fever. It is gradually being replaced by less toxic agents (described later) for infections caused by *Candida albicans* and *Aspergillus* species.

Dosing and Administration

AmB is available for intravenous use only, and contains a vehicle (sodium deoxycholate) to enhance solubility in plasma. It is given once daily in a dose of 0.5 to 1 mg/kg (higher doses may be fl'quired in life-threatening infections). The dose is initially delivered over a 4-hour time period, but this can be reduced to a one-hour infusion if tolerated. Daily infusions are continued until a specified cumulative dose is achieved. The total

AmB dose is determined by the type and severity of the fungal infection: it can be as little as 500 mg (for catheter-related candidemia) or as much as 4 grams (for life-threatening invasive aspergillosis).

INFUSION-RELATED INFLAMMATORY RESPONSE.
Infusions of AmB are accompanied by fever, chills, nausea, vomiting, and rigors in about 70% of instances (7). This reaction resembles a systemic inflammatory response, and the presumed culprit is cytokine release from activated monocytes (6). This reaction is most pronounced with the initial infusion, and often diminishes in intensity with repeated infusions. The following measures are used to reduce the intensity of this reaction (7):

Thirty minutes before the infusion, give acetaminophen (10 to 15 mg/kg orally) and diphenhydramine (25 mg orally of IV). If rigors are a problem, premedicate with meperidine (25 mg IV).

If the premedication regimen does not give full relief, add hydrocortisone to the AmB infusate (0.1 mg/mL).

Central venous cannulation is preferred for AmB infusions to reduce the risk of infusion-related phlebitis, which is common when AmB is infused through peripheral veins (6).

Nephrotoxicity
AmB binds to cholesterol on the surface of renal epithelial cells and produces an injury in the renal tubules that clinically resembles a renal tubular acidosis (distal type), with increased urinary excretion of potassium and magnesium (8) Azotemia is reported in 30% to 40% of patients during daily infusions of AmB (9), and can occasionally progress to acute renal failure that requires hemodialysis (10). The renal impairment from AmB usually stabilize with continued infusions, and improvement is expected if AmB is discontinued. An increase in the serum creatinine above 3.0 mg/dL should prompt cessation of AmB infusions for a few days (7).

Hypokalemia and hypomagnesemia are common during AmB therapy, and the hypokalemia can be difficult to correct until the magnesium deficits are rerlaced (the relationship between magnesium and potassium is described in Chapter 34). Because **magnesium depletion is the seminal event** in both electrolyte disorders, oral magnesium supplementation (300 to 600 mg elemental magnesium daily) is recommended if possible during AmB therapy to replace urinary magnesium losses. However, this can result in hypermagnesemia in the presence of renal insufficiency, so magneslum supplementation is not recommended for patients with progressive azotemia. The nephrotoxic effects of AmB are aggravated by hypovolemia, and by the concurrent use of other nephrotoxic agents (e.g., cyclosporine). The deleterious effects of hypovolemia are explained by the localized vasoconstriction that is obst'rved in AmB nephrotoxicity. Avoiding diuretics and maintaining intravascular volume with isotonic saline infusions is considered essential for reducing the risk of nephrotoxicity.

Liposomal Amphotericin B

Specialized lipid preparations of AmB have been developed to enhance AmB binding to fungal cell membranes and reduce binding to mammalian cells (thereby reducing the risk of renal injury). One of these preparations contains microscopic vesicles like the one depicted in Figure 44.3 to transport amphotericin. These vesicles are made up of phospholipids, and are called li*posomes.* Phospholipid molecules are *amphipathic;* i.e., they have a hydrophilic end and a hydrophobic end. When placed in an aqueous pledium, the phospholipid molecules arrange themselves in bilayers so that the hydrophilic ends are on the surface of the bilayer and hydrophobic ends are in the interior. These bilayers then pinch off to form enclosed vesicles,. The phospholipid bilayer becomes a liposomal membrane, and the amphotericin molecules are intercalated in this membrane. This drug preparation is initially kept as a dry powder, and is hydrated just prior to infusion. The hydration triggers the liposome formation.

Clinical trials comparing liposomal AmB (Ambisome) to standard AmB have shown that both are equally effective, but liposomal AmB is associated with fewer infusion-related side effects and a lower incidence of renal dysfunction (6,9,11). The dose of liposomal AmB needed to produce equivalent antifungal effects is 5 times higher than the dose of standard AmB (6).

The major disadvantage of the lipid formulations is the cost. A comparison of the daily cost of treatment with standard AmB and liposomal AmB (Ambisome) for a 70 kg adult is shown below.

	Standard AmB	Liposomal AmB
Avg. Wholesale Price·	$11.54/50 mg	$118.40/50 mg
Daily Dose	1 mg/kg	5 mg/kg
Daily Cost (70 kg)	$16.16	$828.80

"as quoted in Reference 12.

These estimates place the liposomal preparation at about 50 times the cost of standard AmB. However, an occasional episode of renal insufficiency from standard AmB might even the score.

The lipid formulations of AmB are currently approved for the treatment of fungal infections in patients who are intolerant of standard AmB (e.g., those with renal insufficiency). The liposomal formulation is also approved for empiric antifungal coverage in neutropenic patients with persistent fever (6). The future of these compounds will be determined by the availability of other less expensive alternatives to standard AmB (such as the triazoles described next).

Triazoles

The triazoles are synthetic antifungal agents that are less toxic alternatives to AmB for selected fungal infections. There are three drugs in this class currently in use: fluconazole, itraconazole, and voriconazole. Fluconazole has the most applications in the ICU.

Clinical Uses
The major use for fluconazole in the ICU is the treatment of *Candida* septicemia in patients who are hemodynamically stable and are not immunocompromised (13,14). There is some concern that fluconazole does not adequately cover some species other than *Candida albicans,* such as *Candida krusei* (15), but this organism is involved in only 5% to 10% of cases of invasive candidiasis in the ICU (15). In patients with candidemia who are immunocompromised, fluconazole can be used after an initial course of amphotericin (15). Itraconazole is effective for invasive aspergillosis, but is not favored because of multiple drug interactions (16). Voriconazole is effective for aspergillosis, and for emipiric treatment of neutropenic patients with persistent fever (17).

Dosing
Fluconazole can be given orally or intravenously. The usual dose for confinned infections is 400 to 800 mg daily given as a single dose (the same dose is recommended for oral and intravenous use). The time to reach steady state levels after the start of therapy is 4 to 5 days, and this can be shortened by doubling the initial dose. Adjustments are necessary for renal impairment: if the creatinine clearance is less than 50 mL/min, the dose should be reduced by 50% (6). For the doses of the other triazoles, see reference (6).

Drug Interactions
The triazoles inhibit the cytochrome P450 enzyme system in the liver, and they can potentiate the activity of several drugs. For fluconazole, the significant interactions include phenytoin, cisapride, and the statins (lovastatin, atorvastatin). Fluconazole should not be used with cisapride (Propulsid) or the statins (6). For a list of drug interactions with the other triazoles, see reference (6).

Toxicity
The triazoles are largely devoid of serious toxicity (other than drug interactions). There are rare reports of severe and even fatal hepatic injury associated with fluconazole therapy in HIV patients (18). Asymptomatic elevation of liver enzymes is reported during fluconazole therapy in less than 10% of patients (6).

Echinocandins
The echinocandins are a new class of antifungal agents that are being promoted as a better choice than fluconazole for invasive candidiasis (16). The proposed benefits of these agents include improved coverage for all *Candida* species, less risk of drug interactions, and no dose modification in renal failure. The significance of these advantages is unproven.

Capsofungin
Capsofungin (Cancidas) is the flagship drug in this class. Clinical studies show that capsofungin is comparable to amphotericin for treating

TABLE 44.2 The Generations of Parenteral Cephalosporins

Agent	Generation	Gram+ Cocci*	Gram- Bacilli	P. aeruginosa	B. fragilis	H. influenza
Cefazolin (Ancef)	1	++++	++	-	-	++
Cefoxitin (Mefoxin)	2	++	++++	-	++	++
Ceftriaxone (Rocephin)	3	++	++++	-	-	++++
Ceftazidime (Fortaz)	3	-	++++	++++	-	++++
Cefepime (Maxipime)	4	++	++++	++++	-	++++

"Does not include coagulase-negative or methicillin-resistant enterococci.
Relative antibacterial activity is indicated by number of plus
Adapted from information in References 20

invasive candidiasis (19), and for empiric therapy of neutropenic patients with persistent fever (16). For treating invasive candidiasis, the intravenous dose is 70 mg initially, then 50 mg daily thereafter. Although capsofungin is being promoted as an improvement in antifungal therapy (16), the clinical studies so far reveal only that the drug is equivalent in efficacy to the other antifungal agents.

Cephalosporins

After the first cephalosporin (cephalothin) was introduced in 1964, a small army of other cephalosporins followed, and there are now 20 different cephalosporins available for clinical use (20). These agents are divided into *generations,* and some of the parenteral agents in each generation are shown in Table 44.2 (21,22).

The Family of Cephalosporins

The first-generation cephalosporins are primarily active against aerobic gram-positive cocci, but are not active against *Staphylococcus epidermidis* or methicillin-resistant strains of S. *aureus.* The popular intravenous agent in this group is cefazolin (Ancef).

The second-generation cephalosporins exhibit stronger antibacterial activity against gram-negative aerobic and anaerobic bacilli of enteric origin. The popular parenteral agents in this group are cefoxitin (Mefoxin) and cefamandole (Mandal).

The third-generation cephalosporins have greater antibacterial activity against gram-negative aerobic bacilli, including *P. aeruginosa* and *Haemophilus influenzae,* but are less active against aerobic gram-positive

TABLE 44.3 Parenteral Dosing of Cephalosporins

Agent	Dose for Serious Infections	Dose in Renal Failure*
Cefazolin	1 g every 6 h	1 g every 24 h
Ceftriaxone	2 g every 12 h	2 g every 12 h
Ceftazidime	2 g every 8 h	2 g every 48 h
Cefepime	2 g every 8 h	2 g every 24 h

"From Reference 24.

cocci than the first-generation agents. The popular parenteral agents in this group are ceftriaxone (Rocephin), and ceftazidime (Fortaz). Ceftriaxone is popular for the treatment of severe community-acquired pneumonia, and is active against penicillin-resistant pneumococci and H. *influenzae.* Ceftazidime is a popular antipseudomonal antibiotic, particularly because it is devoid of serious adverse effects.

The fourth-generation cephalosporins retain activity against gramnegative organisms, but add some gram-positive coverage. The only drug in this generation is cefepime (Maxipime), which has the gram-negative antibacterial spectrum of ceftazidime (i.e., it covers *P. aeruginosa),* but is also active against gram-positive cocci (e.g., streptococci and methicillinsensitive staphylococci).

Dosing

The doses for the more popular parenteral cephalosporins are shown in Table 44.3, along with dose adjustments for renal failure. Note that the dose in renal failure is adjusted by extending the dosing interval rather than decreasing the amount of drug given with each dose (22). This is done to preserve concentration-dependent bacterial killing. Note also that ceftriaxone requires no dose adjustment in renal failure.

Toxicity

Adverse reactions to cephalosporins are uncommon and nonspecific (e.g., nausea, rash, and diarrhea). There is a 5 to 15% incidence of cross-antigenicity with penicillin (21), which is why cephalosporins should be avoided in patients with a prior anaphylactic reaction to penicillin.

Comment

The popularity of cephalosporins is definitely on the decline (in fact, no new cephalosporin has appeared since 1996, the year cefepime was introduced). The early generation cephalosporins were once unmatched in popularity for gram-positive coverage, but have taken a back seat to vancomycin because of the emergence of methicillin-resistant S. *aureus.* The later generation cephalosporins such as ceftazidime and cefepime are also on the decline because of emerging resistance (see Fig. 44.2).

The only cephalosporin that seems to be holding ground is ceftriaxone, which is a popular agent for severe community-acquired pneumonia.

THE FLUOROQUINOLONES

The fluoroguinolone era began in 1987 with the introduction of ciprofloxacin. This was followed in the mid-1990s by the appearance of the "newer" fluoroquinolones, beginning with levofloxacin (introduced in 1996). These two generations of quinolones differ somewhat in pharmacokinetic properties and spectrum of activity.

Activity and Clinical Use

The early fluoroquinolones (e.g., ciprofloxacin) were active against (methicillin-sensitive) staphylococci and most of the aerobic gramnegative bacilli, including *Pseudomonas aeruginosa* and were less active against streptococci. Rapidly emerging resistance to these antibiotics (caused in part by the excessive use of ciprofloxacin after it was introduced) has reduced their value in treating serious gram-negative infections, particularly those due to *P. aeruginosa* (see Fig. 44.2).

The newer fluoroguinolones (e.g., levofloxacin, gatifloxacin, moxifloxacin) retain the antibacterial spectrum of the early agents (except for reduced activity against *P. aeruginosa),* but provide added coverage for streptococci, pneumococci (including penicillin-resistant strains) and "atypical" organisms like *Mycoplasma pneumoniae* and *Haemophilus influenzae.* The newer fluoroquinolones are used primarily for communityacquired pneumonia, exacerbations of chronic obstructive lung disease, and urinary tract infections. The inability to cover methicillin-resistant staphylococci, and the limited activity against *P. aeruginosa,* limits their value in the ICU.

Dosing

Table 44.4 shows the recommended intravenous doses for four quinolone antibiotics. The newer quinolones have longer half-lives than ciprofloxacin, and require only one dose daily. Dose adjustments are required for all the agents except moxifloxacin, which is metabolized in the liver (23).

TABLE 44.4 Parenteral Dosing of Fluoroquinolones

Agent	Dose for Serious Infections	Dose in Renal Failure"
Ciprofloxacin	400 mg every 8h	400 mg every 18 h
Levofloxacin	500 mg every 24 h	250 mg every 48 h
Gatifloxacin	400 mg every 24 h	200 mg every 24 h
Moxifloxacin	400 mg every 24 h	400 mg every 24 h

"From References 6.22.

DRUG INTERACTIONS

Ciprofloxacin interferes with the hepatic metabolism of theophylline and warfarin and can potentiate the actions of both of these drugs (24,25). Ciprofloxacin causes a 25% increase in serum theophylline levels, and combined therapy has resulted in symptomatic theophylline toxicity (26). Although no dose adjustments are necessary, serum theophylline levels and prothrombin times should be monitored carefully when ciprofloxacin is given in combination with these two agents.

Toxicity

The fluoroquinolones are relatively safe. Neurotoxic reactions (confusion, hallucinations, seizures) can develop days after starting quinolone therapy in 1 % to 2% of patients (27). Prolongation of the QT interval and polymorphic ventricular tachycardia (torsades de pointes) have been reported in patients receiving all quinolones except moxifloxacin, but only 25 cases were on record as of 2001 (28).

Comment

The emerging resistance of gram-negative pathogens to ciprofloxacin has diminished the value of fluoroquinolones in the ICU. Ciprofloxacin can no longer be viewed as a first-line drug for *Pseudomonas* infections, and there are better antibiotics available to treat other gram-negative infections (e.g., imipenem or meropenem). The newer agents are popular for community-acquired pneumonia, but are not favored drugs for ventilator-associated pneumonia unless the pneumonia is early-onset (within 5 days of admission) and the patient is in the low risk category for colonization with gram-negative pathogens (see Table 41.5).

IMIPENEM

Imipenem is a member of the carbepenem class of antibiotics (the other drug in the class is meropenem, which is mentioned briefly later), and is distinguished by having the broadest spectrum of antibacterial activity of any antibiotic currently available (29).

Activity and Clinical Uses

In short, imipenem is active against all common bacterial pathogens except methicillin-resistant staphylococci. As demonstrated in Figure 44.1 imipenem is one of the most active agents for aerobic gram-negative bacilli, and it is also active against *Pseudomnas aerugillosa* (although less so, as in Fig. 44.2). It provides good coverage for the pneumococcus, methicillin-sensitive staphylococci, and coagulase-negative staphylococci (the latter being a common cause of catheter-related infections). It also proves excellent coverage for anaerobes, and is active against *Bacteroides*

fragi/is and *Enterococcus faeca/is.* Some minor strains of pseudomonads (e.g., *P. cepaciae)* are poorly covered by imipenem, but they are uncommon offenders. There is some acquired resistance by *P. aerugillosa,* but the clinical significance of this is unclear.
Imipenem can be used for virtually any infection that does not involve methicillin-resistant *Staph.aureus.* **It** is well-suited for mixed aerobic/ anaerobic infections such as pelvic and intraabdominal infections. It is also been very effective when used as mono therapy for neutropenic patients with fever (see Table 43.4) (30).

Dosing
Imipenem is inactivated by enzymes on the luminal surface of the proximal renal tubules, so it is impossible to achieve high levels of the drug in urine. To overcome this problem, the commercial preparation of imipenem contains an enzyme inhibitor, cilastatin. The combination imipenem-cilastatin preparation is available as Primaxin. The dose recommendations for imipenem-cilastatin represent the dose of imipenem. The usual intravenous dose in adults is 500 mg every 6 hours. In suspected *Pseudomonas* infections, the dose is doubled to 1 g every 6 hours. In renal failure, the dose should be reduced by 50 to 75% (22).

Adverse Effects
The major adverse effect associated with imipenem is generalized seizures, which occur in 1 to 3% of patients receiving the drug (29). Most patients have a history of a seizure disorder, an intracranial mass, or renal failure. Although this is an uncommon occurrence, a maximum daily dose of 2 g or 25 mg/kg has been recommended (29).

Meropenem
Meropenem is similar to imipenem in its spectrum of antibacterial activity, but does not produce seizures (31). The normal intravenous dose is 1 gram every 8 hours and, in the presence of renal failure, a dose reduction of about 50% is required. Meropenem may, in fact, be slightly superior to imipenem because there is no risk of seizures, but the clinical experience with this drug is limited in comparison to imipenem.

Comment
The ideal antibiotic would be effective against all pathogens and produce no adverse reactions. Imipenem comes closer to this ideal than any antibiotic currently available, with the possible exception of meropenem. This has been my personal favorite for several years because it covers almost everything! The seizure risk is overstated, and is only a concern if you don't adjust the dose in renal failure, or the patient has another reason to have seizures. There is some emerging resistance to imipenem in strains of *P. aeroginosa,* but the significance of this is unclear.

THE PENICILLINS

The penicillin discovered by Alexander Fleming in 1929 is benzylpenicillin, or penicillin G. This substance is active against aerobic streptococci *(S. pneumoniae,* S. *pyogenes)* and anaerobic mouth flora. The emergence of penicillin-resistant pneumococci in recent years has virtually eliminated penicillin G from the ICU.

Extended-Spectrum Penicillins

The penicillins in this category haveanextended antibacterial spectrum that covers aerobic gram-negative bacilli. This category includes the aminopenicillins (ampicillin and amoxicillin), the carboxypenicillins (carbenicillin and ticarcillin), and the ureidopenicillins (azlocillin, mezlocillin, and pipericillin). All groups are active against gram-negative pathogens, but the latter two groups are active against *P. aeruginosa* (32). These agents are also known as *antipseudomonal penicillins.* The most popular drug in this class is pipericillin, which is available in a special combination product (see next).

Pipericillin- Tazobactam

Pipericillin is most often given in combination with tazobactam, a beta-lactamase inhibitor that has synergistic activity when combined with pipericillin. The commercial product (Zosyn) contains pipericillin in an 8:1 ratio with tazobactam. The recommended dose of the combination product is 3.375 grams (3 grams pipericillin and 375 mg tazobactam) IV every 4 to 6 hours. In the presence of renal insufficiency, the dose should be changed to 2.25 grams every 8 hours (33).

Pipericillin-tazobactam can be used for empiric therapy of urinary tract infections and intraabdominal sepsis, and it is one of the antibiotics recommended for empiric therapy of neutropenic patients with fever. However, the performance of this preparation in the susceptibility rates in Figures 44.1 and 44.2 indicate that there are better alternatives for the treatment of gram-negative infections in the ICU.

VANCOMYCIN

Vancomycin is one of the staples of antimicrobial therapy in the ICU, but concerns about the emergence of vancomycin-resistant enterococci (VRE) have prompted a general mandate to curtail its use.

Antibacterial Spectrum

Vancomycin is active against all gram-positive cocci, including all strains of *Staphylococcus aureus* (coagulase-positive, coagulase-negative, methicillin-sensitive, methicillin-resistant) as well as aerobic and anaerobic streptococci (including pneumococcus and enterococcus) (34). It is the drug of choice for penicillin-resistant pneumococci, and is one of the

most active agents against *Clostridium difficile,* the pathogen responsible for antibiotic-associated pseudomembranous colitis. Enterococcal resistance to vancomycin occurs in 1 to 15% of nosocomial isolates (34), and the prevalence in different hospitals varies widely.

Clinical Use

Vancomycin is the drug of choice for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis.* However, as much as 2/3 of the vancomycin used in ICUs is not directed at a specific pathogen, but is used for empiric antibiotic coverage in patients with suspected infections (35). The popularity of vancomycin in empiric antibiotic regimens is a reflection of the prominent role played by MRSA and S. *epidermidis* in ICU-related infections.

Dosing

The usual intravenous dose of vancomycin is 1 gram every 12 hours (34). Each dose must be infused slowly (no faster than 10 mg/min) to prevent infusion reactions (see below). Intermittent dosing is traditional, but continuous infusion also achieves bactericidal drug levels in blood (34). Dose reduction is necessary in renal insufficiency, and is accomplished by increasing the dosing interval. One dose of vancomycin every 4 days is sufficient for hemodialysis patients, and a supplemental dose after dialysis is not required (22).

Serum drug levels are often monitored to limit toxicity and maintain efficacy. Peak levels should be below 40 mg/L to reduce the risk of ototoxicity (for intermittent dosing only), and trough levels should be above 5 mg/L to maintain antibacterial activity (36).

Toxicity

Rapid administration of vancomycin can be accompanied by vasodilation, flushing, and hypotension *(red man syndrome)* as a result of histamine release from mast cells (34). The trigger for this release is unknown, but slowing the infusion rate (to less than 10 mg/minute) usually corrects the problem.

Ototoxicity

Vancomycin can cause reversible hearing loss for high-frequency sounds when serum drug levels exceed 40 mg/L (36). Permanent deafness has been reported when serum levels exceed 80 mg/L (35). Both complications are uncommon, possibly because drug levels are monitored routinely.

Nephrotoxicity

Renal insufficiency of unclear etiology is reported in 5% of patients receiving vancomycin (36). There is no apparent relationship to the dose

of vancomycin, but the incidence is higher when amino glycosides are given concurrently. Renal function usually returns to normal after stopping vancomycin.

Comment
Vancomycin continues to be a solid performer in the ICU. Curtailing its use will be difficult until another antibiotic appears that has the same antibacterial profile as vancomycin. That drug is already here, as described next.

Linezolid
Linezolid (Zyvox) is a synthetic antibiotic that was introduced in 2000 to treat infections caused by resistant gram-positive organisms (37): i.e., MRSA, VRE, and penicillin-resistant pneumococci. Although intended only for cases where vancomycin was ineffective or not tolerated, linezolid is now being considered as a possible replacement for vancomycin. It has the same spectrum of activity, and has proven effective in treating MRSA infections. In fact, one study comparing vancomycin and linezolid for the treatment of MRSA pneumonia showed better results with linezolid (38). Linezolid may be better suited for treating pneumonia because it penetrates into respiratory secretions, while vancomycin does not (34). The recommended intravenous dose of linezolid for serious infections is 600 mg twice daily.
Linezolid is relatively safe when given in short courses. However, prolonged (more than one month) treatment can be associated with thrombocytopenia, peripheral neuropathy, and optic neuropathy (37,39). The optic neuropathy resolves partially, but the peripheral neuropathy is irreversible.

A FINALWORD
The first rule of antibiotics is try not to use them, and the second rule is try not to use too many of them. If antibiotics are needed pending culture results, the combination of vancomycin and imipenem will suffice in most situations. Imipenem covers all of the common bacterial pathogens in the ICU except methicillin-resistant *Staph aureus* (MRSA), hence the vancomycin. If you don't have a problem with MRSA in your ICU, then imipenem alone will suffice. You can then adjust antibiotics according to the culture results. If the cultures are negative and the patient has not improved on antimicrobial therapy, you should stop the antibiotics and rethink your strategy. Remember (from Chapter 40) that fever and leukocytosis are signs of inflammation, not infection, and that about 50% of ICU patients with signs of inflammation will *not* have a documented infection.

References