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Section 2 Clinical Syndromes: Community-Acquired Infections Lionel A. Mandell,

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Pneumonia DEFINITION Pneumonia is an infection of the pulmonary parenchyma. Despite significant morbidity and mortality, it is often misdiagnosed, mis treated, and underestimated. Pneumonia has usually been classified as community-acquired (CAP), hospital-acquired (HAP), or ventilatorassociated (VAP). A fourth category, healthcare-associated pneumonia, should be discontinued because it did not reliably predict infection with resistant pathogens and was associated with increased use of broad-spectrum antibiotics. Rather than relying on a predefined subset of pneumonia cases, it is better to assess patients individually based on risk factors for infection with a resistant organism, such as certain comorbid illnesses, recent hospitalization, or recent antibiotic therapy. Pneumonia caused by macroaspiration of oropharyngeal or gastric contents, usually referred to as aspiration pneumonia, is best thought of as a point on the continuum that includes CAP and HAP. Estimates suggest that aspiration pneumonia accounts for 5–15% of CAP cases, but reliable figures for HAP are unavailable. The airways or pulmonary parenchyma may be involved, and patients usually represent a clinical phenotype with risk factors for macroaspiration and involvement of characteristic anatomic pulmonary locations. In this chapter, we will not be dealing with pneumonia in immuno compromised hosts. PATHOPHYSIOLOGY Pneumonia is the result of the proliferation of microbial pathogens in the alveoli and the host’s response to them. Until recently, it was thought that the lungs were sterile and that pneumonia resulted from the introduction of potential pathogens into this sterile environment. Typically, this introduction occurred through microaspiration of oro pharyngeal organisms into the lower respiratory tract. The overcoming of innate and adaptive immunity by such microorganisms could result in the clinical syndrome of pneumonia. A complex and diverse community of bacteria in the lungs consti tutes the lung microbiota. Awareness of this microbiota has prompted a rethinking of how pneumonia develops. Mechanical factors, such as the hairs and turbinates of the nares, the branching tracheobronchial tree, mucociliary clearance, and gag and cough reflexes, play roles in host defense but are insufficient to effectively block bacterial access to the lower airways. In the absence of a sufficient barrier, microorgan isms may reach the lower respiratory tract by a variety of pathways, including inhalation, microaspiration, and direct mucosal dispersion. The constitution of the lung microbiota is determined by three fac tors: microbial entry into the lungs, microbial elimination, and regional growth conditions for bacteria, such as pH, oxygen tension, and tem perature. The key question, however, is how a dynamic homeostasis among bacterial communities results in acute infection. Pneumonia therefore does not appear to be the result of the invasion of a sterile space by a particular microorganism but is more likely an emergent phenomenon dependent

upon a number of mechanisms, including self-accelerating positive feedback loops. A possible model for pneumonia is as follows. An inflamma tory event resulting in epithelial and/or endothelial injury results in the release of cytokines, chemokines, and catecholamines, some of which may selectively promote the growth of certain bacteria, such as Streptococcus pneumoniae and Pseudomonas aeruginosa. This cycle of inflammation, enhanced nutrient availability, and release of potential

bacterial growth factors may result in a positive feedback loop that further accelerates inflammation and the growth of particular bacteria, which may then become dominant. In cases of CAP and HAP, the trigger may be a viral infection compounded by microaspiration of oropharyngeal organisms. In cases of true aspiration pneumonia, the trigger may possibly be the macroaspiration event itself.

Once triggered, innate and adaptive immune responses can help contain potential pathogens and prevent the development of pneumo nia. However, in the face of continuing inflammation (and especially if a positive feedback loop becomes sustainable), the process may proceed to a full-fledged pneumonia syndrome. Inflammatory mediators such as interleukin 6 and tumor necrosis factor result in fever, and chemo kines such as interleukin 8 and granulocyte colony-stimulating factor increase local neutrophil numbers. Mediators released by macrophages and neutrophils may create an alveolar capillary leak, resulting in impaired oxygenation, hypoxemia, and radiographic infiltrates. Bacte ria themselves may produce toxins that further amplify the inflamma tory response. Moreover, some bacterial pathogens appear to interfere with the hypoxic vasoconstriction that would normally occur with fluid-filled alveoli, possibly resulting in severe hypoxemia. Decreased compliance due to capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bron chospasm all lead to worsening dyspnea. If severe enough, changes in lung mechanics secondary to reductions in lung volume, compliance, and intrapulmonary shunting of blood may cause respiratory failure. PATHOLOGY Classic pneumonia evolves through a series of stages. The initial stage is edema with a proteinaceous exudate and often bacteria in the alveoli. Next is a rapid transition to the red hepatization phase. Erythrocytes in this intraalveolar exudate give this stage its name. In the third phase, gray hepatization, erythrocytes have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with the successful containment of the infection and improvement in gas exchange. In the final phase, resolution, the macrophage reappears as the dominant cell in the alveolar space and the debris of neutrophils, bacteria and fibrin has been cleared, as has the inflammatory response. CHAPTER 131 Pneumonia This pattern has been described best for lobar pneumococcal pneu monia but may not apply to pneumonia of all etiologies. In VAP, respi ratory bronchiolitis may precede the development of a radiologically apparent infiltrate. A bronchopneumonia pattern is most common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and Pneumo cystis pneumonias represent alveolar rather than interstitial processes. COMMUNITY-ACQUIRED PNEUMONIA ■ ■ETIOLOGY Numerous microbes may cause CAP, including a variety of bacteria, viruses, fungi, and protozoa. Newer viral pathogens include metapneumoviruses, the coronavi ruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and the SARS-CoV-2 coronavirus. First described in December 2019, SARS-CoV-2 and its associated clinical disease, COVID-19, reached pandemic proportions and are a cause of significant morbidity and mortality. The COVID-

19 pandemic has changed the etiologic profile of CAP, and the ultimate role that the SARS-CoV-2 virus will play as a cause of CAP remains to be seen. The virus and the disease are discussed in detail in Chap. 205. Although most CAP cases are caused by relatively few pathogens, an accurate determination of their prevalence is difficult because labora tory testing methods are often insensitive and indirect (Table 131-1). Separation of potential agents into “typical” bacterial pathogens and “atypical” organisms may be helpful, although both types of pathogens can lead to similar clinical syndromes. The former group includes S. pneumoniae, Haemophilus influenzae, and, in selected patients, Staphylo coccus aureus and gram-negative bacilli such as Klebsiella pneumoniae and P. aeruginosa. The “atypical” organisms include Mycoplasma pneumoniae,

TABLE 131-1 Microbial Causes of Community-Acquired Pneumonia, by Site of Care HOSPITALIZED PATIENTS OUTPATIENTS NON-ICU ICU Streptococcus pneumoniae Mycoplasma pneumoniae Haemophilus influenzae Chlamydia pneumoniae Respiratory virusesa S. pneumoniae M. pneumoniae C. pneumoniae H. influenzae Legionella spp. Respiratory virusesa S. pneumoniae Staphylococcus aureus Legionella spp. Gram-negative bacilli H. influenzae Respiratory virusesa aInfluenza A and B viruses, SARS-CoV-2 and other coronaviruses, human metapneumovirus, adenoviruses, respiratory syncytial viruses, parainfluenza viruses. Abbreviation: ICU, intensive care unit. Chlamydia pneumoniae, and Legionella species as well as respiratory viruses such as influenza, adenoviruses, human metapneumoviruses, respiratory syncytial virus, and coronaviruses. With the increasing use of pneumococcal vaccine, the incidence of pneumococcal pneumonia is decreasing. M. pneumoniae plays more of a role in ambulatory cases, whereas Legionella tends to be associated with more serious cases and can be found in outbreaks, as well. C. pneumoniae now appears to account for <1% of CAP cases. Viruses are recognized as increasingly important in pneumonia, and polymerase chain reaction (PCR)–based testing indi cates their presence in the respiratory tract of 20–30% of healthy adults and in the same percentage of pneumonia patients, including those who are severely ill. The most common are influenza, parainfluenza, and respiratory syncytial viruses. Whether they are true etiologic pathogens, co-pathogens, or simply colonizers cannot always be determined. Atypi cal organisms cannot be cultured on standard media or seen on Gram stain, but their frequency and importance have significant implications for therapy. They are intrinsically resistant to all β-lactam antibiotics and require treatment with a macrolide, fluoroquinolone, or a tetracycline. In the 10–15% of CAP cases that are polymicrobial, the etiology usually includes a combination of typical and atypical pathogens. PART 5 Infectious Diseases Earlier literature suggested that aspiration pneumonia was caused primarily by anaerobes, with or without aerobic pathogens. A shift, however, has been noted recently: if aspiration pneumonia is acquired in a community or hospital setting, the likely pathogens are those usually associated with CAP or HAP. Anaerobes may still play a role, especially in patients with poor dentition, lung abscess, necrotizing pneumonia, or empyema. S. aureus pneumonia is known to complicate influenza virus infection. However, methicillin-resistant S. aureus (MRSA) has been reported as a primary etiologic agent of CAP. Although cases caused by MRSA are relatively uncommon, clinicians must be aware of its potentially serious consequences, such as necrotizing pneumonia. Two factors have led to this problem: the spread of MRSA from the hospital setting to the community and the emergence of genetically distinct MRSA strains in the community associated with bacterial toxin pro duction. Community-associated MRSA (CA-MRSA) strains may infect healthy individuals who have had no association with health care. Despite a careful history, physical examination, and radiographic studies, the causative pathogen is often difficult to predict with certainty, and in more than half of cases, a specific etiology is not

determined. Nevertheless, epidemiologic and risk factors may suggest certain pathogens (Table 131-2). ■ ■EPIDEMIOLOGY It is estimated that 7 million or more CAP cases occur annually in the United States. The annual incidence in adults ranges from 16 to 23 per 1000 population. The incidence of hospitalization is 650/100,000 but rises dramatically to 2000/100,000 yearly in the elderly. Overall, approximately 30% of patients are hospitalized, resulting in 1.5 million admissions. Along with influenza, CAP is the eighth leading cause of death in the United States, resulting in >60,000 deaths annually. The mortality rate among outpatients is usually <5% but ranges from ~12 to 40% among hospitalized patients. The exact rate depends on whether

TABLE 131-2 Epidemiologic Factors Suggesting Possible Causes of Community-Acquired Pneumonia FACTOR POSSIBLE PATHOGEN(S) Alcoholism Streptococcus pneumoniae, oral anaerobes, Klebsiella pneumoniae, Acinetobacter spp., Mycobacterium tuberculosis COPD and/or smoking Haemophilus influenzae, Pseudomonas aeruginosa, Legionella spp., S. pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae Structural lung disease

(e.g., bronchiectasis) P. aeruginosa, Burkholderia cepacia, Staphylococcus aureus Dementia, stroke, decreased level of consciousness Oral anaerobes, gram-negative enteric bacteria Lung abscess CA-MRSA, oral anaerobes, endemic fungi, M. tuberculosis, nontuberculous mycobacteria Travel to Ohio or St. Lawrence river valley Histoplasma capsulatum Travel to southwestern United States Hantavirus, Coccidioides spp. Travel to Southeast Asia Burkholderia pseudomallei, avian influenza virus Stay in hotel or on cruise ship in previous 2 weeks Legionella spp. Local influenza activity Influenza virus, S. pneumoniae, S. aureus Exposure to infected humans SARS-CoV-2 Exposure to birds H. capsulatum, Chlamydia psittaci Exposure to rabbits Francisella tularensis Exposure to sheep, goats, parturient cats Coxiella burnetii Abbreviations: CA-MRSA, community-acquired methicillin-resistant Staphylococcus aureus; COPD, chronic obstructive pulmonary disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. treatment takes place in or outside the intensive care unit (ICU). In the United States, CAP is the leading cause of death from infection among patients >65 years of age. Moreover, 18% of hospitalized CAP patients are readmitted within 1 month of discharge. The overall yearly CAP cost is estimated at $17 billion. Risk factors for CAP in general and pneumococcal pneumonia in particular have implications for treatment. They include alcoholism, asthma, immunosuppression, institutionalization, and age >70 years. In the elderly, decreased cough and gag reflexes and reduced antibody and Toll-like receptor responses increase the likelihood of pneumonia. Risk factors for pneumococcal pneumonia include dementia, seizure disor ders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease (COPD), and HIV infection. CA-MRSA pneumonia is more likely in patients with skin coloniza tion or infection with CA-MRSA at other sites, and after viral infection. Enterobacteriaceae tend to infect patients recently hospitalized, given antibiotics, or who have comorbidities such as alcoholism, heart failure, or renal failure. P. aeruginosa is a particular problem in patients with severe structural lung disease (e.g., bronchiectasis, cystic fibrosis, or severe COPD). Risk factors for Legionella infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or cruise ship trip. ■ ■CLINICAL MANIFESTATIONS The clinical presentation of pneumonia can vary from indolent to fulminant and from mild to fatal. Manifestations of worsening severity include both constitutional findings and those limited to the lung and associated structures. The patient is frequently febrile and/or tachy cardic and may experience chills and/or sweats. Cough may be non productive or productive of mucoid, purulent, or blood-tinged sputum. Gross hemoptysis is

suggestive of necrotizing pneumonia (e.g., that due to CA-MRSA). Depending on severity, shortness of breath may be present, and pleural involvement may result in chest pain. Up to 20% of

patients may have gastrointestinal symptoms such as nausea, vomiting, or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias. Findings on physical examination vary with the degree of pulmo nary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Palpation may reveal increased or decreased tactile fremitus, and the percussion note can vary from dull to flat, reflecting underlying consolidated lung and pleural fluid, respectively. Crackles, bronchial breath sounds, and possibly a pleural friction rub may be heard. The clinical presentation may be less obvious in the elderly, who may initially display new-onset or worsening confusion, or worsening of a chronic illness, but few other manifestations. Severely ill patients may have septic shock and organ failure. In cases of CAP, symptoms can range from almost nonexistent to severe, and in those with aspiration pneumonia, chest radiographic findings are often in gravity-dependent parts of the lung. ■ ■DIAGNOSIS When confronted with possible CAP, the physician must ask two ques tions: Is this pneumonia, and, if so, what is the likely pathogen? The former question is answered by clinical and radiographic methods, whereas the latter requires laboratory techniques. Clinical Diagnosis The differential diagnosis includes infectious and noninfectious entities, including acute bronchitis, exacerbations of chronic bronchitis, heart failure, and pulmonary embolism. The importance of a careful history cannot be overemphasized. The diag nosis of CAP requires a compatible history, such as cough, sputum pro duction, fever and dyspnea, and a new infiltrate on chest radiography. Unfortunately, the sensitivity and specificity of physical examina tion findings are only 58% and 67%, respectively. Chest radiography is often unable to differentiate CAP from other conditions. Radiographic findings may suggest increased severity (e.g., cavitation or multilobar involvement) and occasionally suggest an etiologic diagnosis, such as pneumatoceles in S. aureus infection or an upper-lobe cavitating lesion in tuberculosis. Computed tomography (CT) may be of value in sus pected loculated effusion or cavitary cases or in postobstructive pneu monia caused by a tumor or foreign body. For outpatients, clinical and radiologic assessments are usually all that is required before treatment is started since most laboratory results are not available soon enough to influence initial management. In certain cases, the availability of rapid point-of-care outpatient tests can be important, such as for rapid diagnosis of influenza infection, and can prompt specific anti-influenza treatment and secondary prevention measures. Etiologic Diagnosis The etiology of pneumonia usually cannot be determined solely on the basis of clinical or radiographic presenta tion. Data from >17,000 emergency department CAP cases showed an etiologic determination in only 7.6%. Except for CAP patients admitted to the ICU, no data exist showing that treatment directed at a specific pathogen is statistically superior to empirical therapy. The benefit of establishing a microbial etiology may be questioned, particularly in light of the cost of diagnostic testing. However, a number of reasons exist for attempting an etiologic diagnosis. Identification of a specific or unexpected pathogen allows focusing of the initial empirical regi men, with a consequent decrease in antibiotic selection pressure and the risk of resistance. Pathogens with important public safety implica tions, such as Mycobacterium tuberculosis, influenza, and SARS-CoV-2 viruses, may be found. Finally, without susceptibility data, trends in resistance cannot be followed accurately, and appropriate empirical therapeutic regimens are harder to devise. GRAM STAIN AND CULTURE OF SPUTUM The main purpose of the sputum Gram stain is to ensure suitability of a specimen for culture. To be suitable, a sputum sample must have >25 neutrophils

and <10 squamous epithelial cells per low-power field. However, staining may also identify certain pathogens (e.g., S. pneumoniae, S. aureus, and gram-negative bacteria). The sensitivity and specificity of the sputum Gram stain and culture are highly variable. Even in cases of proven

bacteremic pneumococcal pneumonia, the positive sputum cultures are ≤50%.

Many patients, particularly elderly individuals, may be unable to produce an appropriate sputum sample. Others may be taking antibiot ics that interfere with culture results. Inability to produce sputum can be caused by dehydration, whose correction may result in increased sputum production and a more obvious infiltrate on chest radiography. For patients admitted to the ICU and intubated, a deep-suction aspirate or bronchoalveolar lavage sample has a high yield on culture when sent to the laboratory as soon as possible. Since pathogens in severe and mild CAP may differ (Table 131-1), the greatest benefit of staining and culturing respiratory secretions is to alert the physician to unexpected and/or resistant pathogens and to permit appropriate modification of therapy. Other stains and cultures (e.g., for M. tuberculosis or fungi) may be useful as well. The sputum Gram stain and culture are recom mended only for hospitalized CAP patients, particularly those with severe cases or those with risks of MRSA or P. aeruginosa infection. BLOOD CULTURES The yield from blood cultures, even when samples are collected before antibiotic therapy, is disappointingly low. Only 5–14% of cultures from hospitalized CAP patients are positive, and the most common pathogen is S. pneumoniae followed by S. aureus and P. aeruginosa. Since recommended empirical regimens all provide pneumococcal coverage, a blood culture positive for this pathogen has little, if any, effect on clinical outcome. However, susceptibility data may allow narrowing of antibiotic therapy in appropriate cases, and such data help to track microbial resistance patterns on a national basis. Because of the low yield and lack of significant impact on outcome, blood cultures are not considered de rigueur for all hospitalized CAP patients. Certain high-risk patients should have blood cultured, includ ing those with neutropenia secondary to pneumonia, asplenia, comple ment deficiencies, chronic liver disease, or severe CAP and those at risk of MRSA or P. aeruginosa infection. CHAPTER 131 URINARY ANTIGEN TESTS Two commercially available tests detect pneumococcal and Legionella urinary antigens. The Legionella pneu mophila test detects only serogroup 1, which accounts for most community-acquired cases of Legionnaires' disease in the United States. Its sensitivity and specificity are 70% and 99%, respectively. The pneu mococcal urine antigen test also is quite sensitive and specific (70% and

> 90%, respectively). Although false-positive results can be obtained for pneumococcus-colonized children, the test is generally reliable. Both tests can detect antigen even after initiation of appropriate antibiotic therapy. Testing for urinary pneumococcal antigen can be reserved for severe cases; Legionella antigen can be sought in severe cases and when relevant epidemiologic factors are present. Pneumonia POLYMERASE CHAIN REACTION PCR tests amplify a microorganism's DNA or RNA, and multiplex PCR panels test for a number of viral and bacterial pathogens. These tests dramatically improve response times, compared to standard cultures, but the contamination of respiratory specimens by upper-airway flora may make semiquantitative or quan titative assays necessary for best results. PCR of nasopharyngeal swabs has become the

> standard for diagnosis of respiratory viral infection, including influenza and coronaviruses. PCR can also detect the nucleic acid of Legionella species, M. pneumoniae, C. pneumoniae, and myco bacteria. The cost-effectiveness of PCR testing, however, has not been definitively established. SEROLOGY A fourfold rise in specific IgM antibody titer between acute- and convalescent-phase serum samples is generally considered diagnostic of infection with a particular pathogen. Until recently, serologic tests were used to help identify atypical pathogens as well as selected unusual organisms such as Coxiella burnetii. However, these tests have fallen out of favor because of the delays in obtaining conva lescent phase results and difficulties with interpretation. BIOMARKERS Two of the most commonly used markers are C-reactive protein (CRP) and procalcitonin (PCT). Levels of these acute-phase reactants increase in the presence of an inflammatory response, par ticularly to bacterial pathogens. Nevertheless, PCT is insufficiently accurate for use in the diagnosis of bacterial CAP, and initial serum

PCT levels should not be used as a basis for withholding initial anti biotic treatment. CRP is considered even less sensitive than PCT for detecting bacterial pathogens. These tests should not be used alone but, in conjunction with findings from the history, physical examination, radiography, and laboratory tests, may facilitate antibiotic stewardship and appropriate management of seriously ill CAP patients.

TREATMENT Community-Acquired Pneumonia SITE OF CARE The decision to hospitalize a patient with CAP has considerable implications. The cost of inpatient management exceeds outpa tient treatment by a factor of 20, and hospitalization accounts for most CAP-related expenditures. However, late admission to the ICU is associated with increased mortality rates. The choice can be difficult: some patients can be managed at home, while others require hospitalization. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, can help to minimize unnecessary hospitalizations. The two most frequently used are the Pneumonia Severity Index (PSI), a prognostic model that identifies patients at low risk of dying, and the CURB-65 criteria, which yield a severity-of-illness score. To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory find ings. Based on the score, patients are assigned to one of five classes with these mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Using the PSI results in lower admission rates for class 1 and 2 patients. Class 3 patients could ide ally be admitted to an observation unit pending further decisions. PART 5 Infectious Diseases The CURB-65 criteria include five variables: confusion (C); urea

> 7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure— systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years. Patients with a score of 0 (a 30-day mortality rate of 1.5%) can be treated as outpatients. With a score of 1 or 2, the patient should be hospitalized unless the score is entirely or in part

attributable to an age of ≥65 years; in such cases, hospitalization may not be neces sary. Among patients with scores of ≥3, mortality rates are 22% overall; these patients may require ICU admission. The PSI score has greater efficacy and has been more robustly validated than the CURB-65 criteria but is more difficult to calculate. In general, if a patient is unable to maintain oral intake, if compliance may be an issue when assessed on the basis of mental condition or living situation (e.g., cognitive impairment or home lessness), or if the patient's O2 saturation on room air is <92%, hospitalization is necessary. If these considerations do not apply, clinical judgment in conjunction with a prediction rule should be used to determine the site of care. Neither PSI nor CURB-65 is accurate in determining the need for ICU admission. Patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation should be admitted directly to an ICU (Table 131-3), and those with three of the nine minor criteria listed in the latter table should be admitted to an ICU or a high-level monitoring unit. Mortality rates were higher among less ill patients who were admit ted to a medical floor but then deteriorated than among equally ill patients initially monitored in the ICU. ANTIBIOTIC RESISTANCE Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Antibiotic misuse results in increased antibiotic selection pressure that can affect resistance locally and globally by clonal dissemination. For CAP, the main resistance issues currently involve S. pneumoniae and CA-MRSA. S. pneumoniae In general, pneumococcal resistance to β-lactams is acquired by (1) direct DNA incorporation and remodeling of penicillin-binding proteins through contact with closely related

TABLE 131-3 Criteria for Severe Community-Acquired Pneumonia Minor criteria Respiratory rate ≥30 breaths/min PaO2/FiO2 ratio ≤250 Multilobar infiltrates Confusion/disorientation Uremia (BUN level ≥20 mg/dL) Leukopenia (WBC count <4000 cells/μL) Thrombocytopenia (platelet count <100,000 cells/μL) Hypothermia (core temperature <36°C) Hypotension requiring aggressive fluid resuscitation Major criteria Respiratory failure requiring invasive mechanical ventilation Septic shock requiring vasopressors Abbreviations: BUN, blood urea nitrogen; PaO2/FiO2, arterial oxygen pressure/ fraction of inspired oxygen; WBC, white blood cell. oral commensal bacteria (e.g., viridans group streptococci), (2) the process of natural transformation, or (3) mutation of certain genes. Susceptibility to penicillins depends upon treatment with intra venous (IV) or oral agents. For IV: Susceptible: minimum inhibitory concentration (MIC) ≤2 μg/mL Intermediate: MIC >2 and ≤4 μg/mL Resistant: MIC ≥4 μg/mL For oral: Susceptible: MIC ≤0.06 μg/mL Intermediate: MIC >0.06 and ≤1 μg/mL Resistant: MIC >1 μg/mL For non–central nervous system pneumococcal infections, decreased susceptibility to penicillin is mitigated by usual doses. In the United States, only 0.6% of pneumococci are resistant to cef triaxone and cefotaxime. Risk factors for penicillin-resistant pneu mococcal infection include recent antimicrobial therapy, age of <2 or >65 years, attendance at a day-care center, recent hospitalization, and HIV infection. In contrast to penicillin resistance, macrolide resistance is increas ing in S. pneumoniae through several mechanisms. Target-site modi fication caused by ribosomal methylation in 23S rRNA encoded by the ermB gene results in high-level resistance (MIC, ≥64 μg/mL) to macrolides, lincosamides, and streptogramin

B–type antibiotics. The efflux mechanism encoded by the mef gene (M phenotype) is usually associated with low-level resistance (MIC, usually <16 μg/mL). These two mechanisms account for ~40% and ~60%, respectively, of resis tant pneumococcal isolates in the United States. High-level resistance to macrolides is more common in Europe, whereas lower-level resis tance predominates in North America. The prevalence of macrolideresistant S. pneumoniae exceeds 25% in some countries; in Canada, it is ~22%, and in the United States approximately 40%. Much of this resistance is high-level, and treatment failures may result. In these situations, a macrolide should not be used as empirical monotherapy. In the United States and Canada, 87.5% of pneumococci are suscep tible to doxycycline. The rate of pneumococcal resistance to fluoroquinolones (e.g., levofloxacin, moxifloxacin, and gemifloxacin) is usually <2%. Changes can occur in one or both target sites (topoisomerases II and IV) and are attributable to mutations in the gyrA and parC genes, respectively. An efflux pump may also play a role in pneu mococcal resistance to fluoroquinolones. Isolates resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered multi drug-resistant (MDR) strains. The propensity for an association of pneumococcal resistance to penicillin with reduced susceptibility to other drugs, e.g. macrolides, tetracyclines, and trimethoprimsulfamethoxazole, is of concern. In the United States, 58.9% of

penicillin-resistant pneumococcal blood isolates are also resistant to macrolides. The most important risk factor for antibiotic-resistant pneumo coccal infection is use of a specific antibiotic within the previous 3 months. A history of prior antibiotic treatment is a critical factor in avoiding the use of an inappropriate antibiotic. CA-MRSA CAP due to MRSA may be caused by the classic hospi tal-acquired strains or by genotypically and phenotypically distinct community-acquired strains. Most infections with the former are acquired either directly or indirectly during contact with the health care environment. However, in some hospitals, CA-MRSA strains are displacing the classic hospital-acquired strains, suggesting that the newer community-acquired strains may be more robust. Methicillin resistance in S. aureus is determined by the mecA gene, which encodes for resistance to all β-lactam drugs At least five staphylococcal chromosomal cassette mec (SCCmec) types have been described. The typical hospital-acquired strain usu ally has a type II or III SCCmec element, whereas CA-MRSA has type IV. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline in addition to vancomycin and linezolid. CA-MRSA strains also carry genes for superantigens such as enterotoxins B and C and PantonValentine leukocidin; the latter is a membrane-tropic toxin that can create cytolytic pores in neutrophils, monocytes, and macrophages. Risk factors for MRSA include colonization or prior infection and MRSA as suggested by gram-positive cocci in clusters on sputum Gram stain. Other factors that may raise suspicion of MRSA infec tion include recent antibiotics, hospitalization, influenza, cavitary or necrotizing pneumonia, or empyema. M. pneumoniae Macrolide-resistant M. pneumoniae has been reported in a number of countries, including Germany (3%), Japan (30%), China (95%), and France and the United States (5–13%). Mycoplasma resistance to macrolides is increasing as a result of binding-site mutation in domain V of 23S rRNA. Gram-Negative Bacilli A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter (see Chap. 166). Fluoroquinolone resistance among community isolates of Escherichia coli is increasing. Enterobacter species are typically resistant to cephalosporins, and the drugs of choice to treat these organisms are usually fluoroquinolones or carbapenems. Similarly, when infections due to bacteria producing extended-spectrum β-lactamases (ESBLs) are documented or suspected, a carbapenem should be

considered. INITIAL ANTIBIOTIC MANAGEMENT Since the etiology of CAP is rarely known at the outset of treatment, initial therapy is usually empirical and designed to cover the likeli est pathogens. In all cases, treatment should be initiated as expedi tiously as possible. CAP treatment guidelines in the United States from the American Thoracic Society (ATS) and the Infectious Dis eases Society of America (IDSA) consider the likely pathogens, risk of antimicrobial resistance, severity of illness, site of care, and risk of infection with specific bacteria such as MRSA and P. aeruginosa (Fig. 131-1, Tables 131-4 and 131-5). In the figure and the tables, the antibiotics are not listed in order of preference. The approach to treatment of aspiration pneumonia is based on a number of factors, including site of acquisition (community vs hospital), normal or abnormal chest radiograph, and additional variables such as illness severity, state of dentition, and risk of infection with an MDR pathogen. Routine coverage of anaerobes is unnecessary unless dentition is poor or there is a lung abscess or necrotizing pneumonia. Our approach to CAP treatment (Tables 131-4 and 131-5) is very similar to the CAP guidelines with the exceptions listed below. Outpatients The exceptions to the CAP guidelines that we follow in treating patients are as follows:

Nonsevere Severe No risk Risk No risk Risk Recent hospitalization and antibiotics (PO or IV) ± local validation* Recent hospitalization and antibiotics (PO or IV) ± local validation* Prior respiratory isolation Prior respiratory isolation Add treatment Add treatment Obtain cultures† Add treatment FIGURE 131-1 Algorithm for assessment of inpatient risk of infection with methicillin-resistant Staphylococcus aureus (MRSA) or Pseudomonas aeruginosa. Underlying lung disease (e.g., bronchiectasis or very severe chronic obstructive pulmonary disease) are also risks for P. aeruginosa infection. *Local validation consists of information on local prevalence, resistance, and risk factors. †Can also use MRSA rapid nasal polymerase chain reaction (PCR) if available. IV, intravenous; PO, oral. • We usually initiate coverage that includes atypical organisms as well as S. pneumoniae. • Generally, we do not consider the risk of infection with P. aeruginosa CHAPTER 131 or MRSA particularly significant in outpatients. • Prior antibiotic use should include both oral and parenteral agents. Patients are stratified into two groups: those without comorbid ity or risk factors for antibiotic resistance and those with comor bidities (e.g., chronic heart, lung, liver, or kidney disease; diabetes; alcoholism; malignancy; or asplenia) with or without risk factors for resistance (Table 131-4). As a general rule, if patients have been treated with a drug from a particular class of antibiotics within the previous 3 months, drugs from a different class should be used to minimize resistance issues. Pneumonia For those without comorbidity or resistance risk factors, amox icillin alone or doxycycline is recommended in the guidelines. Monotherapy with amoxicillin is based on evidence of its efficacy in the treatment of hospitalized CAP patients. This recommenda tion is a change from the 2007 IDSA/ATS CAP guidelines. As a rule, however, we usually tend to initiate treatment that includes coverage for S. pneumoniae as well as the atypical pathogens (Table 131-4). TABLE 131-4 Initial Treatment Strategies for Outpatients with Community-Acquired Pneumonia STATUS STANDARD REGIMEN No comorbidities or risk factors for antibiotic resistancea Combination therapy with amoxicillin (1 g tid) + either a macrolideb or doxycycline (100 mg bid) or Monotherapy with doxycycline (100 mg bid) or Monotherapy with a macrolideb,c With comorbiditiesd ± risk factors for antibiotic resistancea Combination therapy with amoxicillin/clavulanatee or a cephalosporinf + either a macrolideb or doxycycline (100 mg bid) or Monotherapy with a respiratory fluoroquinoloneg aAntibiotic treatment within the past 3 months or contact with the health care system. bAzithromycin (500 mg on day 1, then 250 mg/d for 4 days), clarithromycin (500 mg bid), or clarithromycin ER (1000 mg/d). cIf local prevalence of pneumococcal resistance is <25%. dIncluding chronic heart, lung, liver, or kidney disease; diabetes

mellitus; alcoholism; malignancy; or asplenia. e500/125 mg tid or 875/125 mg bid. fCefpodoxime (200 mg bid) or cefuroxime (500 mg bid). gLevofloxacin (750 mg/d), moxifloxacin (400 mg/d), or gemifloxacin (320 mg/d).

TABLE 131-5 Initial Treatment for Inpatients with or without Risk Factors for Infection with MRSA or Pseudomonas aeruginosa DISEASE SEVERITY, RISK STATUS REGIMEN Nonsevere No risk factors A β-lactama + a macrolideb or A respiratory fluoroquinolonec Prior respiratory isolation Add coverage for MRSAd or Pseudomonas aeruginosae Recent hospitalization, antibiotic treatment, ± LVf Add coverage for MRSAd or P. aeruginosae only if cultures are positive Severe No risk factors A β-lactama + a macrolideb or A β-lactama + respiratory fluoroquinolonec Prior respiratory isolation Add coverage for MRSAd or P. aeruginosae Recent hospitalization, antibiotic treatment ± LVf Add coverage for MRSAd or P. aeruginosae aAmpicillin-sulbactam (1.5–3 g q6h), ceftriaxone (1–2 g/d), cefotaxime (1–2 g q8h), ceftaroline (600 mg q12h), or ertapenem (1 g/d). bAzithromycin (500 mg/d) or clarithromycin (500 mg bid). cLevofloxacin (750 mg/d), moxifloxacin (400 mg/d), or gemifloxacin (320 mg/d). dVancomycin (15 mg/kg q12h, with adjustment based on serum levels) or linezolid (600 mg q12h). ePiperacillin-tazobactam (4.5 g q6h), cefepime (2 g q8h), ceftazidime (2 g q8h), imipenem (500 mg q6h), meropenem (1 g q8h), or aztreonam (2 g q8h). fObtain cultures. MRSA rapid nasal polymerase chain reaction can also be used if available. Abbreviations: LV, local validation (local prevalence, resistance, risk factors); MRSA, methicillin-resistant Staphylococcus aureus. PART 5 Infectious Diseases Monotherapy with a macrolide is recommended in the guide lines only if there are contraindications to amoxicillin or doxy cycline and there is documented low risk of macrolide resistance (<25%). Otherwise, outpatient treatment is quite similar to the regimens recommended in the 2007 IDSA/ATS guidelines. Two relatively newer agents, lefamulin (a pleuromutilin) and omadacy cline (a tetracycline) are possible options for CAP patients unable to take β-lactams and/or wanting to avoid the fluoroquinolones. They are available in the United States but not in Canada. Treatment of influenza (Chap. 206) and COVID-19 (Chap. 205) is discussed in their own chapters. Inpatients Our exceptions to the recommendations in the CAP guidelines are as follows: • As a general rule, when initiating treatment for infection with P. aeruginosa, we use double coverage. • The presence of all three risk factors is not required for drug resistance (recent hospitalization, recent oral or IV antibiotic treatment, ± local validation) (Fig. 131-1, Table 131-5). The main considerations for determining initial empirical treat ment of hospitalized CAP patients are clinical severity and risk of infection with drug-resistant pathogens such as MRSA or

P. aeruginosa. Hospitalization alone is not now considered a sig nificant risk factor for these pathogens. Hospitals should collect local data on MRSA and P. aeruginosa regarding prevalence, risk factors for infection, and antibiotic susceptibilities. Patients can be categorized as having nonsevere or severe CAP (Table 131-3), and those in each category may or may not have risk factors for MRSA or P. aeruginosa (Fig. 131-1). In scenarios involving these variables in hospitalized CAP patients, empirical treatment for either of these pathogens should be added to standard therapy in those previously colonized or infected with these pathogens, but not in the patient who is considered nonsevere and whose only risk factors are recent hospitalization and antibiotic treatment ± local validation data (Fig. 131-1). In this setting, if we begin treatment, we try to de-escalate if appropriate. In most patients, cultures should be performed but treatment usually withheld unless culture results or rapid nasal PCR results for MRSA are positive.

Nonsevere, No Risk Factors For patients with nonsevere infection and no risk factors, treatment should consist of either a combination of a β-lactam and a macrolide or monotherapy with a respiratory fluoroquinolone (Table 131-5). In the event of con traindications to macrolides and fluoroquinolones, a β-lactam plus doxycycline may be used. Treatment with a β-lactam plus macrolide combination or a fluoroquinolone alone results in lower mortality than monotherapy with a β-lactam. Severe, No Risk Factors Patients with severe infection but no risk factors should receive combination therapy with either a β-lactam plus macrolide or a β-lactam and a respiratory fluoroqui nolone (Table 131-5). Observational studies suggest that combina tion therapy with a β-lactam plus macrolide may be preferable to a β-lactam plus fluoroquinolone. Nonsevere and Severe, with Risk Factors To date, there are no prediction rules reliably identifying patients who should be started empirically on treatment for MRSA or P. aeruginosa. Current risk fac tors for infection with these pathogens are hierarchical. Prior isolation of these organisms, especially from the respiratory tract within the previous year, is a more robust risk factor than recent hospitalization and expo sure to parenteral antibiotics. For P. aeruginosa, underlying lung disease (e.g., bronchiectasis or very severe COPD) also is an important risk fac tor. If MRSA or P. aeruginosa has been isolated previously, appropriate empirical therapy should be started in both severe and nonsevere cases

(Table 131-5). We prefer linezolid over vancomycin as first-line treat ment for MRSA because of its inhibition of bacterial exotoxin and better lung penetration. If the organism is not isolated from respiratory secretions or blood and/or the nasal or bronchoalveolar lavage PCR test for MRSA is negative and the patient is improving at 48 h, treat ment may be de-escalated to a standard regimen. If, however, the risk factors are recent hospitalization and anti biotic use within the previous 3 months, appropriate samples should be obtained for culture, and, in severe cases only, extendedspectrum treatment for MRSA or P. aeruginosa should be initiated. Depending on the severity of infection, local data on P. aeruginosa resistance, and antibiotic use within the previous 90 days, single- or double-drug coverage should be used such as antipseudomonal β-lactam plus ciprofloxacin, levofloxacin, or aminoglycoside. If two antipseudomonal agents are started, the drugs should be from different classes. Whenever possible, assessment for possible de-escalation of therapy is urged. If the patient’s illness is not severe, empirical extended treatment should be withheld until culture results are available. Regardless of the site of care, CAP patients with proven influenza should be given anti-influenza treatment (e.g., oseltamivir) as well as appropriate antibacterial therapy. Physicians should be vigilant about possible superinfection with MRSA. If a viral pathogen such as influenza or SARS-CoV-2 is found and no bacterial pathogen is obvious, antibacterial treatment can be discontinued. However, in those with severe illness, the possibility of bacterial-viral coinfection should be considered. Although hospitalized patients have traditionally received initial therapy by the IV route, some drugs, particularly the fluoroqui nolones, are very well absorbed and may be given orally from the outset to select patients. For those initially treated with IV agents, a switch to oral treatment is appropriate when the patient can ingest and absorb the drugs, is hemodynamically stable, and is showing clinical improvement. A 5-day course of treatment is usually suffi cient for uncomplicated CAP, but longer treatment may be required for patients who have not stabilized clinically and for those with bacteremia, metastatic infection, or infection with a more virulent pathogen such as P. aeruginosa or MRSA. There are some data to suggest that in select patients who are doing well and are clinically stable, treatment may be discontinued after 3 days. ADJUNCTIVE MEASURES In addition to appropriate antimicrobial therapy, certain adjunctive measures should be used. Adequate hydration, oxygen therapy for

CHAPTER 131 TABLE 131-6 Microbiologic Causes of Ventilator-Associated Pneumonia NON-MDR PATHOGENS (CORE PATHOGENS) MDR PATHOGENS Streptococcus pneumoniae Other Streptococcus spp. Haemophilus influenzae Methicillin-sensitive Staphylococcus aureus Antibiotic-sensitive Enterobacteriaceae Escherichia coli Klebsiella pneumoniae Proteus spp. Enterobacter spp. Serratia marcescens Pseudomonas aeruginosa Methicillin-resistant S. aureus Acinetobacter spp. Antibiotic-resistant Enterobacteriaceae ESBL-positive strains Carbapenem-resistant strains Legionella pneumophila Burkholderia cepacia Aspergillus spp. Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant. hypoxemia, vasopressor treatment, and assisted ventilation when necessary are critical to successful treatment. Glucocorticoids may be beneficial in cases of severe CAP requiring invasive or noninva sive mechanical ventilation or with shock. Recent data show a mor tality benefit for corticosteroid therapy in those with severe CAP (ventilated and nonventilated), especially if there is a high level of systemic inflammation (CRP >15 mg/dL); therapy is usually con tinued for 8–14 days and given either by intermittent or continu ous infusion. Data support the use of dexamethasone plus a Janus kinase inhibitor or an interleukin 6 inhibitor in COVID-19 patients with rapidly increasing oxygen needs and systemic inflammation. FAILURE TO IMPROVE Patients slow to respond to therapy should be reevaluated at about day 3 (or sooner if their condition is worsening), with several sce narios considered. A number of noninfectious conditions mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient truly has CAP and empirical treatment is aimed at the likely expected pathogens, lack of response may be explained in a number of ways. The pathogen may be resistant to the drug, or a sequestered focus (e.g., lung abscess or empyema) may prevent antibiotic access to the pathogen. The patient may be getting the wrong drug or the correct drug at the wrong dose or frequency of administration. Another possibility is that CAP has been diagnosed correctly but an unexpected pathogen (e.g., CA-MRSA, M. tuberculosis, or a fungus) is the cause. Nosocomial superinfections—both pulmonary and extrapulmonary—are other possible explanations for a hospitalized patient’s failure to improve. In all cases of delayed response or wors ening condition, the patient must be carefully reassessed and appro priate studies initiated, possibly including CT or bronchoscopy. COMPLICATIONS Complications of severe CAP include respiratory failure, shock and multiorgan failure, and exacerbation of comorbid illnesses. Three particularly noteworthy conditions are metastatic infection, lung abscess, and complicated pleural effusion. Metastatic infection (e.g., brain abscess or endocarditis) is unusual and requires a high degree of suspicion and a detailed workup for proper treatment. Lung abscess may occur in association with aspiration pneumonia or with infection caused by pathogens such as CA-MRSA, P. aeru ginosa, or (rarely) S. pneumoniae. A significant pleural effusion should be tapped for diagnostic and therapeutic purposes. If the fluid has a pH <7.2, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L or if bacteria are seen or cultured, drainage is needed. Cardiovascular events with pneumonia, particularly in the elderly and usually in association with pneumococcal pneumonia and influenza, are increasingly recognized. These events, which may be acute or whose occurrence may extend to at least 1 year, include congestive heart failure, arrhythmia, myocardial infarction, or stroke and may be caused by a variety of mechanisms, including increased myocardial load and/or destabilization of atherosclerotic plaques by inflammation. FOLLOW-UP Fever and leukocytosis usually resolve within 2–4 days in otherwise healthy CAP patients, but physical findings may persist longer. Chest radiographic abnormalities

are slowest to resolve (4–12 weeks), with the speed of clearance depending on the patient's age and underlying lung disease, and the etiologic pathogen. Patients may be discharged from hospital once their clinical condition, includ ing any comorbidity, is stable. The site of residence after discharge (nursing home, home with family, home alone) is an important consideration, particularly for elderly patients. For a hospitalized patient, we generally recommend a follow-up radiograph ~4–6 weeks later. If relapse or recurrence occurs, particularly in the same lung segment, the possibility of an underlying neoplasm or other local abnormalities (e.g., focal bronchiectasis) must be considered. For individuals managed as outpatients, routine follow-up chest radiog raphy is not necessary if they are nonsmokers, if they are otherwise well, and if symptoms resolved within 5–7 days. ■ ■PROGNOSIS The prognosis depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient). Young patients without comorbid ity do well and usually recover fully after ~2 weeks. Older patients and those with comorbid conditions may take several weeks longer to recover fully. The overall mortality rate for the outpatient group is <5%. For patients requiring hospitalization, overall mortality ranges from 12% to 40%, depending on the patient category and the processes of care, particularly the timely administration of appropriate antibiotics. Recent data, especially in older patients, show that the 1-year mortality following CAP exceeds the 30-day mortality. ■ ■PREVENTION The main preventive measure is vaccination. Recommendations of National Advisory Committees on Immunization Practices should be followed (Chap. 129). VENTILATOR-ASSOCIATED PNEUMONIA Research on hospital-acquired pneumonia has focused on VAP (onset ≥48 h after mechanical ventilation). However, the same information and principles can also be applied to ventilated HAP and to nonICU HAP. Approximately 70% of HAP cases are acquired outside the ICU and 30% in the ICU; the fact that 35% of all HAP patients need mechanical ventilation defines ventilated HAP as a distinct entity. In nonintubated patients with HAP, an expectorated sputum sample is used for microbiologic diagnosis, but results are confounded by fre quent colonization by oral pathogens. Microbiologic information in VAP and ventilated HAP is obtained from direct access to deep lower respiratory tract samples, which provide reliable microbiologic data; however, these samples can also contain colonizing pathogens. ■ ■ETIOLOGY Potential etiologic agents of VAP include both MDR and non-MDR bacterial pathogens (Table 131-6). The non-MDR group of "core pathogens" is nearly identical to the pathogens found in severe CAP (Table 131-1); it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors (particularly prior antibiotic treat ment), MDR pathogens are a consideration, even early in the hospital course. The relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different criti cal care units within the same institution. Most hospitals have problems with P. aeruginosa and MRSA, but other MDR pathogens are often institution-specific. Less commonly, fungal and viral pathogens cause VAP, usually affecting severely immunocompromised patients. Rarely,

community-associated viruses cause mini-epidemics, usually when introduced by ill health care workers.

■ ■EPIDEMIOLOGY Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia— VAP in the overwhelming majority of cases. Although in recent years the frequency of this infection was declining as a result of effective prevention strategies, with the advent of COVID-

19, there has been an increase in its frequency. The frequency of VAP changes with the dura tion of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. Once a ventilated patient is transferred to a chronic-care facility or to home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia. However, in chronic ventilator units, purulent tracheobronchitis becomes a significant issue, often interfering with efforts to wean patients off mechanical ventilation (Chap. 313). Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and compromise of normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors (Table 131-7). The most important risk factor is the endotracheal tube, which bypasses the normal mechanical factors preventing aspiration. While the presence of an endotracheal tube may prevent large-volume aspi ration, microaspiration is actually exacerbated by secretions pooling above the cuff. The endotracheal tube and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the tube’s surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged dur ing suctioning (done preferably with a closed catheter system) and can reinoculate the trachea, or tiny fragments of a glycocalyx can embolize to distal airways, carrying bacteria with them. The ventilator circuit tubing can harbor pathogenic organisms that can wash back to the patient if manipulated too often; thus, circuits are changed only when soiled and with each new patient. Heat moisture exchangers are changed every 5–7 days or if visibly soiled or malfunctioning. PART 5 Infectious Diseases In a high percentage of critically ill patients, the normal oropharyn geal flora is replaced by pathogenic microorganisms. The most impor tant risk factors are antibiotic selection pressure, cross-infection from other infected/colonized patients or contaminated equipment, severe systemic illness, and malnutrition. Of these factors, antibiotic exposure poses the greatest risk by far. Pathogens such as P. aeruginosa almost never cause infection in patients without prior exposure to antibiotics. The recent emphasis on hand hygiene has lowered the cross-infection rate. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-third of colonized patients develop VAP. Colony counts increase to high levels, sometimes days before the development of clini cal pneumonia; these increases suggest that the final step in VAP devel opment, independent of aspiration and oropharyngeal colonization, is the overwhelming of host defenses by a large bacterial inoculum. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although hyperglycemia and frequent transfusions adversely affect the immune response. ■ ■CLINICAL MANIFESTATIONS The clinical manifestations of HAP and VAP are nonspecific: fever, leukocytosis, increased respiratory secretions, and pulmonary

TABLE 131-7 Pathogenic Mechanisms and Corresponding Prevention Strategies for Ventilator-Associated Pneumonia PATHOGENIC MECHANISM PREVENTION STRATEGY Oropharyngeal colonization with pathogenic bacteria Elimination of normal flora, Avoidance of prolonged antibiotic courses; consider oral chlorhexidinea overgrowth by pathogenic bacteria Large-volume oropharyngeal Short course of prophylactic antibiotics for comatose patients; short course of

prophylactic inhaled aminoglycoside antibioticsb aspiration around time of intubation Gastroesophageal reflux Postpyloric enteral feeding with orally placed feeding tubea; avoidance of high gastric residuals, prokinetic agents Bacterial overgrowth of stomach Avoidance of prophylactic agents that raise gastric pHa; selective decontamination of digestive tract with nonabsorbable antibioticsa Cross-infection from other colonized patients Hand washing, especially with alcoholbased hand rub; intensive infection control educationb; isolation; proper cleaning of reusable equipment Large-volume aspiration Ventilator circuit humidification Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction Change ventilator circuits only when soiled and with new patient; drain ventilator circuit condensate away from patient; replace heat moisture exchanger every 5–7 days or if soiled or malfunctioninga Microaspiration around endotracheal tube Endotracheal intubation Noninvasive ventilationb Prolonged duration of ventilation Daily awakening from sedation,b weaning protocolsb Abnormal swallowing function Early percutaneous tracheostomyb Secretions pooled above Head of bed elevatedb; continuous aspiration of subglottic secretions with specialized endotracheal tubeb; avoidance of reintubation; minimization of sedation and patient transport; prophylactic PEEPc of 5–8 cm endotracheal tube Altered lower respiratory host defenses Tight glycemic controla; lowering of hemoglobin transfusion threshold aStrategies with negative randomized trials or conflicting results. bStrategies demonstrated to be effective in at least one randomized controlled trial. cPositive end-expiratory pressure. consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation. Serial changes in oxygenation may identify pneumonia earlier than other findings and may also be a means to monitor improvement with therapy. ■ ■DIAGNOSIS No single set of criteria is reliably diagnostic of pneumonia in a ven tilated patient. The inability to accurately identify such patients com promises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates. Application of clinical criteria typical for CAP consistently results in overdiagnosis of VAP, largely because of (1) frequent tracheal colo nization with pathogenic bacteria in patients with endotracheal tubes, (2) multiple alternative causes of radiographic infiltrates in mechani cally ventilated patients, and (3) the high frequency of other sources

of fever in critically ill patients. The differential diagnosis of VAP includes atypical pulmonary edema, pulmonary contusion, alveolar hemorrhage, hypersensitivity pneumonitis, acute respiratory distress syndrome, and pulmonary infarction. Findings of fever and/or leu kocytosis may have alternative causes, including antibiotic-associated diarrhea, central line–associated infection, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumo nia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP (fungal or viral pneumonia); or require some additional intervention, such as surgical drainage or catheter removal, for optimal management. This diagnostic dilemma has led to debate and controversy about whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to a clinical approach enhanced by principles learned from quantitative-culture studies. The most recent IDSA/ATS guidelines for HAP/VAP give a weak recom mendation for a clinical approach based on semiquantitative cultures,

with consideration of the availability of resources, cost, and the avail ability of expertise. The guidelines acknowledge that the use of a quan titative approach may result in less antibiotic use, which may be critical for antibiotic stewardship in the ICU. Therefore, the approach at each institution—or potentially for each patient—should be individualized and based on local colonization rates, local diagnostic expertise, and recent history of antibiotic therapy. Quantitative-Culture Approach This method uses quantitative cultures of deep respiratory tract samples to distinguish colonization from true infection. The more distal in the respiratory tree the diagnos tic sampling, the more specific are the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, an endotracheal aspirate yields proximal samples, and the diagnostic threshold is 106 cfu/mL. The protected specimen brush method, in contrast, collects distal samples and has a threshold of 103 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram staining, differential cell counts, staining for intracellular organisms, and detection of local protein levels elevated in response to infection. If the quantitative approach is used, therapy decisions should be linked to culture results (no antibiotics if below the diagnostic thresh old), with antibiotics withheld until results are available unless the patient is critically ill. Studies have documented less antibiotic use with this approach than with the clinical approach, but the results are less clear if antibiotic decisions are not directly linked to culture data. One common limitation of the quantitative approach is that the use of a new and effective antibiotic agent in the 24–48 h prior to sampling can lead to false-negative results. With antimicrobial-sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnos tic threshold. After 3 days, the operating characteristics of the tests improve to the point at which they are equivalent to results obtained when no prior antibiotic therapy has been given. Conversely, colony counts above the diagnostic threshold during antibiotic therapy sug gest that the current antibiotics are ineffective. In addition, quantitative cultures may give results below the diagnostic threshold if samples are collected early in the course of infection or if sampling is delayed until after an effective host response has reduced bacterial counts. Ideally, a specimen should be obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed. Clinical Approach The lack of specificity of a clinical diagnosis of VAP has hampered its utility, but this approach has been improved by the addition of microbiologic and other laboratory data. Tracheal aspirates generally yield at least twice as many potential pathogens as quantitative cultures, but the causative pathogen is almost always pres ent. The absence of bacteria in Gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative

diagnoses possible in patients with suspected VAP, can prevent inap propriate antibiotic overtreatment. Furthermore, the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage, allowing de-escalation of empirical antibiotic therapy. Similarly, with newer and more sensitive molecular diagnostic meth ods, a suspected MDR pathogen can be eliminated as a therapy target if test results are negative. A clinical approach that focuses on careful antimicrobial use and de-escalation of therapy after culture results become available may have an impact on the avoidance of antimi crobial overuse and the consideration of alternative sites of infection similar to that of a quantitative-culture approach.

TREATMENT Ventilator-Associated Pneumonia Many studies have demonstrated higher mortality rates with the delay of initially appropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the resistance patterns of the most likely pathogens in a given patient and consideration of local microbiology. ANTIBIOTIC RESISTANCE Because of a higher risk of infection with MDR pathogens (Table 131-6), VAP is treated with antibiotics different from those used for severe CAP. Antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (e.g., MRSA and Enterobacteriaceae producing ESBLs or carbapenemases) or for intrinsically resistant pathogens (e.g., P. aeruginosa and Acinetobacter species). Frequent use of β-lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and ESBL-positive strains. CHAPTER 131 P. aeruginosa can develop resistance to all routinely used anti biotics, and, even if initially sensitive, P. aeruginosa isolates may develop resistance during treatment. Either derepression of resis tance genes or selection of resistant clones within the large bacterial inoculum associated with most pneumonias may be the cause. Acinetobacter species, Stenotrophomonas maltophilia, and Burkholderia cepacia are intrinsically resistant to many of the empirical antibiotic regimens employed (see below). VAP caused by these pathogens typically emerges during treatment of other infections, and resis tance is always evident at initial diagnosis. EMPIRICAL THERAPY Recommended options for empirical therapy are listed in Table 131-8. Treatment should be started once diagnostic specimens have been obtained. The major factors in the selection of agents are the pres ence of risk factors for MDR pathogens and the predicted risk of death (≤15% is considered low risk). Choices among the various options listed depend on local patterns of resistance and—a very important factor—the patient's prior antibiotic exposure. Knowl edge of the local hospital's—and even the specific ICU's—anti biogram and the local incidence of specific MDR pathogens (e.g., MRSA) is critical in selecting appropriate empirical therapy. Pneumonia The majority of patients without risk factors for MDR infec tion can be treated with a single agent. In fact, mortality is lower with a single agent than with combination therapy for those with a low mortality risk. For these patients, monotherapy options listed in Table 131-8 are active against the core pathogens, as well as nonresistant P. aeruginosa. However, in selected settings, it may be possible to use a nonpseudomonal agent such as cefotaxime or moxifloxacin. Unfortunately, the proportion of patients with no MDR risk factors is <10% in some ICUs and is unknown for HAP patients. The major difference from CAP is the markedly lower incidence of atypical pathogens in VAP; the exception is Legionella, which can be a nosocomial pathogen, especially with local epidem ics due to breakdowns in the treatment of potable water in the hos pital. The standard recommendation for patients with risk factors for MDR infection and a high mortality risk is for three antibiotics:

TABLE 131-8 Empirical Antibiotic Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia NO RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGENa (CHOOSE ONE FROM EACH COLUMN) Piperacillintazobactam (4.5 g IV q6h) Cefepime (2 g IV q8h) Levofloxacin (750 mg IV q24h) Piperacillin-tazobactam (4.5 g IV q6h) Cefepime (2 g IV q8h) Ceftazidime (2 g IV q8h) Imipenem (500 mg IV q6h) Meropenem (1 g IV q8h) Consider newer agentsc Amikacin (15–20 mg/kg IV q24h) Gentamicin (5–7 mg/kg IV q24h) Tobramycin (5–7 mg/kg IV q24h) Ciprofloxacin (400 mg IV q8h) Levofloxacin (750 mg IV q24h) Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg × [1.5 × CrCl + 30] IV q12h) Polymyxin B (2.5–3.0 mg/kg per day IV in 2 divided doses) Risk Factors for MRSAb (Add to above) Linezolid (600 mg IV q12h) or Adjusted-dose vancomycin

(trough level, 15–20 mg/dL) aPrior antibiotic therapy, prior hospitalization, local antibiogram. bPrior antibiotic therapy, prior hospitalization, known MRSA colonization, chronic hemodialysis, local documented MRSA pneumonia rate >10% (or local rate unknown). cNewer agents can have activity against resistant P. aeruginosa (ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, plazomicin), carbapenem-resistant Enterobacteriaceae (ceftazidime-avibactam, imipenem-relebactam, meropenemvaborbactam), metallo-β-lactamase–producing Enterobacteriaceae (ceftazidimeavibactam, cefiderocol), Stenotrophomonas (cefiderocol), and Acinetobacter spp. (cefiderocol, sulbactam-durlobactam). Abbreviations: CrCl, creatinine clearance rate; MRSA, methicillin-resistant Staphylococcus aureus. PART 5 Infectious Diseases two directed at P. aeruginosa and other resistant gram-negative organisms and one directed at MRSA. However, in the absence of septic shock, a single agent may be effective for these patients, provided there is a single agent that is likely to be effective against at least 90% of the gram-negative pathogens in that ICU. Empirical combination therapy enhances the likelihood of initially appropri ate therapy over that with monotherapy. A β-lactam agent provides the greatest coverage, yet even the broadest-spectrum agent—a carbapenem—still constitutes inappropriate initial therapy in up to 10–15% of cases at some centers. The emergence of carbapenem resistance at some institutions requires the addition of polymyx ins to the combination-therapy options. A number of emerging agents may modify our approach to therapy. New antipseudomonal agents include ceftazidime–avibactam, ceftolozane–tazobactam, imipenem–relebactam, and plazomicin. Therapy for carbapenemresistant Enterobacteriaceae can consist of ceftazidime–avibactam, imipenem–relebactam, or meropenem–vaborbactam, while Entero bacteriaceae that produce metallo-β-lactamases can be treated with ceftazidime–avibactam or cefiderocol. Acinetobacter spp. can be treated with cefiderocol (as part of a combination regimen) or with sulbactam-durlobactam, and Stenotrophomonas can be treated with cefiderocol. SPECIFIC TREATMENT Once an etiologic diagnosis is made, broad-spectrum empirical therapy can be modified (de-escalated) to specifically address the known pathogen. For patients with MDR risk factors, antibiotic regimens can be reduced to a single agent in most cases. Only a minority of cases require a complete course with two or three drugs. A negative tracheal-aspirate culture or growth below the threshold for quantitative cultures of samples obtained before any antibiotic change strongly suggests that antibiotics should be discontinued or that an alternative diagnosis should be pursued. Identification of other confirmed or suspected sites of infection may require ongoing antibiotic therapy, but the spectrum of pathogens (and the

corresponding antibiotic choices) may be different from those for VAP. A 7- or 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibioticresistant strains. Exceptions include cases in which initial therapy is inappropriate or consists of second-line antibiotics and cases caused by some more resistant organisms, such as carbapenemase-producing Acinetobacter species. In these situations, serial measurements of procalcitonin may help guide duration of therapy. A major controversy regarding specific therapy for VAP con cerns the need for ongoing combination treatment of Pseudomonas pneumonia. No randomized controlled trials have demonstrated a benefit of combination therapy with a β-lactam and an aminogly coside, nor have subgroup analyses in other trials found a survival benefit with such a regimen. Combination therapy may increase the likelihood of initially appropriate therapy and may have value in bacteremic infection with septic shock, but the benefit may last for only a few days. The unacceptably high rates of clinical failure and death despite combination therapy among patients with VAP caused by P. aeruginosa (see “Failure to Improve,” below) indicate that

better regimens are needed, perhaps including aerosolized anti biotics. In most cases of Pseudomonas pneumonia, current guide lines recommend against continuing combination therapy after the isolate's antimicrobial susceptibility is known. FAILURE TO IMPROVE Treatment failure is not uncommon in VAP, especially that caused by MDR pathogens. VAP caused by MRSA is associated with a 40% clinical failure rate when treated with standard-dose vancomycin. One proposed but unproven solution is the use of high-dose indi vidualized treatment, although the risk of renal toxicity increases with this strategy. In addition, the MIC of MRSA to vancomycin has been increasing, and a high percentage of clinical failures occur when the MIC is in the upper range of sensitivity (i.e., 1.5–2 μg/mL). Linezolid appears to be 15% more efficacious than even adjusted-dose vancomycin and is preferred in patients with renal insufficiency and those infected with high-MIC isolates of MRSA. VAP due to Pseudomonas has a 40–50% failure rate, no matter what the regimen. Therapy-related causes of clinical failure include not using the recommended combination regimen (Table 131-8) and inadequate antibiotic dosing. However, the emergence of β-lactam resistance during therapy is an important problem, especially in infection with Pseudomonas and Enterobacter species. Recurrent VAP caused by the same pathogen is possible because the biofilm on endotracheal tubes allows persistence and reintroduction of the microorganism. Studies of VAP caused by Pseudomonas show that approximately half of recurrent cases are caused by a new strain. Some studies have suggested that treatment failure may be less com mon with optimized β-lactam dosing and use of either prolonged or continuous infusion therapy. Possible causes of treatment failure can be difficult to determine early in the therapeutic course and can include superinfection, the presence of extrapulmonary infection, as well as patient factors such as severe comorbid illness and immunosuppression. Serial quantitative cultures may clarify the microbiologic response, and recent data in ICU patients have shown a role for biomarkers, such as procalcitonin, to guide duration of therapy in conjunction with the patient's initial response to treatment. COMPLICATIONS Apart from death, the major complication of VAP is prolonga tion of mechanical ventilation, with corresponding increases in the duration of ICU and hospital stay. In most studies, the need for additional mechanical ventilation resulting from VAP justifies aggressive efforts at prevention. In rare cases, necrotizing pneumonia (e.g., due to P. aeruginosa or S. aureus) can cause significant pulmonary hemorrhage or empy ema. More commonly, necrotizing infections result in the longterm complications of bronchiectasis and parenchymal scarring leading to recurrent pneumonia. Other long-term complications of

pneumonia can include need for prolonged oxygen therapy, a cata bolic state in a patient already nutritionally at risk, the necessity for ongoing rehabilitation, and—in the elderly—an inability to return to independent function and the need for nursing home placement. FOLLOW-UP Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment, usually with an improve ment in oxygenation. Because findings on chest radiography often worsen initially during treatment, they are less helpful than clinical criteria as an indicator of response to therapy. ■ ■PROGNOSIS VAP is associated with crude mortality rates as high as 50–70%, but the real issue is attributable mortality. Many patients with VAP have underlying diseases that would result in death even if VAP did not occur. Attributable mortality exceeded 25% in one matched-cohort study, while more recent studies have suggested much lower rates (5–10%), although patients with VAP complicating COVID-19 have a higher attributable mortality than those with other forms of VAP. Some variability in VAP mortality rates is clearly related to the type of patient and ICU studied. VAP in trauma patients is not associated with attributable mortality, possibly because many of the patients were otherwise healthy before being injured. The

causative pathogen also plays a major role. Generally, MDR pathogens are associated with significantly greater attributable mortality than non-MDR pathogens. Pneumonia caused by some pathogens (e.g., S. maltophilia) is simply a marker for a patient whose immune system is highly compromised and is therefore at high risk. ■ ■PREVENTION (TABLE 131-7) Because endotracheal intubation is a risk factor for VAP, the most impor tant preventive intervention is to avoid intubation or minimize its dura tion. Successful noninvasive ventilation avoids many of the problems associated with endotracheal tubes. Strategies that minimize the dura tion of ventilation through daily holding of sedation and formal weaning protocols have also been highly effective in preventing VAP. Unfortunately, a tradeoff in risks is sometimes necessary. Aggressive attempts to extubate early may result in reintubation(s) and increase aspiration, posing a risk of VAP. Heavy continuous sedation increases VAP risk, but self-extubation because of insufficient sedation is also a risk. The tradeoffs also apply to antibiotic therapy. Short-course antibi otic prophylaxis can decrease the risk of early-onset VAP in comatose patients requiring intubation, and data suggest that antibiotics decrease VAP rates overall. Conversely, prolonged courses of antibiotics consis tently increase the risk of MDR VAP; pseudomonal VAP is rare among patients who have not recently received antibiotics. In one recent randomized trial, 3 days of daily inhaled aminoglycoside prophylaxis reduced the occurrence of VAP for the next 28 days, with no impact on mortality or antibiotic use. Minimizing microaspiration around the endotracheal tube cuff also can prevent VAP. Simply elevating the head of the bed (at least 30° above horizontal, but preferably 45°) and using specially modified endotracheal tubes that allow removal of the secretions pooled above the cuff can prevent microaspiration. The risk-to-benefit ratio of trans porting the patient outside the ICU for diagnostic tests or procedures should be carefully considered since VAP rates are increased among transported patients. The role played by overgrowth of the normal bowel flora in the stomach—in the presence of elevated gastric pH—in the pathogen esis of VAP is questionable. Therefore, avoidance of agents that raise gastric pH may be relevant only in certain populations, such as liver transplant recipients and patients who have undergone other major intraabdominal procedures or who have bowel obstruction. MRSA and nonfermenters such as P. aeruginosa and Acinetobacter species are not normally part of the bowel flora but reside primarily in the nose and on the skin, respectively. In outbreaks of VAP due to specific pathogens, the possibility of a breakdown in infection control measures (particularly contamination

of reusable equipment) should be investigated. Even high rates of pathogens that are already common in a particular ICU may result from cross-infection. Education and reminders of the need for consis tent hand washing and other infection-control practices can minimize this risk.

HOSPITAL-ACQUIRED PNEUMONIA While less well studied than VAP, HAP in nonintubated patients—both inside and outside the ICU—is similar to VAP. The main differences are the higher frequency of non-MDR pathogens and the generally better underlying host immunity in nonintubated patients. The lower frequency of MDR pathogens allows monotherapy in a larger propor tion of cases of HAP than of VAP. However, the bacteriology and outcome of ventilated HAP patients may be very similar to those of patients with VAP. The only pathogens that may be more common in the non-VAP population are anaerobes because of a greater risk of macroaspira tion and the lower oxygen tensions in the lower respiratory tract of these patients. Anaerobes usually contribute only to polymicrobial pneumonias, and specific therapy targeting anaerobes probably is not needed since many of the recommended antibiotics are active against anaerobes. Diagnosis is even more difficult for HAP in the nonintubated patient than for VAP. Lower respiratory tract samples appropriate for culture are considerably more difficult to obtain from nonintubated

patients. Many of the underlying diseases that predispose a patient to HAP are also associated with an inability to cough adequately. Since blood cultures are infrequently positive (<15% of cases), the major ity of patients with HAP do not have culture data on which antibiotic modifications can be based, and de-escalation is less likely. Despite these difficulties, the better host defenses in non-ICU patients result in lower mortality rates than are documented for VAP and for ventilated HAP. In addition, the risk of antibiotic failure is lower in HAP. CHAPTER 131 Pneumonia GLOBAL IMPACT From the available data, it is virtually impossible to accurately assess the impact of pneumonia from a global perspective. Any differences in incidence, disease burden, and costs across different age, ethnic, and racial groups are compounded by differences among countries in terms of etiologic pathogens, resistance rates, access to health-care and diagnostic facilities, and vaccine availability and use. A standard approach with clearly defined outcome measures is needed before the impact of pneumonia can be accurately evaluated. However, simple extrapolation from U.S. data for CAP and HAP/ VAP shows that pneumonia has a significant impact on quality of life, morbidity, health costs, and mortality rates and that this impact has implications for patients and for society as a whole. Acknowledgment The authors gratefully acknowledge the contributions of Richard Wun derink, MD, to this chapter in a prior edition. ■ ■FURTHER READING Dequin PF et al: Hydrocortisone in severe community–acquired pneu monia. N Engl J Med 388:1931, 2023. Dickson RP et al: Towards an ecology of the lung: New conceptual models of pulmonary microbiology and pneumonia pathogenesis. Lancet Respir Med 2:238, 2014. File TM Jr: Community-acquired pneumonia. N Engl J Med 389:632, 2023. Jain S et al: Community-acquired pneumonia requiring hospitaliza tion among U.S. adults. N Engl J Med 373:415, 2015. Kalil AC et al: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Tho racic Society. Clin Infect Dis 63:e61, 2016. Mandell LA, Niederman MS: Aspiration pneumonia. N Engl J Med 380:651, 2019. Mandell LA et al: Infectious Diseases Society of America/Ameri can Thoracic Society consensus guidelines on the management of

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