Chapter 44: Respiratory Tract Infections, Lower

ACUTE BRONCHITIS

- Bronchitis is frequently classified as either acute or chronic. Acute bronchitis is characterized by inflammation of the epithelium of the large airways resulting from infection or exposure to irritating environmental triggers (eg, air pollution and cigarette smoke).
- Acute bronchitis occurs year-round, but more commonly during the winter months. Viral infections, cold, damp climates, and/or the presence of high concentrations of irritating environmental triggers such as air pollution or cigarette smoke may precipitate attacks.
- Respiratory viruses are the predominant infectious agents associated with acute bronchitis. The most common infecting agents include influenza A and B, respiratory syncytial virus (RSV), and parainfluenza virus. Bacterial pathogens are involved in a minority of cases and involve pathogens often associated with community-acquired pneumonia (CAP).
- Infection of the trachea and bronchi causes hyperemic and edematous mucous membranes and an increase in bronchial secretions. Destruction of respiratory epithelium can range from mild to extensive and may affect bronchial mucociliary function. In addition, the increase in desquamated epithelial cells and bronchial secretions, which can become thick and tenacious, further impairs mucociliary activity. Recurrent acute respiratory infections may be associated with increased airway hyperreactivity and possibly the pathogenesis of asthma and chronic obstructive lung disease.

Clinical Presentation

- Acute bronchitis usually begins as an upper respiratory infection with nonspecific complaints. Cough is the hallmark of acute bronchitis and occurs early. The onset of cough may be insidious or abrupt, and the symptoms persist despite resolution of nasal or nasopharyngeal complaints; cough may persist for up to 3 or more weeks. Frequently, the cough initially is nonproductive, but then progresses, yielding mucopurulent sputum.
- Fever, when present, rarely exceeds 39°C (102.2°F) and appears most commonly with adenovirus, influenza virus, and *Mycoplasma pneumoniae* infections.
- Bacterial cultures of expectorated sputum are generally of limited utility because of the inability to avoid normal nasopharyngeal flora by the sampling technique. For the vast majority of affected patients, an etiologic diagnosis is unnecessary and will not change the prescribing of routine supportive care for the management of these patients.

Treatment

- Goals of Treatment: The goal is to provide comfort to the patient and, in the unusually severe case, to treat associated dehydration and respiratory compromise.
- The treatment of acute bronchitis is symptomatic and supportive. Reassurance and antipyretics alone are often sufficient. Bedrest for comfort may be instituted as desired. Patients should be encouraged to drink fluids to prevent dehydration and possibly to decrease the viscosity of respiratory secretions.
- **Aspirin** or **acetaminophen** (650 mg in adults or 10–15 mg/kg per dose in children with a maximum daily adult dose of <4 g and 60 mg/kg for children) or **ibuprofen** (200–800 mg in adults or 10 mg/kg per dose in children with a maximum daily dose of 3.2 g for adults and 40 mg/kg for children) is administered every 6–8 hours.

- In children under 19 years of age, aspirin should be avoided and acetaminophen used as the preferred agent because of the possible association between aspirin use and the development of Reye syndrome.
- In otherwise healthy patients, no meaningful benefits have been described with the use of oral or aerosolized β_2-receptor agonists and/or oral or aerosolized corticosteroids.
- Persistent, mild cough, which may be bothersome, may be treated with **dextromethorphan**; more severe coughs may require intermittent **codeine** or other similar agents. Codeine is no longer recommended for use in pediatric patients.
- Routine use of antibiotics in the treatment of acute bronchitis is strongly discouraged; however, in patients who exhibit persistent fever or respiratory symptomatology for more than 5–7 days, the possibility of a concurrent bacterial infection should be suspected.
- When possible, antibiotic therapy is directed toward anticipated respiratory pathogen(s) (ie, *Streptococcus pneumoniae* and *Haemophilus influenzae*).
- *M. pneumoniae,* if suspected by history or if confirmed by culture, serology, or PCR may be treated with **azithromycin**. Also, a fluoroquinolone with activity against these pathogens (**levofloxacin** or **moxifloxacin**) may be used empirically, but reserved for patients not responding adequately to supportive care and deemed at risk of associated complications.
- See Chapter 42 for recommendations to treat influenza.

CHRONIC BRONCHITIS

- Chronic bronchitis is a result of several contributing factors, including cigarette smoking; exposure to occupational dusts, fumes, and environmental pollution; host factors (eg, genetic factors); and bacterial or viral infections.
- Chronic bronchitis is defined clinically as the presence of a chronic cough productive of sputum lasting more than 3 consecutive months of the year for 2 consecutive years without an underlying etiology of bronchiectasis or tuberculosis.

Clinical Presentation

- The hallmark of chronic bronchitis is a cough that may range from a mild to severe, incessant coughing productive of purulent sputum. Expectoration of the largest quantity of sputum usually occurs upon arising in the morning, although many patients expectorate sputum throughout the day. The expectorated sputum is usually tenacious and can vary in color from white to yellow-green.
- On physical examination, patients with advanced disease may have cyanosis and clubbing of digits.
- Chest auscultation usually reveals inspiratory and expiratory rales, rhonchi, and mild wheezing with an expiratory phase that is often prolonged. There may be hyperresonance on percussion with obliteration of the area of cardiac dullness. Normal vesicular breathing sounds are diminished.
- Chest radiograph may show increased anteroposterior diameter of the thoracic cage (barrel chest) and depressed diaphragm with limited mobility.
- Laboratory findings may include erythrocytosis (ie, increased hematocrit) in advanced disease.
- Pulmonary function tests may reveal decreased vital capacity and prolonged expiratory flow.
- The diagnosis of chronic bronchitis is based primarily on clinical assessment and history.
- The most common bacterial isolates (expressed in percentages of total cultures) identified from sputum culture in patients experiencing an acute exacerbation of chronic bronchitis are given in **Table 44-1**.

TABLE 44-1

Common Bacterial Pathogens Isolated from Sputum of Patients with Acute Exacerbation of Chronic Bronchitis

Pathogen	Percent of Cultures
H. influenzae[a,b]	45
M. catarrhalis[a]	30
S. pneumoniae[c]	20
E. coli, *Enterobacter* species, *Klebsiella* species, *P. aeruginosa*	5

[a]Often β-lactamase positive.

[b]Vast majority are nontypeable strains.

[c]More than 25% of strains may have intermediate or high resistance to penicillin.

Treatment

- Goals of Treatment: Reduce the severity of symptoms, to ameliorate acute exacerbations, and to achieve prolonged infection-free intervals.
- A complete occupational/environmental history for the determination of exposure to noxious and irritating gases, as well as cigarette smoking must be assessed.
- Attempts must be made to reduce the patient's exposure to known bronchial irritants (eg, reduce smoking and workplace pollution).
- Pulmonary rehabilitation programs (including exercise-training program with resistance and aerobic exercise) individualized for patients with chronic respiratory impairment can improve quality of life by optimizing each patient's physical and social performance and autonomy.
- Chest physiotherapy (pulmonary toilet) can be instituted. Humidification of inspired air may promote the hydration (liquefaction) of tenacious secretions, allowing for more effective sputum production. The use of mucolytic aerosols (eg, *N*-acetylcysteine and deoxyribonuclease) is of questionable therapeutic value.
- For patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), combination therapy with a long-acting β_2-agonist and inhaled corticosteroid led to decreased exacerbations and rescue medication use while it also improved quality of life, lung function, and symptom scores compared with long-acting β_2–agonist monotherapy.

Pharmacologic Therapy

- Patients should be up-to-date with vaccinations, particularly pneumococcal and an annual influenza vaccine.
- For patients who consistently demonstrate clinical limitation in airflow, a therapeutic challenge of a short-acting β_2–agonist bronchodilator (eg, as **albuterol** aerosol) should be considered. Regular use of a long-acting β-receptor agonist (LABA) aerosol (eg, **salmeterol** and **formoterol**) in responsive patients are more effective and probably more convenient than short-acting β_2-receptor agonists. Chronic inhalation of a combination LABA and a corticosteroid (eg, **salmeterol-fluticasone** and **formoterol-mometasone**) improved pulmonary function and quality of life.
- Long-term use of aerosolized corticosteroid is associated with increased side effects including hoarseness, sore throat, thrush, pneumonia, and osteoporosis; however, caution should be exercised in withdrawing inhaled glucocorticoid administration in patients with severe COPD receiving

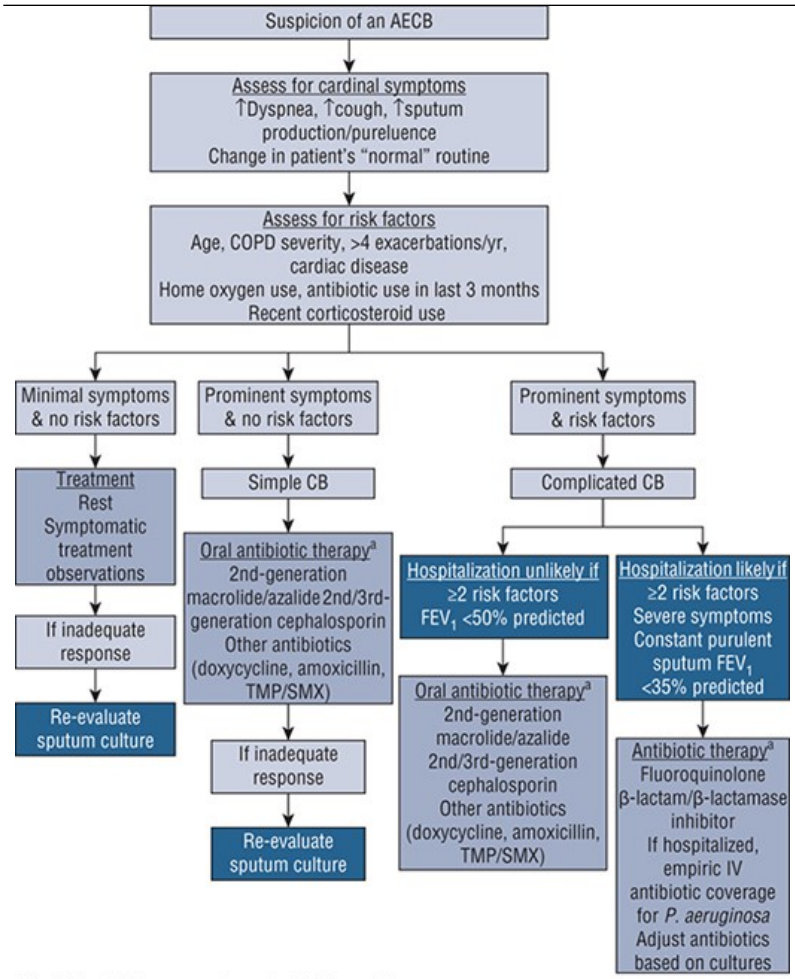
triple inhalation therapy.

- Long-term inhalation of **ipratropium** (or **tiotropium**) decreases the frequency of cough, severity of cough, and volume of expectorated sputum.
- Inhaled long-acting muscarinic antagonists (LAMAs) alone or more frequently, in combination with a LABA, improve lung function and symptom control and reduce the number of acute exacerbations.
- Long-acting **theophylline** remains an effective "add on" therapy, particularly for severe chronic bronchitis/COPD, due to the drug's beneficial effects of bronchodilation, improved ciliary function and increased beat frequency, possibly increased mucus hydration, and low cost.
- The role of **roflumilast** in chronic lung disease is evolving but many guidelines suggest its greatest use is in the more severely affected patients.
- Use of antimicrobials for treatment of chronic bronchitis has been controversial but is becoming more accepted. The goal is to select the most effective antibiotic drug for the patient based on their history of previous exacerbations and response to drug therapy (see **Fig. 44-1**).
- The Anthonisen criteria can be used to determine if antibiotic therapy is indicated. The patient will most likely benefit from antibiotic therapy if two or three of the following are present: (1) increase of shortness of breath, (2) increase in sputum volume, or (3) production of purulent sputum.
- Selection of antibiotics should consider that up to 30%–40% of *H. influenzae* and 95%–100% of *Moraxella catarrhalis* are β-lactamase producers; up to 40% of *S. pneumoniae* demonstrate intermediate susceptibility or resistance to penicillin, with 20% being highly resistant.
- Antibiotics commonly used in the treatment of these patients and their respective adult starting doses are outlined in **Table 44-2**. Duration of symptom-free periods may be enhanced by antibiotic regimens using the upper limit of the recommended daily dose for 5–7 days.

FIGURE 44-1

Clinical algorithm for the diagnosis and treatment of chronic bronchitic patients with an acute exacerbation incorporating the principles of the clinical classification system.

(AECB, acute exacerbation of chronic bronchitis; COPD, chronic obstructive pulmonary disease; CB, chronic bronchitis; TMP/SMX, trimethoprim/sulfamethoxazole.)



[a]See Table 44–2 for commonly used antibiotics and doses.

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 44-2

Oral Antibiotics Commonly Used for the Treatment of Acute Respiratory Exacerbations in Chronic Bronchitis

Antibiotic	Brand Name	Usual Adult Oral Dose (mg)	Dose Schedule (Doses/Day)
Preferred drugs			
Ampicillin	–	250–500	3–4
Amoxicillin	–	500–875	2–3
Amoxicillin–clavulanate	Augmentin®	500–875	2–3
Ciprofloxacin	Cipro®	500–750	2
Levofloxacin	Levaquin®	500–750	1
Moxifloxacin	Avelox®	400	1
Doxycycline	Monodox®	100	2
Minocycline	Minocin®	100	2
Tetracycline HCl	–	500	4
Trimethoprim–sulfamethoxazole	Bactrim DS®/Septra DS®	1 DS	2
Supplemental drugs			
Azithromycin	Zithromax®	250–500	1
Erythromycin	Ery-Tab®/Erythrocin®	500	4
Clarithromycin	Biaxin®	250–500	2
Cephalexin	Keflex®	500	4

DS, double-strength tablet (160-mg trimethoprim/800-mg sulfamethoxazole).

BRONCHIOLITIS

- Bronchiolitis is an acute viral infection of the lower respiratory tract of infants that affects ~50% of children during the first year of life and 100% by 2 years.
- RSV is the most common cause of bronchiolitis, accounting for up to 75% of all cases. Other detectable viruses include parainfluenza, adenovirus, and influenza. Bacteria serve as secondary pathogens in a minority of cases.

Clinical Presentation

- The most common clinical signs of bronchiolitis. A prodrome suggesting an upper respiratory tract infection, usually lasting from 1–4 days, precedes the onset of clinical symptoms. As a result of limited oral intake due to coughing combined with fever, vomiting, and diarrhea, infants are frequently dehydrated.
- The diagnosis of bronchiolitis is based primarily on history and clinical findings. Identification of *respiratory syncytial virus* by PCR should be available routinely from most clinical laboratories, but its relevance to the clinical management of bronchiolitis remains obscure and routine testing is not recommended.

Signs and Symptoms

- Prodrome with irritability, restlessness, and mild fever.
- Cough and coryza.
- Vomiting, diarrhea, noisy breathing, and increased respiratory rate as symptoms progress.
- Labored breathing with retractions of the chest wall, nasal flaring, and grunting.

Physical Examination

- Tachycardia and respiratory rate of 40–80 per minute in hospitalized infants.
- Wheezing and inspiratory rales.
- Mild conjunctivitis in one-third of patients.
- Otitis media in 5%–10% of patients.

Laboratory Tests

- Peripheral white blood cell count normal or slightly elevated.
- Abnormal arterial blood gases (hypoxemia and, rarely, hypercarbia).

Treatment

- Bronchiolitis is a self-limiting illness and usually requires no therapy (other than reassurance, antipyretics, and adequate fluid intake) unless the infant is hypoxic or dehydrated. Otherwise healthy infants can be treated for fever, provided generous amounts of oral fluids, and observed closely for evidence of respiratory deterioration.
- In severely affected children, the mainstays of therapy for bronchiolitis are oxygen therapy and intravenous (IV) fluids.
- Aerosolized β-adrenergic therapy appears to offer little benefit for the majority of patients but may be useful in the child with a predisposition toward bronchospasm. The routine use of systemically administered corticosteroids is not recommended.
- The American Academy of Pediatrics guidelines support the use of nebulized hypertonic saline (eg, 3% saline) for the treatment of bronchiolitis in hospitalized infants and children.
- The American Academy of Pediatrics does not recommend the routine use of **ribavirin** in children with bronchiolitis and most experts recommend reserving use of ribavirin for severely ill patients. Use of ribavirin requires special equipment (small-particle aerosol generator) and specifically trained personnel for administration via oxygen hood or mist tent.

PNEUMONIA

- Pneumonia remains one of the most common causes of severe sepsis and infectious cause of death in children and adults in the United States, with a mortality rate as high as 50%. **Table 44-3** presents the classification of pneumonia and risk factors.

TABLE 44-3

Pneumonia Classifications and Risk Factors

Type of Pneumonia	Definition	Risk Factors
Community-acquired pneumonia (CAP)	Pneumonia developing outside the hospital or <48 hours after hospital admission	• Age >65 years • Diabetes mellitus • Asplenia • Chronic cardiovascular, pulmonary, renal, and/or liver disease • Smoking and/or alcohol abuse
Hospital-acquired pneumonia (HAP)	Pneumonia developing >48 hours after hospital admission	• Witnessed aspiration • COPD, ARDS, or coma • Administration of antacids, H_2-antagonists, or proton pump inhibitor • Supine position • Enteral nutrition, nasogastric tube • Reintubation, tracheostomy, or patient transport • Head trauma, ICP monitoring • Age >60 years • MDR risk (eg, MRSA, MDR *Pseudomonas*) if IV antibiotic use within 90 days
Ventilator-associated pneumonia (VAP)	Pneumonia developing >48 hours after endotracheal intubation	• Same as hospital acquired • MDR risk with IV antibiotics in past 90 days, septic shock, ARDS preceding VAP, acute renal replacement therapy preceding VAP, or 5+ days of hospitalization preceding VAP

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; ICP, intracranial pressure; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; VAP, ventilator-associated pneumonia.

Pathophysiology

- Respiratory pathogens enter the lower respiratory tract by one of three routes: (1) direct inhalation of infectious droplets; (2) aspiration of oropharyngeal contents; or (3) hematogenous spread from another infection site.
- Pneumonia is caused by a variety of viral and bacterial pathogens.
- Pneumonia is categorized as either community-acquired or hospital-acquired. Pneumonia onset outside of the hospital or within 48 hours of hospital admission have CAP. Pneumonia onset in the hospital after at least 48 hours of hospitalization have hospital-acquired pneumonia (HAP). Pneumonia onset following 48 hours of endotracheal intubation have ventilator-associated pneumonia (VAP).
- The causative pathogen in CAP in adult patients is most commonly viral, with human rhinovirus and influenza most common. The most prominent bacterial pathogen causing CAP in otherwise healthy adults is *S. pneumoniae* accounting for up to 35% (12%–68%) of all acute cases. Other common bacterial causes are *H. influenzae*, the "atypical" pathogens including *M. pneumoniae, Legionella* species, *C. pneumoniae*.

- Viral pathogens (RSV and human rhinovirus) predominate in CAP among pediatric patients with a prevalence of up to 80% in those less than 2 years of age.
- HAP is predominantly caused by gram-negative aerobic bacilli and *S. aureus* and is much more likely to be caused by a multidrug-resistant isolate. *P. aeruginosa* and *Acinetobacter* spp. are the most common cause of HAP (about 25%–45%) while *K. pneumoniae* and *E. coli* are also common.
- Aspiration pneumonia has a bacteriology similar to CAP or HAP and anaerobic pathogens are less common and typically seen in patients with specific risk factors such as periodontal disease or alcoholism.

Clinical Presentation

Gram-Positive and Gram-Negative Bacterial Pneumonia

- Classifications of pneumonia are given in **Table 44-3**.
- Blood cultures and noninvasive sputum cultures (ie, expectorated sputum, sputum induction, or nasotracheal suctioning) are recommended for all adult patients with suspected HAP or VAP.
- The chest radiograph and sputum examination and culture are the most useful diagnostic tests for gram-positive and gram-negative bacterial pneumonia. Typically, the chest radiograph reveals a dense lobar or lobular consolidated infiltrates.
- Signs and symptoms: Abrupt onset of fever, chills, dyspnea, and productive cough; Rust-colored sputum or hemoptysis; Pleuritic chest pain; and Dyspnea.
- Physical examination findings: Tachypnea and tachycardia; dullness to percussion; increased tactile fremitus, whispered pectoriloquy, and egophony; Chest wall retractions and grunting respirations; Diminished breath sounds over affected area; and Inspiratory crackles during lung expansion.
- Chest radiograph findings: Dense lobar or segmental infiltrate.
- Laboratory tests: Leukocytosis with predominance of polymorphonuclear cells. Low oxygen saturation on arterial blood gas or pulse oximetry.

Atypical Pneumonia (*M. Pneumoniae and C. Pneumoniae*)

- Pneumonia caused by the atypical pathogens, such as *M. pneumoniae* and *C. pneumoniae*, often has a more gradual onset and overall lower severity compared with other bacterial causes. Patients with atypical pneumonia also commonly have extrapulmonary, constitutional symptoms.

Hospital-Acquired Pneumonia

- The strongest predisposing factor for HAP is mechanical ventilation. Factors predisposing patients to HAP include severe illness, long duration of hospitalization, supine positioning, witnessed aspiration, coma, acute respiratory distress syndrome, patient transport, and prior antibiotic exposure. HAP is exacerbated by the wide use of acid-reducing drugs (eg, H_2-receptor blocking agents and proton pump inhibitors) which increases the pH of gastric secretions and may promote the proliferation of microorganisms in the upper GI tract.
- The diagnosis of nosocomial pneumonia is usually established by the presence of a new infiltrate on chest radiograph, fever, worsening respiratory status, and the appearance of thick, neutrophil-laden respiratory secretions.

Treatment

- Goal of Treatment: Eradication of the offending organism and complete clinical cure. Secondary goals include minimization of the unintended consequences of therapy, including toxicities and selection for secondary infections such a *Clostridioides difficile* or antibiotic-resistant pathogens, and minimizing costs through outpatient and oral therapy when the patient's severity of illness and clinical considerations permit.
- The supportive care of the patient with pneumonia includes the use of humidified oxygen for hypoxemia, fluid resuscitation, administration of

bronchodilators (albuterol) when bronchospasm is present, and chest physiotherapy with postural drainage if there is evidence of retained secretions.

- Important therapeutic adjuncts include adequate hydration (by IV route if necessary), optimal nutritional support, and fever control.
- Severity scoring systems such as CURB-65 are used to guide treatment. For CURB-65, patients receive 1 point for each criterion present: **C**onfusion, **U**remia (BUN >20 mg/dL [7.1 mmol/L]), **R**espiratory rate ≥30 breaths/min, **B**lood pressure (systolic <90 mm Hg, diastolic ≤60 mm Hg), age ≥65 years. Patients with CURB-65 score <2 are generally candidates for outpatient treatment. Patients with a score of 2 are typically admitted to the general ward of the hospital with ICU admission considered for patients with scores ≥3.
- The treatment of bacterial pneumonia initially involves the empiric use of a relatively broad-spectrum antibiotic therapy effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained. Therapy should be narrowed to cover specific pathogens once the results of cultures are known. The minimum duration of therapy for CAP is 5 days although CAP is commonly treated for 7–10 days.
- Appropriate empiric choices for the treatment of bacterial pneumonias relative to a patient's underlying disease are shown in **Table 44-4** for adults and **Table 44-5** for children. Dosages for antibiotics to treat pneumonia are provided in **Table 44-6**. Pathogen-directed antimicrobial therapy for common pneumonia pathogens in adult patients is given in **Table 44-7**.
- Antibiotic concentrations in respiratory secretions in excess of the pathogen minimum inhibitory concentration (MIC) are necessary for successful treatment of pulmonary infections.

TABLE 44-4

Evidence-Based Empirical Antimicrobial Therapy for Pneumonia in Adults[a]

Clinical Setting and/or Patient Characteristics	Usual Pathogens	Empirical Therapy
Outpatient/Community-acquired		
No at-risk comorbidity (diabetes, heart/lung/liver/renal disease, alcoholism, malignancy, asplenia) AND no antimicrobial use in past 3 months	*S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M. catarrhalis*	Macrolide[b] OR doxycycline
At-risk comorbidity (diabetes, heart/lung/liver/renal disease, alcoholism, malignancy, aspelnia) OR immunosuppressive condition/drugs OR antimicrobial use in past 3 months	*S. pneumoniae* (including drug-resistant), *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M. catarrhalis*	Antipneumococcal fluoroquinolone[c] OR β-lactam[d] + EITHER macrolide[b] OR doxycycline
Regions with more than 25% rate of macrolide-resistant *S. pneumoniae*	*S. pneumoniae* (including drug-resistant), *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M.*	Antipneumococcal fluoroquinolone[c] OR β-lactam[d] + EITHER macrolide[b] OR doxycycline

	catarrhalis	
Inpatient/Community-acquired		
Non-ICU	*S. pneumoniae* (including drug-resistant), *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* spp.	Antipneumococcal fluoroquinolone[c] OR β-lactam[e] + EITHER macrolide[b] OR doxycyline
ICU	*S. pneumoniae* (including drug-resistant), *S. aureus*, *Legionella* spp., gram-negative bacilli, *H. influenzae* If MRSA suspected If *P. aeruginosa* suspected If influenza suspected	β-lactam[e] + EITHER azithromycin OR Antipneumococcal fluoroquinolone[c] Add vancomycin or linezolid to above regimen Antipseudomonal, antipneumococcal β-lactam[f] + EITHER (1) ciprofloxacin OR (2) levofloxacin OR (3) aminoglycoside + azithromycin OR (4) aminoglycoside + moxifloxacin Add oral oseltamivir or intravenous peramivir (when oral medications not possible)
Hospital-acquired pneumonia		
Low mortality risk[g] AND No MDR HAP[h] risk factors AND Local MRSA prevalence <20%	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MSSA	Piperacillin–tazobactam, cefepime, levofloxacin, imipenem OR meropenem
Low mortality[g] risk AND No MDR HAP[h] risk factors AND Local MRSA ≥20% OR unknown	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Piperacillin–tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, OR aztreonam + vancomycin OR linezolid
High mortality risk[g] OR MDR risk factor(s)[h]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Double cover *P. aeruginosa* with two of the following, avoiding two from the same class: piperacillin–tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam, gentamicin, tobramycin, amikacin + vancomycin OR linezolid
Ventilator-associated pneumonia		
No MDR VAP risk factors[i] AND Local MRSA and gram-negative bacilli-resistance both <10%[j]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MSSA	Piperacillin–tazobactam, cefepime, levofloxacin, imipenem OR meropenem

No MDR VAP risk factors[i] AND Local MRSA ≥10% or unknown AND gram-negative bacilli-resistance <10%[j]	Non-fermenting gram-negative bacilli, enteric gram-negative bacilli, MRSA	Piperacillin–tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, OR aztreonam + vancomycin OR linezolid
MDR VAP risk factor(s)[i] OR local MRSA and gram-negative bacilli-resistance >10%[j] or unknown	MDR non-fermenting gram-negative bacilli, MDR enteric gram-negative bacilli, MRSA	Double cover *P. aeruginosa* with two of the following, avoiding two from the same class : piperacillin–tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam, gentamicin, tobramycin, amikacin, colistin, polymyxin B + vancomycin OR linezolid
Aspiration pneumonia		
Community-acquired Hospital-acquired	*S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae* *S. aureus*, *P. aeruginosa* enteric gram-negative bacilli *If anaerobes suspected*	Treat as above for CAP Treat as above for HAP Treat as above for CAP/HAP using antibiotic with anaerobic coverage OR add clindamycin OR metronidazole

[a]See the section Selection of Antimicrobial Agents.

[b]Macrolide: erythromycin, clarithromycin, and azithromycin.

[c]Antipneumococcal fluoroquinolone: levofloxacin and moxifloxacin.

[d]Infectious Diseases Society of America recommended outpatient β-lactams: high-dose amoxicillin or amoxicillin/clavulanate preferred, cefpodoxime, cefuroxime, ceftriaxone (intramuscular) alternatives.

[e]Infectious Diseases Society of America recommended inpatient β-lactams: ceftriaxone (intravenous), cefotaxime, ampicillin.

[f]Infectious Diseases Society of America recommended antipneumococcal, antipseudomonal β-lactams: piperacillin/tazobactam, cefepime, meropenem, imipenem.

[g]Indicators of high HAP mortality risk: need for ventilator support due to pneumonia; septic shock.

[h]MDR HAP risk factors: receipt of IV antibiotics in previous 90 days; structural lung disease (bronchiectasis or cystic fibrosis).

[i]MDR VAP risk factors: receipt of IV antibiotics in previous 90 days; septic shock; acute respiratory distress syndrome preceding VAP; ≥5 days hospitalization preceding VAP; acute renal replacement therapy preceding VAP.

[j]Resistance to antibiotic being considered for empiric gram-negative monotherapy.

MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

TABLE 44-5

Empirical Antimicrobial Therapy for Pneumonia in Pediatric Patients[a]

Clinical Setting and/or Patient Characteristics	Usual Pathogen(s)	Empirical Therapy
Outpatient/Community-acquired		
<1 month	Group B *Streptococcus*, *H. influenzae* (nontypeable), *E. coli*, *S. aureus*, *Listeria* CMV, RSV, adenovirus	Ampicillin–sulbactam, cephalosporin,[b] carbapenem[c] Ribavirin for RSV[d]
1–3 months	*C. pneumoniae*, possibly *Ureaplasma*, CMV, *Pneumocystis carinii* (afebrile pneumonia syndrome) *S. pneumoniae*, *S. aureus*	Macrolide/azalide,[e] trimethoprim–sulfamethoxazole Semisynthetic penicillin[f] OR cephalosporin[g]
Preschool-aged children	Viral (rhinovirus, RSV, influenza A and B, parainfluenzae, adenovirus, human metapneumovirus, coronavirus)	Antimicrobial therapy not routinely required
Previously healthy, fully immunized infants and preschool children with suspected mild–moderate bacterial CAP	*S. pneumonia* *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin[b,g] Macrolide/Azalide or fluoroquinolone
Previously healthy, fully immunized school-aged children and adolescents with mild–moderate CAP	*S. pneumonia* *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin,[b,g] or fluoroquinolone Macrolide/Azalide, fluoroquinolone, or tetracycline
Moderate–severe CAP during influenza virus outbreak	Influenza A and B, other viruses	Oseltamivir or zanamivir
Inpatient/Community-acquired		
Fully immunized infants and school-aged children	*S. pneumonia* CA-MRSA *M. pneumoniae*, *C. pneumoniae*	Ampicillin, penicillin G, cephalosporin[b] β-Lactam + vancomycin/clindamycin β-Lactam + macrolide/fluoroquinolone/doxycycline
Not fully immunized infants and children; regions with invasive penicillin-resistant pneumococcal strains; patients with life-threatening infections	*S. pneumoniae*, PCN-resistant MRSA *M. pneumoniae*, other atypical pathogens	Cephalosporin[b] Add vancomycin/clindamycin Macrolide/azalide[e] + β-lactam/doxycycline/fluoroquinolone

[a]See the section Selection of Antimicrobial Agents.

[b]Third-generation cephalosporin: ceftriaxone and cefotaxime. Note that cephalosporins are not active against *Listeria*.

[c]Carbapenem: imipenem–cilastatin and meropenem.

[d]See text for details regarding possible ribavirin treatment for RSV infection.

[e]Macrolide/Azalide: erythromycin and clarithromycin/azithromycin.

[f]Semisynthetic penicillin: nafcillin and oxacillin.

[g]Second-generation cephalosporin: cefuroxime and cefprozil.

CAP, community-acquired pneumonia; CMV, cytomegalovirus; MRSA, methicillin resistant *Staphylococcus aureus*; RSV, respiratory syncytial virus.

TABLE 44-6

Antibiotic Doses for Treatment of Bacterial Pneumonia

		Antibiotic Dose[a]	
Antibiotic Class	**Antibiotic**	**Pediatric**	**Usual Adult Dose**
Penicillin	Ampicillin ± sulbactam Amoxicillin ± clavulanate[b] Piperacillin–tazobactam Penicillin	150–200 mg/kg/day IV 45–100 mg/kg/day orally 200–300 mg/kg/day IV 100,000–250,000 units/kg/day IV	2 g IV every 4–6 h (6 h if ampicillin/sulbactam) 875–2000 mg orally twice daily 3.375–4.5 g IV every 6–8 h 12–24 million units/day in divided doses IV every 4–6 h
Extended-spectrum cephalosporins	Ceftriaxone Cefotaxime Ceftazidime Cefepime Ceftolozane–tazobactam Ceftazidime–avibactam	50–75 mg/kg/day IV 150 mg/kg/day IV 90–150 mg/kg/day IV 100–150 mg/kg/day IV – –	1–2 g IV daily 1–2 g IV every 8 h 1–2 g IV every 8 h 1–2 g IV every 6–8 h 3 g IV every 8 h 2.5 g IV every 8 h
Monobactam	Aztreonam	90–120 mg/kg/day IV	1–2 g IV every 8 h
Macrolide/Azalide	Clarithromycin Erythromycin Azithromycin	15 orally mg/kg/day 30–50 IV or orally mg/kg/day 10 mg/kg × 1 day (×2 days if parenteral), and then 5 mg/kg days 2–5 IV or orally	0.5–1 g orally once or twice daily 500 mg IV or orally every 6–8 h 500 mg × 1 day (×2 days if parenteral), and then 250 mg days 2–5 IV or orally
Fluoroquinolones[c]	Moxifloxacin Levofloxacin Ciprofloxacin	– 8–20 mg/kg/day IV or orally 30 mg/kg/day IV or orally	400 mg IV or orally daily 750 mg IV or orally daily 400 mg IV every 8 h / 750 mg orally twice daily

Tetracycline[d]	Doxycycline Tetracycline HCl	2–5 mg/kg/day IV or orally 25–50 mg/kg/day orally	100 mg IV or orally twice daily –
Aminoglycosides	Gentamicin Tobramycin Amikacin	7.5–10 mg/kg/day IV 7.5–10 mg/kg/day IV 15–20 mg/kg/day IV	7.5 mg/kg IV daily 7.5 mg/kg IV daily 15–20 mg/kg IV daily
Carbapenems	Imipenem Meropenem Meropenem–vaborbactam	60–100 mg/kg/day IV 30–60 mg/kg/day IV	500–1000 mg IV every 6 to 8 h 500–2000 mg IV every 6 to 8 h 2 g/2 g IV every 8 h
Polymyxins	Colistin Polymyxin B	2.5–5 mg/kg/day IV 15,000–30,000 units/kg/day IV	IV: 300 mg × 1, then 150 mg daily/Neb: 150 mg every 8 h IV: 2–2.5 mg/kg × 1, then 1.25–1.5 mg/kg every 12 h
Other	Vancomycin Linezolid Clindamycin	45–60 mg/kg/day IV 20–30 mg/kg/day IV or orally 30–40 mg/kg/day IV or orally	15–20 mg/kg IV every 8–12 h 600 mg IV or orally every 12 h 600 mg IV or orally every 8 h or 450 mg orally every 6 h

[a]Doses can be increased for more severe disease and may require modification for patients with organ dysfunction.

[b]Higher-dose amoxicillin and amoxicillin/clavulanate (eg, 90 mg/kg/day) are used for penicillin-resistant *S. pneumoniae*.

[c]Fluoroquinolones have been avoided for pediatric patients because of the potential for cartilage damage; however, they have been used for MDR bacterial infection safely and effectively in infants and children (see text).

[d]Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years because of tetracycline-induced permanent tooth discoloration.

TABLE 44-7

Directed Antimicrobial Therapy for Common Pneumonia Pathogens in Adult Patients

Pathogen	Preferred Antibiotic Therapy	Alternative Antibiotic Therapy
Penicillin-susceptible *S. pneumoniae* (MIC ≤2 mg/L)	Ampicillin, amoxicillin, penicillin G	Ceftriaxone, cefotaxime, macrolide, levofloxacin, moxifloxacin, doxycycline, clindamycin, vancomycin
Penicillin-resistant *S. pneumoniae* (MIC >2 mg/L)	Ceftriaxone, cefotaxime, levofloxacin, moxifloxacin	High-dose amoxicillin (3 g/day), linezolid, clindamycin, vancomycin
Non-β-lactamase-producing *H. influenzae*	Ampicillin (IV), amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
β-Lactamase-producing *H. influenzae*	Ceftriaxone, cefotaxime, ampicillin–sulbactam, amoxicillin–clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Chlamydophila pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Legionella pneumophila	Fluoroquinolone or azithromycin	Doxycycline
MSSA	Cefazolin, antistaphylococcal penicillin	Clindamycin, vancomycin
MRSA	Vancomycin, linezolid	Telavancin, ceftaroline, quinupristin/dalfopristin, clindamycin, sulfamethoxazole/trimethoprim
P. aeruginosa	Antipseudomonal β-lactam[a] or fluoroquinolone[b] based on antimicrobial susceptibility testing results. Can consider adding aminoglycoside if patient in septic shock or at high mortality risk	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Acinetobacter spp.	Carbapenem OR ampicillin–sulbactam based on antimicrobial susceptibility testing results	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Extended-spectrum β-lactamase-producing gram-negative bacilli	Carbapenem	Piperacillin–tazobactam or cefepime potential options depending on susceptibility/adequate dosing
Carbapenem-resistant organisms	New β-lactam/β-lactamase inhibitors[c] based on antimicrobial susceptibility testing OR IV colistin or polymyxin B + inhaled colistin	

[a]Antipseudomonal β-lactam: piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem/cilastatin, doripenem, aztreonam.

[b]Antipseudomonal fluoroquinolone: ciprofloxacin and levofloxacin

[c]New β-lactam/β-lactamase inhibitors: ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam.

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCN, penicillin.

EVALUATION OF THERAPEUTIC OUTCOMES

- For patients with pneumonia of mild-to-moderate clinical severity, the time to resolution of cough, decreasing sputum production, and fever, as well as other constitutional symptoms of malaise, nausea, vomiting, and lethargy, should be noted. Progress should be observed in the first 2 days, with complete resolution in 5–7 days.
- When discontinuing therapy, patients should be afebrile for 48–72 hours and have no more than one CAP-related sign of clinical instability (ie, tachycardia, tachypnea, hypotension, hypoxia, altered mental status).
- With HAP some resolution of symptoms should be observed within 2 days of instituting antibiotic therapy. If no resolution of symptoms is observed within 2 days of starting seemingly appropriate antibiotic therapy or if the patient's clinical status is deteriorating, the appropriateness of initial antibiotic therapy should be critically reassessed. The clinician should consider the possibility of changing the initial antibiotic therapy to expand antimicrobial coverage not included in the original regimen if the patient's clinical status is worsening or failing to improve after 48–72 hours of therapy.
- De-escalation of antibiotic therapy to be more narrow spectrum in patients with HAP/VAP is strongly recommended. Evidence suggests this approach does not affect clinical outcomes while reducing excess antibiotic use. The recommended duration of therapy for HAP/VAP is 7 days, as the clinical benefit of longer durations of therapy (≥10 days) is not clear based on available clinical evidence.

See Chapter 125, Lower Respiratory Tract Infections, authored by Evan J. Zasowski and Martha G. Blackford, for a more detailed discussion of this topic.