

Infectious Diseases

The number of infectious complications encountered in the intensive care unit (ICU) continues to increase. Patients who otherwise would have not survived in the past are now improving due to new technical advancements. However, the length of stay, as well as the large number of devices employed for this purpose, predisposes patients to difficult and often fatal infections. Clinical characteristics of patients who are treated in the ICU have evolved in recent years. Those who are immunocompromised, post-transplant, and the geriatric population are now regularly treated in the ICU with the consequent increase in morbidity, mortality, and cost.

From the infectious diseases point of view, the approach to a critically ill patient who is admitted to the ICU should immediately differentiate if the patient was transferred from the floor versus if the patient was directly admitted to the ICU from the community. This constitutes a paramount parameter to categorize the etiologic agents, to understand the pathophysiology of their processes, and mostly to decide which therapeutic antimicrobial interventions are needed.

■ I. PNEUMONIA (NOSOCOMIAL)

A. If the patient is transferred to the ICU after being in the hospital for several days, then treatment should address the nosocomial aspect of infection and the following important facts:

1. Mortality rates among these patients are 20–60%.
2. These patients represent 15% of all hospital deaths.
3. Successful treatment depends upon underlying disease, specific causative organisms, and timely institution of therapy.

B. Predisposing Factors

1. Intubation.
2. ICU: Especially the patient who is receiving sedation.
3. Antibiotics: Broad-spectrum agents will rapidly change normal flora of the mouth and gastrointestinal (GI) tract.
4. Surgery: Especially thoracic, abdominal, or neurosurgery, which increases the risk of aspiration.
5. Chronic lung disease.

6. Advanced age.
7. Immunosuppression.

C. Etiologic Agents

1. Common

- Gram-negative bacteria such as: *Klebsiella* sp., *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter* sp., *Acinetobacter* sp.
- Gram positive bacteria: *Staphylococcus aureus*.

2. Less Common

- a. Anaerobic mouth flora (i.e., *streptococci*)
- b. Other gram-negative bacilli (i.e., *Serratia* sp., *Xanthomonas* sp.)
- c. *Haemophilus influenzae*
- d. *Legionella* sp.
- e. *Candida* sp.
- f. *Aspergillus* sp.
- g. Influenza virus
- h. *Streptococcus pneumoniae*
- i. Miscellaneous: according to prevalent organisms in each hospital
- j. Tuberculosis (TB, typical and atypical)

Another helpful approach is to consider the likely pathogens according to the time after hospitalization the pneumonia developed. Late-onset pneumonia (after more than 5 days of hospitalization) is usually characterized with more resistant organisms.

- ### D. Clinical Manifestations.
- Patients in the ICU, especially those who are intubated or sedated, will not manifest the usual symptoms of pneumonia such as cough, chest pain, or dyspnea. Patients who are neutropenic cannot mount an inflammatory response, and, therefore, the sputum will not show purulent material. Subtle changes in oxygenation, fever, and clinical deterioration are clues for the diagnosis of pneumonia in intubated patients. Leukocytosis or leukopenia can be the first manifestation of occult pneumonia. In some instances, i.e., *Pneumocystis* pneumonia, the presence of spontaneous pneumothorax can be the first indication of pulmonary involvement. Thick, foul-smelling sputum is characteristic of anaerobic and aspiration pneumonia.

E. Diagnosis

1. On chest x-ray, look for new or changing infiltrates.
2. Obtain sputum for Gram's stain *immediately* on every patient.
3. Remember the concept of colonization versus true infection; this distinction is sometimes very difficult.
4. Be aggressive in trying to obtain diagnosis (i.e., bronchoalveolar lavage [BAL]). Transtracheal aspirates are not commonly employed.
5. Obtain other stains (i.e., acid-fast bacilli stain [AFB], Giemsa, wet prep).
6. Order serologies, if appropriate (i.e., *Legionella*, fungal serologies, cryptococcal antigen, CIE).
7. Remember the microbiological pattern of your hospital.

F. Treatment Options

1. Empiric options most commonly utilized in the ICU
 - a. Beta-lactam plus aminoglycoside (i.e., piperacillin and tobramycin).
 - b. Cephalosporin plus aminoglycoside (i.e., ceftazidime and gentamicin).
 - c. Clindamycin plus gentamicin.
 - d. Clindamycin plus quinolone (i.e., ciprofloxacin).

- e. Imipenem/cilastatin plus aminoglycoside.
- f. Cephalosporin plus fluoroquinolone.
- g. Add trimethoprim-sulfamethoxazole [TMP-SMX] if *Pneumocystis carinii* pneumonia is suspected.
- h. Add erythromycin or azithromycin 500 mg IV qd or erythromycin 0.5–1 g IV q6 h if *Legionella* is suspected
- i. TMP-SMX 15–20 mg/kg/d TMP
- j. Doxycycline 100 mg IV q12 h
- k. Rifampin 300 mg IV q12 h
- l. Amphotericin B 0.6–1 mg/kg/d

Duration of therapy is not well defined, but most authors agree on treating gram-negative and anaerobic pneumonia for 10–21 days. Gram-positive processes are usually treated between 10 and 14 days, and atypical pneumonias receive 2 weeks of antimicrobial therapy. *Candida* pneumonia requires prolonged treatment with up to 1.5 g of amphotericin B as a total dose.

G. Prevention

1. Preoperative and postoperative measures for prevention of pneumonia
 - a. Identification of high-risk patients
 - b. Treatment of respiratory infections, removal of respiratory secretions
 - c. Instruction and therapy to expand patients' lungs (i.e., chest physiotherapy, incentive spirometry)
2. Proper hand washing
3. Appropriate maintenance of in-use respiratory therapy equipment
 - a. Use of sterile fluids in nebulizers
 - b. Proper use of single-dose and multidose medications for respiratory therapy
4. Proper sterilization and disinfection of reusable respiratory equipment
5. Proper suctioning of the respiratory tract
6. Protection of patients from other infected patients or staff

■ II. COMMUNITY-ACQUIRED PNEUMONIA

A. Common Organisms

1. *Streptococcus pneumoniae*
2. *Mycoplasma pneumoniae*
3. *Haemophilus influenzae*
4. *Klebsiella* sp.
5. Respiratory viruses (Influenza A and B, Adenovirus, Respiratory syncytial virus, Parainfluenza)
6. *Legionella* sp.

B. Other Less Common Organisms

1. *Pneumocystis carinii*
2. *Mycobacterium tuberculosis*
3. *Cryptococcus* sp.
4. *Chlamydia psittaci*
5. *Histoplasma* sp.
6. *Nocardia* sp.

C. Common Manifestations

1. Fever, cough, dyspnea, sputum production usually purulent but not in all cases.
2. Hypoxemia is common.
3. Anxiety.
4. Leukocytosis; also leukopenia in severe infections.

D. Uncommon Presentations in Patients Who Are $\frac{1}{4}$

1. Elderly
2. Immunocompromised (especially neutropenic)
3. Post-transplantation

E. Clinical Clues for Diagnosis

1. Acute onset: bacterial, viral, aspiration, tularemia, *Pneumocystis*
2. Subacute onset: viral, *Legionella*, *Haemophilus* sp., *Mycoplasma*, Q fever, Psittacosis, *Chlamydia*, *Pneumocystis*
3. Aerogenous route: any segment
4. Hematogenous: most commonly in both bases, as blood flow is preferential to these areas

F. Associations

1. Birds: psittacosis
2. Turtles: typhoid
3. Dogs: *Pasteurella multocida*
4. Cattle: Q fever
5. Rabbits: tularemia
6. Air conditioners: *Legionella*
7. COPD and smoking: *H. Influenzae*, *Pseudomonas aeruginosa*
8. Hides: anthrax
9. Foreign travel: *Echinococcus*, paragonimiasis
10. Barracks: *Neisseria meningitidis*, group A *Streptococcus*

G. Treatment. Empiric treatment is usually dictated by the geographical background, clinical presentation, and host status.

- o Levofloxacin 750 mg.

or

- o Ceftriaxone 1 g IV plus azithromycin 500 mg IV

1. *Streptococcus pneumoniae* and *Haemophilus influenzae*
 - a. Quinolone (moxifloxacin or levofloxacin)
 - b. Ertapenem (1 g q24 h)
 - c. Ceftriaxone (1 g q24 h)
2. *Legionella* sp., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*
 - a. Moxifloxacin (400 mg IV qd)
 - b. Levofloxacin (500 mg IV qd)
 - c. Doxycycline (200 mg IV qd)
3. *Pseudomonas aeruginosa*
 - a. Meropenem (2 g IV q8 h)
 - b. Cefepime (2 g IV q8 h) and Amikacin (1 g IV q24 h)
 - c. For multidrug resistant *p. aeruginosa* Colistin (80 mg IV q8 h)
4. Influenza A/B, Avian Influenza
 - a. Oseltamivir (Tamiflu) 75 mg PO q24 h plus Rimantadine 100 mg PO.
 - b. Avian Influenza (Influenza virus type A H₅N₁)—Influenza following close contact with infected poultry. Several outbreaks in humans have been identified in Asia: flu-like symptoms with vague gastrointestinal

complaints that rapidly progress to acute respiratory failure. Diagnosis is by hemagglutinin-specific RT-PCR for avian influenza. Treatment with antivirals should be given early, and it includes: Oseltamivir (150 mg), with amantadine and rimantadine.

H. Complications After 72 h

1. Persistent fever
2. Empyema
3. Obstruction
4. Lung abscess
5. Resistant organism
6. Focus of infection

■ III. SEVERE ADULT RESPIRATORY SYNDROME (SARS)

Term given by the World Health Organization, describes a rapidly progressive respiratory illness with documented outbreaks in China, Hong Kong, Vietnam, Singapore, and Canada. The presumable pathogen is a coronavirus that spreads person to person via droplets, sewage, and water and potentially through human feces. It is hypothesized that bats are the primary reservoir for the disease. The mortality rate from SARS is high (up to 20%). This is a two-stage illness:

1. Prodrome: includes fever, malaise, headache, myalgias, and diarrhea may occur.
2. Respiratory phase: non-productive cough and dyspnea that rapidly progress to respiratory failure.

There is no current treatment available for this illness, except for supportive care in the intensive care unit. Preventive measures against SARS are mainly focused on travel advisories to countries and cities with active outbreaks. Efforts are underway to prepare a vaccine for the prevention of SARS.

■ IV. SEPSIS

- A. More than 750,000 cases of sepsis, with an associated mortality of 20–60%, are estimated to occur annually. Despite improvements in antimicrobial therapy and supportive care, the incidence of and mortality associated with sepsis have not declined. This is, in part, a consequence of an array of medical advances that can place patients at increased risk for development of infection and, potentially, sepsis.
- B. Sepsis and Related Disorders
 1. Definitions
 - a. Bacteremia: Positive blood cultures (may be transient)
 - b. Sepsis: Clinical evidence suggestive of infection *plus* signs of a systemic response to the infection (all of the following):

- (1). Tachypnea (respiration 20 breaths per minute; if patient is mechanically ventilated, minute volume 10 L/min)
 - (2). Tachycardia (heart rate >90 beats per minute)
 - (3). Hyperthermia or hypothermia (core or rectal temperature >38.4°C [101°F] or <35.6°C [96.1°F])
- c. Sepsis Syndrome (may also be considered *incipient septic shock* in patients who later become hypotensive): Clinical diagnosis of sepsis outlined above, plus evidence of altered organ perfusion (one or more of the following):
- (1). PaO₂/FiO₂ no higher than 280 (in the absence of other pulmonary or cardiovascular disease).
 - (2). Lactate level above the upper limit of normal.
 - (3). Oliguria (documented urine output <0.5 mL/kg body weight for at least 1 h in patients with urinary catheters in place).
 - (4). Acute alteration in mental status.
 - (5). Positive blood cultures are not required.
- d. Early Septic Shock: Clinical diagnosis of sepsis syndrome as outlined above, *plus* hypotension (systolic blood pressure <90 mmHg or a 40-mmHg decrease below baseline systolic blood pressure) that lasts for <1 h and is responsive to conventional therapy (intravenous fluid administration or pharmacologic intervention)
- e. Refractory Septic Shock: Clinical diagnosis of the sepsis syndrome outlined above, *plus* hypotension (systolic blood pressure <90 mmHg or a 40-mmHg decrease below baseline systolic blood pressure) that lasts for >1 h despite adequate volume resuscitation and that requires vasopressors
- C. Pathophysiology. Cell walls of gram-negative bacteria contain proteins, lipids, and lipopolysaccharides. Endotoxin (lipopolysaccharide) has three components: an O-specific polysaccharide, the R-core, and lipid A. Lipid A may be the major culprit in initiating the endotoxic symptoms. It is this component of endotoxin that stimulates the release of tissue necrosis factor (TNF) and can also activate the complement pathway. The sepsis syndrome is caused by endothelial damage following endotoxin-stimulated activation of neutrophils, coagulation, complement, and macrophages. Macrophages are stimulated to release TNF, interleukins, leukotrienes, thromboxane, and other cardioactive substances. Endotoxemia markedly increases the risk of myocardial depression and multiple organ failure. In patients who have positive blood cultures, those with severe endotoxemia have 5 times the mortality of those who do not have endotoxemia.
- D. Priorities in the Treatment of Sepsis
- a. Early recognition.
 - b. Cardiovascular/pulmonary support.
 - c. Fluid resuscitation.
 - d. Pressor agents.
 - e. Empiric antibiotic therapy.
 - f. Other immunotherapeutic agents (investigational).
 - g. Corticosteroids are *not effective*.
 - h. Drainage of any foci of infection.
- E. Prognosis. Mortality in sepsis is a function of the severity of physiologic derangements, the duration of illness, and the number of organ system failures. These organ systems include, but are not limited to, the lungs, kidneys, and liver. When the pulmonary system becomes dysfunctional, the resultant clinical entity is known as the adult respiratory distress syndrome (ARDS). The sequence has been

termed the multiple-organ dysfunction syndrome (MODS). MODS is the most common cause of demise in patients who experience uncontrolled inflammation and infection.

- F. Activated protein C. The presence of coagulation abnormalities is a major problem in patients with severe sepsis and septic shock. Some reports suggest that supplementation of activated protein C may produce clinical benefit, by decreasing mortality rate. The greater benefit from activated protein C was observed in acutely ill patients (APACHE II score 25). Some evidence shows that patients receiving activated protein C have lower incidence of multi-organ system failure, but greater risk of serious bleeding (including fatal intracranial hemorrhage). A careful selection of patients should be done in order to identify those that will benefit the most from this therapy.

■ V. TOXIC SHOCK SYNDROME

A. Clinical Case Definition (See Table 8.1)

1. Severe febrile (38.9°C) illness with rash (erythroderma followed by desquamation), hypotension or syncope, and multiple organ system involvement (at least four of the following: mucous membrane, GI, muscular, central nervous system [CNS], renal, hepatic, hematologic, cardiopulmonary, metabolic).
2. Hypotension: probably due to small-vessel and capillary leakage with extravascular accumulation of fluid (edema).
3. Blood cultures are usually negative.
4. Acute episode followed by desquamation
5. No evidence of other causes: scarlet fever, Kawasaki's disease, Rocky Mountain spotted fever, etc.

B. Epidemiology and Other Clinical Features

1. Affects mostly young menstruating women. Tampon use, especially continuous use and Rely brand in some studies. *S. aureus* colonization of vagina. Recurrence rate of 30%. Decrease in the number of reported cases.

Table 8.1. Toxic Shock Syndrome

Criteria for Diagnosis

Temperature <38.9°C

Systolic blood pressure <90 mmHg

Rash with subsequent desquamation, especially on palms and soles

Involvement of >3 of following organ systems:

Gastrointestinal: vomiting or severe diarrhea

Muscular: severe myalgias or fivefold increase in creatine kinase

Mucous membranes: frank hyperemia

Renal insufficiency: serum urea nitrogen, creatinine, double of normal

Liver: enzymes, twice upper limits of normal

Blood: thrombocytopenia <100,000/mm³

CNS: disorientation without focal findings

Negative tests for leptospirosis, Rocky Mountain spotted fever, and measles

2. Also occurs in non-menstruating women, men, and children (colonization or focal infection with *S. aureus*, including postoperative infections). Common occurrence after surgery. Fatality rate: 5–10%.
- C. Etiology. Exotoxin(s) of *S. aureus* appear to cause the disease. Recently, streptococci have been shown to cause the same syndrome.
- D. Differential Diagnosis. Kawasaki's disease, scarlet fever, leptospirosis, Rocky Mountain spotted fever, measles.
- E. Treatment. The most important treatment is volume expansion and correction of hypotension; removal of the tampon, if present, in menstruating women; debridement of wounds, etc.; and administration of antistaphylococcal antibiotics (after cultures have been obtained). Steroids have not been proven to be effective or to alter outcome.

■ VI. MENINGITIS

A. Acute meningitis is a medical emergency that requires early recognition, rapid diagnosis, precise antimicrobial therapy, and aggressive ICU support.

1. Etiologic Agents

- a. *Streptococcus pneumoniae*: The most common cause in adults.
 - b. *Neisseria meningitidis*: Common among groups of young individuals and children.
 - c. *Haemophilus influenzae*: Common in children up to 12 years of age.
 - d. *Staphylococcus aureus* and *S. epidermidis*: Seen in the elderly or postoperatively (CNS shunts).
 - e. *Listeria monocytogenes*: Usually mistaken with diphtheroids or contaminants.
 - f. Streptococci other than *S. pneumoniae*: Especially group B in neonatal disease.
 - g. Gram-negative bacilli: After surgery or trauma.
 - h. *Mycobacterium tuberculosis*: Increasing in frequency.
 - i. *Cryptococcus*: Usually in immunosuppressed patients (i.e., those with acquired immune deficiency syndrome [AIDS], or impaired cell-mediated immunity).
 - j. Syphilis: presentation variable.
 - k. *Herpes simplex*.
 1. Toxoplasma: can present as meningoencephalitis or brain abscess.
 - m. Naegleria: epidemiological history is paramount.
 - n. Other viruses (i.e., echovirus, St. Louis, equine, and Western encephalitis).
- ### 2. Associations: Epidemiology and Organisms
- a. Summer and fall: Coxsackie or echovirus; leptospira
 - b. Previous meningitis: *S. pneumoniae*
 - c. Alcoholism: *S. pneumoniae*
 - d. Young adults: *N. meningitidis*
 - e. Elderly: *S. pneumoniae*, listeria, gram-negative bacilli
 - f. Lymphoma: *Cryptococcus* sp.
 - g. Petechia: *N. meningitidis*, echovirus
 - h. Sinusitis: *H. influenzae*, *S. pneumoniae*, anaerobic bacteria

- i. Cellulitis: aerobic, gram-positive cocci
- j. Brain abscess: mixed flora
- k. Swimming in fresh water: amoebas
- l. Other family members with meningitis: *N. meningitidis*
- m. Water contact: leptospira
- n. Hospital acquired: gram-negative bacilli, staphylococcus, candida
- o. Head trauma
 - (1). Close fracture: *S. pneumoniae*, gram-negative bacilli
 - (2). Craniotomy: gram-negative bacilli, staphylococci
 - (3). Cerebrospinal fluid rhinorrhea: *S. pneumoniae*
- 3. Cerebrospinal Fluid (CSF) Findings (See Table 8.2)
- 4. Diagnostic Approach
 - a. Order antigen detection for *H. influenzae*, *S. pneumoniae*, *N. meningitidis*.
 - b. Obtain high-volume CSF for AFB concentrate and fungal cultures (20–30 mL).
 - c. If CSF is normal or viruses are suspected, repeat lumbar puncture (LP) in 24–36 h.
 - d. Upon admission, obtain serologies for viral infections (i.e., St. Louis encephalitis, California encephalitis).
 - e. Obtain serologies in serum and CSF for fungal infections.
 - f. Polymerase chain reaction (PCR) may be helpful (especially for TB and cytomegalovirus [CMV] infections).
- 5. Treatment

In acutely ill patients, the goal of therapy is to institute treatment before the pathologic process of inflammation can produce irreversible progression and/or death. Time is essential in this situation. Empiric therapy is instituted immediately after diagnosis is made, and it is based on the recognition of a community versus hospital and/or postoperative process. For community-acquired meningitis, usual treatment includes a third-generation cephalosporin (i.e., cefotaxime

Table 8.2. CSF Findings in Meningitis According to Etiology

<i>Bacterial</i>	<i>Tuberculous</i>	<i>Viral</i>	<i>Chronic</i>
Glucose >40 mg/dL (Blood ratio <0.4)	30–45 mg/dL	20–40 mg/dL	30–40 mg/dL
Protein 100–500 mg/dL	100–500 mg/dL	50–100 mg/dL	100–500 mg/dL
White blood cells 1000–10,000/cc ³	100–400/cc ³	10–1,000/cc ³	100–500/cc ³
Gram's stain (+) 60–80% (untreated) 40–50% (previously treated)	AFB smear (+) in up to 40%	Smears are usually negative	Special stains needed: India ink (+) 75% AFB (+) 30%

180 8. Infectious Diseases

3 g IV q6 h or ceftriaxone 2–4 g q12–24 h). Vancomycin should be added to this regimen until culture and susceptibility results are available.

B. Pneumococcal Meningitis

1. Pneumococcal meningitis is still the most common cause of bacterial meningitis in adults. Underlying diseases: sickle cell disease, splenectomy and splenic dysfunction, hypogammaglobulinemia, alcoholism, head trauma (CSF fistula), and chronic pulmonary, hepatic, or renal disease.
2. Associated infections: pneumonia, otitis, bacteremia, endocarditis, mastoiditis.
3. Therapy: Ceftriaxone 4 g/d, Vancomycin 2 g/d should be given if there has been beta-lactam resistance noted locally.

C. Haemophilus Meningitis

1. Underlying disease (adults): alcoholism, compromised host defenses, head trauma.
2. Associated infections: pneumonia, sinusitis, otitis. Secondary cases can occur in close contacts.
3. Therapy: Cefotaxime (2 g IV q6 h), ceftriaxone (2 g IV q12 h), and chloramphenicol (500 mg PO q6 h for 2 weeks) as IV to PO switch.

D. Meningococcal Meningitis

1. Meningococcal meningitis is seen primarily in children, adolescents, and young adults. Secondary infection in close contacts can occur. Predisposing factors include complement defects.
2. Disseminated neisserial infection (often recurrent in persons with C₅-C₈ deficiency). Waterhouse-Frederickson syndrome is an acute, often fatal, syndrome of septic shock associated with massive adrenal necrosis, associated with bacteremia due to this organism. It requires early recognition, antibiotic therapy, and especially aggressive ICU/hemodynamic support.
3. Early antimicrobial therapy is needed. Ceftriaxone 2 g IV q12 h is the preferred IV therapy; as an alternative Meropenem 2 g q8 h can be administered.

E. *Listeria* Meningitis. *Listeria* is an important cause of bacteremia and meningitis, particularly in the elderly. Epidemiological history is important. Therapy is with ampicillin (2 g q4 h) or Meropenem (excellent in vitro activity against *Listeria*).

F. *Staphylococcus aureus* and *Staphylococcus epidermidis*. Infection with these organisms is common after neurosurgery and/or ventricular peritoneal shunt placement.

1. Therapy

- a. Methicillin sensitive: Cefotaxime (3 g IV q6 h) or cefepime (2 g IV q8 h).
- b. Methicillin resistant: Linezolid (600 mg IV q12 h) or vancomycin (2 g IV q12 h).
- c. An infected shunt may need to be removed early in the course of therapy if the patient is not responding. Repeat LP at 2–3 days is needed in order to reach this decision (persistent growth of organisms, despite adequate therapy).

G. Gram-Negative Bacilli

1. Infections with gram-negative bacilli are challenging to treat due to their high morbidity and mortality. Development of resistance can occur while on therapy (especially with *Enterobacter* sp.). Most organisms will respond to ceftriaxone, cefotaxime, or ceftazidime. For *Pseudomonas aeruginosa*, ceftazidime 2 g IV q8 h is the drug of choice. It should be given with gentamicin (1–2 mg/kg/8 h).

H. Complications of Bacterial Meningitis

1. Brain Abscess: Usually follows trauma, contiguous infection, hematogenous dissemination.
 2. Subdural Empyema: Primarily disease of the young but, in elderly, may complicate neurosurgery or subdural hematoma.
 3. Epidural Abscess: Usually accompanied by focal osteomyelitis and subdural empyema.
 4. All of the above are caused by mixed bacteria and usually require drainage, as well as prolonged IV antibiotic therapy.
- I. Herpes Meningitis/Encephalitis. Herpes meningitis/encephalitis is a devastating necrotizing type of encephalitis. Temporal spikes on electroencephalogram (EEG) are characteristic. Treatment is given with acyclovir 15 mg/kg q8 h (high dose) for 2 weeks. Careful attention to hydration is mandatory to avoid renal insufficiency.

■ VII. INFECTIONS IN PATIENTS WITH AIDS

A. Opportunistic infections are the most common causes of morbidity and mortality in patients with human immunodeficiency virus (HIV). Patients with CD4 cells <250 are at risk for developing severe infectious complications. Their approach is depicted in Table 8.3.

B. Summary of Current Therapeutic Approaches

1. Pulmonary Disease

a. Disease due to *Pneumocystis carinii* (*Pneumocystis jirovecii*) pneumonia (PCP) (Table 8.4)

b. Disease due to *M. Tuberculosis*

- (1). Start with at least four drugs, preferably five; INH 300 mg/d, rifampin 600 mg/d, pyrazinamide 15/kg/d, ciprofloxacin 750 mg PO bid, ethambutol 15–20 mg/kg/d.
- (2). If TB is sensitive to INH and/or rifampin, continue for 12–18 months (not in the ICU).
- (3). If TB is resistant to either or both drugs (INH and Rifampin), multiple drug resistant, continue with 5–6 drugs, and adjust according to sensitivities. Prognosis is very poor.
- (4). Follow liver function tests, initially weekly and later monthly.
- (5). If patient cannot use PO drugs, give IV INH and rifampin (same dose) and IM streptomycin (1 g/d).

c. Pulmonary Disease Due to *Histoplasma capsulatum*

- (1). Initiate therapy with amphotericin B at 0.8–1 mg/kg/d.
- (2). Search for other sites of involvement (i.e., bone marrow biopsy, lumbar puncture, chest x-ray, barium enema, and small bowel series).
- (3). Once the patient is stable, switch to fluconazole 200 mg PO bid.

d. Pulmonary Disease Due to *Legionella* sp.

- (1). Initiate therapy with erythromycin 3–4 g IV/d.
- (2). If the patient is not responding, add rifampin (600 mg/d) and/or ciprofloxacin 400 mg IV q12 h.

Table 8.3. Approach to HIV Patients With Opportunistic Infections

<i>Clinical presentation</i>	<i>Common organism*</i>	<i>Diagnostic procedure</i>
Pulmonary infiltrates	<i>P. carinii</i> (PCP); tuberculosis (TB); <i>Mycobacterium avium-intracellulare</i> (MAI); histoplasma, aerobic bacteria, legionella	BAL and/or lung biopsy; appropriate serologies
Seizures, headache, vertigo, facial palsy	Toxoplasma, cryptococcus MAI, herpes, CMV	MRI, head CT, LP, and appropriate serologies
Esophagitis	Candida, herpes, CMV, cryptosporidium	Endoscopy with biopsy and washings
Diarrhea	CMV, <i>cryptosporidium</i> , <i>Giardia</i> , MAI, <i>Isospora</i> , <i>C. difficile</i> , <i>salmonella</i>	Stool culture (initially) [†] AFB stain, colonoscopy, and biopsy
Persistent fever	MAI, <i>histoplasma</i> , TB, <i>cryptococcus</i>	CT abdomen [‡] Bone marrow Blood cultures with special stains (AFB)

* Remember that each one of these syndromes can be caused by non-infectious processes.

[†] Also useful to obtain fecal leukocytes for diagnosis of colitis.

[‡] Performed when fever persists despite initial evolution.

- e. Pulmonary Disease Due to Bacteria. Common Organisms are
 - (1). *Streptococcus pneumoniae*
 - (2). *Haemophilus influenzae*
 - (3). *Pseudomonas* (especially if sinusitis is present)
- f. Add Antibacterial Therapy Empirically on Admission
 - (1). Ticarcillin-clavulanic acid 3.1 g IV q6 h (will also cover anaerobes in the sinuses) or Piperacillin-tazobactam 3.375–4.5 g IV q6 h.
 - (2). Cefuroxime 1.5 g IV q8 h.
 - (3). Adjust when cultures and sensitivities become available.
- g. Pulmonary Disease Due to *M. avium-intracellulare*
 - (1). Ethambutol 15 mg/kg/d PO plus Clarithromycin 500 mg PO q12 h or Azithromycin 500 mg PO q24 h plus Rifampin.
 - (2). Treatment is given for at least 6 months after a negative sputum for MAI.
2. Enteric Pathogens in Patients With AIDS (See Table 8.5)
3. CNS Infections in AIDS
 - a. Cryptococcal Meningitis
 - (1). Acute: amphotericin B 0.7–1 mg/kg/d plus 5-fluorocytosine 25 mg/kg/d until the patient is stable or improving. Then switch to fluconazole 400 mg/d PO for 3 months.
 - (2). Maintenance: fluconazole 200–400 mg/d PO.

Table 8.4. Recommended Management for PCP

<i>Antibiotic</i>	<i>Mild to moderate</i>	<i>Severe (Usually in ICU)</i>
TMP-SMX	2–3 double-strength tabs PO tid for 14–21 days	5 mg/kg IV q6 h for 3 weeks
Pentamidine	3–4 mg/kg IV-IM qd	4 mg IV qd (once a day)
Trimethoprim- dapsone	Trimethoprim 100 mg PO tid Dapsone 100 mg PO Qid	?
Clindamycin- primaquine	Clindamycin 600 mg PO tid Primaquine 30 mg PO qid	900 mg IV q8 h for 3 weeks
Atovaquone	750 mg PO bid	For 2–3 weeks
Trimetrexate- leucovorin	Trimetrexate 45 mg/m ² /d IV for 21 days Leucovorin 30 mg/m ² IV q6 h for 10 days, and then PO q6 h for 14 days	Same as mild to moderate Solumedrol
Corticosteroids adjunctive therapy	?	40 mg IV or (equivalent PO bid) for 5 days Wean gradually over 10 days

b. Toxoplasmosis

- (1). Pyrimethamine 200 mg PO: loading dose followed by 75 mg PO daily with folinic acid 5 mg PO daily. (No IV presentation available.)
- (2). Sulfadiazine 1.5 g PO q6 h; plus Leucovorin 10 mg PO q24 h.

c. CMV (Including Retinitis)

- (1). Ganciclovir 5–10 mg/kg IV q12 h for 14 days (initial therapy)
- (2). Foscarnet 60 mg/kg IV q8 h for 14 days (initial therapy)
- (3). Lifelong suppressive therapy with valganciclovir 900 mg PO q24 h.

d. Herpes Simplex

- (1). Acyclovir 10–15 mg/kg IV q8 h

e. Syphilis

- (1). Crystalline penicillin 24 million U/d for 14 days
- (2). Ceftriaxone 2–4 g/d IV for 14 days

C. Important Facts to Remember in Treating HIV-Infected Patients in the ICU

1. Patients may have more than one infection at the same time.
2. Blood precautions should be instituted *immediately* to avoid unnecessary exposure.
3. Noninfectious processes (i.e., tumors) can mimic infections.

Table 8.5. Enteric Pathogens Commonly Seen in Patients With AIDS

<i>Organism</i>	<i>Antimicrobial agent</i>	<i>Direction of therapy (days)</i>
<i>G. lamblia</i>	Metronidazole 250 mg PO tid	5
<i>E. histolytica</i>	Metronidazole 750 mg tid and diiodohydroxyquin 650 mg PO tid	10
<i>Shigella</i> sp.	Fluoroquinolone IV or PO	3–7
<i>C. jejuni</i>	Ciprofloxacin 500 mg IV q12 h	7
<i>I. belli</i>	TMP-SMX 1 double-strength qd	14
CMV	Ganciclovir 5 mg/kg IV q12 h	30
<i>Herpes simplex</i>	Fluconazole 100 mg PO q24 h	14
Oral thrush	Ketoconazole 200–400 mg/d PO	10
Candida esophagitis	Fluconazole 200–400 mg/d IV	7–10

4. Patients require a full physical examination daily, including mouth, perirectal area, and eyes.
5. Superinfections are common (i.e., fungal and resistant bacteria).
6. When fever persists, consider lumbar puncture, liver, and bone marrow biopsy.
7. Obtain CD4-CD8 counts if not recently clone.
8. Code status needs to be established early.
9. Privacy of and respect toward patient are essential and mandatory.

■ VIII. INFECTIONS IN THE IMMUNOCOMPROMISED HOST

- A. The number of critically ill patients with impaired host defense mechanisms who are admitted to the ICU has dramatically increased in recent years. The knowledge and recognition of the basic deficiency enable the physician to predict the type and site of infection and allow the institution of early empiric therapy (see Tables 8.6 and 8.7).
- B. Immunocompromised patients admitted to the ICU should be categorized according to the time of acquisition of infection.

Hospital-acquired infections have different etiologic agents compared to those from the community, despite having the same basic immunologic defect.

Table 8.6. Selected Immunological Defects and Clinical Presentations

<i>Defect</i>	<i>Organism</i>	<i>Manifestations</i>
Phagocytes/ neutrophils (i.e., neutropenia)	Gram-positive cocci	Bacteremia
	Gram-negative bacilli	Sepsis
	<i>P. aeruginosa</i>	Tissue invasion,
	<i>Candida</i> sp.	Pneumonia, rhinocerebral
	<i>Aspergillus</i> sp.	and cutaneous
	<i>Mucor</i> sp., <i>Absidia</i> sp., <i>Fusarium</i> sp.	
Complement (i.e., C ₅ -C ₈ deficiency)	<i>Neisseria</i> sp.	Fulminant sepsis
	<i>Strep. pneumoniae</i>	Recurrent infection
	<i>H. influenzae</i>	Pneumonia
	<i>P. aeruginosa</i> <i>Brucella</i> sp.	Sepsis Recurrent fever
Antibody (i.e., IgA-IgG deficiency)	Gram-positive cocci	Pneumonia, otitis
	<i>H. influenzae</i>	Meningitis
	Herpes simplex	Encephalitis
	<i>Giardia lamblia</i>	Liver disease Diarrhea
Cell-mediated immunity (i.e., decrease in CD4 counts)	<i>Salmonella</i>	Diarrhea, sepsis
	<i>Listeria</i> sp.	Meningitis
	<i>Mycobacterium</i> sp.	Pneumonia
	<i>Nocardia</i> sp.	CNS/lungs
	<i>Cryptococcus neoformans</i>	Lungs
	<i>Histoplasma capsulatum</i>	Mucocutaneous
	<i>Coccidioides immitis</i>	Disseminated
	Herpes simplex	Pneumonia
	Varicella zoster	CNS/myocardium
	CMV	
	<i>P. carinii</i> <i>Strongyloides stercoralis</i> <i>Toxoplasma gondii</i>	

■ IX. ANTIMICROBIALS (See Table 8.8)

■ X. INFECTIOUS DISEASES “PEARLS” FOR ICU CARE

- A. Hand washing is the single most important procedure to prevent infection.
- B. Improving the nutritional status is of great importance for the outcome of infections.

Table 8.7. Common Clinical Presentations in Compromised Patients in the ICU

<i>Reason for admission</i>	<i>Common pathogen</i>	<i>Initial therapeutic approach</i>
Fever and neutropenia	Early: Gram-negative bacilli Gram-positive cocci (usually catheter related) Late: Resistant gram-negative bacilli Fungi (<i>Candida</i> sp., <i>Aspergillus</i> sp., <i>Fusarium</i> sp., <i>Mucor</i> sp.)	Early empiric therapy mandatory
Sepsis: post-splenectomy	Encapsulated bacterial organisms	Emergency institution of antibacterial therapy
Neurologic deterioration in patient with cell-mediated immune deficit	Intracellular organisms	Obtain CT, LP, and treat for bacteria and possibly for cryptococcus
Sepsis after solid organ transplantation	Immediately after surgery: Common local bacteria Not related to surgery: Virus, fungus, nocardia	Choose antibacterials according to site. Empiric therapy with extensive workup needed
Bilateral pulmonary infiltrates	Organism depends on causative defect	Treat empirically, and obtain BAL and biopsy (if possible)
Diabetic ketoacidosis	Bacterial organisms, mucormycosis, aspergillus	Treat for mixed bacterial infection
AIDS	Depends on sites of infection	See section on AIDS
Postoperative status and malnutrition	Antibiotic-resistant gram-negative bacilli Group D streptococci <i>Candida</i> sp.	Utilize broad-spectrum therapy

- C. Remove bladder catheters as soon as possible.
- D. Complete daily physical examination is mandatory.
- E. Gram's stain is the single best and least expensive test for early diagnosis of several infections (i.e., pulmonary, soft tissue, meningitis).
- F. Hypothermia, especially in elderly patients, suggests sepsis.
- G. Central catheters should be changed every 5–7 days.

Table 8.8. Selected Antimicrobials Commonly Used in the ICU

<i>Drug</i>	<i>Dose</i>	<i>Renal adjustment: Creatinine clearance</i> >80 50–10 <10	<i>Comments and side effects</i>
Aminoglycosides (i.e., gentamicin)	1–2 mg/kg IV q8 h	8–12 h 12 h 24–48 h	Monitor levels, renal function, and hearing
Broad-spectrum penicillin (i.e., piperacillin)	3–4 g IV q8 h	4–6 h 8–12 h 12–24 h	Monitor Na ⁺ and coagulation profile
Imipenem	500 mg to 1 g	6 h 12 h 24 h	Seizures, twitching, facial palsies
Cephalosporins (i.e., ceftazidime)	2 g IV q8 h	6–12 h 12 h 14 h	Penetrates CSF well
Aztreonam	2 g IV q8 h	6–12 h 12 h 24 h	Tolerated in penicillin-allergic patients
Vancomycin	1 g IV q12 h	6–12 h 2–3 d weekly	Monitor levels; interstitial nephritis
Oxacillin	6–12 g IV	4–6 h 6–8 h 8–12 h	Infuse in at least 1 h
Acyclovir	2–3 g/d IV	8 h 12–24 h 24–48 h	Monitor WBC and renal function
Ganciclovir	5 mg/kg IV	12 h 12 h 24–48 h	Monitor bone marrow depression
Clindamycin	600–900 mg IV	8 h 8 h 8 h	Diarrhea
Chloramphenicol	3–4 g IV or PO	6 h 6 h 6 h	Monitor bone marrow function

Table 8.8. *Continued*

<i>Drug</i>	<i>Dose</i>	<i>Renal adjustment: Creatinine clearance</i> >80 50–10 <10	<i>Comments and side effects</i>
Metronidazole	30 mg/kg/d IV or PO	6 h 6 h 6 h	Metallic taste
Amphotericin B	0.5–1 mg/kg IV once a day	24 h 24 h 48 h	Monitor renal function
Fluconazole	200–400 mg q12 h IV or PO	12 h 24 h 48 h	Interacts with anticoagulants
Itraconazole	2–4 g PO	12–24 h 24 h 24 h	
TMP-SMX	4–5 mg/kg IV (TMP) or higher	6–12 h 12–24 h 24–48 h	Monitor WBC; skin rash
Doxycycline	100–200 mg IV	12–24 h 12–24 h 12–24 h	Impairs neutrophil function
Levofloxacin	500–750 mg IV	24 h	Do not use in children
Azithromycin	500 mg IV	24 h	
Erythromycin	1–4 g/d IV	6 h 6 h 6 h	Preferably given through central IV line
Ribavirin	Aerosolized 190 mg/mL at 12.5 L/min over 18 h and the rest over 6 h. Repeat daily for 10 days	? ? ?	Requires special device for medication delivery

- H. Peripheral lines should be changed every 2–3 days.
- I. If prolonged ICU stay is expected, early placement of subcutaneous catheters is recommended.
- J. Patients with high fever require special attention to fluid management.
- K. Antibiotics interact with many other drugs. (See previous tables.)
- L. Drug-induced fever is not uncommon (common agents are antibiotics, H₂-antagonists, and phenytoin).
- M. Fever may last for several days, even when appropriate antimicrobial therapy has been instituted.
- N. Closely follow the clinical situation, which is more important than laboratory results.

■ XI. USEFUL FACTS AND FORMULAS

A. **Antibiotic Kinetics.** The pharmacokinetics of antibiotics depends on several factors.

The *volume of distribution* (V_D) of an antimicrobial is calculated as

$$V_D = \frac{A}{C_p}$$

where A = total amount of antibiotic in the body; C_p = antibiotic plasma concentration.

Repetitive dosing of antibiotics depends on the principle of *minimal plasma concentrations* (C_{\min}):

$$C_{\min} = \frac{D}{(V_D)(2^n - 1)}$$

where D = dose; n = dosing interval expressed in half-lives.

The *plasma concentration at steady state* (C_{ss}) of an antimicrobial can be estimated utilizing the following formula:

$$C_{ss} = \frac{\text{Dose per half - life}}{(0.693)(V_D)}$$

B. **Antibiotic Adjustments.** Renal dysfunction in critically ill patients is common. In those patients receiving aminoglycosides, dosage modification is required according to the *aminoglycoside clearance*:

$$\text{Aminoglycoside clearance} = (C_{cr})(0.6) + 10$$

where C_{cr} = creatinine clearance in mL/min.

Table 8.9. Selected Antibiotics Levels

<i>Antibiotic</i>	<i>Level (μg/mL)</i>	
Amikacin	Peak 20–30	Through <8
Gentamicin	Peak 10–20	Through 5–10
Chloramphenicol	Peak 5–10	Through <2
Tobramycin	Peak 5–10	Through <2
Vancomycin	Peak 30–40	Through 5–10

Table 8.10. Selected Atypical Mycobacteria

<i>Category</i>	<i>Runyon group</i>	<i>Mycobacterial species</i>
Photochromogens	I	<i>M. kansasii</i> <i>M. marinum</i>
Scotochromogens	II	<i>M. scrofulaceum</i>
Nonchromogens	III	<i>M. avium-intracellulare</i>
Rapid growers	IV	<i>M. fortuitum</i> <i>M. chelonae</i> ssp. <i>chelonae</i> <i>M. chelonae</i> ssp. <i>abscessus</i> <i>M. ulcerans</i>

To estimate the *creatinine clearance*, the *Cockcroft and Gault formula* is utilized:

$$C_{cr}(\text{mL}/\text{min}) = \frac{(140 - \text{age}) \times \text{weight}}{\text{Cr} \times 72}$$

where Cr = serum creatinine in mg/dL. Another modification to this formula is the *Spyker and Guerrant method*:

$$C_{cr}(\text{mL}/\text{min}) = \frac{(140 - \text{age}) \times (1.03 - 0.053 \times \text{Cr})}{\text{Cr}}$$

C. Antibiotic Levels. Some of the clinically employed antibiotic levels are depicted in Table 8.9.

D. Other Facts. Some of the atypical mycobacteria commonly encountered in the critical care setting are depicted in Table 8.10.