Chapter 129: Lower Respiratory Tract Infections

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UPDATE SUMMARY

Update Summary

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The following section was updated:

- Minor edits were made to self-assessment questions to improve clarity.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 44, Respiratory Tract Infections, Lower.

KEY CONCEPTS

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1. Respiratory infections remain a major cause of morbidity from acute illness in the United States and represent the most common reasons why patients seek medical attention.

2. The majority of pulmonary infections follow colonization of the upper respiratory tract with potential pathogens, whereas microbes less commonly gain access to the lungs via the bloodstream from an extrapulmonary source or by inhalation of infected aerosol particles. The competency of a patient's immune status is an important factor influencing the susceptibility to infection, etiologic cause, and disease severity.

3. An appropriate treatment regimen for a patient with uncomplicated lower respiratory tract infection can be established by evaluating the patient history, physical examination, chest radiograph, and properly collected sputum for culture interpreted in light of current knowledge of the most common lung pathogens and their antibiotic susceptibility patterns within the community.

4. Acute bronchitis is most commonly caused by respiratory viruses and is almost always self-limiting. Therapy targets associated symptoms such as lethargy, malaise, or fever and may include fluids for rehydration. Routine use of antibiotics should be avoided and medication to suppress cough is rarely indicated.

5. Chronic bronchitis is caused by several interacting factors, including inhalation of noxious agents (most prominent are cigarette smoke and exposure to occupational dusts, fumes, and environmental pollution) and host factors including genetic factors and bacterial (and possibly viral) infections. The hallmark of this disease is a chronic cough, accompanied by excessive production, and expectoration of sputum with a persistent presence of microorganisms in the patient's sputum.

6. Treatment of acute exacerbations of chronic bronchitis includes attempts to mobilize and enhance sputum expectoration (chest physiotherapy, humidification of inspired air), oxygen if needed, aerosolized bronchodilators in select patients with demonstrated benefit, and possibly antibiotics.

7. Respiratory syncytial virus is the most common cause of acute bronchiolitis, an infection that mostly affects infants during their first year of life. In the well infant, bronchiolitis usually is a self-limiting viral illness.

8. The most prominent pathogen causing community-acquired bacterial pneumonia in otherwise healthy adults is *Streptococcus pneumoniae*, whereas the most common pathogens causing hospital-acquired pneumonia are *Staphylococcus aureus* and gram-negative aerobic bacilli.

9. Empiric antimicrobial therapy for pneumonia should consist of antibiotic regimens targeting presumed causative pathogens based on clinical presentation and patient-specific characteristics, local epidemiology, and resistance patterns.

10. Microbiologic tests for pneumonia etiology should be performed when clinically indicated and used along with patient clinical response to tailor antibiotic therapy using evidence-based pathogen-directed therapy when possible.

BEYOND THE BOOK

BEYOND THE BOOK

Create a study chart of the following antibiotics with potential utility in lower respiratory tract infections: ceftazidime-avibactam; ceftolozane-tazobactam; meropenem-vaborbactam; cefiderocol, imipenem-relabactam, plazomicin, eravacycline. On the chart include spectrum of activity, pharmacokinetics (ADME), dosing (including need for adjustment in special populations), adverse effects, Food and Drug Administration (FDA)-approved indication(s), level of evidence supporting use in lower respiratory tract infections (none, in vitro/in vivo, case report/series, observational study, randomized controlled trial), and potential place in therapy of lower respiratory tract infections.

INTRODUCTION

1 Respiratory tract infections remain a major cause of morbidity from acute illness in the United States and most likely represent the single most common reason patients seek medical attention. This chapter focuses on bacterial and viral infections involving the lower respiratory tract, which includes the tracheobronchial tree and lung parenchyma.

2 The respiratory tract has an elaborate system of host defenses, including humoral immunity, cellular immunity, and anatomic mechanisms.[1] When functioning properly, respiratory tract host defenses are markedly effective in protecting against pathogen invasion and removing potentially infectious agents from the lungs. For the most part, infections in the lower respiratory tract occur only when these defense mechanisms are impaired, as in cases of dysgammaglobulinemia or compromised ciliary function, such as that caused by the chronic inflammation accompanying cigarette smoking. In addition, local defenses may be overwhelmed when a particularly virulent microorganism or excessive inoculum invades lung parenchyma. Most pulmonary infections follow colonization of the upper respiratory tract with potential pathogens, which, after achieving sufficiently high concentrations, gain access to the lung via aspiration of oropharyngeal secretions. Less commonly, microbes enter the lung via the blood from an extrapulmonary source or by inhalation of infected aerosolized particles. The specific type of pulmonary infection caused by an invading microorganism is determined by a variety of host factors, including age, anatomic features of the airway, and specific characteristics of the infecting agent.

The most common infections involving the lower respiratory tract are bronchitis, bronchiolitis, and pneumonia. Bronchitis and bronchiolitis are inflammatory conditions of the large and small airways, respectively, of the tracheobronchial tree. The inflammatory process does not extend to the alveoli. Bronchitis frequently is classified as acute or chronic; acute bronchitis occurs in individuals of all ages, whereas chronic bronchitis primarily affects adults. Bronchiolitis is a disease of infancy.

Lower respiratory tract infections in children and adults most commonly result from either viral or bacterial invasion of lung parenchyma. The diagnosis of viral infections rests primarily on the recognition of a characteristic constellation of clinical signs and symptoms. Because treatment of viral respiratory infections is largely supportive, only occasionally does the diagnosis require laboratory confirmation; this is achieved through serologic tests or identification of the organism by culture or antigen detection in respiratory secretions.[2] Laboratory techniques using polymerase chain reaction (PCR), microarrays, and multiplex ligation-dependent probe amplification, to name a few, have emerged to identify specific pathogens rapidly and accurately.[3]

In contrast, because bacterial pneumonia usually necessitates expedient, effective, and specific antibiotic therapy, its management depends, in large part, on an understanding of the risk factors for acquiring pneumonia, predominant pathogens within the community, and, if necessary, isolation of the etiologic agent by culture from lung tissue or secretions.[4-6] The pharynx is colonized with many organisms that can cause pneumonia; therefore, culture of expectorated sputum can be misleading unless the specimen is examined to ensure that it has originated from the lower respiratory tract. The Gram stain provides the easiest method for distinguishing lower from upper respiratory tract secretions; moreover, through determination of the shape and color of the bacteria, the Gram stain frequently narrows the microbiologic differential diagnosis sufficiently to allow accurate initial therapy. Scanned under low-power microscopy, Gram-stained expectorated upper respiratory tract secretions contain many irregularly shaped epithelial cells with little evidence of inflammation and may not reflect the pathogen. In contrast, a lower-tract specimen from a patient with bacterial pneumonia usually contains multiple neutrophils per high-powered field and a single or predominant bacterial species. More aggressive procedures can be performed to more accurately identify responsible pathogens including respiratory secretion samples obtained via bronchoscopy or bronchoalveolar lavage (BAL). Culture of specimens confirmed to originate from the lower tract by Gram stain or collection via BAL provides valuable diagnostic

information for the majority of patients with bacterial pneumonia. In addition, pneumonia promotes the release of inflammatory mediators and acute-phase proteins, such as C-reactive protein, which can be significantly elevated in serum in the presence of respiratory tract infections.[7] Unfortunately except for pathogen identification by culture, elevations in C-reactive protein, changes in sputum color or peripheral white blood count, etc., are not specific for determining viral, bacterial, or fungal etiology. Newer genomic testing may aid tremendously in determining the identity of responsible pathogen(s) and then selection of optimal antimicrobial therapy.

3 An appropriate treatment regimen for the patient with an uncomplicated lower respiratory tract infection usually can be established by history, physical examination, chest radiograph, and properly collected sputum cultures interpreted in light of the most common lung pathogens and their antibiotic susceptibility patterns within the community.[2,5] More sophisticated or invasive diagnostic methods (eg, computed tomography, bronchoscopy, and lung biopsy) are reserved for severely ill patients who are unable to expectorate sputum or who are not responding to empirical therapy or for pulmonary infections occurring in immunocompromised patients.[2]

BRONCHITIS

Acute Bronchitis

Epidemiology and Etiology

Acute bronchitis occurs year-round, but more commonly during the winter months. Cough accounts for more than 6 million ambulatory visits annually, underscoring its major financial impact on the healthcare system.[8] 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 (viral) infection and/or smoking are the most common precipitants of attacks, which usually manifest initially as a persistent cough.

4 Respiratory viruses are the predominant infectious agents associated with acute bronchitis, accounting for 85% to 95% of occurrences. The most common infecting agents include influenza A and B, respiratory syncytial virus (RSV), and parainfluenza virus, whereas the common cold viruses (rhinovirus and coronavirus) and adenovirus are encountered less frequently. Although far less common, bacterial pathogens are involved in a minority of cases and involve pathogens often associated with community-acquired pneumonia (CAP) including *Mycoplasma pneumoniae*, *Streptococcus pneumonia, Haemophilus influenzae, Moraxella catarrhalis*, and less commonly *Chlamydophila pneumoniae* and *Bordetella pertussis*, the agent responsible for whooping cough. Although a primary bacterial etiology for acute bronchitis appears rare, secondary bacterial infection may be involved, particularly in patients with underlying disease(s).[8]

Pathogenesis

4 Since acute bronchitis is primarily a self-limiting illness and rarely a cause of death, few data describing the pathology are available. In general, infection of the trachea and bronchi yields inflammation-induced hyperemic and edematous mucous membranes with 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. The probability of permanent damage to the airways as a result of acute bronchitis remains unclear but appears unlikely. However, epidemiologic evaluations support the belief that recurrent acute respiratory infections may be associated with increased airway hyperreactivity and possibly the pathogenesis of asthma, chronic obstructive pulmonary disease (COPD), or possibly the asthma-COPD syndrome.[9,10]

Clinical Presentation

Acute bronchitis usually begins as an upper respiratory infection with nonspecific complaints.[8,11] 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. In older children and adults, the sputum is raised and expectorated; in the young child, sputum often is swallowed and can result in gagging and vomiting. Substantial discomfort may result from the coughing. Dyspnea, cyanosis, or signs of airway obstruction are observed rarely unless the patient has underlying pulmonary disease, such as emphysema or COPD. Fever, when present, rarely exceeds 39°C (102.2°F) and appears most commonly with

adenovirus, influenza virus, and *M. pneumoniae* infections. The diagnosis typically is made on the basis of a characteristic history and physical examination and should be differentiated from asthma or bronchiolitis as these latter diseases are usually associated with wheezing, shortness of breath, and hypoxemia. Bacterial cultures of expectorated sputum are of limited use because of the inability to avoid normal nasopharyngeal flora by the sampling technique. Similarly, viral cultures are unnecessary. In the absence of important risk factors, including COPD, congestive heart failure, or immune compromise, throat/sputum cultures have no role in the routine care of patients with acute bronchitis. 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

Desired Outcome

In the absence of a complicating bacterial superinfection, acute bronchitis almost always is self-limiting. The goals of therapy are to provide comfort to the patient and, in the unusually severe case, to treat associated dehydration and respiratory compromise.[8]

General Approach to Treatment

4 Treatment of acute bronchitis is symptomatic and supportive in nature. Reassurance and antipyretics frequently are all that are needed. 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. Mist therapy (use of a vaporizer) may promote the thinning and loosening of respiratory secretions.

Pharmacologic Therapy

Mild analgesic–antipyretic therapy often is helpful in relieving the associated lethargy, malaise, and fever. Aspirin or acetaminophen (650 mg/dose in adults [maximum less than 4 g/day] or 10-15 mg/kg/dose in children [maximum 60-75 mg/kg/day or 5 doses/day]) administered every 4 to 6 hours or ibuprofen (200-800 mg/dose in adults [maximum 3.2 g/day] or 10 mg/kg/dose in children [maximum 40 mg/kg/day]) should be administered every 6 to 8 hours. Aspirin should be avoided in children less than 19 years of age with a fever-causing illness and acetaminophen or ibuprofen used as the preferred agents because of a possible, but unclear and unproven association between aspirin use and the possible development of Reye's syndrome.

Patients may present with mild-to-moderate wheezing. In otherwise healthy patients, no meaningful benefits have been described with the routine use of oral or aerosolized β_2-receptor agonists[11,12] and/or oral or aerosolized corticosteroids. Corticosteroids should be avoided in patients with acute bronchitis. There is no evidence to support the routine use of β_2-receptor agonists in either pediatric or adult patients with acute bronchitis; however, adults with airflow obstruction may have a trend toward improvement in cough.[13] Some clinicians, despite no data, may initiate a brief trial (eg, about 5-7 days) of β_2-receptor agonists and even oral or inhaled corticosteroid for patients with a persistent (more than 14-20 days), troublesome cough. This is rarely, if ever, necessary in patients with uncomplicated acute bronchitis and should be avoided. Cough may persist for 3+ weeks and airway hyperresponsiveness for 5 to 6 weeks in as many as 50% of affected patients. In contrast, COPD patients experiencing an acute exacerbation can benefit from a short course of corticosteroid.

Patients suffering from acute bronchitis frequently medicate themselves with nonprescription cough and cold remedies containing various combinations of antihistamines, sympathomimetics, and antitussives despite the lack of definitive evidence supporting their effectiveness.[8,11] The tendency of these agents to dehydrate bronchial secretions could aggravate and prolong the recovery process. Although not recommended for routine use, persistent, mild cough, which may be bothersome, can be treated with dextromethorphan; more severe coughs may require intermittent codeine or other similar agents.[14] In severe cases, the cough may be persistent enough to disrupt sleep, and use of a mild sedative-hypnotic, concomitantly with a cough suppressant (eg, codeine), may be desirable. However, antitussives should be used cautiously when the cough is productive, and codeine is no longer recommended for use in pediatric patients. The primary or supplemental use of expectorants is questionable because their clinical effectiveness has not been well established.[8]

Routine use of antibiotics for treatment of acute bronchitis should be strongly discouraged due to limited benefit.[8,11,15] In previously healthy patients who exhibit persistent fever or respiratory symptoms for more than 5 to 7 days or for predisposed patients (eg, elderly/frail, COPD, and immune compromised), the possibility of a concurrent bacterial infection should be suspected. When possible, antibiotic therapy should be directed toward anticipated respiratory pathogen(s) (eg, *S. pneumoniae* and *H. influenzae*). *M. pneumoniae*, if suspected by history or if confirmed by culture serology

or PCR, can be treated with azithromycin. Alternatively, a fluoroquinolone antibiotic with activity against these suspected pathogens (eg, levofloxacin or moxifloxacin) can be used empirically, but due to the increasing rate of pathogen resistance to current antimicrobial drugs, the use of antibiotics in patients with acute bronchitis should be reserved for only those patients not responding adequately to supportive care and deemed at risk of associated complications. During known epidemics involving the influenza A virus, amantadine or rimantadine may have been effective in minimizing associated symptoms if administered early in the course of the disease; however, treatment with these adamantanes is no longer recommended by the Centers for Disease Control and Prevention (CDC) due to increasing influenza resistance and associated adverse effects (see Chapter 131, "Influenza"). The neuraminidase inhibitors (eg, zanamivir and oseltamivir) and the endonuclease inhibitor baloxavir are active against both influenza A and B viral infections and may reduce the severity and duration of the influenza episode if administered promptly during the onset of the viral infection and are the preferred treatment (see Chapter 131).[12,16] Unfortunately, the incidence of influenza virus resistance to available antiviral drugs is increasing, necessitating reconsideration of how we administer antiviral drugs for prophylaxis and treatment.[12] The concept of antiviral drug combinations has emerged as a successful approach to effectively treat systemic viral infections.[17]

Chronic Bronchitis

Epidemiology and Etiology

Chronic bronchitis, most often a component of COPD, is a clinical diagnosis for a nonspecific, heterogenic disease that primarily affects adults. An in-depth presentation of the spectrum and management of COPD is given in Chapter 45, "Chronic Obstructive Pulmonary Disease"; this section focuses solely on chronic bronchitis. In developed countries, the prevalence of chronic bronchitis is slightly higher in men than in women. Depending on the definition used for chronic bronchitis, 3.4% to 22% of adults have chronic bronchitis and 14% to 74% of COPD patients suffer from chronic bronchitis.[18]

5 Chronic bronchitis is defined 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. The disease is a result of several contributing factors; the most prominent factor is cigarette smoking; however, in nonsmokers who develop chronic bronchitis (4%-22%), other factors may be exposure to occupational dusts, fumes, and environmental pollution, and host factors (eg, genetic factors and bacterial [and possibly viral] infections).[18] The contribution of each of these factors and of others (either alone or in combination) to chronic bronchitis is unknown.[19] Cigarette smoke is a well-known airway irritant and is a predominant factor in the etiology of chronic bronchitis. Although previously assumed the most common etiologic cause of chronic bronchitis, more strict prohibition of public smoking and the resultant decrease in chronic tobacco smokers, particularly in developed countries, underscores the importance of other factors as causes of this chronic disease. Airway irritants including occupational dust, chemicals, or air pollution, either alone or more likely in combination, are also responsible for the pathogenesis of chronic bronchitis and may explain the development in nonsmokers.[18] Furthermore, genomic studies have begun to expand our understanding of the molecular pathways that may have clinical relevance in this heterogeneous disease. Lastly, the influence of recurrent respiratory tract infections during childhood or young adult life on the later development of chronic bronchitis remains obscure, but recurrent respiratory infections may predispose individuals to the development of chronic bronchitis. Whether these recurrent respiratory tract infections are a result of unrecognized anatomic abnormalities of the airways or impaired pulmonary defense mechanisms is unclear.

Chronic bronchitis and emphysema are the two main components of COPD/chronic obstructive lung disease.[20-22] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines document does not distinguish these two diagnoses (eg, emphysema or chronic bronchitis) in the definition of COPD, but it does define COPD as a disease characterized by airflow obstruction that is not fully reversible and progressive. The GOLD guidelines provide a COPD classification scoring system according to severity that can be helpful in staging patients for intensity of therapy, acute/chronic therapy, and prognosis. Unfortunately, differences in definitions between authoritative organizations may cause confusion in the assignment of patients in clinical trials and thus in assessment and application of study results to clinical care.

Pathogenesis

Chronic inhalation of an irritating noxious substance compromises the normal secretory and mucociliary function of bronchial mucosa.[18] Bronchial biopsy specimens in bronchitic patients underscore the importance of T-cell-derived proinflammatory cytokines (eg, interleukins IL-4, IL-5, IL-13, and interferon gamma) in the pathogenesis and propagation of the observed inflammatory changes. In chronic bronchitis, the bronchial wall is thickened,

and the number of mucus-secreting goblet cells on the surface epithelium of both larger and smaller bronchi is increased markedly. In contrast, goblet cells generally are absent from the smaller bronchi of normal individuals. In addition to the increased number of goblet cells, hypertrophy of the mucous glands and dilation of the mucous gland ducts are observed. As a result of these changes, chronic bronchitis has substantially more mucus in the peripheral airways, further impairing normal lung defenses. This increased quantity (overproduction and hypersecretion) of tenacious secretions within the bronchial tree frequently causes mucous plugging of the smaller airways. Accompanying these changes is squamous cell metaplasia of the surface epithelium, edema, and increased vascularity of the basement membrane of larger airways and variable chronic inflammatory cell infiltration. In addition, the amounts of several proteases derived from inflammatory cells are increased and due to COPD-induced defective antiproteases lead to continued destruction of connective tissue. Continued progression of this pathology can result in residual scarring of small bronchi and peribronchial fibrosis augmenting airway obstruction and weakening of bronchial walls.[18]

Clinical Presentation

5 The hallmark of chronic bronchitis is a cough that may range from a mild to a severe and incessant coughing productive of purulent sputum. Coughing may be precipitated by multiple stimuli, including simple, normal conversation. Expectoration of the largest quantity of sputum usually occurs on arising in the morning, although many patients expectorate sputum throughout the day. The expectorated sputum usually is tenacious and can vary in color from white to yellow-green. Patients with chronic bronchitis often expectorate as much as 100 mL/day more than normal. As a result, many patients complain of a frequent bad taste in their mouth and of halitosis. Sputum color provides no prognostic indication of infection or cause of an infectious disease exacerbation, that is, viral versus bacterial cause. Although sputum color of more green and yellow can be a predictor of potentially pathogenic bacteria, this is unreliable clinically.[23] The diagnosis of an acute exacerbation requires consideration of a number of different factors all occurring within a discrete timeframe (eg, increased/worsening respiratory symptoms including dyspnea, sputum volume and/or clearance, and cough). The tracking of the number of acute exacerbations and their consequences (decline in forced expiratory volume in 1 second [FEV1]), persistent/worsening of symptoms annually, is extremely important for prognostication and defining ongoing treatment strategies. Each acute exacerbation of chronic bronchitis results in continual declines in lung function.

The diagnosis of chronic bronchitis is based primarily on clinical assessment and history. Any patient who reports coughing sputum on most days for at least 3 consecutive months each year for 2 consecutive years presumptively has chronic bronchitis.[18] The diagnosis of chronic bronchitis is made only when the possibilities of bronchiectasis, cardiac failure, cystic fibrosis, and lung carcinoma, among others, have been effectively excluded. To be more specific in the diagnosis, some investigators have added the criteria of lost wages for 3 or more weeks. In addition, many clinicians attempt to subdivide their patients based on severity of disease to guide therapeutic interventions. Two primary classification proposals are most often used in an attempt to determine the severity of the underlying disease as well as the occurrence/impending occurrence of an acute exacerbation of chronic bronchitis; for disease severity and acute exacerbations the prognostic tools advocated by GOLD are very helpful including classification based on spirometry (“mild” postbronchodilator FEV1 greater than or equal to 80% predicted to “very severe” postbronchodilator FEV1 less than 30% predicted: see Chapter e43, “Evaluation of Pulmonary Function”); the COPD assessment test (eight-item measure of health status), the Clinical COPD Questionnaire (a measure of clinical control), and the Modified Medical Research Council Questionnaire to predict future mortality. The other simple classification system is that proposed by Anthonisen and colleagues in 1987 that is still used to categorize patients in many therapeutic clinical trials.[24] The use of patient symptom diaries can also be helpful in compliant patients. The importance of accurate classification for grouping patients of similar disease involvement cannot be overemphasized with respect to assessing publications outlining treatment strategies for these patients. These classifications attempt to capture specific phenotypes of chronic bronchitis patients. The typical clinical presentation of chronic bronchitis is listed in Table 129-1. Comparison of the trends in changes in a patient’s physical activity, symptoms, and clinical/physical findings from the patient’s “routine” is extremely helpful in determining the presence and severity of an acute exacerbation.

TABLE 129-1

Clinical Presentation of Chronic Bronchitis

Signs and symptoms
Excessive sputum expectoration
Cough
Cyanosis (advanced disease)
Physical examination
Chest auscultation usually reveals inspiratory and expiratory rales, rhonchi, and mild wheezing with an expiratory phase that is frequently prolonged
Hyperresonance on percussion with obliteration of the area of cardiac dullness
Normal vesicular breathing sounds are diminished
Clubbing of digits (advanced disease)
Obesity
Chest radiograph
Increase in anteroposterior diameter of the thoracic cage (barrel chest)
Depressed diaphragm with limited mobility
Laboratory tests
Erythrocytosis (advanced disease), that is, increased hematocrit
Pulmonary function tests
Decreased vital capacity
Prolonged expiratory flow

In more advanced stages of chronic bronchitis, physical findings associated with cor pulmonale, including cardiac enlargement, hepatomegaly, and edema of the lower extremities, are observed. In general, people with chronic bronchitis tend to maintain at least normal body weight and commonly are obese. Radiographic studies are of limited value in either the diagnosis or follow-up of a patient. The microscopic and laboratory assessments of sputum are used in the overall evaluation of patients with chronic bronchitis. Gram staining of the sputum often reveals a mixture of both gram-positive and gram-negative bacteria, reflecting normal oropharyngeal flora and chronic tracheal colonization (in order of frequency) by non-typable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Table 129-2 lists the most common bacterial isolates identified from sputum culture for patients experiencing an acute exacerbation of chronic bronchitis. For patients with more severe airflow disease (eg, FEV_1 less than 40% predicted), enteric gram-negative bacilli, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa* may be significant pathogens during acute exacerbations.

TABLE 129-2

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 nontypable strains.

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

Treatment

Desired Outcome

The goals of therapy for chronic bronchitis are twofold: to reduce the severity of chronic symptoms and to ameliorate acute exacerbations and achieve prolonged exacerbation-free intervals.

General Approach to Treatment

The approach to treatment of chronic bronchitis is multifactorial.[18] First and foremost, attempts must be made to reduce the patient's exposure to known bronchial irritants (eg, smoking and workplace pollution). A complete occupational and environmental history for determination of exposure to noxious, irritating gases as well as preference toward cigarette smoking must be assessed. Often easier to discuss than accomplish, reasonable attempts should be made with the patient to reduce or eliminate the number of cigarettes smoked daily and to reduce exposure to secondhand smoke. An organized, coordinated, smoking cessation program, including counseling, possibly hypnotherapy, and the adjunctive use of nicotine substitutes (eg, nicotine gum or patch) or other pharmacotherapy (eg, bupropion and varenicline), may promote the reduction or complete withdrawal from cigarette smoking. Often just as difficult is modification of exposure to irritating substances within the home and workplace.

The importance of pulmonary rehabilitation has been realized in improving the quality of life for patients with chronic respiratory diseases.[25] Pulmonary rehabilitation is broadly defined as an interdisciplinary program individualized for patients with chronic respiratory impairment designed to optimize each patient's physical and social performance and autonomy. A personalized exercise-training program including resistance and aerobic exercise is central to these programs. Pulmonary rehabilitation programs relieve dyspnea and fatigue, improve a patient's emotional function, and enhance their sense of control over their disease and life. These improvements are often moderately large and clinically relevant.[25] The challenge for the future is to determine what components of a comprehensive pulmonary rehabilitation program provide the greatest benefit.

6 Measures to provide chest physiotherapy (eg, pulmonary "toilet") can be instituted.[26] Clearly the cost-effectiveness of chest physiotherapy needs to be better described but their short-term effects have been demonstrated and may be of symptomatic value to many patients experiencing an acute exacerbation of the chronic bronchitis. During acute pulmonary exacerbations of the disease, the patient's ability to mobilize and expectorate sputum may be reduced dramatically. In these instances, attempts at postural drainage techniques, with instruction and or active participation from a respiratory therapist, may assist in promoting clearance of pulmonary secretions. In addition, humidification of inspired air may promote the hydration (liquefaction) of tenacious secretions, allowing for removal that is more productive. Use of aerosolized mucolytic aerosols, such as *N*-

acetylcysteine (NAC) and DNAse, is of questionable therapeutic value, particularly considering their propensity to induce bronchospasm (NAC) and their excessive cost. NAC cleaves the disulfide bonds of mucus, decreasing its elastic property that is important for upward mobility and then expectoration. Aerosol mucolytic therapy was associated with a small reduction in acute exacerbations in subjects with chronic bronchitis or COPD and did not cause any harm, improve quality of life, or slow the decline of lung function.[27] The clinical benefit may be greater for chronic bronchitis/COPD patients who have frequent or prolonged exacerbations and are unable to utilize inhaled corticosteroids or long-acting β_2-agonists.[27] Although limited data are available, chronic use of oral or aerosolized bronchodilators may be of benefit by increasing mucociliary and cough clearance. For patients with moderate to severe 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) could be considered; however, there is insufficient evidence to recommend the routine use of pharmaceutical agents for cough relief.[18] Pulmonary function tests should be performed before and after β_2-agonist aerosol administration for more objective determination of a patient's propensity to benefit from supplemental aerosol therapy. Regular use of a long-acting β-receptor agonist aerosol (eg, salmeterol and formoterol) in responsive patients is more effective and probably more convenient than short-acting β_2-receptor agonists.[28] The aerosol route for β_2-receptor agonist and/or corticosteroid administration is favored over systemic formulations for improved patient acceptance and compliance and to minimize the number and magnitude of associated adverse effects. Chronic inhalation of a combination long-acting β-receptor agonist (LABA) and a corticosteroid (eg, salmeterol-fluticasone and formoterol-mometasone) improved pulmonary function and quality of life.[29] 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. A stepwise approach to withdrawing inhaled corticosteroids may minimize the risk for acute exacerbations but a decrease in lung function can still occur after discontinuation.[30]

Inhaled anticholinergic drugs, including ipratropium and tiotropium, have an important role in the chronic management of patients with chronic bronchitis and COPD.[31] Inhaled long-acting muscarinic antagonists (LAMAs) alone or more frequently, when administered in combination with a LABA, improve lung function and symptom control and reduce the number of acute exacerbations. Triple combination inhalation therapy (eg, LABA + LAMA + an inhaled corticosteroid) is being evaluated in patients with more severe COPD with promising findings and its role remains to be defined.[32] Although once prescribed extensively for patients with chronic bronchitis, chronic theophylline therapy is used with decreasing frequency in favor of aerosolized β_2-receptor agonists, LABA, LAMA, etc. Nevertheless, long-acting theophylline remains an effective "add on" therapy for many patients, particularly those with more 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.[18]

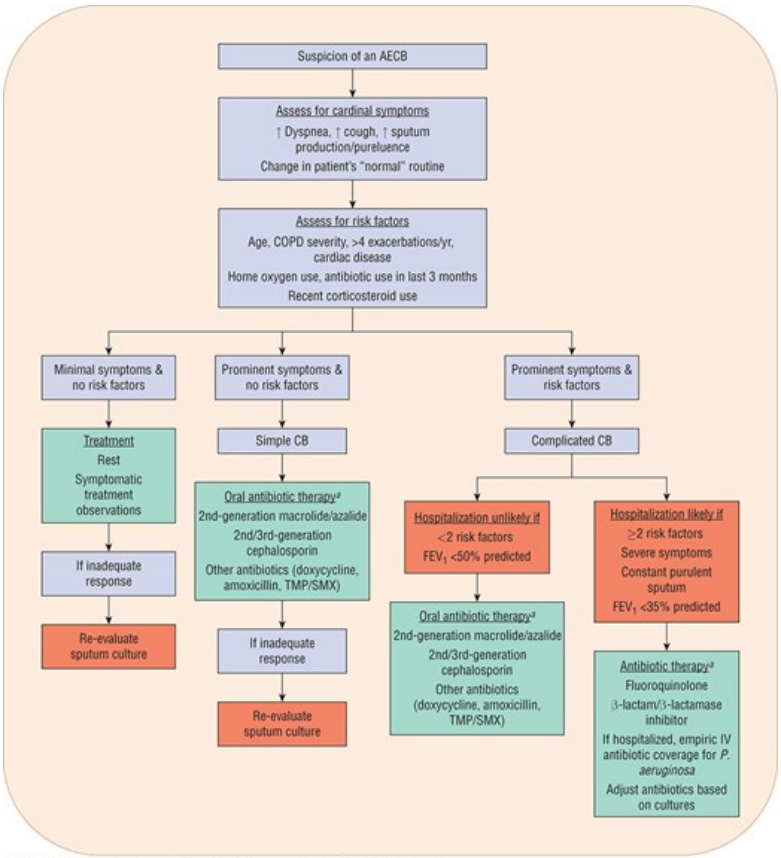
Phosphodiesterase 4 inhibitors (PDE-4), compared with the nonselective phosphodiesterase inhibitor theophylline, only affect phosphodiesterase in the airway smooth muscle, immune cells (eosinophils, monocytes, and neutrophils), and proinflammatory cells. Roflumilast is a highly specific (second generation) PDE-4 inhibitor that is most often reserved for use in patients with moderate to severe COPD. Considering that many of the published studies assessing the viability of second-generation PDE-4 inhibitors in patients with COPD involved patients with chronic cough and increased sputum production, it is inferred that these drugs would be of value in patients with chronic bronchitis as well. The GOLD guidelines suggest roflumilast reduces exacerbations in COPD patients with chronic bronchitis treated with oral glucocorticosteroids. Roflumilast only provides a net benefit to patients at high risk of severe exacerbations.[32,33] A lower 30-day readmission rate in patients hospitalized for COPD with roflumilast therapy was reported.[34] PDE-4 inhibitors improved lung function over placebo and reduced the likelihood of exacerbations; they had little impact on a patient's symptoms or quality of life. Nevertheless, the major limitation to the use of PDE-4 inhibitors is their side effect profiles. Patients receiving roflumilast often experience nausea, vomiting, headache, weight loss, insomnia, and an increased risk of psychiatric events.[35] The exact role of roflumilast in chronic lung disease is evolving but many guidelines suggest its use as add-on therapy for subgroups of patients.[32,35]

Use of antimicrobials for treatment of chronic bronchitis has been controversial, but is becoming more accepted in specific circumstances. Numerous comparative evaluations, including placebo-controlled studies of antibiotic administration for acute and chronic treatment of chronic bronchitis, have suggested clinical benefit. The antibiotics selected most frequently possess variable in vitro activity against the common sputum isolates *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *M. pneumoniae*. Conflicting published results appear independent of the antibiotic used or the regimen compared. A wide disparity that existed in the published results from older studies served as the basis for the enormous controversy about the use of antibiotics for the treatment of acute exacerbations of chronic bronchitis. Overall, good clinical results have been observed with the use of standard short-course antibiotic regimens (eg, macrolides, azalides, oral cephalosporins, and the combination drug amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and tetracyclines).[36,37] 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. The introduction of genome expression profiling of sputum and other biologic fluids can facilitate specific pathogen diagnosis and focused therapy.[38]

A useful paradigm for the assessment and treatment of acute exacerbations of chronic bronchitis and antibiotic decision making is shown in Fig. 129-1.[39] Many clinicians use the so-called Anthonisen criteria to determine if antibiotic therapy is indicated.[24] With the Anthonisen criteria, if a patient exhibits two of the following three criteria during an acute exacerbation of chronic bronchitis (AECB), the patient will most likely benefit from antibiotic therapy and, thus, should receive a treatment course: (a) increase in shortness of breath; (b) increase in sputum volume; and (c) production of purulent sputum. There are greater healthcare costs for patients who are noncompliant with their antibiotic regimen for their AECB.

FIGURE 129-1

Clinical algorithm for the diagnosis and treatment of chronic bronchitis patients with an acute exacerbation incorporating the principles of the clinical classification system. (AECB, acute exacerbation of chronic bronchitis; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; TMP/SMX, trimethoprim/sulfamethoxazole.) [a]See Table 129-3 for commonly used antibiotics and doses. *(Reprinted, with permission, from Hayes DJ, Meyer K. Acute exacerbations of chronic bronchitis in elderly patients: Pathogenesis, diagnosis, and management. Drugs Aging 2007;24:555–572.)*



The increasing resistance of the common bacterial pathogens to first-line agents further complicates antibiotic selection. As many as 30% to 40% of *H.*

influenzae isolates and 95% to 100% of *M. catarrhalis* isolates produce β-lactamases. Moreover, up to 40% of *S. pneumoniae* isolates demonstrate intermediate susceptibility (minimum inhibitory concentration [MIC] 0.125-1 mg/L) or resistance (MIC ≥ 2 mg/L) to oral penicillin, with approximately 20% of isolates being highly resistant (MIC > 2 mg/L). Concern regarding *S. pneumoniae* resistance is increasing, and resistance is now greater than or equal to 30% for macrolides. Despite these changes in bacterial susceptibility, the recommendation is to initiate therapy with first-line antimicrobial agents in less severely affected patients (see Fig. 129-1). For patients with more moderate to severe disease, many clinicians will begin antibiotic therapy with the second-line agents, such as amoxicillin-clavulanate, a macrolide (such as azithromycin or clarithromycin, although they are being used less frequently), or a fluoroquinolone, such as levofloxacin and moxifloxacin (see Fig. 129-1).

Regardless of the antibiotic selected, predetermined outcome measures should be monitored closely for each patient to determine the success or failure of the therapeutic intervention. Oral antibiotics with broader antibacterial spectra (eg, amoxicillin-clavulanate and fluoroquinolones) that possess potent in vitro activity against sputum isolates are increasingly becoming first-line antibiotics as initial therapy for treatment of acute exacerbations of chronic bronchitis.

An important clinical outcome variable directing drug selection and criteria for beginning antibiotics in individual patients is the infection-free period when they are off antibiotics. The length of the infection-free time period and the change in the number of physician office visits and hospital admissions with a particular antibiotic regimen are extremely important to identify, whenever possible, for each patient. The antibiotic regimen that results in the longest infection-free period defines the “regimen of choice” for specific patients for future acute exacerbations of their disease. Long-term prophylactic antibiotic use may provide a slight benefit in decreasing exacerbation rates, but does not appear to decrease mortality, and markedly increase the emergence and colonization of antibiotic-resistant pathogens. For this reason, most guidelines do not support this indication. However, chronic macrolide/azalide use reduces the incidence of acute exacerbations in COPD patients in a clinically significant manner (macrolide and anti-inflammatory activity addressed later).[39,40]

Antibiotics that are effective against responsible pathogens, demonstrate the least risk of drug interactions, and can be administered in a manner that promotes compliance should be selected. Antibiotics, commonly used for treatment of these patients with chronic bronchitis, and their respective adult starting doses are listed in Table 129-3. Doses of antibiotics should be adjusted as needed to the desired clinical effect and the lowest incidence of acceptable side effects. A frequently used clinical strategy to enhance the duration of symptom-free periods incorporates higher-dose antibiotic regimens using the upper limit of the recommended daily antibiotic dose. More clinicians are electing to limit their antibiotic treatment regimen to 5 days as compelling data continue to support equal efficacy, less exposure potentially reducing bacterial resistance development, and possibly less side effects with short-duration antibiotic therapy versus longer treatment regimens (greater than 7 days).

TABLE 129-3

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).

Except for long-term macrolide/azalide administration, chronic antibiotic therapy is rarely indicated in the management of patients with chronic bronchitis. Such approaches lead to marked increase in cost and occurrence of multidrug-resistant (MDR) pathogens. Conversely, long-term macrolide (erythromycin, clarithromycin, and roxithromycin) or azalide (azithromycin) administration has been associated with a clinically significant reduction in the incidence of acute exacerbations in patients with chronic bronchitis and COPD.[39-41] The benefit of these drugs is attributed to their antibacterial, anti-inflammatory, and immunomodulatory activity. These drugs reduce bacterial adherence and toxin production, inhibit biofilm function, and reduce the generation of oxygen-free radicals, modulate mucin gene protein production controlling mucus hypersecretion, and improve mucociliary clearance. These drugs also decrease neutrophil chemotaxis, promote downregulation of adhesion molecule expression, and inhibit transcription factors leading to decreased production of pro-inflammatory cytokines.[41]

The importance of multifactorial cellular oxidative stress in the pathogenesis of chronic bronchitis and COPD has prompted the study of the efficacy of antioxidants and particularly the oral administration of NAC, other mucolytic agents, and antioxidants.[27,42,43] Some guidelines suggest their use for more severely affected patients. Studies with oral NAC have suggested a dose-dependent response with 600 mg once to twice daily and it may slightly decrease the exacerbation rate in COPD patients not using inhaled steroids; however, there does not appear any effect on lung function. The exact role of antioxidant in the care of these patients remains to be defined—no specific recommendations can be provided until more data are available regarding which specific compound (as well as dose and duration of therapy) is optimal.

BRONCHIOLITIS

Epidemiology and Etiology

Bronchiolitis is an acute viral infection of the lower respiratory tract that affects approximately 50% of children during the first year of life and 100% by age 2 years. The occurrence of bronchiolitis peaks during the winter months and persists through early spring. Bronchiolitis remains the major reason for hospital admission during the first year of life.[44]

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis, accounting for up to 75% of all cases. During epidemic periods, the incidence of RSV-induced bronchiolitis may approach 90% of cases. Other frequently detectable viruses include human rhinovirus, coronavirus, parainfluenza, and adenovirus. Bacteria serve as secondary pathogens in a minority of cases.[44]

Clinical Presentation

The clinical presentation of bronchiolitis (Table 129-4) is often preceded by 1 to 4 days of symptoms (eg, nasal congestion, rhinorrhea, cough, and low-grade fever) indicative of an upper respiratory tract infection. Due to limited oral intake because of coughing combined with fever, vomiting, and diarrhea, infants frequently are dehydrated. The increased work of breathing and tachypnea most likely contribute to increased fluid loss. In most cases, bronchiolitis is self-limiting and typically symptoms improve within 7 to 10 days with resolution within 28 days without the need for hospitalization. In patients who require hospitalization, the average length of stay is approximately 3 days.[45]

TABLE 129-4

Clinical Presentation of Bronchiolitis

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)

The diagnosis of bronchiolitis is based primarily on history and clinical findings. It is important for the clinician to attempt to differentiate between

bronchiolitis and a host of other clinical entities affecting infants, which may produce a similar picture of dyspnea and wheezing. Asthma, congestive heart failure, anatomic airway abnormalities, cystic fibrosis, foreign bodies, and gastroesophageal reflux are the primary disease entities that may present with wheezing in children. Isolation of a viral pathogen in the respiratory secretions of a wheezing child establishes a presumptive diagnosis of infectious bronchiolitis. However, identification of specific viral pathogens often is hindered by the limited availability of special virology laboratories. In addition, in the elderly and in immunocompromised patients, antigen detection lacks adequate sensitivity, and patients frequently seek medical care after the acute stage of the infection, thus compromising the ability of the available tests to diagnose RSV. However, the proliferation of commercial enzyme-linked immunosorbent assays and fluorescent antibody staining techniques of nasopharyngeal secretions has increased the ability to identify viral antigens within several hours. Identification of RSV by PCR should be available from most clinical laboratories, but its relevance to the clinical management of bronchiolitis remains obscure and therefore routine testing is not recommended.[45,46]

Multiple clinical laboratory determinations have been used to assist in the management of cases of bronchiolitis. Radiographic evaluation of the chest in children with bronchiolitis yields variable findings and rarely alters therapeutic decisions. Thus, the routine use of chest radiography is not recommended; however, in hospitalized patients who fail to demonstrate expected improvement, they may help to distinguish bronchiolitis from other entities characterized by wheezing so that appropriate treatment may be initiated. In children requiring hospitalization, abnormalities in blood gas tensions are frequent and appear to relate to disease severity. Hypoxemia is common and increases the respiratory drive, whereas hypercarbia is seen in only the most severe cases. Despite the presence of moderate degrees of hypoxemia, clinical cyanosis is unusual.[44]

Treatment

Desired Outcome

In the well infant, bronchiolitis usually is a self-limiting illness, and reassurance, antipyretics, and adequate fluid intake usually are all that are necessary while waiting for resolution of the underlying viral infection. In-hospital support is necessary for the child suffering from respiratory failure or marked dehydration; underlying cardiac and pulmonary diseases potentiate these conditions.[45]

General Approach to Treatment

Almost all otherwise healthy babies with bronchiolitis can be followed as outpatients. Such infants are treated for fever, provided generous amounts of oral fluids, and observed closely for evidence of respiratory deterioration.[44] In severely affected children, the mainstays of therapy for bronchiolitis are oxygen therapy and IV fluids. In a subset of patients, aerosolized bronchodilators may have a role. For selected infants, particularly those with underlying pulmonary disease, cardiac disease, or both, therapy with the antiviral agent ribavirin can be considered.[47]

Pharmacologic Therapy

Aerosolized β_2-adrenergic therapy appears to offer little benefit for most patients and may even be detrimental.[46-48] Given their overall ineffectiveness, neither aerosolized β_2-adrenergic nor nebulized epinephrine therapies are recommended by the American Academy of Pediatrics (AAP) for the treatment of bronchiolitis.[48,49] Multiple studies have supported the AAP recommendations due to insufficient evidence for the effectiveness of bronchodilators in bronchiolitis, although there may be subgroups of patients who might benefit.[48-50]

Similarly, controlled trials of corticosteroids in bronchiolitic infants have not shown therapeutic effects or significant harmful effects, though viral shedding may be prolonged.[45,48] As a result, the routine use of systemically administered corticosteroids is not recommended by the AAP and is therefore discouraged.[46,48] Combination therapy with oral dexamethasone and nebulized epinephrine may act synergistically to reduce hospital admissions and shorten the time to discharge and the duration of symptoms, but the overall clinical benefits is questionable based on study results.[49] Although placing children with bronchiolitis in mist tents has been common practice, no data have documented the effectiveness of this practice.

The AAP guidelines support the use of nebulized hypertonic saline (eg, 3% saline) for the treatment of bronchiolitis in hospitalized infants and children while other international guidelines do not recommend its use.[46,48] As such, although nebulized hypertonic saline has proven to be safe and effective for the symptomatic improvement in patients with bronchiolitis after 1 day of use, there continues to be debate on if it reduces the length of hospital stay.[51]

Ribavirin may offer benefit to a subset of infants with bronchiolitis. Ribavirin, a synthetic nucleoside, possesses in vitro antiviral properties against a variety of RNA and DNA viruses, including influenza A, influenza B, parainfluenza, and adenovirus; it is approved only in aerosolized form against RSV. Use of the aerosol drug formulation requires special equipment (small-particle aerosol generator) and specially trained personnel for administration via oxygen hood or mist tent. Special care must be taken to avoid drug particle deposition and the resulting clogging of respiratory tubing and valves in mechanical ventilators. Among hospital admissions for RSV infection, ribavirin therapy failed to decrease length of hospital stay, number of days in the intensive care unit, or number of days receiving mechanical ventilation. Consequently, the AAP does not recommend the routine use of ribavirin in children with bronchiolitis and most experts recommend reserving use of ribavirin for severely ill patients.[48]

For infants with underlying pulmonary or cardiovascular disease, prophylaxis against RSV may be warranted. When administered monthly during the RSV season, both RSV immune globulin and palivizumab (a monoclonal antibody for RSV) may decrease the number of RSV episodes and the need for hospitalization. Between the two, palivizumab is preferred, given its ease of administration, lack of administration-related adverse effects, and noninterference with select immunizations. Despite continuing research, there is no vaccine marketed for RSV.

PNEUMONIA

Epidemiology

Pneumonia remains one of the most common causes of severe sepsis and the leading infectious cause of death in children and adults in the United States, with a mortality rate as high as 50% depending on the severity of illness.[5,52] Pneumonia occurs throughout the year, with the relative incidence of disease resulting from different etiologic entities varying with the seasons. It occurs in persons of all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill.

Pathogenesis and Etiology

Inspiration of ambient air constantly exposes the lungs to environmental and infectious particulate matter. 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. Respiratory host defenses comprise innate and adaptive immunity pathways. These defense mechanisms are preserved in healthy individuals and respiratory pathogens are effectively removed before infection occurs. Conversely, immunocompromised individuals (such as those with cystic fibrosis or prolonged neutropenia) lack robust defense mechanisms and are at higher risk of severe respiratory infections. Lung infections can also suppress the antibacterial activity of the lung by impairing alveolar macrophage function and mucociliary clearance, thus setting the stage for secondary bacterial pneumonia. Mucociliary transport is also depressed by ethanol and narcotics and by obstruction of bronchi by mucus, tumor, or extrinsic compression. All these factors can severely impair pulmonary clearance of aspirated bacteria. Any alteration of the normal lung microbiome by infection and/or disease can evolve to pneumonia requiring antimicrobial treatment.[53]

Pneumonia is caused by a variety of viral and bacterial pathogens. The causative organism(s) is highly dependent on how and/or where the pneumonia was contacted.[4-6,54] For epidemiologic and treatment purposes, pneumonia is often categorized as either community-acquired or hospital-acquired (Table 129-5).[6] Patients with pneumonia onset outside of the hospital or within 48 hours of hospital admission are considered to have community-acquired pneumonia (CAP). Those with pneumonia onset in the hospital after at least 48 hours of hospitalization are considered to have hospital-acquired pneumonia (HAP). Patients with pneumonia onset following 48 hours of endotracheal intubation are considered to have ventilator-associated pneumonia (VAP).

TABLE 129-5

Pneumonia Classifications and Risk Factors

Type of Pneumonia	Definition	Risk Factors
Community-acquired pneumonia	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	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	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.

Community-Acquired Pneumonia

The causative pathogen in CAP in adult patients is most commonly viral, with human rhinovirus and influenza most common.[55] The most prominent bacterial pathogen causing CAP in otherwise healthy adults is *S. pneumoniae* accounting for up to 35% of all acute cases. It is particularly prevalent and severe for patients with splenic dysfunction, diabetes mellitus, chronic cardiopulmonary or renal disease, or HIV infection. Other common pathogens include *H. influenzae* (2.5%-45%) and the atypical pathogens *M. pneumoniae*, *Legionella* species, and *C. pneumoniae* (about 20%).[55-57] Although generally less common, *S. aureus* is also an important CAP pathogen in children and adults and is often seen in patients with cystic fibrosis and those recovering from an antecedent viral respiratory infection such as influenza. CAP caused by enteric gram-negative bacteria, including *E. coli* and *K. pneumoniae*, is also uncommon but these pathogens are sometimes identified; most frequently among patients with chronic illness, especially alcoholism and diabetes mellitus.[4] Healthcare-associated pneumonia was a classification that had been previously used to distinguish nonhospitalized patients at risk for MDR pathogens from those likely infected with traditional CAP pathogens; however, it is no longer recommended to risk stratify patients using this designation.[4,6]

Even more so than in adult patients, viral pathogens predominate in CAP among pediatric patients with a prevalence of up to 80% in those less than 2 years of age. Respiratory syncytial virus and human rhinovirus comprise the majority of these infections.[58] Other common viruses in children include

parainfluenza, adenovirus, human metapneumovirus, and bocavirus.[5,58] Group B *Streptococcus*, although rare in adults, is the most common cause of bacterial pneumonia among neonates and typically causes a clinical and radiographic picture nearly indistinguishable from hyaline membrane disease.[59] The bacterial causes of CAP outside the neonatal period are generally similar to adults, with *S. pneumoniae* being the major bacterial pathogen in childhood pneumonia.[58] *M. pneumoniae* is also common, particularly among older children. *H. influenzae* type b, once a major childhood pathogen, has become an infrequent cause of pneumonia since the introduction of active vaccination against this organism in the late 1980s.

Hospital-Acquired Pneumonia

HAP occurs most commonly in critically ill patients and is usually caused by bacteria.[6] Factors predisposing patients to the development of HAP include high severity of illness, longer duration of hospitalization, supine positioning, witnessed aspiration, coma, acute respiratory distress syndrome, patient transport, and prior antibiotic exposure (Table 129-5). The strongest predisposing factor, however, is mechanical ventilation (intubation). The length of stay for hospital admissions is increased by a mean of 7 to 9 days for patients who develop HAP.[6]

HAP is predominantly caused by gram-negative aerobic bacilli or *S. aureus* and is much more likely to be caused by an MDR isolate.[6] Collectively, the non-lactose fermenting gram-negative bacilli *P. aeruginosa* and *Acinetobacter* spp. are the most common cause of HAP (about 25%-45%).[6] Enteric gram-negative bacilli such as *K. pneumoniae* and *E. coli* are also common (13%-20%).[6] *S. aureus* is also common (12%-21%) with approximately half of these isolates methicillin-resistant.[6] Patients with longer lengths of hospital admission or IV antibiotic use within the previous 90 days preceding HAP development are more likely to have MDR organisms.[6]

HAP can be subclassified as ventilator-associated pneumonia (VAP), which is pneumonia occurring after 48 or more hours of endotracheal intubation.[6] The risk for developing pneumonia in the hospital increases by 6 to 21 times after a patient is intubated because the natural airway defenses against the migration of upper respiratory tract organisms into the lower tract are bypassed.[6] This situation is exacerbated by the wide use of acid-suppressing drugs (eg, H_2-receptor blocking agents and proton pump inhibitors) in the intensive care unit, which increases the pH of gastric secretions and may promote the proliferation of microorganisms in the upper GI tract. Subclinical microaspirations are events that occur routinely in intubated patients and result in the inoculation of bacteria-contaminated gastric contents into the lung and a higher incidence of nosocomial pneumonia.[60] Although generally similar in etiology to HAP, VAP is more likely to be caused by *S. aureus* (20%-30%) and multidrug resistance is more common.[61,62]

Aspiration pneumonia is classically treated as a separate entity from CAP or HAP. It was predominantly caused by anaerobic bacteria that commonly colonize the oropharynx. The epidemiologic evidence suggests a decreasing importance of anaerobic bacteria in aspiration pneumonia. 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 severe periodontal disease or those with specific clinical findings such as necrotizing pneumonia or lung abscess.[54]

Tuberculosis

The acid-fast bacillus *Mycobacterium tuberculosis* causes tuberculosis and is spread person to person by inhalation of droplets. After years of steady decline, the number of cases of pneumonia caused by *M. tuberculosis* in the United States began to increase in the mid- to late 1980s. The new epidemic was a consequence of an increased incidence among prison inmates, IV drug abusers, immigrants, and, most prominently, HIV-infected patients. It is most prominent in urban neighborhoods afflicted with crowded living conditions and poor access to healthcare; thus, groups prone to tuberculosis include the homeless and patients in chronic care facilities and homes for the elderly. Unlike previous eras in which tuberculosis was seen most frequently in elderly men, infection currently is identified in increasing numbers of young adults. MDR strains of *M. tuberculosis* have become more common, and treatment regimens for these patients should involve consultation with a specialist. (See Chapter 135, "Tuberculosis" for a detailed discussion of tuberculosis pathophysiology, diagnosis, and treatment.)

Clinical Presentation and Diagnosis

The common signs, symptoms, physical exam findings, and diagnostic features of patients with pneumonia are listed in Table 129-6. They are both constitutional (fever, chills, malaise) and respiratory (cough, increased sputum production, dyspnea). These signs and symptoms coupled with physical exam findings suggestive of a pulmonary infiltrate, with or without abnormal whiteblood cell (WBC) count or oxygen saturation, can form the basis of a presumed clinical diagnosis of pneumonia. The diagnosis of pneumonia is preferably further strengthened by radiographic evidence such as

pulmonary infiltrate(s) on chest x-ray or another chest imaging. Clinical practice guidelines recommend a chest radiograph for all adult patients with suspected pneumonia but only in select pediatric patients with severe CAP (eg, inpatient, signs of hypoxia/respiratory distress).[4-6]

TABLE 129-6

Clinical Presentation of Pneumonia

Signs and symptoms
Abrupt onset of fever, chills, dyspnea, and productive cough
Rust-colored sputum or hemoptysis
Pleuritic chest pain
Dyspnea
Physical examination
Tachypnea and tachycardia
Dullness to percussion
Increased tactile fremitus, whisper pectoriloquy, and egophony
Chest wall retractions and grunting respirations
Diminished breath sounds over affected area
Inspiratory crackles during lung expansion
Chest radiograph
Dense lobar or segmental infiltrate
Laboratory tests
Leukocytosis with predominance of polymorphonuclear cells
Low oxygen saturation on arterial blood gas or pulse oximetry

Clinical and radiographic data can begin to shape the differential diagnosis of suspected pneumonia pathogens. 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.[64,65] The exception to this is *Legionella pneumophila*, which is an atypical pathogen that often causes severe illness making it a common pathogen in patients with CAP who require ICU admission.[64,118] Patients with atypical pneumonia also commonly have extrapulmonary, constitutional symptoms.[64,65] Atypical pneumonias often demonstrate patchy infiltrates on chest x-ray that are more extensive than clinical symptoms suggest, hence the term “walking pneumonia.”[66] Chest radiographs in patients with viral etiology are often diffuse, interstitial compared with the classic lobar or lobular consolidated infiltrates of bacterial pneumonia. Staphylococcal pneumonias often demonstrate cavitary or necrotizing lesions on imaging. Although these general clinical and diagnostic characteristics can be useful, there is considerable overlap in clinical presentation between pneumonia etiologies. These data alone are not sufficiently reliable to differentiate between bacterial, atypical bacterial, and viral etiology.[67] Similarly, the use of biomarkers, such as procalcitonin, is not recommended to differentiate between bacterial and viral pneumonia.[4,6]

10 Following a pneumonia diagnosis based on clinical and radiographic evidence, further diagnostic testing to confirm the diagnosis and determine the etiology may be warranted. 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.[6] Blood cultures often provide value in determining the causative pathogen, particularly in VAP where approximately 15% of patients have concomitant bacteremia.[68,69] Emphasis is placed on determining an etiology in HAP and VAP due to the high prevalence of MDR organisms and associated risk of ineffective empiric therapy. This allows adjustment of initial empiric therapy into optimal, pathogen-specific therapy.

Confirmation of etiology is less common in CAP, where a microbiologically confirmed etiology is identified in only 7% of cases in clinical practice.[70] As such, empiric treatment of CAP is often continued for the entire duration of therapy without ever determining the causative pathogen. Cultures are only routinely recommended in patients with more severe CAP where knowledge of the causative pathogen and whether the empiric antibiotic regimen is active are most important. In patients treated in the outpatient setting, sputum cultures are not routinely recommended. The exceptions to this are pediatric patients who have experienced failure of initial antibiotics and adult patients treated with empiric antibiotics that cover MRSA and/or *P. aeruginosa*.[4,5] Blood and sputum cultures are recommended in hospitalized adult patients with severe CAP. This includes, but is not limited to, patients with septic shock requiring vasopressors and/or those with respiratory failure requiring mechanical ventilation (Table 129-7). Blood and sputum cultures are also recommended in hospitalized adult patients receiving empiric therapy covering MRSA and/or *P. aeruginosa* or among considered at risk for these pathogens.[4] Sputum Gram stain and culture are recommended for hospitalized children who can produce a sputum sample along with blood cultures in those with moderate/severe CAP.[5] Urinary antigen tests are also available for *S. pneumoniae* and *L. pneumophila*, and are recommended in adults with severe CAP.[4] These tests are more rapid than traditional microbiologic methods and can detect pathogen antigen days (*S. pneumoniae*) to weeks (*L. pneumophila*) after initiation of antibiotic therapy.[71] These tests have a high specificity (90%-99%) but lower sensitivity (50%-80%). This translates to few false-positives and more false-negatives, making it a useful test to "rule in" these pathogens in adult patients.[63,72,73] Rapid diagnostic tests for viruses, including influenza, are also recommended in children with suspected CAP. Influenza nucleic acid amplification testing is also recommended in adult patients when influenza is circulating in the community. A positive result in combination with an absence of clinical factors strongly suggestive of bacterial infection can be used to reduce unnecessary antibiotic use.[5] It would also be prudent to perform nucleic acid amplification testing for SARS-CoV-2 when it is circulating in the community.

TABLE 129-7

Severe CAP Criteria

Major Criteria – 1 or more defines severe CAP
Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation
Minor Criteria – 3 or more defines severe CAP
Respiratory rate >30 breaths/min
PaO_2/FIO_2 ratio <250
Multilobar infiltrates
Confusion/disorientation
Uremia (blood urea nitrogen level >20 mg/dL [7.1 mmol/L])
Leukopenia (white blood cell count <4,000 cells/mm^3 [4×10^9/L])
Thrombocytopenia (platelet count <100,000/mm^3 [100×10^9/L])
Hypothermia (core temperature <36°C)
Hypotension requiring aggressive fluid resuscitation

Treatment Goals

Eradication of the offending organism through selection of the appropriate antibiotic(s) and subsequent complete clinical cure is the primary goal of therapy of pneumonia. 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.

General Approach to Treatment

Achievement of the goals of therapy for pneumonia treatment requires the provider to follow the principles of good antimicrobial stewardship

while ensuring adequate treatment of the potential infection. Comprehensive principles of optimal antimicrobial therapy and infectious diseases stewardship are discussed in detail in Chapter 127, "Antimicrobial Regimen Selection." In general, antimicrobial stewardship involves provision of the right antimicrobial(s) (or lack thereof when infection is not present); at the right time, at the right dose, for the right duration. This is often a balance between providing therapy broad enough to cover likely pathogens but not overly broad resulting in potentially unnecessary drug toxicity, secondary infection, or antibiotic resistance. This also involves continual monitoring of patient clinical status and diagnostic data to support the decision to either continue empiric therapy, narrow or alter therapy, or discontinue therapy if infection is ruled out. This section discusses the selection of antimicrobial regimens in patients with a suspected or confirmed diagnosis of pneumonia.

Following diagnosis of the pneumonia, one of the first treatment decisions is what level of medical care is necessary (ie, outpatient vs inpatient vs inpatient ICU). This decision is ultimately made by a physician and should be based on the patient's severity of illness and subsequent risk of mortality. However, it is important for pharmacists to be able to perform and understand this severity assessment because it should be used to recommend the appropriate diagnostic monitoring and empiric antimicrobial therapy. Multiple severity scores designed to estimate mortality risk in CAP are available for severity assessment.[74,75] The preferred severity score for determining whether hospital admission is appropriate is the Pneumonia Severity Index (PSI), also known as Pneumonia Outcomes Research Team (PORT) score.[4,76] The PSI score utilizes age, comorbidities, physical exam findings, diagnostic test results, and laboratory test results to compute a patient's mortality risk. The PSI score identifies patients with low mortality risk allowing them to be safely treated in the outpatient setting.[4] The extensive laboratory and physiologic data required to calculate the PSI score is often not readily available upon patient presentation or in the outpatient setting.[76] The CURB-65 or CRB-65 scores may be used in these cases.[74,75] These short, simple point systems can easily be applied at the point of care using readily available clinical data. 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. CRB-65 is a simplified version of CURB-65 that does not require knowledge of serum BUN concentration. Patients with CURB-65 or CRB-65 scores <2 are generally candidates for outpatient treatment.[4] Patients with a score of 2 or more are typically admitted to the general ward or ICU.[4] The severe CAP criteria listed in Table 129-7 are recommended to determine whether ICU care is necessary. Patients with one major criteria should be admitted to ICU. Minor criteria should be used in conjunction with clinical judgment when neither of the major criteria is present. Although guidelines do not state a specific number of minor criteria necessitating ICU admission, data indicate patients with three or more minor criteria are often admitted to the ICU in practice.[4]

Empiric Antimicrobial Treatment

Treatment of bacterial pneumonia, like the treatment of most infectious diseases, initially involves the empirical use of a relatively broad-spectrum antibiotic therapy that is effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained as indicated.[56,77] Therapy should be narrowed to cover specific pathogens after the results of cultures are known in cases where cultures are obtained. Multiple factors can aid in identifying the potential pathogens involved, including when and where the pneumonia was contracted, local pathogen epidemiology and susceptibility patterns, and individual patient factors. These individual patient factors include patient age, previous and current medication history, underlying disease(s), major organ function, and present clinical status. These factors must be evaluated to select an appropriate and effective empirical antibiotic regimen as well as the most appropriate route for drug administration (oral vs parenteral). (For a more detailed discussion on the principles of antibiotic selection, see Chapter 127.)

Because many antibiotics are effective in the treatment of bacterial pneumonia, and superiority of one antibiotic over another is often unclear or difficult to define, there are a variety of recommended empiric antimicrobial regimens for suspected bacterial pneumonia. For a list of potential empiric antimicrobial regimens, based on available clinical practice guidelines, primary literature, and antimicrobial susceptibility and PK/PD, refer to Table 129-8 for adults and Table 129-9 for children. A complete list of antimicrobial agents for specific pathogens is beyond the scope of this chapter and is presented in Chapter 127. Table 129-10 lists dosages for selected antibiotics used for the treatment of bacterial pneumonia.

TABLE 129-8

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)	*S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *M. catarrhalis*	Amoxicillin (preferred) OR Doxycycline (2nd preferred) OR Macrolide[b] (non-preferred)
At-risk comorbidity (diabetes, heart/lung/liver/renal disease, alcoholism, malignancy, asplenia) OR immunosuppressive condition/drugs	*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
Inpatient/Community-Acquired		
Non-severe CAP	*S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* sp.	β-Lactam[e] + EITHER macrolide[b] OR doxycycline OR
	If prior respiratory MRSA (1 year)	Antipneumococcal fluoroquinolone[c]
	If prior respiratory *P. aeruginosa* (1 year)	ADD vancomycin OR linezolid AND obtain cultures, de-escalate in 48 hr if MRSA negative and clinically improving
	If prior hospitalization AND IV antibiotic (90 days) OR	ADD[f] cefepime, piperacillin-tazobactam, ceftazidime, imipenem, meropenem, OR aztreonam AND obtain cultures, de-escalate in 48 hr if *P. aeruginosa* negative and clinically improving
	locally validated risk factor	Obtain cultures, escalate if needed based on results
Severe CAP	*S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* sp.	β-Lactam[e] + EITHER macrolide[b] OR antipneumococcal fluoroquinolone[c]
	If prior respiratory MRSA (1 year)	ADD vancomycin OR linezolid AND obtain cultures, de-escalate in 48 hr if MRSA negative and clinically improving
	If prior respiratory *P. aeruginosa* (1 year)	ADD[f] cefepime, piperacillin-tazobactam, ceftazidime, imipenem, meropenem, OR aztreonam AND obtain cultures, de-escalate in 48 hr if *P. aeruginosa* negative and clinically improving
	If prior hospitalization AND IV antibiotic (90 days)	ADD vancomycin OR Linezolid AND ADD[e] cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, OR aztreonam AND obtain cultures, de-escalate if MRSA/*P. aeruginosa*-negative and clinically improving
Hospital-Acquired Pneumonia		

Low mortality risk[g] AND No MDR HAP[h] risk factors AND Local MRSA prevalence <20%	Non-fermenting gram-negative bacilli[i], 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[i], 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[i], 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	*S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*	Treat as above for CAP
Hospital-acquired	*S. aureus*, *P. aeruginosa* enteric gram-negative bacilli	Treat as above for HAP
	If anaerobes suspected	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, ampicillin-sulbactam, ceftaroline.

[f]If β-lactam-based CAP regimen selected, substitute antipseudomonal β-lactam for standard CAP β-lactam, unless ceftazidime or aztreonam chosen.

[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 129-9

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* (nontypable), *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-to-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-to-moderate CAP	*S. pneumonia* *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin,[b,g] or fluoroquinolone Macrolide/azalide, fluoroquinolone, or tetracycline
Moderate-to-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.

Data from Reference 5.

TABLE 129-10

Antibiotic Doses for Treatment of Bacterial Pneumonia

Antibiotic Class	Antibiotic	Antibiotic Dose[a]	
		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 hr if ampicillin/sulbactam) 875-2,000 mg orally twice daily 3.375-4.5 g IV every 6-8 hr 12-24 million units/day in divided doses IV every 4-6 hr
Extended-spectrum cephalosporins	Ceftriaxone Cefotaxime Ceftazidime Cefepime Ceftolozane-tazobactam Ceftazidime-avibactam Cefiderocol	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 hr 1-2 g IV every 8 hr 1-2 g IV every 6-8 hr 3 g IV every 8 hr 2.5 g IV every 8 hr 2 g IV every 8 hr
Monobactam	Aztreonam	90-120 mg/kg/day IV	1-2 g IV every 8 hr
Macrolide/azalide	Clarithromycin Erythromycin Azithromycin	15 mg/kg/day orally 30-50 mg/kg/day IV or orally 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 to 8 hr 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 hr/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	7.5-10 mg/kg/day IV 7.5-10 mg/kg/day IV	7.5 mg/kg IV daily 7.5 mg/kg IV daily

	Amikacin Plazomicin	15-20 mg/kg/day IV	15-20 mg/kg IV daily 15 mg/kg IV daily
Carbapenems	Imipenem Meropenem Meropenem-vaborbactam Imipenem-relabactam	60-100 mg/kg/day IV 30-60 mg/kg/day IV	500-1,000 mg IV every 6 to 8 hr 500-2,000 mg IV every 6 to 8 hr 2 g/2 g IV every 8 hr 1.25 g every 8 hr
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 hr IV: 2-2.5 mg/kg × 1, then 1.25-1.5 mg/kg every 12 hr
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 hr 600 mg IV or orally every 12 hr 600 mg IV or orally every 8 hr or 450 mg orally every 6 hr

[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.

Community-Acquired Pneumonia

Tables 129-8 and 129-9 provide evidence-based guidelines for the treatment of CAP in adults[4] and children,[5] respectively. The bacterial causes are relatively constant, even across geographic areas and patient populations. Unfortunately, pathogen resistance to standard antimicrobials is increasing (penicillin-resistant *S. pneumoniae,* macrolide-resistant *S. pneumoniae*, etc.) and can vary geographically, necessitating careful attention by the clinician to local and regional bacterial susceptibility patterns.[78] Indiscriminate use of antimicrobials for treatment of pneumonia has contributed to the problem of antimicrobial resistance, underscoring the need for defining the optimal antibiotic regimen for each patient. Thus, initial therapy should be based on presumed antibacterial susceptibility.

Evidence-based empiric therapy for CAP in adults differs between outpatients, hospitalized patients, and hospitalized patients admitted to an intensive care unit (see Tables 129-8 and 129-9).[4,5] In adult outpatients, choice of therapy depends on the individual patient's risk for drug-resistant *S. pneumoniae*. Amoxicillin is the preferred treatment for patients at low risk (ie, no at-risk comorbidities). Patients who cannot receive amoxicillin should be treated with doxycycline. Macrolides (such as azithromycin) should only be used when both amoxicillin and doxycycline are contraindicated and local macrolide-resistant *S. pneumoniae* prevalence is low.[4] In patients with specific comorbidities putting them at risk for treatment failure or drug-resistant *S. pneumoniae*, either anti-pneumococcal fluoroquinolone monotherapy (such as levofloxacin or moxifloxacin) or combination therapy consisting of a β-lactam (Table 129-8) plus either a macrolide or doxycycline is indicated to ensure coverage of resistant strains.[4] Empiric therapy of CAP for inpatients differs from that of outpatients in two ways: first, it is usually IV rather than oral route of administration; and second, coverage against drug-resistant *S. pneumoniae* is given to all patients. This reflects the desire to rapidly achieve adequate systemic antimicrobial exposures and increase the likelihood of providing in vitro active therapy in patients with a higher severity of illness where the importance of early appropriate therapy is increased. In patients with severe CAP, therapy should always consist of a combination regimen with a β-lactam backbone (Table 129-8), as

these regimens are associated with reduced mortality in patients with bacteremic pneumococcal pneumonia.[79-81]

Coverage of less frequent CAP pathogens, such as MRSA and *P. aeruginosa*, may be considered in patients with specific risk factors for these pathogens.[4] Patients with a positive respiratory culture for MRSA and/or *P. aeruginosa* in the past year should receive empiric coverage for that respective pathogen.[4] Respiratory cultures and/or nasal MRSA PCR tests should be obtained in these patients before antibiotic therapy is administered. The empiric MRSA and/or *P. aeruginosa* coverage should be discontinued in 48 hours if these test results are negative for these pathogens and the patient is clinically improving. Patients who have been hospitalized in the past 90 days who also received IV antibiotics are at increased risk for both MRSA and *P. aeruginosa*. Patients meeting this criteria who have non-severe cap should have cultures and nasal MRSA PCR tests performed. Antibiotics covering MRSA and/or *P. aeruginosa* should be added only if these pathogens are identified. Patients who have been hospitalized in the past 90 days who also received IV antibiotics admitted with severe CAP should receive both empiric MRSA and *P. aeruginosa* coverage and have cultures performed. The MRSA and *P. aeruginosa* coverage should be discontinued after 48 hours if culture results are negative and the patient is clinically improving.[4]

Additional treatment considerations for adult patients with CAP include whether to provide coverage for influenza or SARS-CoV-2 and whether adjunctive corticosteroids are necessary. Nucleic acid amplification testing for influenza should be obtained when influenza and/or SARS-CoV-2 is circulating in the community.[4] Treatment with a neuraminidase inhibitor (such as oseltamivir or peramivir) should be administered only if influenza testing is positive. Adjunctive corticosteroids should only be given to patients with septic shock that is refractory to fluid resuscitation and vasopressor support.[4]

Similar to adult patients, empiric antibiotic regimens for CAP in pediatric patients differ between the outpatient and inpatient setting. However, in pediatric patients, choice of empiric therapy is more dependent on patient age group and immunization status rather than comorbidity. For outpatients, choice of therapy is predominantly based on age group and suspected etiology (ie, typical vs atypical bacteria; viral). Among inpatients, those fully immunized against *S. pneumoniae* and *H. influenzae* type B may be treated with a penicillin antibiotic with or without macrolide for typical coverage as indicated based on clinical suspicion for atypical pneumonia.[5] Empiric regimens in unimmunized patients or in areas with a high prevalence of penicillin-resistant *S. pneumoniae* should consist of third-generation cephalosporin (such as ceftriaxone).[5] Similar to CAP in adults, MRSA is sometimes the causative pathogen. Addition of MRSA coverage (with vancomycin or linezolid) should be considered when clinical suspicion is high (post-viral pneumonia, necrotizing/cavitary radiographic findings).[5]

Patient Care Process

Patient Care Process for Pneumonia

Collect

- Patient characteristics (eg, age, sex, pregnancy, drug allergies)

- Patient medical history including comorbid conditions, previous infections, previous hospitalization, and current or recent residence in a nursing facility
- Social history (including tobacco/ethanol/drug use)
- Current and past medications, particularly antimicrobials, immune suppressants, and chemotherapy
- Subjective data
  - Patient-reported risk factors for pneumonia (Table 129-5)
  - Patient-reported pneumonia signs/symptoms (Table 129-6)
  - Timing/location of symptom onset (ie, community vs hospital; time since onset)
- Objective data
  - Temperature, blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation, ventilator settings if applicable
  - Pertinent respiratory physical exam findings (Table 129-6)
  - Diagnostic procedures (such as chest imaging)
  - Labs including CBC and differential, basic metabolic panel, blood gases, and lactate (if sepsis suspected)
  - Current and previous microbiology results including antimicrobial susceptibility when available

Assess

- Likelihood of pneumonia based on history of present illness, physical exam, imaging, and laboratory and microbiologic data
- Severity of illness and mortality risk based on hemodynamics, respiratory status, presence of organ failure, severity score(s) if CAP
- Most likely pathogens and potential for antimicrobial resistance based on age, comorbidities, clinical presentation and diagnostics, pneumonia type (ie, CAP vs HAP vs VAP vs aspiration—Table 129-5), local epidemiology and antimicrobial resistance patterns, previous infections and antibiotic exposure

Plan

- Empiric antimicrobial regimen based on likely pathogen(s) and mortality risk
  - Include drug(s), route of administration, dose, frequency, and duration (Tables 129-8 to 129-10)
- Appropriate monitoring parameters for efficacy, toxicity, and potential modification of therapy (ie, cultures or other tests for etiology when indicated)
  - Include timing (cultures preferably obtained before antimicrobials administered) and frequency
- Provider education including rationale and evidence for recommendation
- Patient education including counseling points/monitoring for efficacy and safety

Implement*

- Clearly and professionally communicate recommendations to prescribers, healthcare team, and/or patient
- Determine consensus treatment plan as an interdisciplinary team

- Follow-up to ensure accurate/appropriate implementation of consensus treatment plan (antimicrobial therapy, diagnostics, and monitoring)

Follow-up: Monitor and Evaluate

- Efficacy monitoring including improvement/resolution of signs/symptoms, physiologic and laboratory data with focus on indicators of infection (temperature, WBC, etc.), respiratory status (RR, oxygenation, ventilator settings), and organ failure/sepsis
- Safety monitoring (including SCr and urine output for nephrotoxicity, etc.)
- Microbiologic cultures and diagnostic tests for etiology
- Assess whether therapy can be narrowed, should be broadened, or requires change based on above monitoring considerations
- When possible, change empiric therapy to pathogen-directed therapy (Table 129-11)
- Design and implement new plan and continual monitoring as needed/appropriate

**Collaborate with patient, caregivers, and other healthcare professionals.*

TABLE 129-11

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.

Hospital-Acquired and Ventilator-Associated Pneumonia

9 Because HAP and VAP have a distinctive epidemiology compared with CAP, empiric antimicrobial regimens for HAP and VAP differ greatly from those for CAP (Table 129-8). Despite this, selection of therapy is based on many of the same principles. As with CAP, knowledge of the local pathogen and antibiotic resistance distribution is important. Antibiotic resistance patterns can vary greatly between institutions in the same city and even within the same institution between hospital units. Because of this, use of institution-specific antibiograms is highly recommended. These antibiograms should ideally also contain separate susceptibility data specific to the ICU population.[6] Along with local susceptibility, patient-specific factors should weigh heavily in the choice of empiric therapy. Individual risk factors for infection with MRSA and MDR gram-negative bacilli are particularly important in HAP and VAP, as is severity of illness and mortality risk.

The vast majority of HAP cases are caused by gram-negative bacilli, predominantly *P. aeruginosa* and the Enterobacteriaceae, or *S. aureus*.[6] As such, all empiric HAP regimens should consist of at least one antibiotic with coverage against these pathogens, usually an antipseudomonal, antistaphylococcal β-lactam (such as piperacillin/tazobactam or cefepime) or an antipseudomonal, antistaphylococcal fluoroquinolone (such as levofloxacin).[6] While aminoglycosides are useful in treating gram-negative pneumonia in combination with another gram-negative-active antibiotic, they should not be used as monotherapy in pneumonia given the lack of data supporting their use in this manner. Patients contracting the pneumonia in a hospital or hospital unit with an MRSA prevalence of 20% or greater should also receive MRSA coverage with either vancomycin or linezolid.[6] Patients with MDR HAP risk factors, such as receipt of IV antibiotics in the past 90 days or structural lung disease, should also receive MRSA coverage in addition to a second antipseudomonal agent to cover for MDR gram-negative bacilli. An empiric antibiotic regimen containing dual pseudomonal and MRSA coverage is also indicated in patients at high risk of mortality, such as those requiring mechanical ventilation as a result of their pneumonia and those in septic shock.[6] This approach is taken to maximize the likelihood of early effective therapy in those patients where the consequences of delayed appropriate therapy in the event the pathogen is resistant to the empiric regimen are greatest.

Empiric antibiotic regimens for patients with VAP are similar to patients with HAP. In patients with no MDR VAP risk factors, who contracted VAP in a unit with a low prevalence of both MRSA (less than 10%-20%) and of gram-negative bacilli resistance (<10% to an antibiotic being considered for use), monotherapy with an antipseudomonal antibiotic with staphylococcal coverage may be used.[6] Higher MRSA prevalence would indicate the addition of vancomycin or linezolid. Likewise, more than 10% resistance to all antibiotics being considered for gram-negative monotherapy would indicate the need for double antipseudomonal coverage (Table 129-8).[6] Patients at risk for MDR VAP, including those receiving IV antibiotics in previous 90 days, those in septic shock, those with VAP onset after 5 or more days of hospitalization, and those with acute respiratory distress syndrome or receiving renal replacement therapy preceding VAP onset should also receive double pseudomonal and MRSA coverage.[6]

Pathogen-Directed Antimicrobial Therapy

10 Tailoring antimicrobial therapy based on diagnostic test results and patient clinical status is an important aspect of the pharmacotherapy of pneumonia. Utilizing a pathogen-directed antimicrobial regimen can optimize patient outcome using evidence-based antimicrobials for a particular pathogen. It can also mitigate potential negative impacts of ongoing broad-spectrum antimicrobial use, including adverse drug reactions, *C. difficile* infection, and development of further MDR infection.[82-84] When tailoring antimicrobial therapy, it is important to consider both diagnostic test results (chest imaging, Gram stain, respiratory cultures), and patient clinical factors (hemodynamics, temperature, respiratory status, white blood cell counts/differential). In patients who are clinically stable with signs of improving infection, narrowing of therapy should be considered, especially if culture results have identified a likely pathogen with associated susceptibility pattern.[6] Recommendations for directed therapy of common pneumonia pathogens can be found in Table 129-11.

Directed Therapy of Important Gram-Positive Pathogens

10 Directed therapy for *S. pneumoniae,* the most common bacterial cause of CAP, primarily depends on penicillin susceptibility. For isolates considered susceptible to intravenous penicillin by the CLSI (MIC ≤2 mg/L), a narrow-spectrum penicillin such as penicillin, ampicillin, or amoxicillin is

preferred.[4] Alternatively, a cephalosporin antibiotic may be used, or in the case of a severe β-lactam allergy, either a macrolide or antipneumococcal fluoroquinolone (Table 129-11).[4] For penicillin-resistant strains, a third-generation cephalosporin or fluoroquinolone is preferred (Table 129-11). High-dose amoxicillin (3 g/day) may be used for penicillin-intermediate strains (MIC = 4 mg/L).[4] High-dose amoxicillin has efficacy in these situations because resistance of *S. pneumoniae* to penicillins is conferred through a change in penicillin-binding protein resulting in decreased affinity of the antibiotic for the binding site. In the case of penicillins and *S. pneumoniae*, this can be overcome by more aggressive dosing that maximizes achievement of adequate time drug concentration is in excess of the MIC ($t >$ MIC) despite the elevated MIC.[85]

Treatment of *S. aureus* pneumonia is dependent on whether the strain exhibits methicillin resistance. Treatment with an antistaphylococcal penicillin, such as oxacillin, nafcillin, or dicloxacillin, is preferred by the CAP guidelines for methicillin-susceptible strains.[4] Cefazolin is an alternative for methicillin-susceptible strains with fewer clinical data in pneumonia. However, it is an equivalent alternative to an antistaphylococcal penicillin on the basis of data from *S. aureus* bacteremia suggesting equivalence or even superiority.[86] Clindamycin or vancomycin may also be used, although these agents are not preferred for treatment of MSSA infections.[87] The treatment of choice for MRSA pneumonia is either vancomycin or linezolid, which are considered equivalent by infectious Diseases Society of America (IDSA) guidelines.[88-90] Vancomycin is often preferred over linezolid in clinical practice to preserve linezolid susceptibility for infections for which linezolid is one of the few remaining treatment options, such as infections caused by vancomycin-resistant enterococci (VRE). Telavancin, while FDA-approved for HAP/VAP caused by *S. aureus*, is often reserved for alternate therapy due to concerns of nephrotoxicity and potentially increased mortality in the subgroup of patients with a creatinine clearance less than 30 mL/min (0.5 mL/s). Additional alternatives for MRSA pneumonia include quinupristin-dalfopristin, ceftaroline, sulfamethoxazole-trimethoprim, and clindamycin. However, clinical evidence for these alternative options remains limited.[91-93]

Directed Therapy of Important Gram-Negative Pathogens

10 For *H. influenzae*, the most common gram-negative cause of CAP, the choice of directed therapy is dependent on whether the strain is β-lactamase producing. Non-β-lactamase-producing strains may be treated with ampicillin (IV) or amoxicillin (oral).[4] A third-generation cephalosporin (such as ceftriaxone) is the treatment of choice for β-lactamase-producing strains. Alternative therapy for *H. influenzae* includes fluoroquinolone, doxycycline, azithromycin, or clarithromycin.[4] Azithromycin is generally preferred to clarithromycin. A larger proportion of *H. influenzae* strains are susceptible to azithromycin relative to clarithromycin and azithromycin has a more favorable drug interaction profile.[94,95]

P. aeruginosa is a notoriously antibiotic-resistant pathogen that utilizes a variety of mechanisms of resistance, resulting in variable susceptibility patterns. Because of this, directed therapy against *P. aeruginosa* pneumonia is highly dependent on antimicrobial susceptibility results. When susceptible, all antipseudomonal agents recommended for empiric therapy are considered equivalent with respect to clinical outcomes in pneumonia.[6] The exception to this is the aminoglycosides, which are not recommended as monotherapy against *P. aeruginosa* pneumonia. Despite equivalence of most antibiotics in this setting, piperacillin-tazobactam, cefepime, and ceftazidime are generally preferred when susceptible. This is to preserve susceptibility of carbapenems, newer β-lactam/β-lactamase inhibitors, and fluoroquinolones for use in more resistant infections. Another consideration in the directed therapy of *P. aeruginosa* is the utility of combination therapy. Patients receiving monotherapy and combination therapy generally have similar outcomes.[6] However, combination therapy may be associated with reduced mortality in patients with septic shock.[96] Directed combination therapy against *P. aeruginosa* only is recommended in patients in septic shock or at high risk of mortality at the time antimicrobial susceptibility testing results become available.[6]

Enterobacterales, particularly *K. pneumoniae* and *E. coli*, are common causes of both HAP and VAP. Although generally susceptible to the gram-negative active agents recommended for empiric therapy of HAP and VAP, Enterobacteriaceae-producing extended-spectrum β-lactamases (ESBL) capable of hydrolyzing many of the β-lactams commonly used for empiric therapy have become increasingly common.[97-99] Because this diverse family of β-lactamases each has variable affinity for different β-lactams, susceptibility to each β-lactam agent can vary depending on the enzyme (ie, CTX-M, TEM, SHV).[100] Further complicating this is the inoculum effect, whereby β-lactams seemingly susceptible in vitro are hydrolyzed in vivo in the presence of a high-inoculum of ESBL-producing organism.[101] This variable susceptibility has resulted in debate regarding the treatment of choice for these infections. Although the limited evidence from observational studies did not demonstrate superiority of carbapenems over piperacillin/tazobactam or cefepime when the organism is susceptible to these agents, carbapenems are often considered the treatment of choice for serious ESBL infections such as pneumonia.[6] Piperacillin/tazobactam was not as effective meropenem for ceftriaxone-resistant *E. coli* or *K. pneumoniae* bloodstream

infections.[102] Based on this, carbapenems will likely continue to be considered the treatment of choice for serious ESBL infections. If piperacillin/tazobactam or cefepime are utilized, it is important to ensure that the isolate is considered fully susceptible by the Clinical and Laboratory Standards Institute (CLSI) and that aggressive dosing strategies to ensure optimal *t* > MIC are employed.

While initially thought of as reliable, last-line antibiotics for resistant gram-negative infections, resistance to carbapenems due to a variety of mechanisms has emerged. Until recently, few antibiotics retained activity against these organisms, resulting in a resurgence in the use of older, more toxic agents such as the polymyxins (colistin, polymyxin B). Availability of three new β-lactam/β-lactamase inhibitor combinations, ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam has provided hope for these infections. Ceftazidime/avibactam and meropenem/vaborbactam have in vitro activity against most carbapenem-resistant Enterobacteriaceae (CRE) acquiring resistance via carbapenemase enzymes.[103,104] Although ceftolozane-tazobactam does not have activity against carbapenemase-producing strains, it is active against many carbapenem-resistant *P. aeruginosa* strains where the primary mechanism of carbapenem resistance is change in cell permeability and/or efflux pumps.[105] Clinical data suggest that these new antimicrobials may be superior and less toxic relative to colistin- and/or aminoglycoside-containing regimens.[106-108,119] Coupled with favorable in vitro susceptibility data it seems reasonable to prefer these novel agents to more toxic polymyxin-containing regimens when the isolate is susceptible. Additional new antibiotic therapies with in vitro activity against many MDR pathogens that commonly cause lower respiratory tract infections and varying levels of clinical evidence include cefiderocol, plazomicin, imipenem-cilastatin-relebactam, and eravacycline. For infections that remain resistant to all other available antibiotics, treatment with inhaled polymyxins or aminoglycosides are recommended.[6] Inhaled antibiotics should be given with systemic antibiotics to which the pathogen is susceptible (ie, if only susceptible to colistin, give both inhaled and IV colistin).

Directed Therapy of Important Atypical Pathogens

10 Treatment of pneumonia caused by atypical bacteria, including *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*, generally consists of either a fluoroquinolone, macrolide, or doxycycline. For *C. pneumoniae* and *M. pneumoniae*, macrolides or doxycycline are preferred agents.[4] Fluoroquinolones or azithromycin is preferred over doxycycline for *Legionella* pneumonia due to the relative paucity of data involving doxycycline for this infection.[4]

Antimicrobial Pharmacokinetic/Pharmacodynamic Considerations

Antimicrobial pharmacokinetics/pharmacodynamics (PK/PD) is an important aspect of optimal antimicrobial therapy for pneumonia. Antibiotic concentrations in respiratory secretions in excess of the pathogen MIC are necessary for successful treatment of pulmonary infections.[109] Thus, ability of an antimicrobial to penetrate into pulmonary secretions is important and must be factored into antimicrobial selection and dosing for pneumonia. The ability of a drug to penetrate respiratory secretions depends on multiple physicochemical factors, including molecular size, lipid solubility, and degree of ionization at serum and biologic fluid pH and the extent of protein binding. Studies evaluating antibiotic concentrations in the pulmonary epithelial lining fluid (ELF) indicate that β-lactams, glycopeptide, and aminoglycosides tend to have ELF to plasma antibiotic concentration ratios less than 1. In contrast, macrolides, fluoroquinolones, and linezolid tend to have ELF to plasma antibiotic concentration ratios much greater than 1. Thus, the latter agents penetrate and concentrate into the ELF to a greater extent.[109]

Although β-lactams, glycopeptides, and aminoglycosides have less extensive ELF penetration, carefully constructed dosing schemes based on PK/PD principles allow these agents to be effective in treating lower respiratory tract infections. Although evidence is conflicting, dosing guided by PK/PD principles may reduce mortality and improve clinical outcome in patients with pneumonia.[6] The use of strategies maximizing antibiotic PK/PD to select antibiotic dosing for HAP and VAP is recommended by the IDSA guidelines.[6] This includes weight-based initial dosing of vancomycin and aminoglycosides followed by measurement of serum antibiotic concentrations to adjust doses through antibiotic therapeutic drug monitoring (TDM) and use of extended or continuous infusion of β-lactams. Dosing and TDM of vancomycin for pneumonia should target achievement of a vancomycin area under the concentration-time curve (AUC) 400-600 mg*hr/L early in the course of therapy.[110,111] This will maximize achievement of AUC/MIC ratios >400 for *S. aureus* isolates with an MIC ≤1 mg/L. Clinical practice guidelines recommend this should preferably be achieved via AUC monitoring.[112] Alternatively, this may be achieved by targeting vancomycin trough concentrations of 15-20 mg/L (10.4-13.8 µmol/L) as surrogate for AUC >400 mg*h/L, although this approach leads to supratherapeutic AUC in a large proportion of patients and a resulting increased risk of vancomycin-associated nephrotoxicity.[13,120] The preferred aminoglycoside dosing strategy for pneumonia, when patient renal function permits, is high-dose once-daily

administration. This approach maximizes the AUC:MIC and peak:MIC ratios for efficacy while allowing undetectable serum trough concentrations for a period of time to minimize nephrotoxicity.[113,114] Aminoglycoside peak:MIC ratios ≥10 are typically targeted clinically for pneumonia. We refer the reader to Chapter e126, "Laboratory Tests to Direct Antimicrobial Pharmacotherapy" and Chapter 127 for more in-depth discussion of antibiotic PK/PD concepts.

PATIENT MONITORING, THERAPY MODIFICATION, AND DURATION OF THERAPY

After therapy has been instituted, appropriate clinical parameters should be monitored to ensure the efficacy and safety of the therapeutic regimen. For patients with bacterial infections of the lower respiratory tract, the time to resolution of initial presenting symptoms and the lack of appearance of new associated symptomatology are important to determine.[115] 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. If the patient requires supplemental oxygen therapy, the amount and need should be assessed regularly. A gradual and persistent improvement in the resolution of these symptoms and therapies should be observed. Initial resolution of infection should be observed within the first 2 days of therapy and progression to complete resolution within 5 to 7 days (usually no more than 10 days). Because cultures for causative organism are rarely obtained except for more severe CAP cases, empiric therapy is typically continued for the duration of therapy provided the patient is responding adequately. When cultures are obtained, tailoring therapy to be pathogen-directed as described above is recommended. The majority of hospitalized patients with CAP should be switched from IV to oral therapy when hemodynamically stable, improving clinically as described above, have normal gastrointestinal tract function, and be able to ingest oral medications.[4] The minimum duration of therapy for CAP is 5 days, although CAP is commonly treated for 7 to 10 days.[4] When discontinuing therapy, patients should be afebrile for 48 to 72 hours and have no more than one CAP-related sign of clinical instability (ie, tachycardia, tachypnea, hypotension, hypoxia, altered mental status). Discontinuation of therapy using these criteria starting at day 5 of therapy decreases the duration of antibiotic therapy without reducing cure rates or increasing readmission in non-ICU CAP patients.[116]

For patients with HAP, substantial underlying diseases, or both, additional parameters can be followed, including the magnitude and character of the peripheral blood WBC count, chest radiograph, and blood gas determinations. Similar to patients with less severe disease, 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 patient should be evaluated carefully for deterioration of underlying concurrent disease(s). Additionally, 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 to 72 hours of therapy. The results of initial and follow-up diagnostic tests, such as respiratory cultures, should also be used alongside clinical response to streamline therapy. De-escalation of antibiotic therapy to be more narrow spectrum in patients with HAP/VAP is strongly recommended. This approach may not affect clinical outcomes while reducing excess antibiotic use.[6] 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.[6] Serum procalcitonin concentrations in combination with clinical response criteria can be used in the decision to discontinue antibiotic therapy.[6]

Prevention of Pneumonia

Prevention of some cases of pneumonia is possible through the use of vaccines and medications against selected infectious agents. Polyvalent polysaccharide vaccines are available for two of the leading causes of bacterial pneumonia, *S. pneumoniae* and *H. influenzae* type b. Children should be vaccinated against *S. pneumoniae*, *H. influenzae* type b, pertussis, and influenza while caregivers for infants less than 6 months should also be vaccinated against influenza and pertussis. Immune prophylaxis for RSV is only recommended for high-risk infants during RSV season. To minimize the risk of developing VAP, healthcare providers should seek to minimize colonization of the aerodigestive tract, prevent aspiration (head raised 45 degrees), and limit the length of mechanical ventilation of patients.[60] (See Chapter 131 for a full discussion of influenza postexposure prophylaxis and Chapter 147, "Vaccines, Toxoids, and Other Immunobiologics" for vaccines.)[117]

ABBREVIATIONS

AAP	American Academy of Pediatrics
ADME	absorption, distribution, metabolism, and excretion
AECB	acute exacerbation of chronic bronchitis
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
CAP	community-acquired pneumonia
CLSI	Clinical and Laboratory Standards Institute
COPD	chronic obstructive pulmonary disease
CRE	carbapenem-resistant Enterobacteriaceae
ELF	epithelial lining fluid
FEV_1	forced expiratory volume in the first second of expiration
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
LABA	long-acting β-receptor agonist
LAMA	long-acting muscarinic antagonist
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NAC	*N*-acetyl cysteine
PCR	polymerase chain reaction
PDE4	phosphodiesterase 4
PK-PD	pharmacokinetics/pharmacodynamics
RSV	respiratory syncytial virus
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus

TDM	therapeutic drug monitoring
VAP	ventilator-associated pneumonia
VRE	vancomycin-resistant enterococci
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. In the absence of a complicating bacterial infection, which of the following is the most appropriate approach to treating acute bronchitis?
   A. Prescribing broad-spectrum antibiotics
   B. Routinely recommending non-prescription cough and cold preparations
   C. Providing symptomatic and supportive care
   D. Discouraging hydration and bed rest
2. Which of the following is true regarding chronic bronchitis?
   A. The majority of patients who suffer from chronic bronchitis have a negative smoking history.
   B. *N*-acetylcysteine should be routinely prescribed to treat associated bronchospasm.
   C. Given the low incidence of bacterial resistance, broad-spectrum antibiotics are rarely employed.
   D. During acute exacerbations, the use of antimicrobial is controversial; however, patients with prominent symptoms may benefit.
3. Which of the following is the most common cause of bronchiolitis?
   A. Respiratory syncytial virus
   B. Parainfluenza virus
   C. Mycoplasma
   D. Adenovirus
4. Which of the following statements is true regarding the treatment of bronchiolitis?
   A. The routine use of systemic corticosteroids should be encouraged.
   B. The use of aerosolized albuterol is associated with significant improvement in a majority of patients.
   C. Due to its clinical efficacy, ribavirin should be routinely prescribed.
   D. Hypertonic saline has proven efficacy after 1 day of use.
5. Community-acquired bacterial pneumonia is most commonly caused by:

A. *Staphylococcus aureus*

B. *Listeria monocytogenes*

C. *Legionella* species

D. *Streptococcus pneumoniae*

6. Which of the following would be the most appropriate empiric therapy for hospital-acquired pneumonia in a patient who has not received antibiotics in the past 90 days in a hospital with an MRSA prevalence of 10%?

A. Ceftriaxone

B. Vancomycin

C. Piperacillin/tazobactam

D. Cefepime + vancomycin

7. Which of the following pathogens should be highly suspected when prescribing empiric antimicrobial therapy to a newborn?

A. *Mycoplasma*

B. Group A *Streptococcus*

C. Group B *Streptococcus*

D. *Pseudomonas*

8. Which of the following is a risk factor for multidrug-resistant hospital-acquired pneumonia?

A. Receipt of intravenous chemotherapy in the past 90 days

B. Receipt of corticosteroids in the past 90 days

C. Receipt of intravenous antibiotics in the past 90 days

D. Receipt of highly active antiretroviral therapy (HAART) in the past 90 days

9. Which of the following would be the most appropriate therapy for the treatment of *Mycoplasma* pneumonia in a patient with compliance issues and currently receiving theophylline?

A. Erythromycin

B. Azithromycin

C. Clindamycin

D. Clarithromycin

10. Which of the following would be the most preferred antimicrobial agents in the treatment of aspiration pneumonia in a hospitalized patient with a necrotizing lesion on chest radiograph?

A. Clindamycin and ceftriaxone

B. Piperacillin/tazobactam and vancomycin

C. Cefepime

D. Ceftriaxone

11. Which of the following is NOT a risk factor for multidrug-resistant ventilator-associated pneumonia?

A. Receipt of intravenous antibiotics in the past 90 days

B. Acute respiratory distress syndrome preceding VAP onset

C. Receipt of a blood transfusion in the past 90 days

D. Receipt of renal replacement therapy prior to VAP onset

12. Which of the following would be appropriate empiric antibiotic therapy for a patient being admitted to the intensive care unit requiring mechanical ventilation due to community-acquired pneumonia?

A. Ceftriaxone

B. Ceftriaxone + azithromycin

C. Levofloxacin

D. Levofloxacin + azithromycin

13. Which of the following is appropriate empiric therapy for a patient with VAP who is currently in septic shock?

A. Vancomycin + piperacillin/tazobactam

B. Piperacillin/tazobactam + tobramycin

C. Linezolid + ertapenem + ciprofloxacin

D. Vancomycin + cefepime + tobramycin

14. Which of the following is considered a first-line antibiotic therapy for ESBL *E. coli* pneumonia?

A. Ertapenem

B. Tobramycin

C. Cefepime

D. Ceftriaxone

15. Which of the following is considered a first-line antibiotic therapy for MRSA pneumonia?

A. Daptomycin

B. Clindamycin

C. Linezolid

D. Telavancin

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Acute bronchitis is typically self-limiting and management involves symptomatic and supportive care. Antipyretics/analgesics, increasing fluid intake, and resting are the primary management options. Patients may use non-prescription cough and cold products; however, there is limited

evidence supporting their efficacy. Routine use of antibiotics also has limited benefit. See sections on "Acute bronchitis - General Approach to Treatment" and "Pharmacologic Therapy".

2. **D.** Acute exacerbations of chronic bronchitis may benefit from antimicrobial therapy if patients have two of the three symptoms: increase in shortness of breath, increase in sputum, and increase in purulent sputum (see Fig. 129-1). Use of antimicrobials should also take into account risk factors and severity of symptoms. Inhaled NAC can cause bronchospasms, and bacterial resistance to antibiotics is increasing so broad-spectrum antibiotics are becoming first-line.

3. **A.** Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis accounting for up to 75% of cases.

4. **D.** Management of bronchiolitis includes symptomatic and supportive care options based on the severity of symptoms. Hypertonic (3%) saline has been proven to be safe and effective after 1 day of use; however, there is debate regarding it shortening the length of hospital stay. The use of bronchodilators and steroids have not shown significant benefit and may cause harm. Ribavirin is not recommend for routine use but may be considered for severely ill patients. See sections on "Bronchiolitis - Treatment" for further information.

5. **D.** *Streptococcus pneumoniae* is the most common cause of community-acquired-bacterial pneumonia in both children and adults according to numerous epidemiologic studies. See sections on "Community-Acquired Pneumonia - Pathogenesis and Etiology - PNEUMONIA."

6. **C.** Coverage for MSSA and single antipseudomonal coverage is recommended in patients with HAP who are at low mortality risk (no septic shock or mechanical ventilation secondary to pneumonia), have no MDR risk factors (IV antibiotics in the past 90 days or structural lung disease), and a hospital MRSA prevalence < 20% (see Table 129-8). Only choice C provides coverage for both MSSA and *P. aeruginosa* without providing unnecessary MRSA coverage.

7. **C.** Group B *Streptococcus* is the most common cause of bacterial pneumonia in neonates. This is because Group B *Streptococcus* is a normal colonizing bacteria of the vaginal epithelium in many women.

8. **C.** Only IV antibiotics in the past 90 days is a consistently proven risk factor for multidrug-resistant HAP among the listed choice. The other choices may result in immune-compromise but are not risk factors for multidrug-resistant pathogens.

9. **B.** The recommended treatment of *Mycoplasma* pneumonia is a macrolide. Azithromycin is preferred, especially in this case, because it avoids a drug-drug interaction with theophylline. Both clarithromycin and erythromycin have been shown to increase serum concentrations of theophylline and increase the risk of theophylline toxicity. See section on "Directed Therapy of Important Atypical Pathogens."

10. **B.** Coverage *P. aeruginosa* is required in this patient because the aspiration occurred in the hospital. Coverage of MRSA is also required because the hospital MRSA prevalence is unknown at this time. Anaerobic coverage is indicated in patients with aspiration pneumonia who have signs of anaerobic pneumonia on imaging, such as a necrotizing lesion or abscess. Piperacillin-tazobactam plus vancomycin is the only answer choice that provides the recommended spectrum of activity for this patient.

11. **C.** Receipt of IV antibiotics in the 90 days preceding VAP, acute respiratory distress syndrome preceding VAP, and receipt of renal replacement therapy prior to VAP onset are all MDR VAP risk factors. Receipt of a blood transfusion is not a risk factor for MDR bacterial infection. See Table 129-5.

12. **B.** The patient has severe CAP because they require mechanical ventilation due to the CAP. Empiric treatment of severe CAP should consist of combination therapy with a β-lactam backbone such as choice B.

13. **D.** Empiric therapy for patients with VAP who are currently in septic shock should cover MRSA and double cover *P. aeruginosa* because septic shock is considered an MDR risk factor in patients with VAP (see Table 129-8). Choice D is the only answer choice that provides this coverage.

14. **A.** Carbapenems are considered first-line therapy for serious ESBL infections including ESBL pneumonia.

15. **C.** Vancomycin and linezolid are the only antibiotics that are considered first-line for MRSA pneumonia because they are the most evidence-based options.