8

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, posttransplant, and the geriatric population are now regularly treated in the ICU with the consequent increase in morbidity, mortality, and cost.

From the infectious disease 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.

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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., and *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/day TMP.
(j) Doxycycline 100 mg IV q12 h.
(k) Rifampin 300 mg IV q12 h.
(l) Amphotericin B 0.6–1 mg/kg/day.
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 handwashing
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)
6. Adenovirus, respiratory syncytial virus, parainfluenza
7. *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.
5. Pulmonary consolidation and presence or absence of pleural effusion.

D. Uncommon Presentations in Patients Who Are $^{1}/_{4}$
1. Elderly
2. Immunocompromised (especially neutropenic)
3. Posttransplantation

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.
- Levofloxacin 750 mg IV daily
  or
- Ceftaroline 600 mg IV q 12 h (adjust in renal dysfunction patients)
  or
- Ceftriaxone 1 g IV plus azithromycin 500 mg IV
  1. *Streptococcus pneumonia* and *Haemophilus influenza*
     (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 H_5N_1)—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 which 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%). In severe cases, respiratory function may worsen during the second week of illness and progress to ARDS. This is a two-stage illness:

1. Prodrome (2–7 day): Includes fever, malaise, headache, and myalgias, and diarrhea may occur
2. Respiratory phase (8–12 day): Nonproductive cough and dyspnea that rapidly progress to respiratory failure

A rapid diagnosis of SARS can be made by reverse transcriptase PCR of respiratory tract, samples, and plasma early in illness.

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. PaO_2/FiO_2 no higher than 280 (in the absence of other pulmonary or cardiovascular diseases).
         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 five 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.* However, if the patient has acute adrenal insufficiency due to sepsis, steroid replacement therapy is a must.
   (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.

■ 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 the 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/mm^3
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 meningitis:* 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.

Table 8.2. CSF findings in meningitis according to etiology

Bacterial	*Tuberculous*	*Viral*	*Chronic*
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 1,000–10,000/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%

   (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.*
   (l) 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. meningitis*
   (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*, and *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 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/day and vancomycin 2 g/day 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 C_5–C_8 deficiency). Waterhouse–Friderichsen 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/day, rifampin 600 mg/day, pyrazinamide 15/kg/day, ciprofloxacin 750 mg PO bid, ethambutol 15–20 mg/kg/day.
         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 five to six 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/day).
      (c) Pulmonary Disease Due To *Histoplasma capsulatum*
         1. Initiate therapy with amphotericin B at 0.8–1 mg/kg/day.
         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.

Table 8.3. Approach to HIV patients with opportunistic infections

Clinical presentation	*Common organism*[a]	*Diagnostic procedure*
Pulmonary infiltrates	*P. carinii* (PCP); tuberculosis (TB); *Mycobacterium avium–intracellulare* (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, *Cryptosporidium, Giardia*, MAI, *Isospora*, *C. difficile, Salmonella*	Stool culture (initially)[b] AFB stain, colonoscopy, and biopsy
Persistent fever	MAI, *Histoplasma*, TB, *Cryptococcus*	CT abdomen[c] Bone marrow Blood cultures with special stains (AFB)

[a]Remember that each one of these syndromes can be caused by noninfectious processes
[b]Also useful to obtain fecal leukocytes for diagnosis of colitis
[c]Performed when fever persists despite initial evolution

Table 8.4. Recommended management for PCP

Antibiotic	*Mild to moderate*	*Severe (usually in ICU)*
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/day 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 Solu-Medrol
Corticosteroid adjunctive therapy	?	40 mg IV or (equivalent PO bid) for 5 days Wean gradually over 10 days

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

(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/day 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/day *plus* 5-fluorocytosine 25 mg/kg/day until the patient is stable or improving. Then switch to fluconazole 400 mg/day PO for 3 months.
2. Maintenance: Fluconazole 200–400 mg/day PO.

(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)

Table 8.5. Enteric pathogens commonly seen in patients with AIDS

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

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/day for 14 days
2. Ceftriaxone 2–4 g/day 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.
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 cloned.
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

Defect	*Organism*	*Manifestations*
Phagocytes/neutrophils (i.e., neutropenia)	Gram-positive cocci	Bacteremia
	Gram-negative bacilli	Sepsis
	P. aeruginosa	Tissue invasion, pneumonia, rhinocerebral and cutaneous
	Candida sp.	
	Aspergillus sp.	
	Mucor sp.	
	Absidia sp.	
	Fusarium sp.	
Complement (i.e., C_5–C_8 deficiency)	*Neisseria* sp.	Fulminant sepsis
	Strep. pneumoniae	Recurrent infection
	H. influenzae	Pneumonia
	P. aeruginosa	Sepsis
	Brucella sp.	Recurrent fever
Antibody (i.e., IgA-IgG deficiency)	Gram-positive cocci	Pneumonia, otitis
	H. influenzae	Meningitis
	Herpes simplex	Encephalitis
	Giardia lamblia	Liver disease
		Diarrhea
Cell-mediated immunity (i.e., decrease in CD4 counts)	*Salmonella*	Diarrhea, sepsis
	Listeria sp.	Meningitis
	Mycobacterium sp.	Pneumonia
	Nocardia sp.	CNS/lungs
	Cryptococcus neoformans	Lungs
	Histoplasma capsulatum	Mucocutaneous
	Coccidioides immitis	Disseminated
	Herpes simplex	Pneumonia
	Varicella zoster	CNS/myocardium
	CMV	
	P. *carinii*	
	Strongyloides stercoralis	
	Toxoplasma gondii	

Table 8.7. Common clinical presentations in compromised patients in the ICU

Reason for admission	*Common pathogen*	*Initial therapeutic approach*
Fever and neutropenia	Early: Gram-negative bacilli and gram-positive cocci (usually catheter related) Late: Resistant gram-negative bacilli Fungi (*Candida* sp., *Aspergillus* sp., *Fusarium* sp., *Mucor* sp.)	Early empiric therapy mandatory
Sepsis: postsplenectomy	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 *Candida* sp.	Utilize broad-spectrum therapy

■ IX. ANTIMICROBIALS (See Table 8.8)

Table 8.8. Selected antimicrobials commonly used in the ICU

Drug	*Dose*	*Renal adjustment: creatinine clearance* >80 50–10 <10	*Comments and side effects*
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 days 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/day 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

(continued)

Table 8.8. (continued)

Drug	*Dose*	*Renal adjustment: creatinine clearance >80 50–10 <10*	*Comments and side effects*
Metronidazole	30 mg/kg/day 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 q12 h IV or PO	200–400 mg	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/day 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

■ X. INFECTIOUS DISEASES: "PEARLS" FOR ICU CARE

A. Handwashing is the single most important procedure to prevent infection.
B. Improving the nutritional status is of great importance for the outcome of infections.
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.
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, H_2-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 and 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.

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

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

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

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

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.

Table 8.9. Selected antibiotic levels

Antibiotic	*Level (μg/mL)*	
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

Category	*Runyon group*	*Mycobacterial species*
Photochromogens	I	*M. kansasii*
		M. marinum
Scotochromogens	II	*M. scrofulaceum*
Nonchromogens	III	*M. avium–intracellulare*
Rapid growers	IV	*M. fortuitum* *M. chelonae* ssp. *chelonae M. chelonae* ssp. *abscessus M. ulcerans*