COVID-19
Special Offer for Healthcare Professionals

Expires May 31, 2021

This Special Offer includes:

The Coronavirus Disease (COVID-19) Pandemic
Sepsis: Diagnosis and Management
Pneumonia

NetCE
Continuing Education

The Coronavirus Disease (COVID-19) Pandemic

At the time of publication, this outbreak was ongoing. As the situation evolves, updated information will be incorporated online at https://www.NetCE.com.

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- Read the enclosed course.
- Complete the questions at the end of the course.
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Faculty

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure

The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, and other healthcare professionals who may identify or educate patients regarding coronavirus infection.

Accreditations & Approvals

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NetCE designates this continuing education activity for 2 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 2 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 2.4 hours for Alabama nurses.

AACN Synergy CERP Category A.

NetCE designates this activity for 2 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-20-067-H04-P and JA4008164-0000-20-067-H04-T.

Social Workers participating in this intermediate to advanced course will receive 2 Clinical continuing education clock hours.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement
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Course Objective
The purpose of this course is to provide physicians, nurses, and other healthcare professionals an overview of the 2019–2020 global outbreak of novel human coronavirus (SARS-CoV-2) infection, including background epidemiology, clinical features, mode of transmission, epidemic potential, and the clinical and public health measures recommended to limit the spread of infection and control the outbreak.

Learning Objectives
Upon completion of this course, you should be able to:

1. Differentiate between the common, ubiquitous strains of human coronavirus and novel (outbreak) strains with respect to epidemiology, modes of transmission, spectrum of illness, and public health implications.
2. Characterize the clinical and public health experience gained from the two prior novel human coronavirus epidemics, SARS and MERS, and how that informs our understanding and response to the current Pandemic.
3. Recognize the clinical manifestations of COVID-19 and systemic complications associated with a dysregulated immune response, and discuss the dynamics of transmission and advise patients regarding prevention of infection, with special attention to those with risk factors for severe disease.
4. Access and implement guideline recommendations for clinical assessment, diagnostic testing, appropriate isolation precautions, and monitoring of a patient with recent exposure to, suspected infection with, or newly diagnosed COVID-19.

Pharmacy Technician Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the background of coronaviruses.
2. Describe the response to the 2019–2020 novel coronavirus disease (COVID-19) outbreak.

BACKGROUND

CORONAVIRUS

Coronaviruses (a subfamily of Coronaviridae) are enveloped, single-stranded RNA viruses that are broadly distributed among humans, other mammals, and birds. Under electron microscopy, the outer envelope of the virion shows club-like surface projections that confer a crown-like appearance to the virus, which accounts for the name given to this family of viruses. The nucleocapsid is a long, folded strand that tends to spontaneous mutations and frequent recombination of the genome, which may account, in part, for changes in transmissibility and pathogenicity that permit a new (novel) form of coronavirus infection in humans.

In addition to four specific subtypes of coronavirus commonly found in humans, other strains have been detected in many different species of animals, including bats, cats, camels, and cattle. On rare occasions, an animal coronavirus is responsible for zoonotic infection in humans, meaning that a novel coronavirus is transmitted from an animal host to one or more humans, producing clinical illness that may result in secondary spread among persons in close contact. The wide distribution, genetic diversity, and frequent shifts in the genome, combined with unique human-animal interface activities, are considered important factors in the periodic emergence of new coronavirus outbreaks in human populations [1; 2].

HUMAN CORONAVIRUS INFECTION

Common Strains

Human coronavirus (HCoV) was first identified in 1965, isolated from a patient with what was described as the common cold [3]. Subsequently, four types of HCoV have been detected commonly in respiratory secretions of children and adults in scattered regions of the globe, labeled HCoV-229E, -NL63, -OC43, and -HKU1. These agents are a common cause of mild-to-moderate upper respiratory illness, such as the common cold, bronchitis,

bronchiolitis in infants and children, and asthma exacerbation. On occasion, as with influenza, HCoVs can cause serious lower respiratory tract infection (viral pneumonia), a complication more common to persons with underlying cardiopulmonary disease or weakened immune systems.

Novel Coronavirus Outbreaks

In addition to the seasonal infections caused by the ambient, adaptive HCoVs described, widespread outbreaks of novel (new) coronavirus infection have occurred in each of the past two decades, and the 2019–2020 Wuhan, China, outbreak poses the third threat of a severe novel coronavirus epidemic on a global scale [1; 4]. The common epidemiologic feature of these outbreaks is an initial point source cluster of zoonotic infection followed by secondary spread of the virus via human-to-human transmission. Among the factors thought to be conducive to the emergence of such outbreaks are the following: genomic recombination in an animal CoV capsid that renders the virus better adapted to human infection (and perhaps more virulent); and dietary practices and cultural determinants that bring humans into close contact with livestock or raw meat and carcasses of wild animals and birds, thereby facilitating transmission from an infected animal host to humans. After infection is established, secondary viral transmission occurs through close person-to-person contact by way of droplet nuclei propelled into the air during coughing and sneezing. The first two known novel coronavirus outbreaks, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, are considered to be zoonotic in origin and were associated with serious, sometimes fatal illness.

Severe Acute Respiratory Syndrome (SARS-CoV)

Infection with SARS-CoV was first recognized in China in November 2002, and signs of an outbreak in Asia were evident by February 2003 [3]. Epidemiologic investigation found that early cases of SARS-CoV represented zoonotic infection involving transmission from civet cats to humans. Over the next several months, SARS-CoV spread to countries in North America, South America, Europe, and other parts of Asia before the global outbreak was contained later in the same year.

SARS-CoV infection began with fever, headache, malaise, and arthralgia/myalgia followed in two to seven days by cough, shortness of breath, and in most patients, signs of pneumonia [3].

According to the World Health Organization (WHO), the 2002–2003 outbreak caused 8,098 probable cases of SARS worldwide and 774 deaths. Just eight cases were identified in the United States. Since 2004, there have been no additional known cases of SARS-CoV infection reported anywhere in the world [3].

In response to the 2003 global SARS outbreak, the Centers for Disease Control and Prevention (CDC), working in concert with the WHO, developed a strategy for controlling the epidemic that included the following elements [3]:

- Activated the Emergency Operations Center to provide around-the-clock coordination and response.
- Committed more than 800 medical experts and support staff to work on the SARS response and to assist with ongoing investigations around the world.
- Provided assistance to state and local health departments in investigating possible cases of SARS in the United States.

- Conducted extensive laboratory testing of clinical specimens from patients with SARS to identify the cause of the disease.
- Initiated a system for distributing health alert notices to travelers who may have been exposed to cases of SARS.

This experience provided a blueprint for responding to the 2019–2020 coronavirus outbreak in China.

Middle East Respiratory Syndrome (MERS-CoV)

MERS-CoV was first reported in Saudi Arabia in 2012, and all cases to date have been linked to countries in or near the Arabian Peninsula. Travel-associated MERS-CoV infection has been reported from many countries around the world, including two imported cases diagnosed in the United States in 2014 involving unlinked healthcare providers who had recently lived and worked in Saudi Arabia. There is epidemiologic evidence for two modes of transmission: zoonotic infection from an animal reservoir to humans (with camels acting as the intermediate host), and person-to-person transmission via close contact with an index case, as described in association with a family case cluster and a nosocomial outbreak [5; 6; 7].

Most persons with confirmed MERS-CoV infection have had moderately severe respiratory illness manifest by fever, cough, and shortness of breath, often complicated by pneumonia and respiratory failure. The case-fatality rate approaches 40%. Most deaths have been in patients with pre-existing chronic conditions such as diabetes, cancer, or heart, lung, or renal disease. Sporadic cases of MERS-CoV continue to appear in various parts of the Middle East [3].

THE 2019–2020 NOVEL CORONAVIRUS OUTBREAK: A GLOBAL THREAT

In December 2019, Chinese physicians in Hubei Province, China, began an investigation of a cluster of cases of severe viral pneumonia in area hospitals linked to exposure to a large seafood and live animal wholesale market in Wuhan City. In the weeks following, it became evident that a large outbreak of respiratory illness was rapidly emerging within Wuhan City and nearby communities, reaching the thousands by mid-January.

On January 24, Chinese scientists reported the results of viral diagnostic studies conducted on bronchoalveolar lavage specimens obtained from three Wuhan City patients hospitalized in December with severe bilateral interstitial, alveolar pneumonia [2]. The investigation identified a viral genome matched to lineage B of the genus betacoronavirus, showing more than 85% match with a SARS-like CoV genome previously described in bats. Ultrathin sections of infected human airway epithelial cells showed inclusion bodies filled with virus particles in membrane-bound vesicles in the cytoplasm. On electron microscopy, the observed morphology of the virion is consistent with the Coronaviridae family.

This newly identified coronavirus is now known to be the etiologic agent responsible for the Wuhan, China, outbreak and is named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The resultant disease is referred to as COVID-19. Like SARS-CoV and MERS-CoV, SARS-CoV-2 is a betacoronavirus that likely has its origin in bats, with one or more animals serving as the intermediate host for zoonotic infection in humans. According to CDC reports, virus sequences from imported cases in this country are similar to the one initially posted by China, suggesting a likely single, recent emergence of this virus from an animal reservoir [12].

The rapid accumulation of many new cases in Wuhan City during the months of December 2019 and January and February 2020, combined with evidence of spread to persons from other nearby provinces in central China and reports of acute infection in healthcare workers, point to facile human-to-human transmission of SARS-CoV-2 as the key factor responsible for continued propagation of the COVID-19 outbreak.

CLINICAL MANIFESTATIONS OF COVID-19

The incubation period of SARS-CoV-2 infection is 5 to 7 days on average, with a range of 2 to 14 days. It is estimated that 97.5% of persons with COVID-19 who develop symptoms will do so within 11.5 days of infection [15; 18]. The onset and progression of illness is variable, with most patients experiencing some combination of fever, cough, fatigue, anorexia, myalgias, and shortness of breath. Less common presenting symptoms include rhinorrhea, sudden loss of smell (anosmia) and/or taste (ageusia), and sore throat. Atypical presentations have been described whereby some patients experience diarrhea or nausea and vomiting prior to the onset of fever and respiratory symptoms and signs. As with other infections, elderly persons may present with weakness and confusion. Older adults and persons with medical comorbidities may have delayed onset of fever and respiratory symptoms [15].

In a study designed to better characterize the symptom profiles of patients with COVID-19 in the United States, especially among nonhospitalized patients, the CDC used an optional questionnaire to collect detailed information from a sample of confirmed COVID-19 cases reported from 16 participating states [60]. Among 164 symptomatic patients with onset of illness between January 14 and April 4, 2020, a total of 158 (96%) reported fever, cough, or shortness of breath. Of 57 hospitalized adult patients, 39 (68%) reported all three of these symptoms, compared with 25 (31%) of the 81 nonhospitalized adult patients. Each of the following symptoms was reported by more than half of patients: cough (84%), fever (80%), myalgia (63%), chills (63%), fatigue (62%), headache (59%), and shortness of breath (57%). Gastrointestinal symptoms were relatively common, most frequently diarrhea (38%) and least frequently vomiting (13%). Shortness of breath was more common in patients who required hospitalization (82%) than in nonhospitalized patients (38%). Anosmia and ageusia were reported by a higher percentage of nonhospitalized patients (22%) than hospitalized patients (7%) [60].

Although most symptomatic patients with COVID-19 experience a mild-to-moderate illness with slow convalescence, there is substantial risk of progression to bilateral pneumonia complicated by respiratory failure and death. In February 2020, the overall case fatality rate for confirmed cases of COVID-19 reported from China was approximately 3%. As the pandemic has progressed, reported case fatality rates have varied considerably among countries and regions, ranging from 3% to as high as 14%. Multiple factors account for this variance, including available health resources and access to care, differences in public health mitigation strategies, lack of uniformity in the way deaths are attributed to COVID, and the extent to which testing and contact tracing identifies asymptomatic infections. Based on reported cases and attributable deaths through mid-July, the COVID-19 case fatality rate in the United States is 3.6% [8].

SEVERITY AND PROGRESSION OF ILLNESS

The first report describing the clinical features of hospitalized patients with COVID-19-related pneumonia in Wuhan City was published online January 24, 2020 [9]. As of January 2, 41 admitted patients had been identified as having laboratory-confirmed 2019-nCoV infection; 30 (73%) were men and 27 (66%) had been exposed to the open-air Huanan Seafood Market. The median age was 49 years, and fewer than half of the patients had a history of underlying chronic disease. Common symptoms at onset of illness were fever (98%), cough (76%), and myalgia or fatigue (44%).

Dyspnea developed in 22 patients (55%), with a median time from illness onset to dyspnea of eight days. Common laboratory abnormalities included leukopenia, lymphopenia, and mild hepatic enzyme elevations. All 41 patients were reported to have pneumonia, and all save one had radiographic evidence of bilateral involvement. The typical findings on chest computed tomography (CT) images of intensive care unit (ICU) patients were bilateral multilobar and segmental areas of consolidation. Acute respiratory distress syndrome developed in 12 (32%) patients, 13 (32%) were admitted to an ICU, and 6 died (15%).

A larger retrospective study examined the clinical characteristics of COVID-19 in a cohort of 1,099 hospitalized patients in China during the first two months of the outbreak [17]. The most common symptoms were fever (43.8% on admission, 88.7% during hospitalization), cough (67.8%), and fatigue (38.1%) [17]. The most common patterns on chest CT were ground-glass opacification (36.4%) and bilateral patchy shadowing (51.8%). Some degree of radiographic or CT abnormality was evident in 82% of patients with nonsevere disease and 97% of patients with severe disease. Lymphocytopenia was present in 83.2% of the patients on admission. Sixty-seven patients (6.1%) were admitted or transferred to the ICU, 2.3% required mechanical ventilation, and 1.4% died [17].

In a summary of 72,314 cases reported to the Chinese Center for Disease Control and Prevention, the severity of illness ranged from mild to critical with approximately the following distribution [15; 23]:

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnea, hypoxia or >50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan dysfunction): 5%

The majority of cases (81%) were characterized as mild, with no or mild pneumonia [23]. The overall case-fatality rate was 2.3%, with higher rates among patient subgroups. Specifically, the case-fatality rate was 49% among critical patients, and all reported deaths occurred in critical patients [23].

Risk Factors

Risk factors for severe disease include advanced age, obesity (body mass index ≥30), and comorbidities such as hypertension, diabetes, cardiovascular disease, cancer, and chronic lung disease. Among more than 70,000 cases reported in China through February 11, 2020, 87% occurred in persons 30 to 79 years of age [23]. The proportion of case fatalities among patients 70 to 79 years of age was 8%, and among those 80 years of age or older, the rate was 14.8%. Case fatality for patients with comorbidities was elevated as well, specifically for those with cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6%), and cancer (5.6%). Only 2% of cases were in persons younger than 20 years of age, and no deaths were reported in those younger than 10 years of age.

Atypical presentations have been described, and older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms [15]. Headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea have been reported but are less common (<10%). Some persons with COVID-19 have experienced gastrointestinal symptoms such as diarrhea and nausea prior to developing fever and lower respiratory tract signs and symptoms. Anosmia or ageusia preceeding the onset of respiratory symptoms has been anecdotally reported, but more information is needed to understand its role in identifying COVID-19. Several studies have documented SARS-CoV-2 infection in patients who never develop symptoms (asymptomatic) and in patients not yet symptomatic (presymptomatic) [15].

In June 2020, the CDC issued an epidemiologic report on 1,320,488 laboratory-confirmed COVID-19 cases in the United States and territories, reported to CDC between January 22 and May 30, 2020 [55]. Cumulative incidence (403.6 cases per 100,000 persons) was similar among males (401.1) and females (406.0), highest among persons 80 years of age or older (902.0), and lowest among children younger than 9 years of age (51.1). Among 599,636 cases with known information on both race and ethnicity, 36% of persons were non-Hispanic white, 33% were Hispanic, 22% were black, 4% were Asian, and 1.3% were American Indian or Alaska Native. Among 287,320 cases with sufficient data on underlying health conditions, the most frequently reported were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an ICU, and 71,116 (5%) died. The hospitalized rate was six times higher among patients with a reported underlying condition (45.4%) than among those without reported underlying conditions (7.6%). The mortality rate was 12 times higher among patients with reported underlying conditions (19.5%) compared with those with none reported (1.6%). Approximately 4% of reported cases were asymptomatic. Among 373,833 cases with data on individual symptoms, 70% noted fever, cough, or shortness of breath; 36% reported muscle aches; and 34% reported headache. Overall, 31,191 (8%) persons reported loss of taste or smell [55].

During the course of the COVID-19 pandemic in the United States, obesity has emerged as an important independent risk factor for severe disease, especially among adult patients younger than 60 years of age. Multiple reports, ranging from single-center studies to analyses of records from large patient care networks, have consistently found that severe obesity (body mass index >35) is associated with higher rates of hospitalization, respiratory failure, and mortality from COVID-19 [77; 78]. The risk varies directly with degree of obesity and is independent of obesity-associated comorbidities. The impact is more striking among men than women. There are multiple mechanisms by which obesity may contribute to adverse outcomes in patients with COVID-19. In addition to obstructive pulmonary physiology and sleep apnea, severe obesity is associated with immune dysfunction (depression of anti-inflammatory signaling and increased pro-inflammatory signaling), alterations in vascular endothelium, and renin-angiotensin stimulation, which together may worsen lung inflammation and alveolar damage [78].

SYSTEMIC COMPLICATIONS OF COVID-19

At the cellular level, infection by a virus requires some affinity of the virion for the host cell combined with a mechanism that facilitates attachment and entry into the cell. Cell entry of SARS-CoV-2 depends on binding of the viral surface spike protein to angiotensin-converting enzyme (ACE2) receptors and activation of the spike protein by host cell transmembrane protease serine 2 [30]. ACE2 is highly expressed by epithelial cells in the nasopharynx and type II alveolar cells in the lung. ACE2 is also expressed in the heart, kidney, vascular endothelium, and intestinal epithelium, which may explain, in part, the propensity for multiorgan dysfunction and vascular complications increasingly recognized in patients with severe COVID-19. In an autopsy series of 27 patients reported from Germany, SARS-CoV-2 was detected in multiple organs, including the lungs, pharynx, kidney, heart, liver, and brain [31]. In a further analysis of renal involvement, SARS-CoV-2 viral load was detected in all kidney compartments examined, with preferential targeting of glomerular cells.

Based upon recent reports from clinical centers caring for a high volume of hospitalized patients, renal and cardiac complications are relatively common in severe COVID-19. In a retrospective study from China, 251 of 333 (75%) hospitalized patients with COVID-19 pneumonia exhibited some degree of renal involvement, as evidenced by proteinuria or hematuria, and 35 (10%) met criteria for acute kidney injury [32]. In another case series of 138 hospitalized COVID-19 patients, 7% overall and 22% of those admitted to the ICU developed elevated troponin levels or electrocar-

diogram abnormalities indicative of myocarditis or cardiac injury some time during hospitalization [33]. Myocardial injury is estimated to affect more than one-quarter of COVID-19 cases classified as critical and presents in two patterns: acute myocardial injury and dysfunction on presentation, and myocardial injury that develops as illness severity intensifies [34]. While headache and confusion are seen in some patients presenting with severe COVID-19, there is no evidence that SARS-CoV-2 causes primary infection of the central nervous system (e.g., encephalitis). In an autopsy series of 18 consecutive patients who died 0 to 32 days after onset of COVID-19, histopathologic examination of brain specimens did not show encephalitis or other specific brain changes referable to the virus [56].

Coagulopathy

Hospitalized patients with advanced COVID-19 often exhibit laboratory signs of a coagulopathy and are at increased risk for arterial and venous thromboembolic complications [15; 39; 40]. The pathogenesis is unknown but may involve some combination of systemic inflammation, endothelial dysfunction, platelet activation, immobility, and stasis of blood flow [40]. The early and most consistent abnormalities are elevated D-dimer levels and mild thrombocytopenia, followed by increased fibrin degradation products and prolongation of the prothrombin time as disease progresses. Laboratory measure of coagulation factors in a patient hospitalized with COVID-19 can provide an indication of disease severity. The presence of an elevated D-dimer on admission carries a poor prognosis and has been associated with increased risk of requiring mechanical ventilation, ICU admission, and mortality [40; 41]. The most frequently reported complications of COVID-19 coagulopathy are deep venous thrombosis (DVT) and pulmonary emboli (PE). In a prospective study of 150 critically ill patients from two centers in France, 25 patients developed PE and 3 developed DVT despite prophylactic anticoagulation [42]. In a report of 184 patients with severe COVID-19 from three centers in the Netherlands, the cumulative incidence of venous thromboembolism was 27%, including PE in 80% of the cases affected [43]. Other centers have reported lower rates. Among 393 patients from New York, venous thromboembolism was diagnosed in only 13 patients (3.3%), 10 of whom were on mechanical ventilation [44]. These differences point to the need for studies that control for clinical severity, underlying comorbidities, prophylactic regimen, and COVID-19-related therapies. At present, there are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolic complications in patients with COVID-19 [15]. One source of interim guidance recommends regularly monitoring hemostatic markers—namely D-dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19 and prophylactic use of low-molecular-weight heparin in all hospitalized patients, unless there are contraindications [40]. The National Institutes of Health has developed guidelines for antithrombotic therapy in patients with COVID-19, available at https://covid19treatmentguidelines.nih.gov/antithrombotic-therapy.

RECOVERY FROM COVID-19

Convalescence following SARS-CoV-2 infection follows a variable course, and symptomatic recovery from severe COVID-19 may take weeks to months. A report from Italy describes a cohort of 143 patients with moderate-to-severe COVID-19, 87% of whom had persistent symptoms two months or more after discharge from hospital [68]. The mean duration of hospitalization was 13.5 days; 73% had evidence of interstitial pneumonia, 15% received noninvasive respiratory support, and 5% required mechanical ventilation. Follow-up clinical assessment was conducted a mean of 60 days after onset of the first COVID-19 symptom. At evaluation, 18 (13%) were symptom free; of the remaining participants, 32% had one or two symptoms and 55% had three or more symptoms. The most common persistent symptoms were fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). None had fever or signs of acute illness. Of the total, 44% reported persistence of the decline in quality of life imposed by COVID-19.

A multistate survey conducted by the CDC found that persistent symptoms three weeks after diagnosis of SARS-CoV-2 infection was common among outpatients with milder illness [69]. Of 270 respondents who were symptomatic at diagnosis, 95 (35%) had not returned to their usual state of health 14 to 21 days from the test date, including 26% of those 18 to 34 years of age and 47% of those older than 50 years of age. Among respondents reporting cough, fatigue, or shortness of breath at the time of testing, 43%, 35%, and 29%, respectively, continued to experience these symptoms at the time of the interview. These results indicate that COVID-19 can cause prolonged illness and slow convalescence, even among young adults without any underlying chronic medical conditions [69].

COVID-19 IN CHILDREN

The CDC provides information for pediatric healthcare providers and guidance for the evaluation and care of neonates at risk for COVID-19 [45]. Acute SARS-CoV-2 infection in childhood tends to be asymptomatic or relatively mild, consisting of transient fever, cough, and other signs common to an upper respiratory viral syndrome. Severe manifestations of COVID-19 have been reported in children of all ages, though the incidence is far less common than in adults and fatalities following acute childhood infection are rare. According to data from more than 2,000 pediatric cases in China, 4% were asymptomatic, 51% had mild symptoms, 39% were moderately ill with some evidence of pneumonia, and 5% were severely ill with dyspnea, hypoxia, and central cyanosis [45]. Only 0.6% developed respiratory failure, shock, or multi-organ dysfunction. In the United States, about 2% of confirmed cases of COVID-19 are among persons younger than 18 years of age, and data from the New York State Department of Health show that only 1% of patients hospitalized with COVID-19 were younger than 20 years of age [46].

PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME

Reports from the United Kingdom, Italy, and New York describe a serious inflammatory disorder in children linked to COVID-19, with many features common to Kawasaki disease and toxic shock syndrome [46; 47; 48]. The term applied to this condition is multisystem inflammatory syndrome in children (MIS-C). Kawasaki disease is an acute vasculitis of unknown cause that affects infants and young children, first described in Japan and thought to involve an aberrant immune response to an unidentified pathogen in persons with a genetic predisposition [47]. Children with COVID-related MIS-C present with signs of a diffuse inflammatory disorder, including persistent fever, abdominal complaints, rash, leukocytosis, elevated C-reactive protein, and evidence of single or multiple organ dysfunction [49]. Hypotension on presentation is common, and myocarditis and other cardiovascular changes (e.g., mitral regurgitation, coronary artery dilatation) may be seen. The majority of patients have tested positive for recent SARS-CoV-2 infection by molecular diagnostic and/or antibody testing. The onset of MIS-C may come days or weeks after what appears to have been an asymptomatic or mild case of COVID-19.

During a 10-day period in mid-April 2020, pediatricians at an intensive care hospital in England noted an unprecedented cluster of eight children with hyperinflammatory shock and other clinical features similar to atypical Kawasaki disease [47]. All had been previously well, and five of the children were boys. Four of the children had known family exposure to SARS-CoV-2. Clinical presentations were similar, with unrelenting fever, variable rash, conjunctivitis, peripheral edema, and warm shock refractory to volume repletion and eventually requiring vasopressors. There was no clinical or virologic evidence of lower respiratory involvement. All patients were treated with IV immunoglobulin (IVIG); seven recovered and one died following arrhythmia, shock, and cerebral infarction. During the course of the COVID-19

epidemic in northern Italy, physicians in Bergamo observed 10 children (median age: 7.5 years) in the span of two months with a severe form of Kawasaki-like disease, a 30-fold increase in incidence when compared to the previous five years [48]. All were positive for recent SARS-CoV-2 infection. As of June 3, 2020, the New York State Department of Health was investigating 195 reported cases of MIS-C and 3 deaths in children. Of these patients, 28% are younger than 5 years of age and 69% are between 5 and 19 years of age [46]. Of the 195 cases, 93% have tested positive for COVID-19. A targeted surveillance for MIS-C in pediatric health centers across the United States identified 186 cases in 26 states during a five-week period between March and May [61]. The median age was 8.3 years, 165 (62%) were male, and 131 (70%) tested positive for SARS-CoV-2 infection by rT-PCR or serologic antibody test.

The clinical features in the MIS-C cases investigated by the New York Department of Health have been reported [62]. Of 191 patients in the study, all presented with fever and tachycardia, 80% were admitted to the ICU, and 62% required vasopressor support. Abdominal complaints and gastrointestinal symptoms were common (62%), as was rash (60%), conjunctival injection (56%), and mucosal changes (27%). Laboratory markers of inflammation included elevated levels of C-reactive protein in all patients, positive D-dimer (91%), and elevated troponin (71%). Evidence of myocarditis was present in 53% of patients. At least one echocardiogram was obtained for 93 patients (94%); 51 (52%) had some degree of ventricular dysfunction, 32 (32%) had pericardial effusion, and 9 (9%) had a documented coronary artery aneurysm. The majority of patients were treated with IVIG and/or glucocorticoids in addition to vasopressors. The median duration of hospitalization was six days. Two patients died. As in Italy, MIS-C cases in New York followed the peak of the COVID-19 epidemic in that state and nearly all patients tested seropositive for recent SARS-CoV-2 infection [62].

Early recognition of MIS-C and prompt referral to an inpatient unit of care is essential. Approximately 50% to 60% of children and adolescents with MIS-C present with signs of cardiovascular involvement leading to warm shock and a need for vasopressor support, compared with about 5% of children with Kawasaki's disease [61; 62]. Cardiac abnormalities are common, including a 9% incidence of coronary artery aneurysm. Echocardiography is recommended in all patients presenting with MIS-C, and until more is known about long-term cardiac sequelae of MIS-C, providers should consider follow-up imaging at one to two weeks and four to six weeks after treatment [61]. Clinical evaluation should include inquiry as to recent COVID-19 illness or known exposure to persons with COVID-19. There are currently no published guidelines or CDC recommendations regarding treatment for MIS-C and no studies comparing efficacy of various treatment options. Based on published reports, principles of care include close observation, correction of hemodynamic instability, diagnostic evaluation to exclude serious bacterial infection (e.g., streptococcal or staphylococcal sepsis, toxic shock syndrome), and consideration of treatment with IVIG. The CDC recommends that patients younger than 21 years of age meeting MIS-C criteria be reported to local, state, and territorial health departments. The CDC case definition for MIS-C is [49]:

- An individual younger than 21 years of age presenting with fever (>38.0°C for at least 24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin-6, elevated neutrophils, reduced lymphocytes, and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (at least two) organ involvement; AND

- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms

All individuals should be reported if they meet the case definition for MIS-C, regardless of whether they fulfill criteria for Kawasaki disease. In addition, MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection.

DIAGNOSTIC TESTING FOR SARS-CoV-2

There are two types of diagnostic tests for determining active SARS-CoV-2 infection: molecular tests that use the real-time reverse transcription-polymerase chain reaction (RT-PCR) to detect viral RNA, and antigen tests that detect specific proteins on the surface of the virion. The most widely used and reliable of these is RT-PCR, which can be applied to mucus specimens from the upper or lower respiratory tracts and to serum samples. SARS-CoV-2 viral RNA can be detected more readily in secretions taken by swab from the nasopharynx than in samples obtained by throat swab [15]. RT-PCR testing of deep nasopharyngeal swab specimens has become the standard procedure for the laboratory diagnosis of active SARS-CoV-2 infection [79; 80]. This test is highly accurate and results can be obtained within one or two days. Antigen tests for the diagnosis of active SARS-CoV-2 infection are also performed on nasal or throat swab specimens and have the advantage of providing results much faster than the RT-PCR test (often less than one hour) [80]. However, antigen tests are less sensitive than molecular tests, which detect viral nucleic acids, and the amount of antigen in a sample decreases as the duration of illness increases. Specimens collected after day 7 of illness are considered more likely to be negative compared to a RT-PCR assay [80]. Thus, a positive antigen test result is highly reliable, but a negative test may need to be confirmed with RT-PCR.

The availability of safe, reliable, and timely SARS-CoV-2 diagnostic testing is essential for effective public health measures to control the COVID-19 pandemic. The nasopharyngeal swab specimen collection method involves close interaction between healthcare workers and patients, requires personal protective equipment, and entails a measure of discomfort for the test subject—all disadvantages to community drive-through diagnostic testing and contact tracing. Self-collected saliva could prove to be a simple, less expensive alternative that alleviates the need for personal protective equipment. There is growing evidence that the molecular test detection rate in saliva specimens from symptomatic and asymptomatic SARS-CoV-2 infected individuals is comparable to deep nasopharyngeal swab specimens. Yale investigators found that among 70 inpatients with confirmed COVID-19 and 495 asymptomatic healthcare workers, the use of self-collected saliva specimens for SARS-CoV-2 molecular diagnostic testing compared favorably with nasopharyngeal swab specimens collected by personnel [81]. In another study of 354 patients presenting to a drive-through testing center with at least one symptom consistent with COVID-19, the SARS-CoV-2 positivity rate was 22.6% for nasopharyngeal swab specimens compared with 22.9% for salivary specimens [82]. Between nasopharyngeal swab specimens and salivary specimens, the positive percent agreement was 93.8% and the negative percent agreement 97.8%.

COVID-19 diagnostic testing in the United States is available at all state and local public health laboratories and at commercial laboratories authorized by the U. S. Food and Drug Administration (FDA) [16; 80]. Although in some cases viral nucleic acid can be detected in nasopharyngeal specimens for weeks after infection, studies show that SARS-CoV-2 viral cultures are usually negative within 8 to 10 days after onset of infection. Shedding of live virus may persist longer in severely ill, hospitalized patients (median range of viral shedding: 12 to 20 days) [15]. Information on specimen collection, handling, and storage is available online at https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html.

ANTIBODY TESTING

SARS-CoV-2 antibody assays are useful for epidemiologic investigation of prevalence in the general population and to identify groups at risk for infection. Unlike RT-PCR and antigen detection tests that identify acute infection, antibody tests determine whether there is evidence of prior infection, even if the person being tested never developed symptoms. The FDA has not authorized the use of serology to detect active SARS-CoV-2 infection, and the CDC does not recommend antibody testing for routine diagnosis of acute infection [79]. However, antibody testing in conjunction with viral RT-PCR may be used to support clinical assessment of persons who present late in the course of COVID-19, or a patient suspected of having a post-infectious syndrome caused by recent SARS-CoV-2 infection (e.g., MIS-C).

Following SARS-CoV-2 infection, IgM and IgG antibodies appear almost simultaneously in the serum within two to three weeks after symptom onset, at which time infectiousness likely is greatly decreased and some degree of immunity from future infection has developed [83]. Thus, early IgM assay without IgG testing is of little value. The duration of detectable antibody is unknown, and the absence of detectable IgM or IgG antibodies does not necessarily rule out previous infection. Several commercially marketed serologic assays for SARS-CoV-2 have emergency use authorization (EUA) by the FDA, which has independently reviewed their performance. A list of all tests authorized for emergency use under EUA is maintained on the FDA website [84]. All currently authorized tests are qualitative (providing a result that is positive, negative, or indeterminate) rather than quantitative (providing a quantitative assessment of antibody levels). It is important to minimize false-positive test results by choosing an assay with high specificity and by testing individuals with an elevated likelihood of previous exposure to SARS-CoV-2 [83].

TREATMENT OPTIONS AND VACCINE DEVELOPMENT

There is no established antiviral therapy of proven efficacy for the treatment of COVID-19 and, as yet, no vaccine for prevention of SARS-CoV-2 infection. Care is supportive and, for the purposes of limiting spread, should be carried out in a controlled environment under Isolation Precautions.

After China published the viral genome on a public database in mid-January 2020, the National Institutes of Health immediately began research efforts to develop better diagnostics, treatments, and vaccines against SARS-CoV-2 [10]. As noted, the CDC has already developed a diagnostic test based on genetic sequencing of the virus shared by Chinese investigators. Two antiviral agents—remdesivir, a drug tried unsuccessfully in the Ebola outbreak, and lopinavir/ritonavir (Kaletra), a combination antiviral used for treatment of human immunodeficiency virus (HIV)—were provided on a compassionate use basis in China. However, one study of hospitalized patients with COVID-19 in China found no difference in time to clinical improvement and no difference in eventual outcome with lopinavir/ritonavir treatment [20].

An accelerated effort is underway in the United States and other countries to develop a vaccine against SARS-CoV-2 utilizing the genetic sequencing shared by China as well as genetic material derived from viral isolates obtained in the West [10]. Preliminary trials to assess vaccine safety began in the first quarter of 2020, followed by trials to determine vaccine effectiveness.

INVESTIGATIONAL THERAPEUTICS

Antiviral Therapy

Remdesivir

Remdesivir, an investigational antiviral drug that inhibits viral RNA polymerases, has been shown to have in-vitro activity against SARS-CoV-2 [15]. An early report described the clinical outcomes for a cohort of patients with COVID-19 who were treated with a 10-day course of intravenous remdesivir as part of a compassionate use program [26]. The study enrolled patients from the United States, Canada, Europe, and Japan who were hospitalized with confirmed SARS-CoV-2 infection and signs of lower respiratory tract disease severe enough to require some degree of oxygen supplementation and/or ventilatory support. Of 53 patients with sufficient data for analysis, 32 (68%) showed significant improvement in oxygen support status with use of remdesivir; the overall mortality was 13% over a median follow-up of 18 days, including 18% among those who were receiving invasive ventilation and 5% among those who were receiving noninvasive oxygen support. The authors observed that while there was no randomized control group and the patients in this study are not directly comparable, the observed mortality was considerably less than that reported contemporaneously in other COVID-19 case series and reports [26].

On October 22, 2020, the FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older (weighing at least 40 kg) for the treatment of COVID-19 when hospitalization is required [90]. The approval was supported by an analysis of three randomized, controlled clinical trials that showed remdesivir shortens the time to recovery and decreases progression of respiratory illness in adult patients hospitalized with COVID-19 [90]. The data analysis included final results from an NIH-sponsored study, a double-blind, placebo-controlled remdesivir trial involving hospitalized patients with moderate-to-severe COVID-19 [35]. In this study, a total of 1,062 patients were randomized to receive intravenous remdesivir or placebo for 10 days. The primary outcome was time to recovery, defined by discharge from hospital or resolution of need for clinical care (hospitalization for infection-control purposes only). The median time to recovery was 10 days for the remdesivir group, compared with 15 days for the placebo group. In an analysis of secondary outcomes, patients who received remdesivir were more likely than those who received placebo to have clinical improvement at day 15. The proportion of serious adverse events related to respiratory failure and the need for higher levels of respiratory support were lower among patients in the remdesivir group. Kaplan-Meier estimates of mortality showed a trend in favor of the treatment group: 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% versus 15.2% by day 29 [35].

As of October 9, 2020, the NIH Treatment Guidelines Panel (NIH Panel) recommends remdesivir for treatment of COVID-19 in hospitalized patients with SpO2 <94% on ambient air or those who require supplemental oxygen, and in patients who need any form of mechanical ventilatory support [57]. The recommended duration of treatment and the advisability of combining remdesivir with a glucocorticoid vary in relation to severity of illness and level of ventilatory support. For patients who require supplemental oxygen but have no need for delivery of oxygen through a high-flow device, the recommended regimen is remdesivir 200 mg IV for one day, followed by 100 mg daily for four days or until hospital discharge, whichever comes first. The duration of remdesivir therapy may be extended up to 10 days when there is no substantial clinical improvement by day 5.

Hydroxychloroquine

In-vitro studies show that chloroquine phosphate and hydroxychloroquine sulphate (commonly used to treat malaria) interfere with the replication cycle of coronaviruses, including SARS-CoV-2, and thus may offer some therapeutic efficacy for treatment of COVID-19 [21]. Randomized controlled clinical trials of hydroxychloroquine are underway in the United States. Based on small case studies and anecdotal reports of possible efficacy,

many clinicians have been inclined to administer hydroxychloroquine to patients with COVID-19 who are so ill as to require hospitalization and having risk factors for severe disease (i.e., age older than 65 years, underlying medical conditions, and/or signs of viral pneumonia). On March 28, 2020, the FDA issued an EUA that allowed chloroquine phosphate or hydroxychloroquine sulphate to be used for the treatment of patients hospitalized with COVID-19 when clinical trials are not available or participation is not feasible [36]. However, this letter was revoked in June 2020 [58]. If used, hydroxychloroquine is generally preferred as it is better tolerated. The suggested dosage regimen is hydroxychloroquine sulphate administered orally in a loading dose of 400 mg twice daily (for one day) then 200 mg twice daily for four days [22]. Potential adverse effects include cardiac conduction QT-prolongation and a number of drug-drug interactions.

An observational study examined the association between hydroxychloroquine use and clinical outcomes, analyzing data from 1,376 consecutive patients with COVID-19 admitted to a clinical center in New York City between March 7 and April 8, 2020 [37]. To assess potential benefit or detrimental effect, the primary end point selected was a composite of intubation or death in a time-to-event analysis, comparing outcomes in patients who received hydroxychloroquine with those who did not. A total of 811 patients (59%) were treated with hydroxychloroquine for a median of five days, 60% of whom also received azithromycin. After adjusting for severity of illness, the investigators found no significant difference in the rate of the composite end point of intubation or death over a median follow-up of 22.5 days. Thus, the risk of intubation or death was not significantly different among hospitalized patients with COVID-19 who received hydroxychloroquine than among those who did not [37].

Randomized, controlled clinical trials to assess efficacy of hydroxychloroquine in patients hospitalized with COVID-19 have not shown a benefit. A multicenter study of hospitalized patients with mild-to-moderate COVID-19 found that hydroxychloroquine, alone or in combination with azithromycin, was no more effective than standard care in improving clinical status at 15 days [70]. Preliminary analysis of data from a multicenter, randomized trial in the United Kingdom found no reduction in 28-day mortality among those treated with hydroxychloroquine when compared with the control group [71]. Hydroxychloroquine use was associated with increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation. An NIH-sponsored, controlled clinical trial was halted (after the fourth interim analysis) because hydroxychloroquine was found unlikely to be beneficial to hospitalized patients with COVID-19 [72]. Whether hydroxychloroquine has a role in outpatient treatment of mild COVID-19, or would be effective as primary or secondary prophylaxis against SARS-CoV-2 infection, remains to be determined by randomized controlled trials designed to assess these possibilities.

On June 15, 2020, the FDA revoked the EUA that allowed for chloroquine and hydroxychloroquine donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was not available or feasible [58]. This decision was based on an ongoing analysis of emerging data indicating that these drugs are unlikely to be effective for patients hospitalized with COVID-19. As of July 2020, the NIH Panel recommends against the use of hydroxychloroquine or chloroquine for the treatment of COVID-19 except in a clinical trial [57].

Approaches to Disease Modification

Severe SARS-Cov-2 infection results in progressive interstitial-alveolar pneumonia and respiratory failure. The disease process is closely linked to activation of the innate immune system and dysregulation of adaptive immune responses, with release of proinflammatory cytokines and chemokines. Death from COVID-19 is often preceded by signs of a hyperimmune inflammatory response ("cytokine storm") that leads to ARDS, multiorgan dysfunction, and circulatory collapse. Laboratory markers of heightened inflammation include elevated C-reactive protein, ferritin, and interleukin-6. Novel approaches to disease management seek to modify disease progression and prevent or ameliorate pulmonary and systemic complications of cytokine storm, in hope of reducing mortality from COVID-19.

COVID-19 Convalescent Plasma

Passive immunization with plasma obtained from surviving patients has been used in the past to treat life-threatening infections absent specific therapy. There is emerging evidence that intravenous transfusion of convalescent plasma with high SARS-CoV-2 antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19 pneumonia. In a preliminary, uncontrolled case series of five critically ill Chinese patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in clinical status, including resolution of ARDS in four patients at 12 days after transfusion [27].

Convalescent plasma treatment has been widely utilized in the United States since early April 2020 under the Mayo Clinic's Expanded Access Protocol (EAP). A report from the Mayo EAP involving 35,322 registered patients found that plasma infusion is relatively safe and may reduce COVID-19 mortality when administered early after hospitalization [76]. A subset analysis showed a gradient of mortality in relation to IgG antibody levels in transfused plasma. The risk of dying from COVID-19 was lower among patients who received convalescent plasma units containing high titer anti-SARS-CoV-2 antibody than among those who received plasma containing low antibody levels. The pooled relative risk reduction among patients transfused with high antibody level plasma units versus low-level antibody plasma was 35% at 7 days and 23% at 30 days. The Mayo EAP report is an analysis of registry data and not a randomized controlled study.

On August 23, 2020, the FDA granted an EUA of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients [73]. This decision was based on historical evidence derived from the use of plasma in prior outbreaks of respiratory virus infection, small case series, and nonrandomized clinical trials conducted during the current outbreak. The FDA provides a COVID-19 convalescent plasma fact sheet with information and instructions for healthcare providers [73]. Randomized clinical trials are needed to confirm efficacy and define patient selection criteria for convalescent plasma use in moderate-to-severe COVID-19.

The FDA website provides information and directions for donation of convalescent COVID-19 plasma [28]. People who have fully recovered from COVID-19 for at least two weeks are encouraged to consider donating plasma, which may help save the lives of other patients. COVID-19 convalescent plasma can only be collected from recovered individuals if they are eligible to donate blood. A potential donor must have had a prior diagnosis of COVID-19 documented by a laboratory test and meet other donor criteria. Complete resolution of symptoms for at least 28 days is required before an individual may donate plasma, or alternatively have had no symptoms for at least 14 days prior to donation and have a negative lab test for active COVID-19 disease [28]. Persons interested in becoming donors should contact the American Red Cross or ask the local blood center about options to donate convalescent plasma in their area.

On April 10, 2020, the FDA granted EUA for an extracorporeal blood purification system to treat adult patients with COVID-19 admitted to an ICU with confirmed or imminent respiratory failure [29]. This device filters the blood for removal of cytokines and other inflammatory mediators associated with cytokine storm, then returns filtered blood to the patient.

Monoclonal Antibody to SARS-CoV-2

Modern immunologic techniques enable the identification of pathogen-specific memory B cells and recovery of immunoglobulin genes that can be expressed to produce monoclonal antibodies [85]. The clinical application of monoclonal antibodies has been relatively safe, and FDA-approved monoclonal antibody products are available to treat or prevent respiratory-syncytial virus, anthrax, and *Clostridioides difficile*. Several laboratories have used B cells from patients recovering from COVID-19 to produce neutralizing monoclonal antibodies to SARS-CoV-2. These antibodies are directed against surface spike glycoprotein, preventing entry of virus into host cells. Passive immunization with monoclonal antibodies has potential for prevention of COVID-19 in vulnerable people and for early augmentation of the immune response (to block disease progression) in COVID-19 patients at risk for severe illness. Given the long half-life of immunoglobulin (approximately three weeks), a single infusion of monoclonal antibodies to SARS-CoV-2 should suffice for either prevention or treatment of COVID-19 [85]. As of October 2020, several SARS-CoV-2 monoclonal antibody products have entered clinical trials.

Tocilizumab

Tocilizumab, a monoclonal antibody directed against the interleukin-6 receptor, has been used to mitigate cytokine storm syndrome associated with COVID-19. A retrospective cohort study of hospitalized patients who required ICU support found that treatment with tocilizumab was associated with reduced mortality [74]. Of 630 patients selected for analysis, 358 (57%) died—102 (49%) who received tocilizumab and 256 (61%) who did not receive tocilizumab. The primary multivariable Cox regression analysis showed an association between receiving tocilizumab and decreased hospital-related mortality. This association was also noted among subgroups requiring mechanical ventilation and with baseline C-reactive protein of 15 mg/dL or higher. In contrast to findings from this and other observational studies of COVID-19 pneumonia, randomized clinical trials have not reported a mortality benefit from tocilizumab therapy [91]. Tocilizumab has been reported to reduce the requirement for mechanical ventilation in some patient populations, thereby alleviating the demand on ICU-level care for management of severe COVID-19. A published editorial assessment concluded that newly released randomized trials suggest a potential role for tocilizumab in COVID-19 but do not show clear evidence of efficacy [91]. As of October 2020, the NIH Panel recommends against the use of tocilizumab for COVID-19 except in the context of a clinical trial [57].

Dexamethasone

Preliminary results of a large multicenter therapeutic trial show that dexamethasone (a glucocorticoid) improves survival in patients hospitalized with COVID-19 who require some degree of respiratory support [63]. In this ongoing study platform, patients are randomly assigned to a group of different therapies and efficacy is assessed using a single end-point: mortality within 28 days after randomization. A total of 2,104 patients were assigned to receive dexamethasone at a dose of 6 mg daily, and 4,321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1,110 patients (25.7%) in the usual care group died within 28 days after randomization. The observed differences in mortality varied according to the level of respiratory support patients required upon entry to the study. Among patients receiving mechanical ventilation, the 28-day mortality was significantly lower in the dexamethasone group (29.3%) than that in the usual care group (41.4%).

Among patients receiving supplemental oxygen without mechanical ventilation, the observed benefit was less pronounced but also significant, 23.3% in the dexamethasone group and 26.2% in the usual care group. There was no demonstrable benefit from dexamethasone treatment in patients who did not require oxygen.

The NIH Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but not mechanical ventilation [57]. If dexamethasone is not available, equivalent doses of another glucocorticoid may be used, such as prednisone 40 mg/day or methylprednisolone 32 mg/day. Dexamethasone is the preferred glucocorticoid to use in pregnant women with COVID-19 who require respiratory support, because of the potential benefit of decreased maternal mortality and the known low risk of fetal adverse effects associated with short-course maternal dexamethasone therapy [57]. Patients receiving dexamethasone at the time of hospital discharge should be given a prescription to complete the specified 10-day course. The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen.

Potential adverse effects of glucocorticoid use include hyperglycemia and opportunistic infection. Clinicians should be aware that *Strongyloides* hyperinfection syndrome has been reported as a complication of modest-dose and short-duration dexamethasone regimens [75]. Patients who may be at risk are those who have previously resided in South America, the Caribbean, the Middle East, Africa, or Asia. Clinical clues to subclinical or unrecognized *Strongyloides* infection include peripheral eosinophilia and unexplained gram-negative bacteremia [75].

VACCINE CANDIDATES

As of October 2020, more than 130 potential vaccines are in preclinical studies around the world and at least 30 candidate vaccines are currently in clinical trials designed to assess immunogenicity and safety. Reports highlight promising early results from two of these candidate vaccines. In a phase 1 trial, a messenger RNA (mRNA) SARS-CoV-2 vaccine was administered to 45 healthy adults (18 to 55 years of age) at one of three dose levels (25, 100, and 250 mcg) given as two vaccinations 28 days apart [64]. All participants developed an immune response. Following the second dose, antibody titers increased and serum neutralizing activity was detected with values similar to those measured in a control panel of convalescent serum samples. Adverse events such as fatigue, myalgia, feverishness, and pain at injection site were reported in half the participants, more commonly after the second injection and at the highest dose. The study group concluded that immunogenicity and safety findings supported expansion of the trial to include older adults and advancement of this vaccine to later-stage clinical trials. In a follow-up report of 40 older adults (50% 56 to 70 years of age and 50% older 70 years of age) administered the mRNA vaccine, the safety profile and immunogenicity were comparable to results in the younger cohort of participants [86]. Enrollment in a phase 3 trial began in late July 2020.

A report from the University of Oxford describes early results of a clinical trial using a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCov-19) expressing the SARS-CoV-2 spike protein [65]. In a phase 1/2 randomized controlled trial, 1,077 healthy adults were assigned to receive either the candidate vaccine or a meningococcal conjugate vaccine as control. Preliminary results show that after a single dose, ChAdOx1 nCoV-19 elicited spike-specific T-cell responses that peaked on day 14, and anti-spike IgG antibody responses by day 28. Strong humoral and cellular immune responses persisted at day 56 of the ongoing trial. Neutralizing

antibody responses were detected in 32 (91%) of 35 participants after a single dose, and in 10 (100%) of 10 participants who received a booster dose. Adverse events such as discomfort at injection site, fever, malaise, and headache were common but mild or moderate and self-limiting. There were no serious adverse reactions. Progression into phase 2 and 3 trials is underway, recruiting older age groups with comorbidities, healthcare workers, and those at higher risk for SARS-CoV-2 exposure [65].

GLOBAL PUBLIC HEALTH CONCERNS AND WHO RESPONSE

WHO DAILY SITUATION REPORT

Beginning in January 2020, and in association with travel to and from China, cases of confirmed SARS-CoV-2 infection began to be reported from multiple countries around the world, including the United States. The WHO monitors developments and tracks the progress of the epidemic, providing daily Situation Reports at its website [8]. In an effort to curb the spread of infection, the WHO and national agencies have developed clinical criteria to guide the evaluation and management of persons with significant exposure and/or compatible illness.

In the initial weeks of the outbreak, cases reported in countries outside China were occurring primarily in returning travelers who had visited Wuhan City or nearby locales in central China. With time, the extent of person-to-person spread unrelated to travel has become increasingly clear; local transmission and community spread is now evident in most countries. As of October 27, 2020, there were more than 42 million confirmed cases and more than 1.1 million deaths globally [8]. More than 150 countries have been impacted. The Americas is the region most severely impacted, and the United States is by far the country with the greatest number of cases with more than 8.5 million confirmed cases reported to the WHO.

Advice to the Public

The WHO has posted standard recommendations for the general public designed to reduce exposure to, and transmission of SARS-CoV-2 [11]. In addition, the CDC has developed guidelines for the public on how to best protect themselves and others [24]:

- Wash hands often with soap and water for at least 20 seconds, especially after having been in a public place or after coughing, sneezing, or blowing your nose. If soap and water are not readily available, a hand sanitizer that contains at least 60% alcohol may be used.
- Avoid touching eyes, nose, and mouth with unwashed hands.
- Avoid close contact with people who are sick, and stay home as much as possible
- Put distance (at least 6 feet) between yourself and other people.
- Cover your mouth and nose with a cloth face cover when around others (i.e., in public). Note: This recommendation does not apply to children younger than 2 years of age, persons with breathing difficulties, or those who are unable to remove the mask unassisted.
- Cover coughs and sneezes.
- Clean and disinfect frequently touched surfaces daily, including tables, doorknobs, light switches, countertops, handles, desks, phones, keyboards, toilets, faucets, and sinks.

WHO and CDC guidance on the use of a face covering, whether by prefabricated mask or fashioned from cloth, is predicated on the growing evidence that asymptomatic and presymptomatic individuals infected with SARS-CoV-2 can transmit the virus to others in close proximity by coughing, sneezing, or speaking [54]. Therefore, anyone out in public should consider that he or she could, unwittingly, be an agent of transmission to others. The face covering serves as a means of source control, and although the primary function is to prevent inadvertent transmission to others, it may also provide a degree of barrier protection for the one wearing

it. The CDC recommends wearing cloth face coverings in public settings in which other social distancing measures are difficult to maintain (e.g., grocery stores, pharmacies), especially in areas experiencing significant community-based transmission. Detailed guidance on the construction, proper usage, and cleaning of cloth face coverings is provided on the CDC website [12].

As public health restrictions are lifted, professional and social interactions in the community present more opportunities for spread of SARS-CoV-2. The risk of transmission varies in proportion to how closely a person interacts with an infected individual and for how long. Studies confirm that wearing face masks or double-layer cloth face coverings reduces the risk of transmission for medical personnel, patients, and the general public when in social and community settings, especially when social distancing is not possible [66; 67; 68]. A CDC report of a contact investigation involving a hair salon where universal face covering was practiced is illustrative. Two stylists with COVID-19 symptoms had worked closely with 139 clients over an eight-day period before learning of the COVID-19 diagnosis, yet there was no evidence of secondary transmission [67]. None of the clients developed COVID-19 symptoms and of 67 individuals tested for SARS-CoV-2, all were negative. Both stylists and 98% of of the clients interviewed had followed posted company policy and city ordinance requiring face coverings by employees and clients in businesses providing personal care services.

TRANSMISSION: PUBLIC HEALTH IMPLICATIONS

The rapidity with which the outbreak spread locally in China provided early evidence that human-to-human transmission from close contact with persons having mild, nonspecific symptoms is the primary means by which SARS-CoV-2 spreads within the community. Epidemiologic studies suggest that infected droplet nuclei expelled during coughing, sneezing, loud talking, or singing is the primary mode of transmission. Sustained close personal contact (being within 6 feet for at least 15 minutes) with an infected person increases the risk of transmission. Limiting the time and lengthening the distance reduces the risk [87]. Recovery of replication-competent virus from the upper respiratory tract begins to decline after onset of symptoms. For patients with mild-to-moderate COVID-19, replication-competent virus has not been recovered after 10 days following symptom onset [88]. Recovery of replication-competent virus between 10 and 20 days after symptom onset has been documented in some patients with severe COVID-19.

Unlike the 2003 SARS-CoV, whereby replication occurs primarily in the lower respiratory tract and shedding is temporally associated with symptom onset, SARS-CoV-2 is characterized by high levels of replication and shedding in the upper respiratory tract, even during the pre-symptomatic phase of infection [38]. Newly infected individuals are most infectious one to two days before and for a few days after the onset of symptoms. This means that persons with asymptomatic and pre-symptomatic SARS-CoV-2 infection may have high viral loads in nasopharyngeal secretions that render them efficient vectors of person-to-person transmission, and a strategy for prevention that relies solely on symptom-based detection and isolation of COVID-19 cases is likely to have limited effectiveness. In a study of skilled nursing facility residents infected with SARS-CoV-2 from a healthcare worker, half were asymptomatic or pre-symptomatic at the time of contact tracing evaluation and testing [15].

These considerations have important public health implications. Close personal contact implies touching and the sharing of common utensils; it is also defined by a proximity of 6–8 feet—the distance respiratory droplets travel after coughing or sneezing. As noted, the risk of infection is greatest for persons who have prolonged, unprotected close contact (i.e., within 6 feet for 15 minutes or longer) with someone recently diagnosed with SARS-CoV-2 infection, regardless of whether the patient has symptoms [89]. A CDC contact investigation demonstrated that even brief periods of unprotected close contact, if repeated and cumulative (exceeding 15 minutes) over the course of a day, significantly increases the risk [92]. This highlights the importance of avoiding congregate settings (e.g., assisted living facilities, college dormitories, family gatherings, indoor dining and bars) because of the increased likelihood of repetitive or sustained close contact. People can reduce the community spread of SARS-CoV-2 by practicing social distancing, wearing face coverings in public, and washing their hands.

On October 21, 2020, the CDC definition of "close contact" was revised for purposes of contact investigation [59]. Close contact describes someone who was within 6 feet of an infected person for a cumulative total of 15 minutes within a 24-hour period starting from two days before illness onset (or, for asymptomatic patients, two days prior to test specimen collection) until the time the patient is isolated. The cumulative 15-minute exposure refers to any combination of individual exposures (e.g., three 5-minute exposures) over a 24-hour period. Factors to consider when assessing close contact include proximity, duration of exposure, whether the individual has symptoms (as the period around onset of symptoms is associated with highest levels of viral shedding), whether the infected person was likely to generate aerosols (e.g., was coughing, shouting, singing), and other environmental factors (e.g., crowding, adequacy of ventilation, whether exposure was indoors or out of doors) [59].

Several emerging reports and epidemiologic studies indicate that children younger than 10 years of age may play only a small role in transmission of SARS-CoV-2. An investigation of 36 childhood COVID-19 cases in China found that 89% acquired the infection from exposure to an older household family member [50]. A population-based surveillance study in Iceland, drawing from a nationwide random sample, found that of 848 children younger than 10 years of age, none tested positive for SARS-CoV-2, whereas 100 of 12,232 (0.8%) adolescents and adults tested positive [51]. Contact tracing in relation to a cluster of COVID-19 among family and friends in France revealed that despite several days of potential exposure to a symptomatic pediatric case, there was no evidence of secondary transmission among 172 school contacts [52]. One possible explanation for these observations is the finding that gene expression of ACE2 in nasal epithelium is age-dependent; it is significantly lower in young children and increases as one develops into adulthood [53]. Lower ACE2 expression in children relative to adults could impact transmission dynamics and may help explain why COVID-19 is less prevalent in children.

The stability of SARS-CoV-2 on environmental surfaces has been studied in an effort to assess whether surface contamination could play a role in virus transmission. After application of aerosols containing a standard dose of SARS-CoV-2, viable virus was detected up to 72 hours on plastic and stainless steel, though the virus titer was greatly reduced; on cardboard, no viable SARS-CoV-2 was measured after 24 hours [19]. These data should be interpreted with caution, as it is unclear to what extent environmental detection of virus in much reduced titer at a given interval, experimentally, can be equated with actual risk of transmission from common environmental surfaces.

The public health strategy of mitigation (preventing spread within communities) has become paramount in order to decisively limit spread and blunt the COVID-19 epidemic curve. These measures include the following: suspension or cancellation of events having large public gatherings, such as cinema, theatre, concerts, and collegiate and professional sports competition; closure of schools and cancellation of classes at colleges and universities; the practice of social distancing in smaller venues such as restaurants and churches; the wearing of masks or cloth face coverings at indoor commercial venues and social gatherings. By slowing the degree and pace of virus transmission, effective mitigation helps to protect those most vulnerable and to ensure that the clinical case load does not overwhelm local hospital and critical care resources.

SHELTERING IN PLACE

Federal and state government officials, upon the advice of the CDC and other public health leaders, have implemented a mitigation strategy that includes measures designed to protect vulnerable individuals and limit the spread of SARS-CoV-2 infection in public places [12]. This begins with the admonition to "shelter in place"—to stay in and work from home as much as possible; when it is necessary to go out in public one should observe the precautions outlined in Advice to the Public.

CDC MONITORING AND GUIDANCE FOR HEALTHCARE PROFESSIONALS

The CDC is closely monitoring the COVID-19 outbreak and is providing updated epidemiologic data and clinical guidance for healthcare providers, laboratories, health facilities, and public health professionals [12]. Included are recommendations for the evaluation of persons/patients under investigation, laboratory specimen transport, and protection of healthcare workers. Recommendations for patient assessment and care in hospitals and other healthcare facilities emphasize the importance of strict adherence to patient isolation and barrier precautions, including the proper use of personal protective equipment (PPE).

The CDC website provides data on reported cases of COVID-19 in the United States, updated regularly. As of October 28, there were more than 8.8 million confirmed or probable positive cases and more than 222,100 deaths reported from 50 states, the District of Columbia, Puerto Rico, Guam, the U.S. Virgin Islands, and the Northern Mariana Islands. Ethnic minority populations appear to be disproportionately affected [12]. Person-to-person transmission is considered the greatest risk.

Selected materials from the CDC website, including recommendations for travelers, interim guidance for healthcare professionals, infection control, and healthcare worker safety, are reproduced in the following sections. Please note that language and/or cultural barriers may impede assessment and education on the topic, and interpreters and translated materials are recommended, when appropriate.

CDC Travel Notice

The CDC has established geographic risk-stratification criteria used to provide updated information about COVID-19 risk for travelers and to guide public health management decisions with respect to travel-related exposures to COVID-19 [13]. The CDC no longer recommends persons returning from domestic or international travel to self-quarantine for 14 days. Returning travelers from any destination are encouraged to observe standard precautions, monitor health, and follow state, territorial, tribal, and local recommendations or requirements after travel [13]. The CDC travel notice is updated regularly in response to new developments. Individuals who must travel should [13]:

- Avoid contact with sick people.
- Avoid touching your eyes, nose, or mouth with unwashed hands.
- Wash hands often with soap and water for at least 20 seconds or use an alcohol-based hand sanitizer that contains at least 60% to 85% alcohol.

- Avoid traveling if you are sick.
- Wear a cloth face covering in terminals and other public venues.
- Cover coughs and sneezes.
- Pick up food at drive-throughs, curbside restaurant service, or stores.

Recommended Criteria to Guide Evaluation of Patients Under Investigation for COVID-19

The CDC provides guidance for who should be tested for COVID-19 and encourages clinicians to use their judgment in determining if a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested [14]. Symptoms to be considered include fever, chills, cough, sore throat, muscle aches, shortness of breath, new loss of taste or smell, and vomiting or diarrhea. As noted, SARS-CoV-2 can cause asymptomatic, pre-symptomatic, and minimally symptomatic infection, leading to virus shedding that may result in transmission to others who are particularly vulnerable to severe disease and death. Special attention should be paid to older adults and to patients with underlying conditions or immunosuppressed states. Even mild signs and symptoms of COVID-19 should be evaluated among potentially exposed healthcare personnel because of their extensive contact with vulnerable patients in healthcare settings.

The CDC has established priorities for COVID-19 diagnostic testing [14]. High priority for testing applies to hospitalized patients with compatible clinical features, healthcare facility workers and those who work in congregate living settings with symptoms, and residents in long-term care facilities (including prisons and shelters) with symptoms. Priority designation for testing applies to any person in the community with symptoms of potential COVID-19. In addition, persons without symptoms may be prioritized by health departments or clinicians for reasons such as public health monitoring, sentinel surveillance, or screening purposes.

Clinicians should work with their local and state health departments to coordinate testing through public health laboratories or work with commercial or clinical laboratories using SARS-CoV-2 diagnostic tests granted an Emergency Use Authorization by the FDA. Patients should be evaluated and discussed with public health departments on a case-by-case basis if their clinical presentation or exposure history is equivocal.

Other considerations that may guide testing include epidemiologic factors (e.g., close contact with an individual who in the past 14 days has tested positive for SARS-CoV-2) and the occurrence of local transmission or a cluster of COVID-19 within a specific community setting (e.g., nursing home, manufacturing facility) [14]. Close contact is defined as one of the following:

- Being within approximately 6 feet (2 meters), or within the room or care area, of a novel coronavirus case for a prolonged period of time while not wearing recommended personal protective equipment or PPE (e.g., gowns, gloves, certified disposable N95 respirator, eye protection); close contact can include caring for, living with, visiting, or sharing a healthcare waiting area or room with a novel coronavirus case.
- Having direct contact with infectious secretions of a novel coronavirus case (e.g., being coughed on) while not wearing recommended personal protective equipment.

Any patient with fever and severe acute lower respiratory illness (e.g., pneumonia, ARDS) requiring hospitalization and without alternative explanatory diagnosis (e.g., influenza) should be evaluated for COVID-19, even if no source of exposure has been identified [14].

A symptomatic patient should be provided a surgical mask and placed on respiratory isolation, preferably in an airborne isolation negative pressure room. Caregivers should observe enhanced precautions (i.e., wear gloves, gown, eye protection device [other than prescription eye glasses], and N95 respirator). For information on the management of patients with COVID-19, see https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

Diagnostic Testing

The CDC recommends that healthcare providers should immediately notify both infection control personnel at their healthcare facility and their local or state health department in the event of a newly diagnosed or suspected case of COVID-19.

Confirmation of COVID-19 is performed using the RT-PCR assay for SARS-CoV-2 on respiratory specimens (which can include nasopharyngeal or oropharyngeal aspirates or washes, nasopharyngeal or oropharyngeal swabs, bronchoalveolar lavage, tracheal aspirates, or sputum) and serum. The FDA has worked to expedite the availability of tests through emergency authorization of commercial laboratories that have developed SARS-CoV-2 testing capability. Information on specimen collection, handling, and storage is available at https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. After initial confirmation of COVID-19, additional testing of clinical specimens can help inform clinical management, including discharge planning. Additional guidance for collection, handling, and testing of clinical specimens is available at the CDC website [12].

Infection with both SARS-CoV-2 and with other respiratory viruses has been reported, and detection of another respiratory pathogen does not rule out COVID-19 [15].

Interim Clinical Guidance for Management of Patients with Confirmed COVID-19

Interim clinical guidance and additional resources for clinicians caring for patients with COVID-19 is provided and updated at the CDC website, selected aspects of which are reproduced in this section [15].

As noted, the clinical presentation of COVID-19 can range from asymptomatic to critically ill, and older patients and those with comorbidities are considered at greater risk for more severe disease. Among patients who developed severe disease, the median time to dyspnea was 5 to 8 days, the median time to ARDS was 8 to 12 days, and the median time to ICU admission was 10 to 12 days. Clinicians should be aware of the potential for some patients to rapidly deteriorate one week after illness onset. Among all hospitalized patients, 26% to 32% of patients were admitted to the ICU [15]. Only 3% to 17% of all patients with COVID-19 develop ARDS, but this increases to 20% to 42% for hospitalized patients and 67% to 85% for patients admitted to the ICU. Mortality among patients admitted to the ICU ranges from 39% to 72%, depending on the study [15]. The median length of hospitalization among survivors was 10 to 13 days.

Remdesivir is the only FDA-approved antiviral therapy for COVID-19 currently available , though multiple trials involving a variety of therapeutic agents are being conducted at many clinical centers throughout the United States. Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated [15]. The NIH and the Infectious Diseases Society of America provide updated COVID-19 management guidelines, including specific recommendations for the use of remdesivir and dexamethasone in hospitalized patients [10; 57].

Healthcare personnel should care for patients in an airborne infection isolation room. Isolation Precautions should be used when caring for the patient. For more detailed recommendations, see the CDC's Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings at https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html.

Patients with a mild clinical presentation may not initially require hospitalization [15]. However, clinical signs and symptoms may worsen with progression to lower respiratory tract disease in the second week of illness; all patients should be monitored closely. As noted, possible risk factors for progressing to severe illness may include, but are not limited to, older age, obesity (body mass index >35), and underlying chronic medical conditions (e.g., lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, diabetes, immunocompromising conditions, pregnancy).

The CDC advises that the decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This decision will depend not only on the clinical presentation, but also on the patient's ability to engage in monitoring and the risk of transmission in the patient's home environment. For more information, see the CDC's Criteria to Guide Evaluation of Patients Under Investigation (PUI) for COVID-19 at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html.

The CDC recommends that for most patients with confirmed SARS-CoV-2 infection the decision to discontinue transmission-based precautions should be made using a symptom-based strategy [25]. In general, patients with mild-to-moderate COVID-19 who are not immunocompromised may discontinue isolation once 10 days have passed since onset of illness, respiratory symptoms have improved, and at least 24 hours have passed since resolution of fever (without the use of fever-reducing medications). For patients who were asymptomatic throughout their infection, precautions may be discontinued when at least 10 days have passed since the date of their first positive viral diagnostic test. Additional considerations apply to patients who have sustained severe or critical illness and to those who are significantly immunocompromised [25].

Summary of the CDC Response to the COVID-19 Outbreak

The CDC is working with the WHO and state and local public health partners to respond to this emerging public health threat. The goal of the ongoing U.S. public health response is to contain this outbreak and prevent sustained spread of COVID-19 in this country.

The CDC and Customs and Border Protection (CBP) continue to conduct enhanced entry screening of travelers who have been in an affected area within the past 14 days at 20 designated U.S. airports. Passengers having symptoms compatible with COVID-19 and a history of travel to an affected area are being referred to CDC staff for evaluation.

As of May 2020, the CDC has produced more than 80 guidance documents on infection control, hospital preparedness assessments, PPE supply planning, and clinical evaluation and management for the outbreak.

OTHER AVAILABLE RESOURCES

CDC Travelers' Health:
Global COVID-19 Pandemic Notice
https://wwwnc.cdc.gov/travel/notices/warning/coronavirus-global

CDC Information for Healthcare Professionals about Coronavirus (COVID-19)
https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html

CDC Coronavirus Disease 2019 (COVID-19) Resources for Health Departments
https://www.cdc.gov/coronavirus/2019-ncov/php/index.html

World Health Organization Coronavirus Disease 2019 (COVID-19) Pandemic
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

Johns Hopkins University and Medicine Coronavirus Resource Center
https://coronavirus.jhu.edu

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Sepsis: Diagnosis and Management

HOW TO RECEIVE CREDIT

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Faculty

Patricia Lea, RN, DNP, MSEd, CCRN, received a Bachelor of Science degree in Nursing in 1973 from Houston Baptist University in Houston, Texas. She returned to graduate school to complete a Master's degree in Education, specifically Health Education, in 1996 from Baylor University in Waco, Texas, and a Doctorate in Nursing Practice in Executive Leadership in 2014 from American Sentinel University in Aurora, Colorado. Dr. Lea specializes in critical care nursing, with an emphasis on heart failure and sepsis. She started her career at the Houston Methodist Hospital in the cardiovascular ICU and opened an acute dialysis unit at what is now Baylor St. Luke's Medical Center in the Houston Medical Center. Dr. Lea was a Cardiovascular Clinical Coordinator and Director of the Heart Failure Clinic at Hillcrest Baptist Medical Center in Waco, Texas. In 2004, Dr. Lea returned to Houston and was employed as a Senior Research Clinical Nurse Specialist at the Texas Heart Institute coordinating stem cell and cardiac stent trials. She is currently Associate Professor and Baccalaureate Senior Level Program Director at the University of Texas Medical Branch School of Nursing in Galveston, Texas.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, Patricia Lea, RN, DNP, MSEd, CCRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure

The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare professionals who work with patients who present with sepsis, including nurses and physicians.

Accreditations & Approvals

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This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

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Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 4 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals with a current review and updated, evidence-based guidance for the diagnosis and management of sepsis and septic shock. The objective is to address knowledge gaps, enhance clinical skill, and enable effective strategies of collaborative care to improve patient outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define the various stages of sepsis, and describe the history and incidence of sepsis relative to mortality.
2. Identify risk factors associated with the development and progression of sepsis.
3. Describe the pathogenesis of SIRS, including the five phases of development, and the pathophysiology of sepsis.
4. Anticipate and assess emerging organ dysfunction associated with septic shock.
5. Recognize clinical and laboratory parameters of sepsis, and implement a strategy for antimicrobial therapy and incremental resuscitation that incorporates fluids, inotrope-vasopressors, and the selective use of corticosteroids.
6. List the diagnostic criteria of suspected SIRS in the pediatric patient.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION AND DEFINITIONS

Sepsis is a systemic pathophysiologic and clinical syndrome caused by infection and manifest by signs of inflammation, host immune response, and organ dysfunction. The causes of sepsis are myriad, and the scope of illness is broad. Most cases of sepsis syndrome arise from bacterial infection, but certain viral (e.g., Ebola and other hemorrhagic fevers) and fungal (e.g., candidiasis, histoplasmosis) infections induce a sepsis syndrome as well.

In simple terms, infection is the invasion of normally sterile host tissue by a microorganism; clinically, infection is recognized by the constellation of symptoms and signs that issue from the host response to the invading microorganism. Bacteremia is defined as the demonstrable presence (e.g., by culture) of viable bacteria within the general circulation.

Historically, there has been some confusion and a lack of consensus with respect to the definition of the various degrees of systemic infection and to the best way to manage the patient along the spectrum of illness and complications induced by sepsis. This lack of consensus prompted the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to convene a conference for the purpose of agreeing on definitions for sepsis and its sequelae. The ACCP/SCCM published their definitions in 1992 [1].

A second task force, international in scope, was convened in 2001. The purpose of this conference (sponsored by the ACCP, SCCM, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society) was to modify, where appropriate, the original ACCP/SCCM definitions to reflect current understanding of the pathophysiology of sepsis. Apart from recommending that the list of signs and symptoms of sepsis be expanded to reflect clinical bedside experience, the task force found insufficient evidence to support alternative definitions of sepsis [2]. This international effort has spawned the global Surviving Sepsis Campaign, comprised of 29 sponsoring clinical specialty societies that convene at regular intervals to review the clinical literature and provide evidence-based guidelines for management of severe sepsis [62; 65].

According to these task forces, sepsis was defined as a systemic inflammatory response arising from known or suspected infection, leading to widespread tissue injury and manifested by two or more of the following conditions [1; 2]:

- Fever (temperature greater than 38.3°C [100.6°F])
- Hypothermia (core temperature less than 36°C [96.8°F])
- Tachycardia (heart rate greater than 90 beats per minute in adults)
- Tachypnea (respiratory rate greater than 20 breaths per minute)
- Altered mental status
- Hyperventilation (partial pressure of carbon dioxide [$PaCO_2$] less than 32 mm Hg)
- Leukocytosis (leukocyte count greater than 12,000 cells per mm^3)
- Leukopenia (leukocyte count less than 4,000 cells per mm^3)

This emphasis on the systemic signs of inflammation as the marker for sepsis requires the recognition that other, noninfectious, pathophysiologic conditions also cause tissue injury and inflammation with systemic ramifications. Systemic inflammatory response syndrome (SIRS) includes any serious, ongoing inflammatory process resulting in end-organ damage and multisystem failure. SIRS encompasses a continuum of escalating inflammatory responses to infectious or noninfectious stimuli; end-organ dysfunction and mortality increase with each stage of the advancing inflammatory process. While sepsis is a common and important form, SIRS may also be seen in association with noninfectious insults, including trauma, burns, pancreatitis, anaphylaxis, adrenal insufficiency, pulmonary embolism, myocardial infarction, massive hemorrhage, and cardiopulmonary bypass [1; 3; 4].

Severe sepsis has been defined as sepsis associated with organ dysfunction and tissue hypoperfusion. Signs of tissue hypoperfusion are hypotension (systolic blood pressure <90 mm Hg or a drop in systolic pressure of >40 mm Hg), lactic acidosis, oliguria, and acute alteration in mental status. Organ dysfunction results from falling blood pressure and widespread microvascular injury caused by circulating toxic byproducts of infection and the inflammatory immune response. Common manifestations include acute lung injury, renal failure, disseminated intravascular coagulation (DIC), and laboratory signs of liver dysfunction. In clinical practice, "septic shock" (a subset of sepsis) is present when there is persistent hypotension requiring vasopressor therapy, after adequate fluid resuscitation has been administered [1; 5].

In 2014, the European and American societies of critical care medicine convened a third task force (Sepsis 3) to re-examine current concepts and definitions of sepsis and septic shock in light of improved understanding of the pathobiology, epidemiology, and management of sepsis. After a synthesis of evidence, the task force determined that previous definitions (as presented by the previous task forces) are limited by an excessive focus on inflammation. The task force also concluded that the model of sepsis following a continuum through severe sepsis to shock is misleading; that the SIRS criteria have inadequate specificity and sensitivity for defining sepsis; and that the term "severe sepsis" is redundant. The Sepsis 3 report and new consensus definitions for sepsis and septic shock were published in 2016 [6]. The new Sepsis 3 definitions are intended to provide greater clarity and specificity while emphasizing the life-threatening nature of sepsis syndrome. The aim is to improve clinical recognition and achieve greater consistency in diagnosis, therapy, and clinical investigation of sepsis.

The Sepsis 3 task force emphasized that sepsis is the primary cause of death from infection and thus requires early recognition, urgent attention, and prompt treatment. Following infection, the clinical characteristics of sepsis may emerge gradually over time, shaped by the interplay of pathogen factors and host factors such as genetic determinants, age, comorbidities, and environment. Sepsis is differentiated from infection by the presence of an aberrant or dysregulated host response accompanied by organ dysfunction. Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained acute-onset organ dysfunction should thus raise the possibility of underlying infection. The clinical and biologic expression of sepsis may be modified by pre-existing illness, chronic comorbidities, medication, and interventions. Specific infections may result in organ dysfunction without generating a dysregulated systemic host response [6].

The Sepsis 3 report defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. This new definition emphasizes the loss of adaptive homeostasis in response to infection, the potential lethality of infection when any degree of organ dysfunction is present, and the importance of urgent assessment and prompt treatment. Because even modest organ dysfunction has been found to confer a mortality risk in excess of 10%, sepsis is inherently a serious condition and the term "severe sepsis" is no longer considered useful [6].

The presence and extent of organ dysfunction can be assessed with various scoring systems that rely on clinical and laboratory parameters, such as the following [6; 7; 62]:

- Acute lung injury: A ratio of arterial oxygen tension to fraction of inspired oxygen of 280 or less
- The presence of a metabolic acidosis (e.g., lactate >2 mmol/L)

- Oliguria: Urinary output of less than 0.5 mL/kg body weight/hour for at least two hours in a patient with a urinary catheter in place
- Coagulation abnormalities: International normalized ratio (INR) >1.5
- Thrombocytopenia: Platelet count <100,000 cells/mcL
- Elevated bilirubin: >2 mg/dL
- Acute alteration in mental status

The scoring system currently used in most critical care units is the Sequential Organ Failure Assessment (SOFA) score, which grades abnormality by organ system and accounts for clinical interventions [7]. A higher SOFA score is associated with an increased probability of mortality. Organ dysfunction can be identified by an acute change in SOFA score ≥2 points consequent to the infection [6].

Working from a model derived from a large data base, the task force was able to identify and validate a simple "bedside" clinical measure that can be used to identify which patients with suspected infection are at risk for developing sepsis, referred to as the quick SOFA (qSOFA). This measure consists of three elements:

- Respiratory rate ≥22 per minute
- Altered mentation
- Systolic blood pressure ≤100 mm Hg

Data analysis has demonstrated that patients with infection who are positive for two or more of these elements are likely to have a prolonged intensive care unit (ICU) stay (i.e., three or more days) or die in the hospital. Physicians and nurses can employ the qSOFA in the office, emergency department, or hospital ward to quickly identify which patients with an infection are on the clinical threshold of sepsis and thus at risk of further clinical deterioration. The task force suggests that positive qSOFA criteria be used to prompt clinicians to further investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider referral to critical care [6].

Sepsis 3 defines septic shock as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Within the clinical construct of sepsis, the patient with septic shock can be identified by the presence of the following two criteria:

- Persisting hypotension requiring vasopressors to maintain mean arterial blood pressure (MAP) ≥65 mm Hg
- Blood lactate >2 mmol/L despite adequate volume resuscitation

The hospital mortality rate for patients meeting these criteria is in excess of 40%, or four times greater than for patients with sepsis [6].

The Surviving Sepsis Campaign provides a screening tool to assist when evaluating patients in the hospital emergency department, medical/surgical/telemetry wards, or in the ICU. This may be accessed at http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx.

EPIDEMIOLOGY AND BURDEN OF SEPSIS

The first description of multiple organ failure appeared in 1973 in a discussion of three patients who died of distal organ failure that followed ruptured aortic aneurysms. Multiple organ failure was subsequently described as multiple, progressive, or sequential systems organ failure. It was noted that shock or infection alone did not cause the distal organ dysfunction. Other severe insults could set in motion an underlying reaction that would lead to widespread endothelial damage, edema resulting from increased vascular permeability, and impaired availability of oxygen [8; 9; 10].

Sepsis, septic shock, and multiple organ failure are major causes of morbidity and mortality in the United States, resulting in at least 800,000 hospitalizations and 250,000 deaths annually. It is estimated that 9.3% of all deaths in the United States, and nearly half of hospital deaths, are a result of sepsis, which equals the number of deaths resulting from myocardial infarction and far exceeds the mortality rates from acquired immune deficiency syndrome (AIDS) or breast cancer. The aggregate hospital cost of care for patients with septicemia totaled nearly $23.7 billion in 2013 [11; 16; 71].

A study of hospital emergency department visits between 1999 and 2005 found that of the 750,000 hospitalizations, more than two-thirds may have initially presented to an emergency department. Cases of suspected sepsis account for more than 570,000 emergency department visits annually. The average length of stay in the emergency department is 4.7 hours. However, more than 20% of patients with sepsis had a length of stay that exceeded six hours, resulting in a substantial burden on facilities nationwide in providing sepsis care [12; 13].

The incidence of septicemia more than doubled between 1993 and 2009, increasing by an annual average of 6% [11]. Between 1993 and 2003, 8.4 million cases of sepsis and 2.4 million cases of severe sepsis were reported. The percentage of severe sepsis cases among all sepsis cases increased from 25.6% to 43.8% during the same time period [15].

The reported incidence rates of sepsis increase with advanced age. Two-thirds of all sepsis cases occur in people 65 years of age and older, with case fatality rates as high as 40% [16]. Age-adjusted rates for sepsis hospitalization and mortality increased annually by 8.2% and 5.6%, respectively, between 1993 and 2003, whereas the fatality rate decreased by 1.4% [15]. Sepsis is more common among men than women, and the fatality rate is greater in men and nonwhite populations [22].

Mortality from sepsis of gram-negative etiology is the cause of 20% to 50% of the overall total number of septic deaths. The figures are now similar for sepsis of gram-positive etiology [18]. Mortality has been reported as high as 60% in patients with underlying medical problems. Among patients who develop the complications of shock and organ failure, mortality can reach 90% [20]. Extent of organ failure contributes to the prognosis, with a greater survival rate in patients with fewer than three failing organs. The risk of death increases as each organ fails [20].

Sepsis is among the leading causes of hospitalization and ranks as the most expensive inpatient condition treated in U.S. hospitals [66]. Data from the 2008 National Hospital Discharge Survey show that the rate of hospitalization for sepsis increased from 11.8 to 24 per 10,000 population during the period 2000 through 2008 [66]. Compared with other conditions, the hospital stay for sepsis was 75% longer and the likelihood of dying during hospitalization was eight times higher. The estimated annual cost of hospitalization for sepsis and septicemia in 2008 was $14.6 billion and increasing at the rate of 11.9% each year [66].

Despite immense clinical effort and high treatment expenditures, mortality rates remain high. Those who survive often sustain permanent organ damage, some degree of physical disability, and long-term cognitive impairment [67].

RISK FACTORS AND PREVENTION

Factors considered important in the development of sepsis include: inappropriate broad-spectrum antibiotic therapy; immunosuppressive treatments, such as cancer chemotherapy; invasive procedures; transplantations; fungal organisms; burns or other trauma; anatomic obstruction; intestinal ulceration; age (the very young and the very old); and progressive clinical conditions, such as malignancy, diabetes, or AIDS [24].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Institute for Health and Care Excellence, risk factors for sepsis include very young (younger than 1 year) and older (older than 75 years) age; frailty; impaired immune systems and/or function; administration of chemotherapy, long-term steroids, or immunosuppressant drugs; history of surgery or other invasive procedures in the past six weeks; any breach of skin integrity; injection drug use; and indwelling lines or catheters.

(https://www.nice.org.uk/guidance/ng51. Last accessed July 13, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Healthcare-associated infections are a major cause of sepsis among severely ill patients. Increased risk of nosocomial infection is associated with the presence of underlying chronic disease, alteration in host defenses, prolonged hospital stay, and the presence of invasive catheters or monitoring devices [27]. Pulmonary, urinary tract, gastrointestinal, and wound infections predominate [28; 29]. In hospitalized adult patients, the etiology of sepsis has shifted from being predominantly gram-negative nosocomial infections (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa*) to gram-positive infections (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*). The incidence of sepsis caused by gram-positive infections has increased by 26.3% per year over the last three decades [17]. Multidrug-resistant pathogens, such as *S. aureus*, now account for more than half of all sepsis cases. *S. aureus* is singly responsible for 40% of ventilator-associated pneumonia episodes and most cases of nosocomial pneumonia [17; 25]. Group B streptococcus is a leading cause of neonatal sepsis in the United States [30].

Vascular and monitoring catheters and infusion sets may become contaminated and lead to the development of nosocomial infections and sepsis. The risk of catheter-related sepsis is increased when the IV catheter is placed in a central vein, particularly if the catheter remains in place longer than three to five days or if the catheter is used for blood sampling [31]. For this reason, consideration should be given to changing the catheter and possibly the insertion site after 72 hours. The risk of contamination of arterial catheters is higher than that observed with venous catheters. Contamination can occur if the system is entered frequently for blood sampling, if the infusate remains in place for more than 48 hours, or if inflammation develops near the catheterized artery [32]. Urinary catheters left in the bladder longer than two weeks often cause infection. Therefore, increased surveillance for signs of urinary tract infections when catheters remain in place beyond a few days is necessary [33].

Central venous catheters (CVCs) are increasingly used in the pediatric population, leading to an increase in CVC-related complications. Implanted ports may be the device of choice when long indwelling times are expected, with consideration given to the patient's age and need for sedation and analgesia during the insertion procedure. Radiograph following the insertion procedure is recommended to ensure correct catheter positioning. Full sterile barrier precautions, strict protocols for catheter care, and prompt removal of the catheter when it is no longer needed are recommended to prevent infectious complications [34].

Bacterial contamination of platelet units (estimated at 1 in 1,000–3,000) results in many occurrences of transfusion-associated sepsis in the United States each year. The AABB (formerly the American Association of Blood Banks) adopted a new standard in 2004 requiring member blood banks and transfusion services to implement detection measures and limit bacterial contamination in all platelet components [35].

Patients who live with malignancy are commonly hospitalized due to infection. Immunosuppresive treatments (or the malignancy itself) can lead to severe infection, which is a frequent cause of death among cancer patients. One in six patients with sepsis has underlying disease [36].

PATHOGENESIS OF SIRS

The natural defense of the body to an infection, or other assault, involves a number of cellular and humoral factors. They include B and T lymphocytes, macrophages, neutrophils, platelets, tumor necrosis factor (TNF), interleukins, the coagulation factors, and probably several other products [26; 37; 38]. There are five rather distinct phases that describe how these biologic products work together to overcome the assault and, paradoxically, how they can interact to cause SIRS and potentially lead to critical organ failure [26; 39].

FIRST PHASE: THE LOCAL RESPONSE

An infection, injury, burn, or similar process can initiate a response that causes the release of various proinflammatory mediators in the immediate area of involvement. Among others, these include the cytokines, eicosanoids, and platelet-activating factors. In an attempt to limit or ameliorate the local injury, these mediators act to remove damaged tissue, stimulate new tissue growth, and combat the spread of neoplastic cells, pathogenic organisms, and antigens. To counteract the effects of these mediators and prevent them from causing damage, the body soon produces a set of anti-inflammatory substances, such as interleukins and TNF receptors [26; 39].

SECOND PHASE: THE EARLY SYSTEMIC RESPONSE

If the initial injury or insult is severe enough, the proinflammatory and anti-inflammatory mediators can appear in the systemic circulation. This may occur by direct entry into the bloodstream in the case of massive trauma, by spillover from the local site in the event of a severe infection, or by other means. The presence of these mediators in the general circulation is a sign that the local region is incapable of handling the situation and that assistance is needed. The proinflammatory response brings additional neutrophils, platelets, lymphocytes, coagulation factors, and other materials to the local site. This should eventually lead to a compensatory anti-inflammatory response that down regulates and controls the proinflammatory actions. In the typical situation, this will occur and no significant untoward effects are seen [26].

THIRD PHASE: PROINFLAMMATORY EXCESS

In some patients, control of the proinflammatory process fails to develop, resulting in a systemic reaction that produces tachycardia, abnormal body temperature, and, in time, hypotension. These are the early signs of SIRS and are thought to be due to: increased microvascular permeability with transudation into organs; platelet sludging, causing capillary blockage and ischemia; reperfusion injury; dysregulation of vasodilatory and vasoconstrictive mechanisms; and maldistribution of blood flow. Persistent hypotension and shock may supervene unless homeostasis is restored, leading to organ dysfunction or organ failure. In an acutely ill patient, altered function in more than one major organ constitutes multiple organ dysfunction syndrome (MODS). While emphasis has been placed on the role of the proinflammatory state in SIRS, an important alternative mechanism may involve an imbalance in the amount or effectiveness of proinflammatory and anti-inflammatory mediators [26].

FOURTH PHASE: EXCESSIVE IMMUNOSUPPRESSIVE RESPONSE

In some patients who survive an initial massive infection or other inflammatory process, there may be a compensatory, but excessive, anti-inflammatory response that results in immunosuppression [40]. This may explain the increased susceptibility to infection in patients with severe burns, trauma, hemorrhage, or pancreatitis. The process is thought to involve impaired monocyte function, altered T- and B-cell activity, diminished proinflammatory cytokines, and several other factors. This process can be self-limiting, and the immunosuppression can resolve without further consequences. If it does not resolve, patients may experience the final, life-threatening complication of MODS [26].

FIFTH PHASE: TRANSITION TO MODS

This phase indicates that there has been an overwhelming, dysregulated host response to the biologic insult. It can take varied forms, depending on the character and severity of critical organ failure. The progression to MODS is common in patients with late-stage SIRS and carries a high mortality risk. If the immune system cannot recover, organ failure and death may follow. In another group of patients, there may be an oscillating effect, with periods of severe inflammation, immunosuppression, and then another proinflammatory response, resulting in increased mortality rates. This has been seen in patients with severe burns, whose levels of cytokines fluctuate widely for several weeks after injury [26; 38].

The nature of the insult can significantly affect the degree of local inflammation and tissue injury. The balance between the expression of pro- and anti-inflammatory mediators often determines the magnitude of early tissue injury and risk of subsequent infectious complications. High levels of the proinflammatory mediators can initiate remote organ injury as a result of organ cross talk. Organ failure and death will occur in patients in phase five unless homeostasis can be maintained and there is a balance between pro- and anti-inflammatory forces [26; 41; 42].

PATHOPHYSIOLOGY OF SEPSIS

A complex, dynamic, and bidirectional interaction occurs between pathogens and the body's immune defense mechanisms during the course of invasive infection. If the defenses are breached successfully, the result can be sepsis [20].

As noted, in the United States, the etiology of sepsis has shifted from a predominance of gram-negative bacteria to a predominance of gram-positive, drug-resistant bacteria [25]. This shift has led to a re-evaluation of basic assumptions about the pathogenesis of sepsis (e.g., there may or may not be differences in the host response to gram-negative organisms compared with the response to gram-positive organisms) [44; 45]. It is important to note that discrimination between gram-negative and gram-positive organisms is based on the recovery of specific pathogens from blood or the presumed site of infection rather than from any specific immunologic criterion. In 30% to 50% of sepsis cases, the inciting organism is not identified [18; 25].

MICROBE RECOGNITION

The innate immune system recognizes invading pathogens and initiates an inflammatory or septic response. Gram-positive and gram-negative bacteria activate the immune response through unique cellular constituents referred to as pattern-associated molecular patterns (PAMPs) or microbial-associated molecular patterns (because they are also common in nonpathogenic bacteria). PAMPs bind to immune system receptors called pattern recognition receptors (PRRs), which are expressed on the surface of host cells. PRRs are essential for initiating the host's immune response and regulating the adaptive immune response to infection or tissue injury, yet PRRs can also contribute to harmful systemic inflammation and tissue damage in organs [5; 25].

Toll-like receptors (TLRs) are the most common class of PRRs. Each of the known TLRs has unique binding properties that allow for the differentiation between gram-negative and gram-positive bacteria. When the TLR system recognizes a pathogen, a response is generated that is both generalized (similar response to dissimilar stimuli) and specific (pathogen is recognized by multiple TLRs simultaneously). The result is an immune system response that is tailored to the pathogen [25; 46]. The degree to which TLRs mediate the outcome of sepsis in individual patients is not yet fully understood [5].

TLRs can detect danger signals both inside and outside the cell [25]. TLRs induce the production of inflammasomes (multiprotein complexes) in response to the products of bacteria and damaged cells. This in turn activates caspase-1, which is important in the process of inflammation and apoptosis (a counter-regulator of the initial inflam-

matory response in sepsis). Caspase-1 activation is considered to be a prerequisite for an adequate immune response. Like other proinflammatory products, caspase-1 can have both positive and negative effects on the course and outcome of sepsis [5].

Nod-like receptors (NLRs) are a less well understood class of PRRs. NLRs can detect danger elements (e.g., microbial motifs, live bacteria, host-derived molecules) inside the cell [25].

ENDOTOXINS AND OTHER BACTERIAL TOXINS

Endotoxin was identified more than 100 years ago, but its potential role in the development of sepsis was not identified until 1951. Experimental studies using endotoxin reproduced some of the features of septic shock in animals, but they did not represent the features of septic shock characteristic to humans. Evidence that endotoxin might play a pathogenic role in humans was discovered accidentally in 1991, but its precise role in sepsis remains elusive. Endotoxin is often found in the blood of critically ill patients, making its measurement of limited diagnostic value. In addition, other bacterial toxins (e.g., gram-positive peptidoglycans) can induce the production of mediators associated with sepsis [18].

COAGULATION SYSTEM

The coagulation system plays an important role in the sepsis-induced inflammatory cascade. Coagulation is the inflammatory reaction to tissue injury and is activated independent of the type of microbe (e.g., gram-positive and gram-negative bacteria, viruses, fungi, or parasites). Coagulation contributes to the outcome in sepsis by down-regulating fibrinolysis and the anticoagulant systems. The collaboration between clotting and inflammation, which works to wall off damaged and infected tissues, is an important host survival strategy. Coagulation induced by inflammation can in turn contribute to further inflammation. A key to determining survival in sepsis is to limit the damage while retaining the benefits of localized clotting and controlled clearance of pathogens [5; 14; 47].

A continuum of coagulopathy in sepsis has been suggested, extending from the appearance of coagulation abnormalities prior to the onset of any clinical signs of sepsis to consumption of anticoagulant proteins and suppression of the fibrinolytic system. Depletion of anticoagulant and fibrinolytic factors contributes to the microvascular deposition of fibrin that is associated with organ dysfunction. Coagulation abnormalities in sepsis contribute significantly to organ dysfunction and death [5; 14; 48].

MANIFESTATIONS OF SEPSIS

Any patient with sepsis who has evidence of dysfunction in one organ in the absence of an obvious cause such as traumatic injury may have incipient dysfunction of other organs. The manifestations of sepsis may be seen in the cardiovascular, pulmonary, central nervous, renal, gastrointestinal, and hematologic systems of the body (most frequently in the lungs and circulatory system) [20].

The following signs and symptoms should not be thought of merely as the manifestations of sepsis but as clear evidence that MODS may be developing. The host response may be more important in the genesis of MODS than the specific bacterium, virus, or traumatic injury. In most patients, the extent of systemic changes corresponds to the extent of shock [19; 20; 49].

CARDIOVASCULAR

In addition to hypotension, a variety of other cardiovascular manifestations may be seen. Tachycardia is common. In addition, the left and right ventricles are dilated, ejection fractions are often depressed, and the Frank-Starling and diastolic pressure-volume relationships are altered [24].

Before the onset of shock, the patient's condition is usually hyperdynamic. The skin is warm and flushed, pulse volume is increased, and pulse pressure is wide. Cardiac output is typically elevated, and systemic vascular resistance (SVR) is usually decreased. Despite the increase in cardiac output, serum lactate levels are often elevated. Anaerobic metabolism occurs because of inadequate nutrient blood flow [24].

As shock sets in, SVR drops precipitously, although cardiac output continues to increase. In the later phases of shock cardiac output declines, which exacerbates the effects of hypoperfusion and allows lactate to accumulate. The decrease in cardiac output can result in a subsequent elevation of the SVR [24].

PULMONARY

Tachypnea, with a respiratory rate of more than 20 breaths per minute, is often the earliest pulmonary sign of sepsis, occurring before hypoxemia. Hypoxemia is usually present, although it may be masked by hyperventilation. The cause of hypoxemia is usually ventilation-perfusion mismatch.

As sepsis continues, marked respiratory alkalosis often ensues; $PaCO_2$ may be 30 mm Hg or less. The hypoxemia progresses rapidly. The result is often pulmonary edema and respiratory failure. Other pulmonary manifestations of sepsis include respiratory muscle dysfunction and bronchoconstriction. The onset of either acute respiratory distress syndrome (ARDS) or persistent pulmonary hypertension is an ominous sign [19; 49; 50].

CENTRAL NERVOUS SYSTEM

Altered mental status may be the most common and most overlooked manifestation of sepsis. This causes elderly patients to be at particularly high risk. Early changes include withdrawal, confusion, irritability, or agitation. In patients with severe infection, one may see disorientation, lethargy, seizures, or frank obtundation [21; 50].

Eventually, symptoms and signs of encephalopathy, including nonfocal neurologic manifestations, may be seen, and some patients may become comatose. In addition, evidence of polyneuropathy, including impaired deep tendon reflexes, muscle weakness, and wasting, may be present [19; 49; 50].

Patients with sepsis and encephalopathy are more likely to be bacteremic and have concomitant renal and hepatic dysfunction than are patients with sepsis and normal mental status. Furthermore, the risk of death increases as the encephalopathy worsens [21].

RENAL

The renal manifestations of sepsis include oliguria and azotemia. Urinary sediment may contain red blood cells, casts, and protein. The urinary excretion of sodium may be markedly reduced (less than 20 mEq/L), and urinary osmolality may be increased (greater than 450 mOsm/kg). Protracted oliguria may reflect acute tubular necrosis, often reversible, or diffuse microvascular injury, often resulting in fixed renal failure [19; 49].

GASTROINTESTINAL

Impaired motility is the most common gastrointestinal problem. Often, this manifests as abnormal gastric emptying or as a dynamic ileus. Stress ulceration is another common problem, although it may be seen less often now than in the past. There is some evidence that stress ulcers are less likely to develop when patients are given adequate fluid resuscitation, although this has not been proven conclusively [53].

HEPATIC

Large but transient elevations in serum transaminase levels may follow an episode of severe shock or hypoxemia. Less severe increases, often in association with mild-to-moderate hyperbilirubinemia, suggest focal hepatic necrosis. In the final states of sepsis, patients may have evidence of frank hepatic insufficiency, including hypoprothrombinemia, jaundice, lactic acidosis, and hypoglycemia [2; 49; 50].

HEMATOLOGIC

Leukocytosis, usually accompanied by a shift to the left (>10% immature cells), is the most common hematologic manifestation of sepsis. Multifactorial anemia is common in late-stage sepsis. Decreased maturity and/or survival of red blood cells may contribute to anemia. Thrombocytopenia and coagulation abnormalities (elevated prothrombin or partial thromboplastin times) are often seen in sepsis. Thrombocytopenia is more common than overt DIC in sepsis. DIC is a manifestation of advanced-stage sepsis and carries a poor prognosis [2; 17; 49; 54; 55].

DIAGNOSIS AND MANAGEMENT

Methods to identify critically ill patients who are likely to die as a result of sepsis have become clearer, and increased awareness that sepsis is more common and lethal than previously understood has helped to promote the development of an organized approach to care. While the early diagnosis of sepsis continues to be a challenge (primarily because a rapid, sensitive, and specific diagnostic test is lacking), research indicates that improvements in outcomes are possible when treatment protocols are applied in a timely manner [48].

As discussed, an international consortium of critical care specialty societies has worked to standardize the definition and clinical parameters of sepsis and to develop evidence-based guidelines for optimal management of sepsis and septic shock. This is an ongoing effort, the goal of which is to improve care and reduce mortality worldwide. Clinical care guidelines have been developed by the Surviving Sepsis Campaign and published by the Society of Critical Care Medicine (SCCM) in 2008, 2013, and 2016. Detailed management strategies are provided for rapid diagnostic evaluation and antimicrobial treatment, fluid resuscitation, and the use of vasopressors in septic shock [62; 65; 72]. Initial funding of the Surviving Sepsis Campaign was provided by the SCCM. The ongoing work and the campaign's guidelines have no direct or indirect connection to industry support. The 2016 international guideline for the management of sepsis and septic shock are available online at http://www.survivingsepsis.org/Guidelines/Pages/default.as [72].

The 2016 guideline recommendations are graded for strength ("strong" or "weak") and for quality of evidence (indicated by a letter). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system uses the letters A through D to reflect an assessment of the quality of evidence, ranging from high (A) to very low (D). As an example, it is recommended that antimicrobial therapy be initiated within three hours of the time a patient presents or as soon as possible upon recognition of sepsis (grade strong, C) and within one hour of the time there is documented hypotension (grade strong, B).

MANAGEMENT OF SEPSIS

Fluid Resuscitation and Diagnosis

The SCCM guideline emphasizes that sepsis and septic shock are medical emergencies; treatment and resuscitation should begin immediately upon recognition. Intravenous fluid resuscitation of a patient with sepsis-induced shock (defined as tissue hypoperfusion) should be initiated as soon as the hypoperfusion is recognized (i.e., not delayed pending admission to an ICU).

The principal recommendations for fluid resuscitation are [72]:

- Intravenous fluid resuscitation should be started immediately, beginning with crystalloids (grade strong, B).
- In the setting of sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid should be given within the first three hours (grade strong, B),
- It is suggested that albumin be added when patients require substantial amounts of crystalloids (grade weak, C).
- Fluid resuscitation should initially target a MAP of 65 mm Hg in patients with septic shock requiring vasopressors (grade strong, B).

It is recommended that, following initial fluid resuscitation, additional fluid administration be guided by frequent reassessment of hemodynamic status. A reasonable set of treatment goals suggested for the first six hours of resuscitation are [65; 72]:

- Central venous pressure of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients)
- MAP of 65 mm Hg or greater
- Urine output of 0.5 mL/kg/hour or greater
- Central venous or mixed venous oxygen saturation of at least 70% or 65%, respectively

Antibiotic Therapy and Source Control

The SCCM recommends obtaining appropriate cultures before beginning antimicrobial therapy, but the process of doing so should not delay antibiotic administration. At least two sets (aerobic and anaerobic) of blood cultures should be obtained, including one drawn through any indwelling vascular catheter or device in place prior to onset of infection. Cultures from other suspected sites should be obtained as well. The guideline committee also recommends that imaging studies be performed to confirm the source of infection, assuming the patient's condition allows it [62; 65; 72].

Intravenous antimicrobial therapy should be started as early as possible, ideally within the first hour of recognition of sepsis or septic shock (grade strong, B). Clinical studies have shown that delay in antimicrobial therapy for serious infection and sepsis prolongs morbidity, lengthens hospital stay, and increases mortality [68]. A retrospective cohort study involving 2,731 patients with sepsis showed that initiation of antimicrobial therapy within the first hour of documented hypotension was associated with increased survival to discharge. Moreover, each hour of delay conferred an approximately 12% decreased probability of survival [69].

The initial choice of antibiotics will depend on the most likely pathogens associated with the source of infection as well as the prevalent micro-organisms in the local community and hospitals. The clinician should assess risk factors for multidrug-resistant pathogens, including prior hospitalization, health facility residence, recent antimicrobial use, and evidence of prior infection with resistant organism. The anticipated susceptibility profile of prevalent local pathogens and the ability of the antibiotic to penetrate to the source of the infection must also be considered. A combination of drugs with activity against all likely pathogens should be administered initially, but the regimen should be reassessed in light of culture results, the goal being to identify a single, narrow-spectrum antibiotic that will best control the infection [53; 57]. It has been found that combining an extended-spectrum beta-lactam antibiotic (e.g., penicillins, cephalosporins) with an aminoglycoside (e.g., gentamicin) was no more effective in reducing mortality than using the beta-lactam agent alone. In addition, the combination carries an increased risk of renal damage [53; 57]. A common approach is to initiate empiric therapy with a carbapenem or extended-spectrum penicillin/beta-lactamase inhibitor (e.g., ticarcillin/tazobactam) to cover gram-negative enteric bacilli and *Pseudomonas*, often in combination with vancomycin to cover *S. aureus* pending culture results.

The empirical antimicrobial regimen should be narrowed as soon as the pathogen has been identified and sensitivities are known. The duration of therapy will depend on the nature of the infection and other considerations specific to a given case. As a general rule, a 7- to 10-day course of bactericidal antimicrobial therapy is considered adequate for most serious infections associated with sepsis [72]. In the event that the syndrome is due to something other than an infectious cause, such as trauma, antibiotics should be discontinued as soon as possible.

Source control requires that a specific anatomic diagnosis of infection (e.g., skin/soft tissue infection, pyelonephritis, cholangitis, peritonitis) be identified, or excluded, as soon as possible and preferably within the first six hours after presentation. Radiographic imaging is often necessary and should be undertaken promptly as soon as the patient's condition permits and antimicrobial therapy has been administered. Source control may be achieved by percutaneous drainage of an infected cyst or abscess, debridement of infected tissue, or removal of an infected device or catheter (removal should be prompt after other vascular access has been established) [53; 72]. If necessary, surgical exploration and drainage should be undertaken within 12 hours of diagnosis (grade strong, C) [65].

Vasopressors and Inotropic Therapy

If hypotension persists after intravascular volume repletion, then vasopressors may be required to restore and maintain adequate blood pressure and tissue perfusion (goal MAP ≥65 mg Hg). Such patients are considered to have the combination of vasodilation and reduced cardiac contractility, a condition best managed with a combined inotrope-vasopressor agent. In order to monitor arterial pressure accurately, it is suggested that all patients requiring vasopressors have an arterial catheter placed as soon as practical, if resources are available [72].

Historically, norepinephrine, dopamine, and epinephrine were three inotrope-vasopressor used to correct hypotension in septic shock [53]. Based on comparison studies and a meta-analysis of six randomized trials, norepinephrine is considered superior to dopamine and is now the recommended first choice for vasopressor therapy in septic shock (grade strong, B) [65; 70; 72]. If a second agent is needed to maintain blood pressure, epinephrine is preferred (grade 2B). Dopamine is not recommended, as there are concerns that side effects (e.g., tachyarrhythmia) may be detrimental to patients in septic shock. Low-dose dopamine should not be used for renal protection [72]. For patient safety and effectiveness, intravenous vasopressor therapy should be administered via a central venous catheter.

As an alternative second drug, or to decrease the required effective dose of norepinephrine, vasopressin (up to 0.03 units/minute) may be added to norepinephrine [62; 65; 72]. Vasopressin should not be administered as the initial agent in septic shock.

Phenylephrine is a pure vasopressor that may be used in very select cases of septic shock [62; 65]. It reduces cardiac stroke volume, which can have deleterious effects in the patient with low cardiac output, and thus is not recommended as initial or additive therapy. Phenylephrine is reserved for the unusual case in which tachyarrhythmia limits norepinephrine use or the patient has known high cardiac output. Intravenous phenylephrine should be administered only by properly trained individuals familiar with its use [53; 56; 60].

Inotropic therapy may involve the use of dobutamine if the cardiac output remains low. If dobutamine is used, it should be combined with the vasopressors. All patients requiring vasopressors should have an arterial line placed for monitoring blood pressure [53; 56].

Monitoring Serum Lactate

If elevated, serum lactate provides a marker of tissue hypoperfusion, and serial measurements (of lactate clearance) can be used to monitor progress in resuscitation of the patient with sepsis or early septic shock. In cases in which elevated lactate levels are used as a marker of tissue hypoperfusion, it is recommended that resuscitation efforts target serum lactate with the goal to achieve normalization as rapidly as possible (grade weak, C) [62; 65; 72].

Corticosteroids

Prior to the 1990s, there was evidence that the overall 28-day mortality was not impacted by the use of corticosteroids; consequently, their use was not advised. A review of studies conducted between 1992 and 2003 concluded that corticosteroids did not change the 28-day mortality in patients with sepsis and septic shock, but that the use of low-dose corticosteroids did reduce the all-cause mortality [58]. According to the 2016 guideline, corticoste-

roids are not recommended in adult patients with sepsis if hemodynamic stability has been achieved with fluid resuscitation and vasopressor therapy.

The patient with persistent hypotension despite fluids and vasopressors should be assessed for adrenal responsiveness and may benefit from corticosteroid therapy. If corticosteroids are to be given, the 2016 SCCM guideline suggests IV hydrocortisone at a dose of 200 mg per day, in divided doses or by continuous infusion (grade weak, D) [72]. In 2017, a multispecialty task force of 16 international experts in critical care medicine, endocrinology, and guideline methods, all members of the SCCM and/or the European Society of Intensive Care Medicine, published a guideline for the management of corticosteroid insufficiency in critically ill patients. This group suggests using IV hydrocortisone <400 mg/day for three or more days at full dose in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy. They suggest not using corticosteroids in adult patients with sepsis without shock [73].

Recombinant Human Activated Protein C

Drotrecogin alpha (activated), or recombinant human activated protein C (rhAPC), has been studied in patients with sepsis due to its antithrombotic, anti-inflammatory, and profibrinolytic properties. It was voluntarily withdrawn from the market in 2011 due to studies showing no improvement in mortality with treatment [59].

Blood Product Administration

In some cases, blood product administration may be required. The 2016 guideline recommends RBC transfusion if the hemoglobin level falls below 7.0 g/L [72]. The routine use of erythropoietin is not recommended for treatment of anemia in patients with sepsis unless other conditions are present, such as the compromise of red blood cell production induced by renal failure. Prophylactic platelet transfusion is suggested when the platelet count is <10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding and when counts are <20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding [72].

Patients who require invasive procedures or surgery typically require a platelet count that is in excess of 50,000/mm^3 [53]. The routine use of fresh frozen plasma is not recommended unless there is active bleeding or planned surgery. Direct administration of antithrombin agents for the treatment of sepsis or septic shock is not advised [53].

SUPPORTIVE THERAPY FOR SEPSIS AND SEPTIC SHOCK

Mechanical Ventilation

Patients who develop sepsis-induced acute lung injury (ALI) or ARDS may require assisted ventilation. The routine use of pulmonary artery catheters for patients with ALI/ARDS is not recommended, and it is important to remember to avoid high pressures and volumes.

The SCCM guideline committee recommends a target goal for maximum end-inspiratory plateau pressures of 30 cm H_2O and a target tidal volume of 6 mL/kg predicted body weight in adult patients with sepsis-induced ARDS (grade strong, A). In addition, the use of lower tidal volumes over higher tidal volumes is suggested for adult patients with sepsis-induced respiratory failure without ARDS [72].

Unless contraindicated, it is recommended that mechanically ventilated patients be kept with the head of the bed elevated (30–45 degrees is suggested) to limit aspiration and prevent the development of ventilator-associated pneumonia. In hospitals with advanced experience and equipment, it may be advantageous to treat patients with ARDS in a prone position if higher pressures are required and the patient's condition allows for the positional change [53; 72].

A protocol for weaning patients from the ventilator should be developed for use following a successful spontaneous breathing trial. Extubation should be considered if the breathing trial is successful. A successful breathing trial is characterized by the following criteria [53]:

- Patient is arousable.
- Patient is hemodynamically stable (without vasopressor agents).
- Patient has developed no new potentially serious conditions.
- Ventilatory and end-expiratory pressure requirements are low.
- Fraction of inspired oxygen requirements are able to be safely delivered with a face mask or nasal cannula.

The SCCM recommends a conservative fluid strategy for patients with established ARDS and no evidence of tissue hypoperfusion in order to minimize fluid retention and weight gain (which have been shown to prolong mechanical ventilation and lengthen ICU stay) [72].

Sedation, Analgesia, and Neuromuscular Blockade

Sedation, whether intermittent or by continuous infusion, may be required for patients who are mechanically ventilated. In such cases, the practice of daily interruption or lightening of the sedation, preferably by established protocol, will serve to maintain the minimum degree of necessary sedation.

Neuromuscular blockade agents are sometimes used in the ICU to improve chest compliance, reduce airway pressures, and facilitate mechanical ventilation. Neuromuscular blockade agents should be used with caution in the patient with sepsis and only for brief periods, so as to avoid the risk of prolonged blockade when the drug is discontinued. The SCCM 2016 guideline suggests using neuromuscular blockade agents for 48 hours or less in adult patients with sepsis-induced ARDS and a PaO_2/FiO_2 ratio <150 mm Hg (grade weak, B).

Glucose Control

Glucose control includes a regimen of appropriate nutrition, beginning with IV glucose and advancing early to enteral feeding for the first seven days in critically ill patients with sepsis [72]. Following initial stabilization, patients with hyperglycemia should receive IV insulin therapy to reduce blood glucose levels. SCCM guidance strongly recommends that blood glucose management in ICU patients with sepsis be done by protocol [72]:

- Insulin dosing to commence when two consecutive blood glucose levels are greater than 180 mg/dL
- Target an upper blood glucose ≤180 mg/dL rather than an upper blood glucose ≤110 mg/dL (grade strong, A)
- Monitor blood glucose every one to two hours until glucose values and insulin infusion rates are stable, then every four hours while patients are receiving insulin infusions

Note: A 2009 study demonstrated more frequent episodes of hypoglycemia and higher mortality when tight glucose control was attempted in critically ill patients [63].

Bicarbonate Therapy and Deep Vein Thrombosis Prophylaxis

Bicarbonate therapy to improve hemodynamics or reduce vasopressor requirements in patients with sepsis-induced lactic acidemia is not recommended for those patients with a pH equal to or greater than 7.15 [72]. The use of bicarbonates in SIRS requires additional study.

The use of anticoagulants to prevent deep vein thrombosis (DVT) has been well studied. For patients with sepsis, the SCCM guideline committee recommends the administration of low-dose unfractionated heparin (UFH), two to three times per day, or low-molecular-weight heparin (LMWH), once daily, unless there are contraindications, such as active bleeding, thrombocytopenia, or severe coagulopathy. LMWH has been found to be superior to UFH and is preferred in high-risk patients if there are no contraindications [53; 72].

When contraindications exist, other preventive measures, such as graduated compression stockings or an intermittent compression device, are recommended. In very high-risk patients, such as those who have sepsis and a history of DVT, trauma, or orthopedic surgery, a combination of both therapies is suggested [53; 56].

Stress Ulcer Prophylaxis

The SCCM guideline recommends stress ulcer prophylaxis for patients with sepsis who have risk factors for gastrointestinal bleeding, using either a proton pump inhibitor or a histamine-2 antagonist. It is recommended that stress ulcer prophylaxis not be used for patients without risk factors for gastrointestinal bleeding [72].

Communication

Also included in the supportive therapy points of care is the SCCM recommendation that advance care planning, including the communication of likely outcomes and realistic goals of treatment, be discussed with patients and families [53; 72]. As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because communication with patients and families is considered an essential aspect of care, it is each practitioner's responsibility to ensure that information regarding goals and potential outcomes are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

SEPSIS BUNDLE

Reducing mortality due to sepsis requires an organized process that guarantees early recognition and consistent application of evidence-based practice. To this end, carefully designed protocols and measurable quality indicators should be incorporated into hospital practice. Beginning in 2005, the Surviving Sepsis Campaign converted its guideline into protocols, with sets of quality indicators that could be implemented by hospitals working to improve outcomes. The Sepsis Bundles are a series of therapies that, when implemented together, have been proven to achieve better outcomes than when implemented individually [62]. In conjunction with the 2013 guideline, two bundles (resuscitation and management) were released.

In order to reflect the changes in the 2016 guideline, in 2018 the Surviving Sepsis Campaign published the Hour-1 Bundle, taking the place of the previously separate resuscitation and management bundles [62]. This new bundle emphasizes the importance of beginning resuscitation and management immediately, then escalating care seamlessly (e.g., by adding vasopressor therapy) on the basis of ongoing clinical parameters rather than waiting or extending resuscitation measures over a longer period. The Hour-1 Bundle consists of five elements that are intended to be initiated within the first hour after the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis or septic shock. The five elements are [62]:

- Measure lactate level. Re-measure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

More than one hour may be required for resuscitation to be completed, but initiation of resuscitation and treatment should begin immediately [62]. The Hour-1 Bundle, based on the 2016 guideline, is evidence-based and intended for use by emergency department, hospital, and ICU staff as a tool for improving the care of patients with sepsis and septic shock.

PEDIATRIC CONSIDERATIONS

Sepsis is the leading cause of pediatric death worldwide. In the United States alone there are 72,000 children hospitalized for sepsis annually, with a reported mortality rate of 25% [75].

In 2002, an international panel of experts met to revise the definitions of sepsis and septic shock to include and reflect the developmental stages of children and age-specific norms of vital sign and laboratory data. The panel also modified the adult criteria for SIRS and proposed dividing the pediatric population into the following six distinct age groups to account for age-specific risks [51]:

- Newborn: 0 days to 1 week of age
- Neonate: 1 week to 1 month of age
- Infant: 1 month to 1 year of age
- Toddler and preschool: 2 to 5 years of age
- School-age child: 6 to 12 years of age
- Adolescent and young adult: 13 to 17 years of age

The panel's definition of SIRS for children includes the presence of at least two of the following criteria (one of which must be abnormal temperature or leukocyte count) [51]:

- Core temperature greater than 38.5°C or less than 36°C (measured by rectal, bladder, oral, or central catheter probe). Hypothermia may indicate serious infection (especially in infants).
- Tachycardia greater than two standard deviations above normal for the child's age in the absence of external stimulus; or unexplained persistent elevation over a four-hour time period; or, for children younger than 1 year of age, bradycardia (as defined by the panel); or unexplained persistent depression over a 30-minute time period. Bradycardia is not a sign of SIRS in older children but may be a sign in the newborn.
- Mean respiratory rate greater than two standard deviations above normal for the child's age or mechanical ventilation
- Leukocyte count that is either elevated or depressed for the child's age; or greater than 10% immature neutrophils

Because many pediatric disease processes present with symptoms of tachycardia and tachypnea, a diagnosis of SIRS should not be based solely on elevated heart and respiratory rates; abnormalities in temperature or leukocyte count must be present. Biomechanical markers of inflammation (e.g., elevated sedimentation rate, C-reactive protein, interleukin-6) have not been proven specific enough to be included in the diagnostic criteria [51].

The following definitions have also been proposed for use in the pediatric population [51]:

- Sepsis: SIRS in the presence of or as a result of suspected or proven infection
- Severe sepsis: Sepsis plus cardiovascular organ dysfunction, ARDS, or two or more other organ dysfunctions (as defined by specific criteria)
- Septic shock: Sepsis plus cardiovascular organ dysfunction

The diagnosis of sepsis and impending septic shock in neonates and children should be suspected when the usual inflammatory triad of fever, tachycardia, and vasodilation is accompanied by changes in mentation. Altered mentation may manifest as inability to be aroused, inconsolable irritability, or lack of interaction with parents. Children may present with hyper- or hypothermia, signs of decreased perfusion, and/or decreased urinary output. Because children often maintain their blood pressure until they are severely ill, hypotension is not necessary for the diagnosis (as in adults), but if present, it helps confirm a suspected case of septic shock. It is also important to note that shock in children may occur long before hypotension occurs [51].

Neonatal ICU (NICU) nurses play a key role in the early recognition and prompt treatment of infection/sepsis in the newborn. A published critical care nursing guide for understanding issues of sepsis in the NICU emphasizes the following goals [74]:

- A high index of suspicion for risk of infection
- An ability to recognize signs of infection and sepsis in infants
- A low threshold for reporting related concerns to the physician or advanced practice nurse
- Being an advocate on behalf of the infant to ensure a timely assessment and prompt therapeutic intervention

The most widely utilized guidance for management of sepsis in the pediatric age group is the 2012 Surviving Sepsis Campaign guidelines [65; 75]. When the clinical diagnosis of sepsis is made in a child, best care practice calls for prompt collection of appropriate cultures, initiation of fluid resuscitation, and administration of empiric antimicrobial therapy within one hour. If hypotension supervenes, or persists, despite completion of the initial fluid resuscitation protocol, inotropic support should be started and the patient assessed and treated for adrenal insufficiency. About 25% of children with septic shock have adrenal insufficiency and will benefit from corticosteroid therapy [75].

EVIDENCE-BASED PRACTICE RECOMMENDATION

If a neonate with sepsis requires intravenous fluid resuscitation, the National Institute for Health and Care Excellence recommends the use of glucose-free crystalloids that contain sodium in the range 130–154 mmol/L, with a bolus of 10–20 mL/kg over less than 10 minutes.

(https://www.nice.org.uk/guidance/ng51. Last accessed July 13, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Clinically, pediatric septic shock takes two forms. In hyperdynamic shock, the child has rapid capillary refill and bounding pulses. In hypodynamic shock, there is prolonged capillary refill, mottled cool extremities, and diminished pulses. In both types, immediate resuscitation involves maintaining necessary circulation with fluid replacement, assuring proper ventilation, and maintaining threshold heart rates. Suggested therapeutic end points include a capillary refill of less than two seconds, warm extremities, urine output greater than 1 mL/kg/hr, normal blood pressure, normal mental status, and normal pulses with no differential between peripheral and central pulses. Frequent monitoring is required as rapid changes may occur in the status of a child with sepsis [52; 53].

The international consensus panel also developed criteria for MODS in the pediatric population based on scoring systems previously described in the literature. These systems include the Pediatric Logistic Organ Dysfunction score, Pediatric-MODS score, and Multiple Organ System Failure score. The panel also considered the criteria used in the open-label rhAPC study in their development of criteria for pediatric MODS [51].

The panel's goal was to identify criteria that would optimize the enrollment of children with severe sepsis in clinical studies. To that end, they specified the following [51]:

- Cardiovascular and respiratory organ dysfunction must be present (and mechanical ventilator support for respiratory failure, if used).
- Other organ dysfunctions should be monitored during clinical studies.
- The usefulness of organ dysfunction-free days as a primary end point should be confirmed.
- Documenting organ dysfunction should be achieved with a pediatric MODS scoring system.

Experts generally agree that additional evidence-based studies are needed to understand and accurately define pediatric sepsis by accounting for the physiologic variables, age-specific norms, and risk factors of this population [23; 43; 75].

CONCLUSION

Sepsis and septic shock present the clinician with a difficult management situation. Patients are usually unstable and may rapidly progress to ARDS, MODS, and death. There are several possible causes of sepsis, including traumatic injury, infections, and burns. Gram-negative and gram-positive organisms associated with nosocomial infections account for many cases. Other bacteria, viruses, fungi, and noninfectious etiologies account for the remaining [17; 19]. The mortality rate from sepsis is approximately 30%, and it was the tenth leading cause of death in the United States in 2005 [22; 61].

The pathophysiology of sepsis involves multiple organ systems and is often related to an abnormal proinflammatory and/or anti-inflammatory response to a bodily insult. Management includes proper antibiotic treatment plus maintenance of hydration, ventilation, and overall homeostasis.

Evidence-based practice guidelines are available to assist in the diagnosis and treatment of these disorders. This course outlines some of the current recommendations and suggestions provided by the SCCM and other experts experienced in treating patients with these disorders.

CASE STUDY

Patient A is a woman, 50 years of age, who was admitted to the emergency department after a motor vehicle accident. She incurred massive abdominal injuries and was transported to the emergency department unconscious and hypotensive upon arrival. She was receiving 35% O_2 via oxygen mask. Her respiratory rate was 28 breaths per minute, and lung sounds were clear bilaterally. She had a sinus tachycardia with a heart rate of 150 beats per minute. Her blood pressure was 80/45 mm Hg. The patient had a 40 pack-year history of cigarette smoking and had been taking medications to control hypertension.

She was transported via stretcher to radiology for a computed tomography scan, which revealed bleeding in the peritoneum. She was taken immediately to surgery. Following surgery, she was taken to the ICU. Three liters of Ringer's lactate had been infused in surgery. Estimated blood loss was 2500 cc, and she received 6 units of whole blood in surgery. Despite fluid resuscitation, the patient was hypotensive during much of the surgical procedure. To assess fluid management, a pulmonary artery catheter was placed while in surgery. A variety of data was obtained upon arrival to the surgical ICU.

Vital Signs	Hemodynamic Parameters	Arterial Blood Gases (ABGs)	Laboratory Values	Ventilator Settings
BP: 100/50 mm Hg Pulse: 120 beats per minute Respirations: 14 breaths per minute on ventilator Temperature: 96.5°F	CVP: 5 mm Hg PAP: 25/15 mm Hg PAWP: 13 mm Hg CO: 3.2 SVR: 1,100 SvO_2: 72%	pH: 7.45 $PaCO_2$: 36 PO_2: 80 HCO_3: 28 SaO_2: 95%	Sodium: 130 Potassium: 4.5 Chloride: 95 Glucose: 140 Hemoglobin: 11.5 Hemocrit: 35 WBC: 11,000	Rate: 14 on assist control FiO_2: 40% Tidal Volume: 800

BP: blood pressure; CI: cardiac index; CO: cardiac output; CVP: central venous pressure; HCO_3: bicarbonate; FiO_2: fraction of inspired oxygen; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PO_2: partial pressure of oxygen; SaO_2: oxygen saturation; SvO_2: venous oxygen saturation; SVR: systemic vascular resistance; WBC: white blood cells.

Patient A was hemodynamically stable following surgery. She awakened slowly and was able to be extubated and put on a 40% O_2 mask.

POST-OPERATIVE DAY 3

Three days after surgery, the patient's level of consciousness began to deteriorate. She was obtunded and only awoke when her name was called. Her skin was warm to touch and appeared flushed, and she had 4+ bounding pulses.

Vital Signs	Hemodynamic Parameters	ABGs on 40% O_2 Mask	Laboratory Values
BP: 110/72 mm Hg Pulse: 118 beats per minute Respirations: 28 breaths per minute Temperature: 104°F	CVP: 6 mm Hg PAP: 20/12 mm Hg PAWP: 10 mm Hg CO: 6.0 CI: 4.2 SVR: 850 SvO_2: 85%	pH: 7.48 $PaCO_2$: 30 PO_2: 85 SvO_2: 85%	Hemoglobin: 9.8 Hemocrit: 28.8 WBC: 25,000 Platelets: 168,000

Urine output was 15 cc per hour for the last three hours. Cultures of sputum, urine, and blood were obtained. Antibiotic therapy was initiated.

Analysis

1. Identify the term that best describes Patient A's condition at the present moment.

   Sepsis is caused by bacteria, viruses, or fungi in the blood. It is a clinical continuum ranging from bacteremia through septicemia to septic shock. Patient A is presently displaying signs of septicemia. Her blood pressure and cardiac output are within an acceptable range. Chemical mediators are being released and causing the physiologic changes.

POST-OPERATIVE DAY 5

On the 5th post-operative day, Patient A's blood pressure dropped to 84/58 mm Hg; her respirations were 32 breaths per minute, heart rate was 130 beats per minute, and temperature was 97°F. Despite 3000 cc fluid resuscitation, Patient A's condition continued to deteriorate. She was re-intubated and connected to a ventilator.

Hemodynamic Parameters
CVP: 3 mm Hg
PAP: 15/7 mm Hg
PAWP: 5 mm Hg
CO: 3.0
CI: 1.6
SVR: 1,597
SvO_2: 68%

Analysis

1. List the risk factors applicable to Patient A's case.

   Trauma

   Cigarette smoking

   Hypertension

   Abdominal injuries

   Multiple invasive lines

   Surgery

2. Patient A is in what stage of septic shock? Describe the symptoms to support your answer.

   Patient A is in the hypodynamic (cold) phase of septic shock. This phase is characterized by decreased cardiac output, increased SVR, hypotension, and inadequate tissue perfusion.

3. What are some of the causative organisms associated with sepsis in a post-operative, hospitalized patient?

   Escherichia coli

   Klebsiella

   Enterobacter

   Pseudomonas aeruginosa

   Staphylococcus aureus

POST-OPERATIVE DAY 8

On post-operative day 8, Patient A's skin was cool and cyanotic, and mottling was noted in the extremities. She responded only to painful stimuli.

Vital Signs	Hemodynamic Parameters	ABGs	Laboratory Values
BP: 38/40 mm Hg Pulse: 170 beats per minute Respirations: 14 breaths per minute on ventilator. She is not assisting. Temperature: 95.6°F	CVP: 6 mm Hg PAP: 38/20 mm Hg PAWP: 18 mm Hg CO: 2.0 SVR: 1746 SvO_2: 48%	pH: 7.28 $PaCO_2$: 48 PO_2: 40 SvO_2: 52% SaO_2: 80%	Sodium: 160 Potassium: 6.8 BUN: 48 Creatinine: 3.0 Platelets: 72,000 PT: 21 PTT: 100.5
BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time.			

Analysis

1. Patient A's temperature is 95.6°F. Is this to be expected in the hypodynamic phase and why?

   Yes. Hypothermia is common during the hypodynamic phase. Metabolic and myocardial activity are greatly reduced.

2. What is the physiologic cause of increased SVR in the hypodynamic phase?

   In the hypodynamic phase, SVR is caused by decreased cardiac output and elevated serum lactate levels.

3. What management would be appropriate in this phase?

   Afterload reduction and myocardial support are of great importance at this point. Before the use of vasodilators, cautious fluid administration with hemodynamic monitoring is essential to provide normovolemia as the vascular capacitance increases. If fluid resuscitation proves unsuccessful, the use of vasodilators in combination with a positive inotrope may be attempted.

POST-OPERATIVE DAY 10

Patient A died on the 10th post-operative day due to the complications of septic shock: renal failure and hepatic failure complicated by DIC and ARDS.

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Pneumonia

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Faculty

Carol Whelan, APRN, has been working in nursing education since 2000. She received her Master's degree in psychiatric/mental health nursing from St. Joseph College in West Hartford, Connecticut, and completed post-graduate nurse practitioner training at Yale University. Ms. Whelan is an Associate Clinical Professor and Lecturer at Yale University and works as an APRN at the Department of Veterans' Affairs in Connecticut, where she also serves as the Vice President of Medical Staff. She has authored many articles, textbook chapters, and books.

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Faculty Disclosure

Contributing faculty, Carol Whelan, APRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide primary care clinicians and other members of the healthcare team with the knowledge and skills necessary to appropriately diagnose, treat, and prevent pneumonia. It is designed to enhance clinical skills, improve outcomes, and foster an interprofessional collaborative practice consistent with published guidelines.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the epidemiology, scope, and classification of pneumonias.
2. Predict the likely etiology (pathogens) in a given case of pneumonia, based on epidemiologic features, clinical setting, and risk factor assessment
3. Assess the diagnostic probability of pneumonia in a given patient, using careful history and clinical examination findings.
4. Determine, by clinical criteria and severity of illness score, which patients with pneumonia require hospitalization or admission to an intensive care unit.
5. Develop a management plan for community-acquired pneumonia, including selection of initial antibiotic therapy appropriate to clinical context and site of care, in accordance with established guidelines.
6. Outline the diagnosis and management of community-acquired pneumonia in pediatric patients.
7. Devise a strategy for prevention of community-acquired pneumonia, including risk factor reduction and recommended immunization protocols.
8. Identify the epidemiology and risk factors of hospital-acquired, ventilator-associated, and nursing home-acquired pneumonia.
9. Anticipate the likely pathogens and antibiotic-sensitivity patterns associated with pneumonia that arises in healthcare facilities.
10. Initiate the management of patients with hospital-acquired or ventilator-associated pneumonia, including guideline-adherent selection of empiric antibiotic therapy.
11. Develop a strategy to reduce the risk of pneumonia for patients in healthcare facilities.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

HISTORICAL BACKGROUND

Hippocrates first described the clinical picture of pneumonia in 400 B.C.E., including the presence of fever, chest pain, productive cough, rales, and dyspnea [1]. However, the disease was recognized even before Hippocrates' time. The disease has resulted in a serious public health and mortality burden over the years, with Osler referring to pneumonia as the "captain of the men of death" in the early 1900s. During this same period, pneumonia surpassed tuberculosis as a leading cause of death.

However, dramatic changes in the past century, namely the introduction of effective antibiotics and vaccinations and improved medical and surgical techniques, have changed the clinical picture of pneumonia dramatically. These developments have resulted in vast improvements in morbidity and mortality from pneumonia in developed countries. Despite these advances, pneumonia remains a major health concern, and the emergence of multidrug-resistant organisms has led to renewed interest and research on this ancient disease.

DEFINITIONS

Pneumonia is defined as a lower respiratory tract, parenchymal infection of the lung. The usual clinical presentation is that of acute- or subacute-onset fever, productive cough, pleuritic chest pain, localized rales and signs of consolidation, and a new pulmonary opacification on chest radiograph. For clinical purposes, acute pneumonia that develops in the nonhospitalized patient is designated as either community-acquired (CAP) or healthcare-associated (HCAP) depending on whether there has been significant exposure to a healthcare environment (e.g., hospital, nursing home, dialysis clinic) within the previous 90 days. Pneumonias that develop as a complication of hospitalization are termed "nosocomial" and are further divided into hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). These are

DISCHARGES FROM HOSPITAL WITH A FIRST-LISTED DIAGNOSIS OF PNEUMONIA, BY AGE			
Age	**Rate (per 10,000)**		
	1990	**2000**	**2009–2010**
18 to 44 years	12.5	10.9	9.5
45 to 64 years	33.5	35.3	32.6
65 to 74 years	98.1	121.3	83.8
75 to 84 years	224.6	263.5	179.3
85 years and older	501.0	514.9	355.3

Source: [6] *Table 1*

important distinctions, as HCAP and nosocomial pneumonias carry a greater risk for less common, multidrug-resistant bacterial infection.

The term "pneumonia" is sometimes used in reference to other inflammatory conditions of the lung when a component of infection is known or suspected. An example is "aspiration pneumonia," whereby a focal chemical pneumonitis (lung injury) is followed rapidly by bacterial overgrowth and incipient infection (pneumonia).

EPIDEMIOLOGY AND SCOPE

Pneumonia is a substantial healthcare concern, ranking among the most common reasons for emergency department and outpatient visits, hospitalizations, and deaths among both adults and children [2; 3; 4; 5; 6]. The World Health Organization (WHO) estimates that 57 million people die from pneumonia every year [228]. Collected data consistently demonstrate a bimodal distribution of mortality, with peaks in children younger than 5 years of age and adults older than 75 years of age. Worldwide, pneumonia was responsible for an estimated 920,000 deaths in children younger than 5 years of age in 2015, mainly in developing countries [228]. In the United States, pneumonia is the leading cause of death from infectious disease and the eighth most common cause of death overall. There is seasonal variation in the incidence of pneumonia, with most cases occurring in the winter months.

U.S. hospital discharge statistics show that the rate of hospitalization for pneumonia varies with age, being highest among adults 75 to 84 years of age. In recent decades, the rate of hospitalization for pneumonia has been relatively stable for adults younger than 65 years of age and has declined somewhat for adults older than 65 years (***Table 1***) [6]. In 2010, there were 1.1 million U.S. hospital discharges for which the leading discharge diagnosis was pneumonia, and the average length of stay for these patients was 5.2 days [2].

The mortality rate for pneumonia and influenza combined has decreased substantially in the United States over the past 20 years, falling from 36.8 per 100,000 in 1990 to 16.1 per 100,000 in 2016 [6]. Two important public health factors, which may account for this trend, are the increased utilization of pneumococcal and influenza vaccines among adults and children and the decline in cigarette smoking [220; 221].

Despite advances made in prevention, treatment, and clinical outcomes, the impact on healthcare delivery systems and the aggregate cost of caring for patients with pneumonia are expected to increase in years to come. This is because of an aging U.S. population, the very group in whom the rate of pneumonia is highest. Using a decision analytic model that assumes no targeted intervention, a population medicine study group projected the incidence of pneumococcal pneumonia in the United States will increase by 38% between 2014

and 2040, with hospitalizations for pneumococcal pneumonia increasing by 96% (from 401,000 to 790,000) in that same period. As a result, healthcare costs associated with pneumonia are expected to increase by $2.5 billion and demand for healthcare services for pneumonia is expected to double [14].

GUIDELINE-DIRECTED MANAGEMENT AND PREVENTION OF PNEUMONIA

In the past two decades, clinical guidelines for the management of pneumonia have been developed by infectious disease and pulmonary medicine societies to improve outcomes and decrease the cost of care. Unfortunately, adherence to guideline-directed management protocols has been low, despite studies demonstrating that lack of adherence is associated with higher rates of adverse outcomes and inappropriate use of antimicrobials [15; 16; 17; 18; 20; 21]. Attention to guidelines varies across hospitals, clinical settings, and specialty practices. Adherence rates tend to be lower among non-pulmonologists and in relation to patient variables such as presence or absence of comorbidities and recent use of antibiotics [20; 22; 23]. Several barriers to guideline adherence have been identified, including lack of familiarity, concern over the practicality and perceived cost of recommended antibiotics, limited documentation of improved outcomes, and potential conflict with other guidelines [23]. The time spent on continuing education activities appears to have a direct correlation with a positive attitude toward, and propensity to follow, published clinical guidelines.

Success in reducing the incidence of pneumonia relies on effective strategies to prevent disease. The primary preventive strategy for CAP is immunization with influenza and pneumococcal vaccines, especially for high-risk groups (i.e., young children, older individuals, and people with compromised immune systems). Targeted immunization has been shown to decrease the rate of hospitalization for pneumonia and influenza and to decrease the risk of long-term morbidity and mortality [7; 9; 10; 218]. However, vaccine utilization rates are low, especially pneumococcal vaccination among high-risk groups and influenza vaccination among children [6; 11].

Prevention of HCAP focuses on care measures to preserve healthy pulmonary defense mechanisms and to reduce transmission of healthcare-associated, often multidrug-resistant, bacterial pathogens. The adherence to guidelines for the prevention of pneumonia that arises in the hospital setting has also been low, with approximately 39% to 66% of hospitals reporting full compliance and up to one-half of nurses reporting that they do not routinely adhere to recommended prevention practices [12; 13].

Decreasing the incidence of pneumonia and its associated morbidity and mortality requires a multifaceted approach and a strategy that includes a concerted effort to improve rates of pneumococcal and influenza vaccinations, especially among high-risk populations; better adherence to guideline-recommended treatment; systems-level approaches to improve the appropriate use of antibiotics; and performance improvement initiatives to reduce healthcare-associated infections. This course is designed to assist healthcare professionals provide better care to their patients by highlighting guideline-recommended diagnosis, treatment, and prevention of pneumonia.

TYPES OF PNEUMONIA	
Type	**Definition**
Community-acquired	New infection in a patient residing in the community, with no recent exposure to a healthcare setting or antibiotics
Hospital-acquired	New infection occurring more than 48 hours after hospital admission
Ventilator-associated	New infection occurring more than 48 to 72 hours after endotracheal intubation
Healthcare-associated	Infection developing within 90 days after hospitalization in an acute care facility for 2 days or more Infection in a resident of a nursing home or long-term care facility Infection after receiving care in an outpatient setting (e.g., hemodialysis or intravenous therapy clinic) Infection occurring with 30 days after home care (e.g., intravenous antibiotic therapy, chemotherapy, or wound care)
Source: [28]	*Table 2*

PATHOGENESIS AND CLASSIFICATION OF PNEUMONIA

Pneumonia is an acute inflammatory condition within the parenchyma of the lung caused by infection that reaches the lower respiratory tract. In most cases, pneumonia develops as a consequence of bacterial colonization/infection of the upper respiratory tract, followed by microaspiration of infected secretions at a time of impaired host pulmonary defense mechanisms [217]. The prime host defenses against foreign particulate matter that reaches the lower respiratory tract are the cough reflex, tracheobronchial (mucociliary) clearance, and alveolar macrophage phagocytosis. Activation of the humeral (antibody) immune response provides augmentation of phagocytosis and the acute cellular response. One or more of these defense mechanisms may be impaired by a variety of factors, including underlying cardiopulmonary and neurologic disease, sedative medication, bronchial obstruction, concurrent active viral and mycoplasma bronchitis, and toxic/metabolic conditions such as alcohol excess, acidosis, and hypoxia. Individuals with an impaired immune system, such as occurs from immunosuppressive drugs, human immunodeficiency virus (HIV), chronic disease, or old age, are more susceptible to infection [4].

Clinically, pneumonia is often described in reference to suspected or established causative pathogens (i.e., viral, bacterial, fungal, or parasitic); however, the specific etiology cannot be identified in more than half of cases in which testing is done [9; 24; 25]. Classifying pneumonia according to the setting in which it develops is more useful for clinical purposes because the most common pathogens, as well as the outcomes, are similar within distinct clinical settings [26; 27]. Pneumonia was once broadly classified as either community-acquired (developing outside of a hospital or other healthcare facility) or nosocomial (developing 48 hours or more after hospital admission, usually postoperatively). In its 2005 guideline, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) noted three distinct categories within the broader classification of pneumonia associated with healthcare facilities: HAP, VAP, and HCAP (***Table 2***) [3; 28]. These three categories of pneumonia are similar in that they often result from colonization, then infection, by resistant gram-negative bacilli and methicillin-resistant *Staphylococcus aureus* (MRSA), necessitating broader empiric antibiotic therapy than that commonly used for CAP [27].

As noted, the cause of pneumonia varies according to setting and patient age. Viruses are the most common cause in young children, whereas bacteria are the more frequent cause among older children and adults [29; 30; 31]. Studies have shown that respiratory viral pathogens play a greater role in the pathogenesis of pneumonia than once thought; many cases of pneumonia, both pediatric and adult, involve a combination of bacterial and viral pathogens or two or more viral pathogens [9; 24; 30; 32]. The increase in the number of viral infections is thought to be related, in part, to better diagnostic testing methods, most notably, polymerase chain reaction (PCR)-based techniques [24; 33; 34].

Pyogenic bacterial infection is the cause of nearly all cases of HAP and VAP, and the distribution of pathogens varies among institutions [26; 28; 29]. Mixed infection appears to be common, as more than one pathogen is frequently isolated from sputum cultures in these cases [28]. Bacteria isolated from cases of early-onset HAP (within four days after admission) are usually sensitive to available drugs [28]. In contrast, late-onset HAP (i.e., more than five days after admission) is likely to be caused by multidrug-resistant pathogens, such as *Pseudomonas* spp., MRSA, and *Acinetobacter* spp. [26; 35]. Viral and fungal pathogens rarely cause HAP or VAP [28].

COMMUNITY-ACQUIRED PNEUMONIA

EPIDEMIOLOGY

Determining accurate incidence rates for CAP is challenging for a variety of reasons, including the facts that "pneumonia" is not a reportable disease, case definition varies across studies, and national databases often link pneumonia with influenza. The epidemiology relies primarily on estimates derived from community-based cohort studies and surveillance networks. Approximately 5 to 6 million cases of pneumonia are diagnosed annually, with about 1 million occurring in older adults [36]. Approximately 4.2 million adult outpatient visits are related to CAP every year, and the mortality rate is less than 1% for adults treated on an outpatient basis [37].

The burden of disease is considerably greater for patients hospitalized with pneumonia. A prospective cohort study of adult residents living in Louisville, Kentucky (population 587,000 adults), recorded 7,449 unique patients hospitalized with CAP between June 2014 and June 2016 [232]. The annual age-adjusted incidence was 649 patients hospitalized with CAP per 100,000 adults, which extrapolates to nearly 1.6 million annual adult CAP hospitalizations in the United States. The observed mortality during hospitalization was 6.5%. An earlier report placed the average overall mortality rate for hospitalized adults at 12%, but the rate is higher—about 30% to 40%—for adults who require admission to an intensive care unit (ICU) [37]. The estimated direct and indirect financial costs are $3.7 billion and $1.8 billion, respectively [38].

The burden of pneumonia is greatest among the elderly (65 years of age and older). In one study of 46,237 people 65 years of age and older, the overall rate of CAP was 18.2 cases per 1,000 person-years for people 65 to 69 years of age, increasing to 52.3 cases per 1,000 person-years for those 85 years of age or older [39].

The mortality rate for adults with pneumonia has decreased substantially over the past two decades. In a review of more than 2.6 million Medicare claims for pneumonia between 1987 and 2005, the age- and sex-adjusted mortality rate dropped from 13.5% to 9.7% [40].

The rate of pediatric outpatient visits for CAP has been reported to be 35 to 52 per 1,000 children 3 to 6 years of age and 74 to 92 per 1,000 children 2 years of age and younger [10]. The hospitalization rate for children up to 18 years of age is 201.1 per 100,000; the highest rate is for infants younger than 1 year of age (912.9 per 100,000) and lowest for teenagers (62.8 per 100,000) [4]. According to data from the Centers for Disease Control and

Prevention (CDC), 525 infants and children (up to 15 years of age) in the United States died as a result of pneumonia (or another lower respiratory tract infection) in 2006 [30].

RISK FACTORS

The primary risk factors for CAP are age, smoking history, and chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD]) and other comorbidities. Occupational dust exposure and history of childhood pneumonia have also been associated with an increased risk, as has male gender, unemployment, and single marital status [39; 41]. As noted earlier, the risk for pneumonia is higher for individuals 65 years or older compared with younger adults, with the risk further increasing for those 85 years and older [39]. Alcoholism and chronic diseases, such as respiratory disease, cardiovascular disease, or kidney disease, also increase the risk for pneumonia, especially in the older population [3; 42; 43]. In the pediatric population, very young children are at increased risk because their immune systems have not fully developed. Conditions of frailty, dementia, alcohol use, and sedative medication all lead to diminished or ineffectual cough and the propensity for aspiration, thereby increasing the risk for pneumonia. Diseases or medications that suppress the immune system increase the risk among all ages [39; 42].

The airways of normal lungs are sterile, and pulmonary defense mechanisms (e.g., mucociliary clearance, alveolar macrophage phagocytosis) work in concert to maintain this sterility. Smoking cigarettes eventually leads to bronchial inflammation and disrupts host defense mechanisms to such an extent that "colonization" of the airways by microbial pathogens is established early in the course of many persons with COPD [44]. The pathogens most commonly implicated are adenovirus, *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. Bacterial colonization in this setting represents low-grade chronic infection, which, in combination with clinical exacerbations, augments airway inflammation, and contributes to pathogenesis and disease progression.

Proton pump inhibitors (PPIs) may increase the risk of pneumonia, but the data are somewhat unclear. One study found that only treatment with PPIs within the past 30 days (and not long-term use) was associated with increased risk, but a later meta-analysis showed that the risk was increased among people taking PPIs or histamine2 receptor antagonists [44; 45].

Among the nursing home population, older age and male gender are risk factors for pneumonia. Other risk factors for this population include swallowing difficulty, inability to take oral medications, profound disability, bedridden state, and urinary incontinence [42].

ETIOLOGY

Given the right conditions, a great many microorganisms are capable of infecting the lung. In general, however, a relatively small collection of viruses and bacteria account for most cases of CAP in adults and children. For a given case, the clinical setting and the patient's age, comorbidity, and risk factors are useful predictors of causation. Viral pneumonia (e.g., influenza) is most commonly linked to community outbreaks.

The most common cause of CAP is *S. pneumoniae*, accounting for approximately one-third of all cases and 40% to 50% of all culture-confirmed bacterial pneumonia cases that require hospitalization [9; 29; 30; 46]. The most common causative pathogen varies in relation to the patient's age, illness severity, and clinical context (***Table 3***) [29; 30; 47].

Clues to the etiology of the pneumonia can often be found in the patient's past medical or social history (***Table 4***). Persons with chronic bronchitis/COPD frequently have tracheobronchial colonization with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*, and when pneumonia supervenes, it is usually with one of these pathogens. Heavy alcohol use carries the risk for anaerobic pleuropulmonary infection (e.g., lung abscess, empyema) and pneumococcal or gram-negative bacillary (e.g., *Klebsiella pneumoniae*, *Proteus* spp.) pneumonia.

MOST LIKELY ETIOLOGIES OF COMMUNITY-ACQUIRED PNEUMONIA ACCORDING TO PATIENT AGE AND SETTING	
Age and/or Setting	**Most Likely Pathogens**
Adults	
Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Haemophilus influenzae* Respiratory viruses *Legionella* spp.
Inpatient, not intensive care unit	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* spp. Respiratory viruses
Intensive care unit	*S. pneumoniae* *Staphylococcus aureus* *Legionella* spp. Gram-negative bacilli *H. influenzae*
Children	
Birth to 3 weeks	Group B streptococci *Listeria monocytogenes* Gram-negative bacilli Cytomegalovirus
3 weeks to 3 months	*S. pneumoniae* Respiratory viruses *Bordetella pertussis* *S. aureus* *Chlamydia trachomatis* (transnatal exposure)
4 months to 4 years	*S. pneumoniae* Respiratory viruses *M. pneumoniae* (in older children) Group A streptococci
5 to 15 years	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae*
Source: [29; 47]	*Table 3*

Other epidemiologic clues to the etiology of pneumonias include seasonal and geographic considerations. Influenza outbreaks are associated with a seasonal increase in secondary *S. pneumoniae*, *S. aureus*, and *H. influenzae* pneumonias. Legionellosis is acquired through inhalation of an aerosol arising from contaminated water; cases present sporadically or as cluster outbreaks related to a point source exposure such as a reservoir, water tower, or air conditioning system [229].

COMORBIDITY AND EXPOSURE IN RELATION TO AT-RISK PATHOGENS	
Patient Characteristic	**Suspect Pathogen(s)**
Alcoholism	Oral anaerobes *Streptococcus pneumoniae* Gram-negative bacilli
COPD, tobacco use	*Haemophilus influenzae* *S. pneumoniae* *Moraxella catarrhalis*
Nursing home resident	*S. pneumoniae* Gram-negative bacilli *H. influenzae* *Staphylococcus aureus*
Poor dental hygiene	Oral anaerobes
Recent exposure to contaminated plumbing or water	*Legionella* organisms
Exposure to exotic birds and/or decaying bird nesting sites	*Chlamydia psittaci* *Histoplasma capsulatum* (histoplasmosis)
HIV infection	*Pneumocystis carinii* *S. pneumoniae* *H. influenzae* *Mycobacterium tuberculosis*
Exposure to excreta of wild rodents	Sin nombre virus (hantavirus pulmonary syndrome)
COPD = chronic obstructive pulmonary disease.	
Source: Adapted with permission from File TM, Tan JS, Plouffe JF. Community-acquired pneumonia: what's needed for accurate diagnosis. Postgrad Med. 1996;99(1):102. ©1996 McGraw-Hill. *Table 4*	

Bacterial Pathogens

Bacterial causes of CAP predominate, accounting for at least half of all adult cases, including older individuals [9; 42]. *S. pneumoniae* is the leading cause of CAP in any adult age-group, with or without comorbid conditions [6; 7; 10]. It is estimated that pneumococcal infection accounts for 20% to 60% of all hospitalized patients with pneumonia [6]. Common bacterial pathogens other than *S. pneumoniae* include *H. influenzae* type b, *S. aureus*, and gram-negative bacilli [25; 26; 29; 48]. *H. influenzae* type b is a small, pleomorphic gram-negative rod known for causing pneumonia in older adults and patients with underlying lung disease.

Atypical pneumonia (and the pathogens associated with this syndrome) is so labeled because the onset of illness tends to be subacute and the clinical exam and radiographic features lack the classical findings seen with typical cases of pneumonia. The most common atypical pathogens are *Mycoplasma pneumoniae* and *C. pneumoniae*, followed by *Legionella* spp. [9]. *M. pneumoniae* is a tiny bacterium that lacks a rigid cell wall. It is spread by droplet nuclei, and transmission within a community proceeds slowly over many weeks. *Mycoplasma* infection is a disease of adolescence and young adulthood, and it is the most common cause of atypical pneumonia in those younger than 40 years of age [66]. Small cluster outbreaks of pneumonia have been observed in large families, schools, nursing homes, and other closed population. There are about 60 different species of *Legionella*, but most disease is caused by *Legionella pneumophila*, a gram-negative rod usually transmitted via inhalation of aerosolized water contaminated with the bacteria [229].

The distribution of etiologic agents accounting for pneumonia varies in relation to illness severity and management setting. In cases of relatively mild illness that permit treatment as an outpatient, blood cultures are rarely positive and the diagnosis is usually made by sputum culture and/or serial serology. In a Canadian study of CAP in the ambulatory setting, designed to determine the frequency of usual and atypical bacterial pathogens, an etiologic diagnosis was established in 48% of patients examined [222]. Of the 419 patients who had blood cultures, 7 (1.4%) were positive, all for *S. pneumoniae*. The atypical pathogen group (*M. pneumoniae* or *C. pneumoniae*) accounted for 29% of cases, *S. pneumoniae* for 6%, and *Haemophilus* spp. for 5%. The etiologic role of viruses was not studied [222].

A similar distribution and frequency was observed in a well-studied series from Spain, comparing pneumonia microbial etiology in three clinical management settings: outpatient, inpatient on the general care ward, and inpatient admissions to the ICU [29]. Among outpatients with CAP, the most frequently identified etiology was the atypical pathogen group (36%), followed by *S. pneumoniae* (35%), viruses (9%), and mixed etiologies (9%). As the severity of illness increased, marked by admission to the hospital general ward and ICU, the likelihood of mycoplasma or chlamydia etiology decreased substantially (14%) and the frequency of *S. pneumoniae* (43%), mixed bacterial pathogens (22%), *S. aureus*, *Pseudomonas*, and other gram-negative bacteria infection increased.

In general, *S. aureus* is an uncommon cause of CAP but should be suspected during influenza outbreaks and in any patient with sepsis syndrome and multifocal pulmonary infiltrates. The role of *S. aureus*, and MRSA specifically, was examined in an observational study of 627 CAP cases admitted to 12 university-affiliated hospitals during the winter months (influenza season) of 2006–2007 [49]. Of the 595 patients from whom blood and sputum cultures were collected, a bacterial pathogen was identified in 107 (17%). The most common pathogen identified was *S. pneumoniae* (57 cases), followed by *S. aureus* (23 cases, 14 of which were MRSA). Thus, *S. aureus* accounted for 5% of the total and 22% of the cases in which the etiology was identified. Of the 23 patients with staphylococcal pneumonia, blood cultures were positive in 39% and sputum culture in 89%. Clinical features observed to be highly associated with *S. aureus* infection were multiple pulmonary infiltrates, altered mental status, illness severity requiring ICU admission, and intubation [49].

Viral Pathogens

Studies have indicated that 5% to 20% of adult CAP may be caused by a viral pathogen [50]. However, as noted earlier, the role of respiratory tract viral infection in pneumonia is complex and perhaps underestimated. Studies utilizing newer diagnostic methods such as PCR have demonstrated rates of viral infection as high as 39% in patients presenting with pneumonia [9; 34]. Because these studies rely on specimens and washings taken from the nasopharynx, rather than directly from the lung, it is not clear to what extent viral isolates in this setting represent primary pneumonia pathogens or concomitant viral upper respiratory infection that may impair pulmonary defense mechanisms and thus predispose to bacterial pneumonia.

Clinical and pathologic studies of pneumonia during influenza seasons have demonstrated clearly that influenza virus (types A and B) is an important cause of primary viral CAP [25; 47]. Other common respiratory viruses associated with pneumonia in adults are respiratory syncytial virus (RSV), rhinovirus, adenovirus, and parainfluenza virus [31; 34; 47]. RSV and rhinovirus are especially common among older adults and nursing home residents [31]. Clinical studies that utilize viral culture for case definition have demonstrated that RSV can be recovered from 3% to 10% of older adults with pneumonia [30]. The paramyxovirus hMPV, first isolated in 2001 from children hospitalized with acute respiratory infection, has now been reported in all age groups and with varying stages of disease, from asymptomatic carrier states to severe bronchitis and pneumonia [30].

Mixed Pathogens

Mixed viral-bacterial infection has been observed in 30% of adult cases of CAP in some studies [9; 31; 34]. Most commonly, *S. pneumoniae* is identified in combination with rhinovirus, influenza A, or RSV [34]. On rare occasions fungal and parasitic pathogens are isolated in association with CAP syndrome.

DIAGNOSIS IN ADULT PATIENTS

Clinical Features

The diagnosis of CAP in adults is challenging because its presentation is similar to other acute respiratory illnesses such as pulmonary embolism/infarction and congestive heart failure [3; 51; 52]. Diagnosis relies primarily on clinical features combined with radiographic findings; however, both the clinical presentation and chest x-ray abnormalities are variable and in part nonspecific, particularly in the elderly [3; 29]. Common presenting symptoms and signs are:

- Productive cough, purulent sputum
- Fever with rigors (shaking chills)
- Dyspnea
- Pleuritic chest pain
- Tachypnea
- Tachycardia
- Hypoxemia
- Signs of consolidation (e.g., crackles, bronchial breath sounds, egophony)
- Signs of pleural effusion (e.g., absent fremitus, dullness to percussion, decreased breath sounds)

Pneumonia in the elderly may present without a history of chills or fever, little cough, and a paucity of findings on exam and chest x-ray. Often in such cases, some combination of tachypnea, tachycardia, and altered mental status is the only sign [31; 42].

Physical examination should focus on the chest, with auscultation to detect localized crackles (rales), bronchial breath sounds, and other signs of consolidation or pleural effusion [47]. Pulse oximetry should also be done. The most clinically significant individual findings are (in descending order) egophony, bronchial breath sounds, and dullness on percussion [53].

Chest Radiography

When pneumonia is suspected on the basis of these clinical features, chest radiography is the standard for confirming the diagnosis, and posteroanterior and lateral radiographs are recommended [3; 29]. The IDSA/ATS guideline notes that evidence of an infiltrate on chest radiograph or other imaging study is required for a diagnosis of pneumonia [47]. In addition to establishing the diagnosis, the chest radiograph can help differentiate pneumonia from other conditions with similar signs and symptoms. Some degree of infiltrate is almost always demonstrated on chest radiographs of patients who have been ill longer than 24 to 48 hours, although the appearance may be subtle or absent on initial presentation [29; 47]. Pneumonia is described according to its anatomic distribution on chest radiographs as either lobar, multifocal/lobar, bronchopneumonic, or interstitial.

The American College of Radiology asserts chest x-ray is the imaging modality of choice for complicated pneumonia.

(https://acsearch.acr.org/docs/69446/Narrative. Last accessed August 22, 2018.)

Strength of Recommendation: 9

The characteristic symptoms and signs, combined with radiographic findings of an infiltrate, establish the clinical diagnosis of pneumonia. One validated prediction tool commonly used assigns 1 point for each of five clinical features present in conjunction with an infiltrate on chest radiography [54]:

- Temperature >37.8°C (100.04°F)
- Heart rate >100 beats per minute
- Crackles on auscultation
- Decreased breath sounds
- Absence of asthma

A score of 4 or 5 indicates a 25% to 50% probability of pneumonia; a score of 2 or 3 indicates a probability of 3% to 10%; and a score of 0 or 1 represents a probability of 1% or less [29; 54]. Neither clinical nor radiographic features can reliably differentiate primary viral from bacterial or combined viral-bacterial pneumonia [9; 31; 32]. There are some features that, if present, aid in making the distinction. The presence of a viral epidemic in the community, such as influenza or RSV, increases the likelihood of a viral etiology [32]. The patient's age can also help identify the most probable cause; as noted previously, viral infections have been found more often in young children and adults older than 60 years of age compared with younger adults [9; 24]. Chest pain is significantly more frequent in adults with bacterial pneumonia than in those with viral pneumonia [9]. Radiographic findings are generally not useful in identifying a specific pathogen, although multilobar infiltrates suggest infection with *S. pneumoniae*, *S. aureus*, or *L. pneumophila*, and patchy, interstitial infiltrates suggest a viral or mycoplasmal etiology [47; 49].

Atypical Pneumonia

The first use of the term atypical pneumonia was in 1938 to describe a series of seven patients who had developed an unusual form of tracheobronchitis [65]. There had also been descriptions of outbreaks of pneumonia that behaved atypically in Europe in the 1920s. In general, these outbreaks were milder and had higher recovery rates than expected for the typical case of pneumonia.

At the present time, atypical pneumonia is encountered, and managed, primarily in the outpatient setting. The causative pathogen most commonly identified in such cases is *M. pneumoniae*. According to CDC estimates, *Mycoplasma* infections occur at the rate of 2 million cases each year and are responsible for between 1 and 10 of every 50 cases of CAP [66].

Atypical pneumonia syndrome, best represented by mycoplasma infection, presents with a subacute prodrome of malaise, low-grade fever, headache, myalgia, and non-productive cough. Symptoms progress slowly over days to weeks; often patients are thought to have an upper respiratory infection or bronchitis and appear less ill than those with typical bacterial pneumonia [65; 66]. The physical examination usually reveals fine rales but no signs of lung consolidation. In the early stage, there may be a maculopapular skin eruptions and, on examination of the ear canal, bullous myringitis of the tympanic membrane. Chest x-ray reveals patchy alveolar densities or inhomogeneous segmental infiltrates, often bilateral involving the middle lobe and lingual. The white blood cell count may be normal or only slightly elevated. Full recovery is expected with no residual effects in a previously healthy individual. However, the disease can be severe in those with sickle cell anemia, older adults, and those with immunosuppression [65].

In younger patients, *C. pneumoniae* (TWAR strain) infection may present as atypical pneumonia. Outbreaks tend to occur in communal settings such as military units and college dormitories [231]. The illness is similar to that seen with mycoplasma infection, except that laryngitis is a prominent feature and nonexudative pharyngitis is common [26]. Chest x-ray may show patchy consolidation, interstitial infiltrates, or funnel-shaped lesions. The white blood cell count is usually normal.

Legionellosis

The first recorded outbreak of legionellosis occurred in 1976 at an annual convention of the American Legion in Philadelphia. A total of 182 of the delegates (many of whom were elderly) became ill, and 146 were hospitalized. The mortality rate was 16%. Because the conference ended prior to the development of significant symptoms in many patients, hospitals all over the United States admitted one or more of the patients who had attended the convention. Despite an outpouring of resources, it took six months to isolate the organism, later named *L. pneumophila*. The pneumonia caused by the organism is commonly known as Legionnaires' disease [65].

L. pneumophila is a small gram-negative bacillus, atypical in its clinical presentation and for its lack of susceptibility to ß-lactam antibiotics. There are about 60 identified species of *Legionella*, although *L. pneumophila* is the primary pulmonary pathogen [230]. *Legionella* accounts for an estimated 8,000 to 18,000 cases of pneumonia requiring hospitalization in the United States each year [229; 230]. Suspicion for infection with *Legionella* organisms should be high in older adults, in those with chronic underlying disease, and in all patients with pneumonia severe enough to require hospitalization.

Legionella bacteria are found in common sources of freshwater but not usually in sufficient numbers to cause disease. However, in commercial water systems such as those found in large buildings, storage tanks, cooling towers, decorative fountains, or hot tubs, *Legionella* growth exceeds the threshold required for transmission to susceptible hosts via aerosolization [229]. Because hotels, resorts, and cruise ships often use large, complex water systems and other aerosol-generating devices, travel is a risk factor for disease. This is also true for hospitals and long-term care facilities.

The onset of infection is marked by dry cough, fever of 38.3°C–38.8°C (101°F–102°F), then progressive symptoms and signs of pneumonia accompanied by multi-organ involvement—vomiting, diarrhea, headache, and altered mental status. Chest x-ray reveals rapidly progressive, asymmetric infiltrates without signs of consolidation. Prompt diagnosis relies on clinical suspicion, urine antigen assay, and specialized culture techniques.

Laboratory Diagnosis

The challenge of diagnosis is complicated by the lack of cost-effective, reliable, and rapidly available tests to discriminate between viral and bacterial pneumonia [37]. The IDSA/ATS guideline notes that routine cultures of sputum and blood are not recommended for patients treated in the ambulatory setting, as results rarely impact management decisions [47]. The primary reason for cultures and serologic testing is to identify specific pathogens suspected on the basis of clinical and epidemiologic findings or cases in which the results of testing will substantially alter the empirical treatment of the patient [47]. Testing may be useful when evaluating a critically ill patient, a patient in whom a drug-resistant or unusual organism is suspected (e.g., *Legionella*), or a patient whose condition is deteriorating or who is not responding within 72 hours after treatment.

Blood Culture

Blood cultures are optional and not recommended as a routine diagnostic test for CAP managed in the ambulatory setting. The principle reason is that the yield is low, and studies show that a positive culture leading to a change in antimicrobial therapy occurs in about 3% or fewer cases [55; 56; 222]. The IDSA/ATS guideline recommends blood cultures before treatment only for patients hospitalized with one of the following conditions [47]:

- Cavitary infiltrates
- Leukopenia
- Active alcohol abuse

- Chronic severe liver disease
- Asplenia
- Positive test result for pneumococcal urinary antigen
- Pleural effusion
- Illness severity requiring admission to the ICU

Blood cultures are indicated for patients who have severe CAP, as they are more likely to have infection with a pathogen other than *S. pneumoniae* [47].

The ATS and the American College of Emergency Physicians (ACEP) also note that blood cultures need not be obtained routinely in all patients admitted with CAP [57]. Similarly to IDSA/ATS, ACEP adds that blood cultures should be considered for patients at higher risk, such as persons who have compromised immune systems, significant comorbidities, severe disease, or another risk factor for infection with resistant organisms [57].

Sputum Culture and Gram Stain

Sputum stain and culture are also considered optional, but are recommended when specific conditions are present [47]:

- Cavitary infiltrates
- Active alcohol abuse
- Severe obstructive/structural lung disease
- Positive result for urinary *Legionella* antigen test
- Positive result for urinary pneumococcal antigen test
- Pleural effusion

Sputum culture and Gram stain should also be performed for all hospitalized patients who are moderately ill or who warrant admission to an ICU [47]. The IDSA/ATS note that examination and culture of respiratory secretions should be performed only on specimens that meet quality performance measures for collection, transport, and processing of samples.

The diagnostic utility of sputum Gram stain and culture has been demonstrated in patients hospitalized with proven (bacteremic) pneumococcal pneumonia. In a series of 58 patients, from whom good quality sputum specimens (>10 inflammatory cells per epithelial cell) were submitted before or within six hours after initiation of antibiotic therapy, pneumococci were identified by Gram stain in 63% and by culture in 89% of cases [224].

Newer Diagnostic Techniques

Assays for the detection of antigen and other components of bacterial and viral pathogens have become a useful adjunct for establishing the etiology of pneumonia. Among these is the detection of bacterial antigen in the urine of patients with CAP. In a clinical series report, an assay for *S. pneumoniae* cell wall polysaccharide in urine was positive in 64% of patients with pneumococcal pneumonia; the sensitivity increased to 88% in patients who were bacteremic [225].

In a meta-analysis of published studies, the assay for detection of *Legionella* antigen in the urine of patients with pneumonia has been shown to have excellent specificity (99%) but only modest sensitivity (74%) [226]. Thus, a urine *Legionella* antigen assay is very useful to "rule in" the diagnosis but does not rule it out—a negative result should be interpreted with caution. Urine samples for *Legionella* antigen assay should be submitted in all cases of CAP with severe illness, suspicion of *Legionella* infection, or with risk factors such as COPD, HIV, immunosuppressive therapy, or organ transplantation. Isolation of *Legionella* from sputum can be accomplished on selective media. Serologic diagnosis requires acute and convalescent serum; it is useful to confirm a case, but of little value in early diagnosis.

Testing for Viruses

Viral culture remains the criterion standard for diagnosis of viral pneumonia, but because of limitations such as the need for prompt transportation, time needed for viral detection, and the lack of sensitivity for all viruses, rapid antigen testing is often done. In adults, rapid testing has a sensitivity of 50% to 60% and a specificity of at least 90% [31]. Testing of nasal swab specimens is slightly less sensitive than testing of wash specimens, but wash specimens can be difficult to obtain in frail or cognitively impaired adults. Rapid RSV tests are usually not useful for adults, as the level of virus titers shed is low [31].

Molecular diagnostic testing of sputum holds promise for providing a rapid and accurate etiologic diagnosis. Studies show that real-time PCR is significantly more sensitive and specific for the detection of the common respiratory viruses that cause CAP, as well as *M. pneumoniae* and *C. pneumoniae* [24; 33]. However, molecular assays are expensive and not currently widely available [31].

Biomarkers

Over the past several years, researchers have been evaluating biomarkers for their utility in diagnosis and for determining duration of empirical therapy for presumed bacterial pneumonia. Procalcitonin has been shown to be superior to other commonly used markers for its specificity for bacterial infection and its ability to distinguish CAP from asthma and COPD [58; 59]. This marker has predictive value; however, no biomarker should be used on its own and, if used, should be considered within the context of clinical and laboratory findings [59].

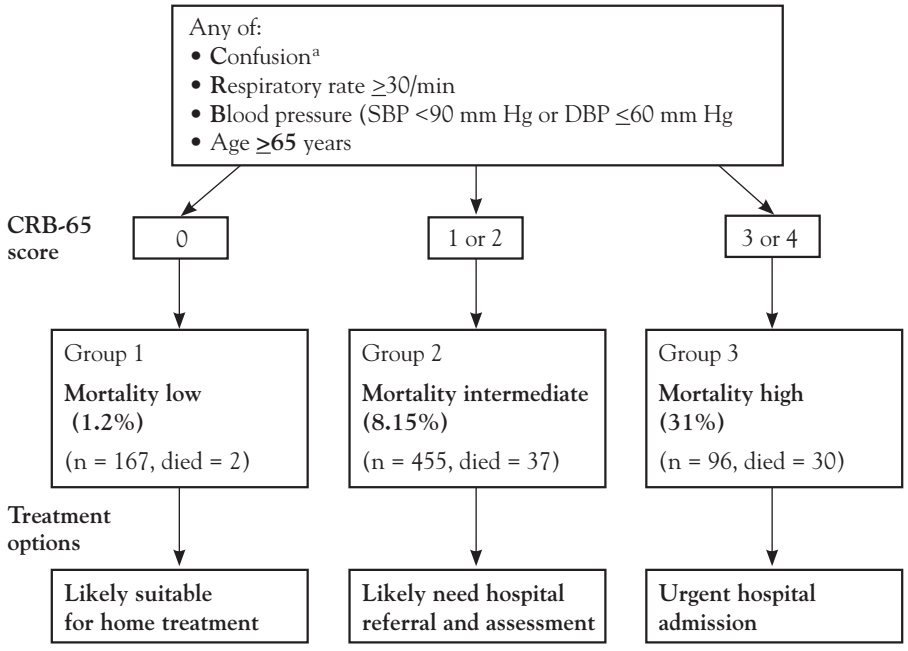
MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

Guidelines for the management of pneumonia in adults were first developed independently by the ATS and the IDSA, with each publishing guidelines in the 1990s and early 2000s [36; 63; 64]. The recommendations in each guideline differed somewhat, but the principles were the same [36]. To eliminate the confusion associated with separate guidelines, the IDSA and ATS jointly developed the current guideline for CAP, published in 2007 (update in progress as of 2018) [47]. The IDSA/ATS guideline focuses on decision making about site of care; the empirical selection of antibiotics; and issues in the delivery of antibiotics, such as the timing of the first dose of antibiotics, the timing of switch therapy (from parenteral to oral antibiotics), and the duration of therapy [47]. The treatment of symptoms associated with CAP is not addressed in the guideline. A systematic review published in 2012 found insufficient evidence to determine if there is benefit to over-the-counter medications (e.g., mucolytics, cough suppressants) for cough associated with acute pneumonia [67].

Site of Care

One of the most important decisions in the management of CAP is determining the site of care—that is, outpatient or inpatient and, if the latter, a general care floor or an ICU [68]. Many physicians admit patients to the hospital when they could be managed effectively on an outpatient basis [47]. This decision requires a careful evaluation of the severity of illness in the context of the personal and social well-being of the patient. Objective severity-of-illness scores and prognostic models can aid in identifying patients who may require hospitalization or admission to an ICU. The most widely used scales are the CRB-65 (confusion, respiratory rate, blood pressure, age 65 years or older) (***Figure 1***), the CURB-65 severity score (which adds urea level to the CRB-65 criteria), and the Pneumonia Severity Index (PSI) (***Table 5***). These assessment tools are recommended by the IDSA/ATS as an aid to clinical judgment in determining the site of care [47; 69; 70]. The scales have been compared, and they do not differ significantly in overall performance [71]. However, each scale has advantages and disadvantages, and none factor in all clinical considerations (such as comorbidities or social factors) [68]. CURB-65 and CRB-65 are easier to score as they have fewer variables and are more likely

CLINICAL SEVERITY ASSESSMENT IN THE COMMUNITY SETTING: THE CRB-65 SCORE



[a]Defined as a Mental Test Score of 8 or less or new disorientation in person, place, or time.

Source: Reprinted with Permission from Lim W, van der Eerden MM, Laing R, et al. Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-382. *Figure 1*

to correctly classify high-risk patients (i.e., high positive-predictive value) [72]. In contrast, the PSI is more sensitive and is better at determining which patients do not require hospitalization (i.e., low false-negative rate). About 30% to 60% of patients at low risk are unnecessarily admitted to the hospital according to the PSI score [68].

The PSI, CURB-65, and CRB-65 were developed to predict the risk of death. Because this risk does not always equate to the need for hospitalization and/or ICU admission, other scales have been developed. For example, SMART-COP provides a score based on a composite of systolic blood pressure, multilobar involvement on chest radiograph, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH [73]. SMART-COP was found to accurately predict the need for intensive respiratory or vasopressor support. Another tool, the Severe Community-Acquired Pneumonia (SCAP) score, includes points assigned to eight variables: arterial pH, systolic pressure, confusion, blood urea nitrogen level, respiratory rate, chest radiograph findings, pulmonary arterial oxygen tension (PaO_2), and age (older than 80 years) [74]. SCAP has identified a larger proportion of patients as low risk compared with the PSI, CURB-65, and CRB-65, and is better than or as accurate as those scores at predicting adverse outcomes in hospitalized patients [74; 75]. The IDSA/ATS guideline notes that the results of these objective criteria should always be accompanied by clinical judgment, including consideration of subjective factors, such as the availability of outpatient support resources and the patient's ability to safely and reliably take oral medication [47].

PNEUMONIA SEVERITY INDEX: POINT SCORING SYSTEM FOR STEP 2 OF THE PREDICTION RULE FOR ASSIGNMENT TO RISK CLASSES II, III, IV, AND V	
Characteristic	**Points Assigned[a]**
Nursing home resident	+10
Demographic factor (age)	
Men	Age (yr)
Women	Age (yr)-10
Coexisting illnesses[b]	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical-examination findings	
Altered mental status[c]	+20
Respiratory rate ≥30 breaths/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125 beats/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg/dL	+20
Sodium <130 mmol/L	+20
Glucose ≥250 mg/dL	+10
Hematocrit <30%	+10
Partial pressure of arterial oxygen <60 mm Hg[d]	+10
Pleural effusion	+10

[a]A total point score for a given patient is obtained by summing the patient's age in years (age minus 10 for women) and the points for each applicable characteristic. The points assigned to each predictor variable were based on coefficients obtained from the logistic-regression model used in step 2 of the prediction rule. A score <70 is risk class II, 71–90 is risk class III, 91–130 is risk class IV, and >130 is risk class V. Higher risk classes are associated with increased mortality.
[b]Neoplastic disease is defined as any cancer except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.
[c]Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.
[d]In the Pneumonia PORT cohort study, an oxygen saturation of less than 90% on pulse oximetry or intubation before admission was also considered abnormal.

Source: Reprinted with permission from Fine M, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243-250. *Table 5*

It is estimated that admission to an ICU is needed for 10% to 20% of patients hospitalized with CAP [76]. The IDSA/ATS guideline establishes major and minor criteria for direct admission to an ICU [47]. The major criteria are septic shock requiring vasopressors or acute respiratory failure requiring intubation and mechanical ventilation. The presence of at least three of the following minor criteria suggests the need for ICU admission [47]:

- Increased respiratory rate (≥30 breaths per minute)
- Low PaO_2/fraction of inspired oxygen ratio (≤250)
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level ≥20 mg/dL)
- Leukopenia (white blood cell [WBC] count <4,000 cells/mm^3)
- Thrombocytopenia (platelet count <100,000 cells/mm^3)
- Hypothermia (core temperature <36°C [96.8°F])
- Hypotension requiring aggressive fluid resuscitation

These criteria were validated as being useful for predicting the severity of CAP [77; 78].

Selection of Antibiotics

The goal of antibiotic treatment of pneumonia is to eradicate the infection or to reduce the bacterial load that the patient's own immune response is able to limit spread and speed recovery. The choice and duration of therapy is based on consideration of known or suspected etiology, age and severity of illness, comorbidities, and knowledge of resistance patterns in the community. One should strive to tailor therapy and avoid unnecessarily prolonged treatment so as to minimize the potential for the development of resistance [37].

Pending results of culture or serologic testing, the initial treatment is empirical and is selected according to patient variables and clinical setting (***Table 6***) [47]. Patients with mild illness and no serious coexisting disease may be managed as outpatients. The ATS/IDSA guideline recommends a macrolide for outpatient treatment of CAP, provided the patient has not received antimicrobials within the previous three months and the prevalence of macrolide resistance among pneumococci in the community is <25% [47]. *S. pneumoniae* resistance to macrolides is four times more likely in adult patients who have received this class of drug within the previous three months, in which case a fluoroquinolone or ß-lactam plus macrolide combination should be selected. A respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended for adults who have comorbidities or a compromised immune system [47]. Fluoroquinolones should not be used routinely, as widespread use increases the possibility that resistance will develop. Alternatively, a ß-lactam plus a macrolide can be used.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Infectious Diseases Society of America (IDSA) recommends empirical therapy for MRSA pending sputum and/or blood culture results for hospitalized patients with severe community-acquired pneumonia defined by any one of the following: a requirement for ICU admission, necrotizing or cavitary infiltrates, or empyema.

(https://academic.oup.com/cid/article/52/3/e18/306145. Last accessed August 22, 2018.)

Level of Evidence: A-III (Good supporting evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

RECOMMENDED EMPIRICAL ANTIMICROBIAL THERAPY ACCORDING TO 2007 IDSA/ATS GUIDELINE FOR THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA			
Site of Care and Patient Characteristics	**Recommended Drug Class**	**Specific Drug Options**	**Level of Evidence**
Previously healthy outpatient, no exposure to antibiotics within past three months	Macrolide	Azithromycin, clarithromycin, or erythromycin	Strong recommendation, level I evidence
	Tetracycline	Doxycycline	Weak recommendation, level III evidence
Outpatients with comorbidities[a] or exposure to antibiotics within the previous three months[b]	Respiratory fluoroquinolone	Moxifloxacin, gemifloxacin, or levofloxacin	Strong recommendation, level I evidence
	ß-lactam + macrolide	High-dose amoxicillin or amoxicillin-clavulanate	Strong recommendation, level I evidence
		Alternatives: ceftriaxone, cefpodoxime, or cefuroxime	Level II evidence
	ß-lactam + tetracycline	High-dose amoxicillin and doxycycline	Level II evidence
Inpatient (not ICU)	Respiratory fluoroquinolone	—	Strong recommendation, level I evidence
	ß-lactam + macrolide	—	Strong recommendation, level I evidence
Inpatient (ICU)	ß-lactam + azithromycin OR ß-lactam + respiratory fluoroquinolone Alternative for penicillin allergy: respiratory fluoroquinolone and aztreonam	Cefotaxime, ceftriaxone, or ampicillin-sulbactam	Strong recommendation, level I and II evidence
[a]Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignant disease; or asplenia or use of immunosuppressant drugs. [b]If patient has been exposed to antibiotics within previous three months, a different drug from a different class should be used.			
Source: [47]			*Table 6*

The selection of a respiratory fluoroquinolone or a ß-lactam plus macrolide combination is recommended also for patients with CAP who are hospitalized on a general floor [47]. Adults admitted to an ICU need empiric treatment for *S. pneumoniae* and *Legionella* spp., as well as consideration of coverage for *S. aureus* and gram-negative bacteria infection, pending sputum and blood culture results. This is achieved with a regimen that combines a broad-spectrum ß-lactam with either azithromycin or a respiratory fluoroquinolone, adding vancomycin or linezolid to cover MRSA if there is clinical suspicion of *S. aureus* infection. Aztreonam, a monobactam, may be substituted for gram-negative bacteria coverage in patients allergic to ß-lactams [47]. The IDSA/ATS guideline also specifies antibiotic selection in reference to specific pathogens (***Table 7***) [47].

For adults who present with presumed viral CAP, it is unclear whether antibiotic treatment is beneficial. When there is epidemiologic, clinical, or laboratory evidence of active influenza, a neuraminidase inhibitor should be administered [32].

RECOMMENDED ANTIBIOTIC THERAPY FOR SPECIFIC PATHOGENS ACCORDING TO 2007 IDSA/ATS GUIDELINE FOR THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA		
Pathogen	**Preferred Antibiotic**	**Alternative Options**
Streptococcus pneumoniae, not penicillin resistant	Penicillin G, amoxicillin	Macrolide, cephalosporins, clindamycin, doxycycline, respiratory fluoroquinolone
Streptococcus pneumoniae, penicillin resistant	Based on susceptibility (cefotaxime, ceftriaxone, fluoroquinolone)	Vancomycin, linezolid, high-dose amoxicillin
Haemophilus influenzae, non-ß-lactamase producing	Amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Haemophilus influenzae, ß-lactamase producing	Second- or third-generation cephalosporin, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae/ *Chlamydophila pneumoniae*	Macrolide, a tetracycline	Fluoroquinolone
Legionella spp.	Fluoroquinolone, azithromycin	Doxycycline
Pseudomonas aeruginosa	Antipseudomonal ß-lactam plus ciprofloxacin or levofloxacin or aminoglycoside	Aminoglycoside plus ciprofloxacin or levofloxacin
Acinetobacter spp.	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
Staphylococcus aureus, methicillin susceptible	Antistaphylococcal penicillin	Cefazolin, clindamycin
Staphylococcus aureus, methicillin resistant	Vancomycin or linezolid	Trimethoprim/sulfamethoxazole
Source: [47]		*Table 7*

Timing of Initial Antibiotic Therapy

The time to the first dose of antibiotics for adults with CAP has engendered debate. A 2003 guideline developed by the IDSA recommended initiation of antibiotic therapy within four hours after hospitalization. Quality measures linked to this timeframe were developed by the Joint Commission and the Centers for Medicare and Medicaid Services [2; 66; 79; 80]. Experts have criticized the timeframe requirement, with some noting that it has the potential to result in less-than-optimal care and others adding that diagnosis of pneumonia in the emergency department is challenging, especially in older patients who have an atypical presentation [51; 52; 79; 80]. In a survey of 121 emergency physicians, 55% of the respondents said they had prescribed antibiotics to patients they did not believe had pneumonia in an effort to comply with the Centers for Medicare and Medicaid Services quality measure; 42% of these respondents said they had prescribed as such more than three times a month [80]. Sixty percent of the respondents said they did not believe that the guideline improves patient care. The results of a systematic review and a large-scale study have shown no decrease in mortality with a first dose administered within four hours [57; 81; 82].

As emphasized by the IDSA/ATS guideline committee, the recommendation at present is to begin antibiotic treatment promptly, without delay, administering the initial dose at the site of care (e.g., emergency department, clinic, office) where the diagnosis is first made [47].

Duration of Therapy

With the availability of well-absorbed, effective oral antibiotics, hospitalized adults do not require intravenous antibiotics for the duration of treatment. Intravenous therapy can be changed to an oral regimen when the patient is hemodynamically stable, improving clinically, and able to take oral medications safely [47]. For patients on a general

ward floor, this transition can often be made by the third hospital day; patients in the ICU usually reach this point within seven days. It is recommended that the oral antibiotic be either the same drug or within the same drug class as the intravenous antibiotic [47]. Patients can be discharged from the hospital as soon as clinical stability has been achieved, provided they have no comorbidities requiring inpatient care and have a safe home environment and reliable follow-up. The IDSA/ATS note the following criteria for determining clinical stability [47]:

- Temperature ≤37.8°C (100.04°F)
- Heart rate ≤100 beats per minute
- Respiratory rate ≤24 breaths per minute
- Systolic blood pressure ≥90 mm Hg
- Arterial oxygen saturation ≥90% or partial pressure of oxygen ≥60 mm Hg on room air
- Ability to maintain oral intake
- Normal mental status

The IDSA/ATS recommend that antibiotic therapy be given for a total of at least five days. The duration of therapy should be extended at least 48 to 72 hours beyond resolution of fever, assuming significant clinical improvement and no more than one pneumonia-associated active clinical sign [47]. A five- to seven-day course should suffice for most uncomplicated cases that show a prompt and satisfactory response to treatment.

The duration of treatment for gram-negative bacillary and staphylococcal pneumonia bears further comment. Unlike pneumococcal pulmonary infection, which usually heals without residual damage, these pathogens often cause destructive changes and small cavities in the lung, which clear slowly and heal by fibrosis. Thus, a more prolonged course of therapy (two to three weeks) should be considered, depending on severity of illness and response to therapy.

Treatment Failure

The clinical response to initial antibiotic therapy is unsatisfactory in approximately 15% of adults with CAP [47]. Failure to respond has no clear definition, and the IDSA/ATS guideline suggests using a systematic classification of cases, with attention to timing and character of response, as a guide to further evaluation and management. In general, treatment failures may be classified as persistent or non-responding, as a delay in achieving clinical stability, or as progressive pneumonia with clinical deterioration. Some clinical deterioration during therapy is not uncommon in the first 24 hours of treatment; as many as 45% of adults admitted to the hospital later require transfer to the ICU [47]. When the diagnosis of CAP is correct and guideline-recommended therapy has been used, the most common reason for treatment failure is an inadequate host response. For these patients, the appropriate management depends on individual case considerations, such as comorbidities, adequacy of pulmonary toilet, and whether the intravenous regimen has been reliably and consistently administered [47].

Benefits of Guideline-Adherent Antibiotic Therapy

Guideline-directed management of CAP has been associated with many benefits. In one study, use of guideline-recommended antibiotics was associated with a significantly shorter time to clinical stability; clinical stability was achieved by seven days in 71% of patients treated with guideline-recommended antibiotics and in 57% of those treated with nonadherent regimens [15]. Adherence to recommendations guiding the selection of antibiotics was also associated with a significantly shorter length of stay (8 vs. 10 days) and a significantly lower overall in-hospital mortality rate (8% vs. 17%) [15]. In a Canadian study of adults (mean age: 51 years) who, in the main, had mild pneumonia, guideline-adherent selection of antibiotic treatment was associated with a lower mortality rate (1%) than that found when treatment selection

that was not adherent to guidelines (6%) [83]. The mortality rate associated with the use of macrolides was also significantly lower than that with the use of fluoroquinolones (0.2% vs. 3%) [83]. In a large study of 54,619 patients who were hospitalized at 113 community hospitals (not in the ICU), use of guideline-adherent treatment was associated with a lower in-hospital mortality rate, lower rate of sepsis and renal failure, and shorter length of stay and duration of parenteral therapy [17]. Decreased mortality has also carried over to populations with more severe disease, with nonadherent therapy being associated with an increase in inpatient mortality (25% vs. 11%) among older adults (median age: 71 years) who were admitted to an ICU [16]. In addition to the higher rates of adverse outcomes, the low rate of adherence has also resulted in the inappropriate use of antimicrobials in at least half of cases [21].

Despite the benefits of guideline-directed treatment and the wide dissemination of the guidelines for management of pneumonia in adults, adherence has been low, especially with regard to antibiotic selection, with rates ranging from 9% to 82% [15; 16; 17; 18; 20]. In a study of more than 34,000 patients in a managed care organization, adherence to the 2003 IDSA guidelines in ambulatory settings was 52% for patients who were previously healthy and had not had recent exposure to antibiotics [20]. The rate of adherence was better (82%) for patients who had comorbidities and no recent exposure to antibiotics [20]. One study found that most cases of guideline-discordant use of antibiotics for older adults represent undertreatment [15]. The use of recommended antibiotics in the emergency department significantly increased from 1993 through 2008, but the percentage of patients receiving these drugs is still not optimal, with 60% to 70% of patients not receiving recommended antibiotics [84].

Strategies to Enhance Adherence to Therapeutic Guidelines

As the low rate of guideline adherence demonstrates, disseminating clinical practice guidelines alone is not enough to change practice. Physician education should address barriers to guideline adherence, including lack of familiarity, concerns about the practicality of recommended antibiotics, increased cost, lack of documented improved outcomes, and potential conflict with other guidelines [23]. Physician practices and healthcare systems should implement strategies that have changed physician behavior in other health condition settings, such as face-to-face educational outreach, use of local opinion leaders, and individualized audit with peer-comparison feedback [85]. In a study of six Dutch hospitals, significant increases in adherence to guideline-recommended care were achieved with an intervention that included the establishment of a local committee, a lecture by a respected opinion leader, feedback on performance, and critical care pathway pocket cards [86]. The intervention also included a second phase that focused on aspects of treatment in most need of improvement. In another study, weekly e-mail reminders listing performance data on antibiotic administration recommendation for individual emergency physicians helped to increase guideline adherence [87]. The use of a standardized evidence-based order set was associated with a decrease in mortality and was also cost-effective [88].

Follow-Up Care

Evidence suggests that severe pneumonia is a cause of long-term morbidity and excess mortality among adults. In a population-based follow-up study of adults with CAP in Canada, conducted over a median of four years, the re-hospitalization rate for pneumonia was 16% to 72% for all causes [9].

The PSI classification and the time to clinical stability can both help predict adverse outcomes. Mortality has been reported to be higher for people originally classified as PSI class V than PSI classes I and II, with rates of 82% compared with 15% [9].

A time to clinical stability of more than 72 hours has been associated with a significantly higher rate of adverse outcomes than shorter times [90]. Overall, severe CAP has been associated with a 30-day re-hospitalization rate as high as 20%, a 30-day mortality rate as high as 23%, and all-cause mortality within one year as high as 28% [76].

These findings indicate that adults with severe pneumonia should be followed up closely to monitor for adverse events after discharge. The time to clinical stability is a useful guide for a follow-up plan; patients in whom clinical stability is not achieved until more than 72 hours after admission should be seen in follow-up soon after discharge [3; 90]. Strategies to prevent influenza and pneumonia should also be emphasized for all hospitalized patients. When indicated, immunization against pneumococcal infection should be initiated before or shortly after discharge, as recommended by the Advisory Committee on Immunization Practices (ACIP) and others [47; 91; 94; 227].

Patient and Family Education

After a diagnosis of pneumonia has been made, patient education should include directions for use of the antibiotic and information on potential untoward effects of the drug. Follow-up instructions, depending on the clinical situation, may include 24-hour telephone contact or follow-up in the office after 24 to 48 hours. This will improve adherence to the prescribed therapy, provide an opportunity to address side effects of drug therapy, and allow progress to be monitored. The need for hospitalization should be assessed throughout the course of the illness. Education should also include instructions to drink plenty of fluids and to use an antipyretic to control fever and myalgias when needed. Use of cough suppressants should be avoided, as the cough reflex and sputum expectoration enhance removal of thick secretions. However, in the event of a constant, nonproductive cough, as found especially with mycoplasmal infection, a narcotic such as codeine at night may allow for more restorative sleep.

Provisions for patients with limited English language proficiency are required under federal law, and the U.S. Department of Health and Human Services and the Office of Civil Rights view a lack of adequate interpretation as discrimination, based on the Civil Rights Act of 1964 [19]. According to U.S. Census Bureau data, more than 60 million Americans speak a language other than English at home, with more than 25 million (8.6% of the population) reporting that they speak English less than "very well" [127]. Immigrant patients with chronic illness may feel unable to return to their home countries due to a lack of available medical care. Changes in healthcare law restricting federal funding of services to only legal residents may cause significant problems for certain facilities, with conflicts arising from providing life-saving care for patients who have no means of reimbursement and no medical services waiting for them in their home countries.

ILLUSTRATIVE CASE

A semi-retired man, 68 years of age, presents one Sunday morning to the emergency department with malaise, fever, productive cough, and right pleuritic chest pain of less than 24 hours duration. He has been active, works as a custodian, has never been hospitalized, takes no medications, and does not regularly see a physician. On review of systems, the patient states that he gave up smoking years ago, has a mild chronic cough and morning sputum production, and has noted mild dyspnea on exertion for the past six months. He drinks only beer, never after work, but every Saturday afternoon he likes to take a six-pack out into the backyard, where he relaxes in his lounge chair. When asked whether there was anything different about the Saturday before the onset of the illness, his wife relates that he consumed two six-packs and failed to come in that evening. She found him later, after dark, asleep in his lounge chair, and helped him in to bed. He awoke this morning with fever and chills. On exam, the patient's temperature is 102.6°F, blood pressure 154/80 mm Hg, pulse 94 beats per minute, and respiration 20 breaths per minute. He is alert,

with signs of mild emphysema and crackles audible over the right lower posterolateral chest. The chest x-ray shows patchy alveolar opacification in the right lower lobe and slight cardiomegaly.

The working diagnosis here is CAP, likely caused by S. pneumoniae or H. influenzae, as the patient has no prodromal upper respiratory symptoms to suggest viral or mycoplasma infection.

Why is this happening now? COPD/chronic bronchitis appears to have developed in recent years. Such patients have damaged, poorly functioning mucociliary epithelium and rely on compensatory cough to promote tracheobronchial clearance. Moreover, they often have colonization with pneumococcus and H. influenzae. An additional risk factor in this patient may be mild heart failure with ambient alveolar edema in the basal segments of the lower lungs. Excessive beer consumption the evening before onset of illness made him somnolent and suppressed his cough reflex, thus rendering him vulnerable to aspiration and retention of upper tract secretions (if not gastroesophageal reflux and aspiration). Encumbered by alveolar edema, and perhaps impaired by the metabolic effects of alcohol, pulmonary macrophages in the basal segment of the right lung were simply overwhelmed.

What is the best site of care and treatment for this patient? While he does not meet the criteria for ICU admission, his age, comorbidities, degree of illness, and social situation taken together suggest the need for hospital admission, parenteral antibiotic therapy, and close observation, anticipating a short hospital stay. He was treated with a β-lactam and macrolide, improved rapidly, and was discharged day 3 on a matching oral regimen, to complete a 10-day course of therapy.

What preventive measures were taken to reduce the risk of this happening again? The 23-valent polysaccharide vaccine (PPSV23) (Pneumovax) was administered prior to discharge and arrangements were made for primary care follow-up. The patient and his wife were educated regarding the need for yearly influenza vaccination. The role of alcohol was discussed, as well as the importance of keeping the Saturday afternoon beer consumption within clearly defined limits.

PNEUMONIA IN THE PEDIATRIC PATIENT

Etiology

Viral pathogens are reported to be responsible for most cases of CAP in preschool-aged children and as many as 80% of cases in children younger than 2 years of age [30]. In children younger than 2 years of age, the most common viral pathogen, occurring in up to 40% of cases, is RSV; other viral pathogens include adenoviruses, bocavirus, human metapneumovirus, influenza A and B viruses, parainfluenza viruses, coronaviruses, and rhinovirus [9; 29; 30; 32].

RSV infection is common in infants and young children; it is estimated that most children have had RSV by 2 years of age [31]. It is leading cause of pneumonia in infants younger than 1 year of age, with 25% to 40% of those infected developing signs of pneumonia or bronchiolitis [29]. Premature birth, very young age, compromised immune system, and impaired lung or heart function are all risk factors for RSV-related pneumonia in infants. In contrast to preschool-aged children, the percentage of viral cases is much lower among older children and adolescents (10 to 16 years of age), and pneumonia caused by RSV is rare in this population.

In older children, viral and atypical bacterial infection account for most mild CAP managed in the ambulatory setting, while pyogenic respiratory bacterial infection is responsible for the majority of CAP in seriously ill, hospitalized children [30]. *S. pneumoniae* is the most common bacterial pathogen in school-aged children. Studies show that atypical pathogens account for 3% to 23% of cases, most commonly mycoplasma in older children and chlamydia in infants and young children [30]. A 2009 European study examining causative agents in hospitalized pediatric patients with radiographic evidence of pneumonia found bacterial infection in 53% of patients and viral pathogens in 67% of patients, with 33% of children in the study showing evidence of both [63]. *S. pneumoniae* was the

most common bacterial pathogen (46%), followed by *M. pneumoniae* and *C. pneumoniae*. The primary viral pathogens identified were influenza A or B, parainfluenza, rhinovirus, RSV and, human metapneumovirus [63].

As with adults, severe CAP caused by *S. aureus* is encountered during outbreaks of influenza [223]. *Legionella* spp. and fungal pathogens are uncommon in children. A combination of viral and bacterial pathogens occurs in up to half of children with CAP [30; 32].

Clinical Features and Diagnosis

The clinical presentation of CAP in children is similar to that in adults, but can vary according to age and developmental stage. For example, cough productive of purulent sputum may be elicited in older children, but nonproductive cough is common in young children and infants [30; 60]. Nonspecific irritability and restlessness may be the primary symptoms in infants.

During the physical examination of pediatric patients, the clinician should look for signs of hypoxia and dehydration, as well as retractions, tachypnea, and use of accessory muscles of respiration [60]. The clinician should also evaluate the upper respiratory tract for evidence of rhinorrhea, otitis media, and pharyngitis [60]. Auscultation of the chest should be carried out, and the Pediatric Infectious Diseases Society (PIDS)/IDSA guideline recommends pulse oximetry for children with suspected hypoxemia [30].

One of the most common reasons for pediatric emergency room visits is fever, and fever is present in 88% to 96% of identified pneumonia cases in developed countries [70]. However, children with fever and wheezing commonly have either upper respiratory disease or reactive airway disease. As with pneumonia in adults, the accuracy of any one sign or symptom in predicting the likelihood of pneumonia is limited [61]. Nonspecific symptoms such as vomiting and abdominal discomfort are common. Careful attention should be given to the chest exam, as diminished breath sounds and fine end-inspiratory crackles are subtle, important clues to the presence of pneumonia in the pediatric patient. In one study, non-specific crackles were present in more than 90% of children with pneumococcal or mycoplasma pneumonia [70]. Infants with pneumonia commonly present with poor feeding and irritability as well as tachypnea, retractions, grunting, and hypoxemia; cough is rare [64].

Several clinical rules have been developed for predicting the likelihood of pneumonia in children on the basis of discernable clinical signs. The presence of at least two of the following signs—fever, tachypnea, and reduced oxygen saturation—is associated with a high probability of the disease; the absence of all three indicates a low probability [61]. Other signs of respiratory distress, such as cough, nasal flaring (in infants), rales, and decreased breath sounds, have also been found to be independent predictors of pneumonia in infants and children [60; 62]. Bronchial breath sounds, rales, and dullness to percussion are more likely to occur in older children and adolescents [60].

Unlike diagnosis in adults, a chest radiograph is not the diagnostic standard to be applied for all CAP in children. The PIDS/IDSA guideline notes that routine chest radiographs are not necessary for children who can be treated as outpatients [30]. However, postero-anterior and lateral chest radiographs should be obtained when there is fever and respiratory distress suspected or documented hypoxemia, or illness severe enough to warrant hospitalization [30]. In a study of 99 children hospitalized with what was later determined to be pneumonia, the most common abnormal finding was "diminished" breath sounds; only 21% were described as having "normal" breath sounds. Radiographic evidence of pulmonary consolidation was present in 79% of patients, and correlation between diminished breath sounds and a positive chest x-ray was 60.2% [63].

Laboratory Tests

Unlike the situation in adults, titers of shed virus in children are high [31]. Thus, rapid antigen testing of nasal or throat swabs for influenza and other respiratory viruses should be done for infants and young children [30]. However, it should be noted that negative results of influenza virus on rapid antigen tests do not conclusively rule out infection with influenza virus. Testing for *C. pneumoniae* is not recommended.

Blood cultures are not routinely needed but should be obtained in children hospitalized for moderate-to-severe pneumonia that is presumed to be bacterial [30]. Urinary antigen detection tests often have false-positive results in children and are therefore not recommended for the diagnosis of pneumococcal pneumonia.

Management of Community-Acquired Pneumonia in Children

The PIDS/IDSA guidelines, published in 2011, addresses the management of CAP in children 3 months of age and older who are otherwise healthy; the guideline does not provide guidance for neonates and infants younger than 3 months of age or children with comorbidities [30]. The guidelines were developed in an effort to decrease morbidity and mortality, as had been shown with the guideline for adults. Similar to the IDSA/ATS guideline, the management issues addressed in the PIDS/IDSA guidelines are site of care and selection and duration of antibiotic therapy, as well as adjunctive surgical and nonantibiotic treatment for complications. As with the guideline for adults, treatment of pneumonia-related symptoms is not included in the pediatric guideline. The discussion here is limited to site of care and antibiotic therapy.

Site of Care

To aid in making site-of-care decisions, the PIDS/IDSA guidelines recommend that a child or infant with CAP be hospitalized if any of the following factors are present [30]:

- Moderate-to-severe illness, as defined by several features, including respiratory distress and hypoxia
- Suspected or documented infection caused by a pathogen with increased virulence, such as community-associated MRSA
- Uncertainty about care at home or availability for follow-up

Most children with pneumonia do not require care in an ICU. The guideline states that a child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child [30]:

- Requires invasive ventilation via a non-permanent artificial airway (endotracheal tube)
- Has impending respiratory failure or sustained tachycardia, inadequate blood pressure, or need for pharmacologic support of blood pressure or perfusion
- Has altered mental status as a result of pneumonia
- Has a pulse oximetry measurement <92% on inspired oxygen of ≥0.50
- Requires acute use of noninvasive positive pressure ventilation

Selection of Antibiotics or Antivirals

The PIDS/IDSA guideline recommends empiric antibiotic therapy according to patient age, immunization status, and site of care. Among infants and children 3 months to 5 years of age, antibiotic therapy is not routinely recommended because viral infection is the predominate cause of CAP in this age group [30]. When the cause is thought to be an influenza virus, influenza antiviral therapy should be started as soon as possible, as maximal benefit has been found when treatment begins within 48 hours after symptomatic infection. (Treatment should not be delayed while waiting for the results of viral testing.) The PIDS/IDSA guideline recommends three U.S. Food and Drug Administration (FDA)-approved influenza anti-

EMPIRIC ANTIBIOTIC THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN ACCORDING TO PIDS/IDSA GUIDELINE		
Site of Care, Patient Characteristics	**Presumed Bacterial Pneumonia**	**Presumed Atypical Pneumonia**
Outpatient		
<5 years	Amoxicillin Alternative: amoxicillin clavulanate	Azithromycin Alternatives: clarithromycin or erythromycin
≥5 years	Amoxicillin[a] Alternative: amoxicillin clavulanate	Azithromycin Alternatives: clarithromycin, erythromycin, doxycycline (children >7 years)
Inpatient (all ages)		
Fully immunized[b] and minimal local penicillin resistance in invasive strains of pneumococcus	Ampicillin or penicillin G Alternatives: ceftriaxone or cefotaxime (with vancomycin or clindamycin if MRSA suspected)	Azithromycin (with ß-lactam if atypical pneumonia is doubtful) Alternatives: clarithromycin, erythromycin, doxycycline (children >7 years), or levofloxacin (children who have reached growth maturity or who cannot tolerate macrolides)
Not fully immunized and/or significant local penicillin resistance in invasive strains of pneumococcus	Ceftriaxone or cefotaxime (with vancomycin or clindamycin if MRSA suspected) Alternative: levofloxacin (with vancomycin or clindamycin if MRSA suspected)	Azithromycin (with ß-lactam if atypical pneumonia is doubtful) Alternatives: clarithromycin, erythromycin, doxycycline (children >7 years), or levofloxacin (children who have reached growth maturity or who cannot tolerate macrolides)
[a]A macrolide plus ß-lactam can be used for children 5 years of age and older with presumed bacterial pneumonia who have clinical, radiographic, or laboratory evidence to distinguish bacterial from atypical pneumonia. [b]Has received conjugate vaccines for *Haemophilus influenzae* b and *Streptococcus pneumoniae*.		
Source: [30]		*Table 8*

viral therapies: oseltamivir (Tamiflu), zanamivir (Relenza), and amantadine (Symmetrel) [30]. A fourth antiviral therapy, rimantadine (Flumadine), is included in the guideline, with a note that the agent is FDA-approved for prophylaxis—not treatment—in children 1 year of age and older [30]. The guideline adds that data on the safety and efficacy of the agent for children 1 year of age and older have been published.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Pediatric Infectious Diseases Society and the IDSA, influenza antiviral therapy should be administered as soon as possible to children with moderate-to-severe community-acquired pneumonia consistent with influenza virus infection during widespread local circulation of influenza viruses, particularly for those with clinically worsening disease documented at the time of an outpatient visit. Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed until confirmation of positive influenza test results.

(https://academic.oup.com/cid/article/53/7/e25/424286. Last accessed August 22, 2018.)

Strength of Recommendation/Level of Evidence: Strong recommendation; moderate-quality evidence

As in adults, *S. pneumoniae* is the most common bacterial cause of CAP in children; thus, if a bacterial pathogen is thought to be the cause, amoxicillin or amoxicillin/clavulanate is recommended as first-line therapy for mild-to-moderate illness in previously healthy children 3 months to 5 years of age who are up-to-date with immunization [30]. Several alternatives can be used for children who are allergic to amoxicillin (***Table 8***). Amoxicillin is also the preferred antibiotic for mild-to-moderate CAP in adolescents and children 5 years of age and older [30]. For children of all ages, especially children older than 5 years of age and adolescents, a macrolide is recommended if an atypical bacterial pathogen is thought (or documented) to be the cause.

For fully immunized infants and school-aged children who are hospitalized, treatment with ampicillin or penicillin G is recommended when local epidemiologic data show a low level of penicillin resistance to *S. pneumoniae* [30]. For children who are not fully immunized or are hospitalized in an area with a high level of penicillin-resistant *S. pneumoniae*, treatment with a third-generation cephalosporin (ceftriaxone or cefotaxime) should be given intravenously. If *M. pneumoniae* or *C. pneumoniae* is strongly suspected, treatment should include a macrolide (orally or intravenously) with a ß-lactam and diagnostic testing should be done as soon as possible [30]. The PIDS/IDSA guideline also recommends antimicrobial treatment for specific pathogens; however, a discussion of all possible pathogens is beyond the scope of this course.

According to a systematic review, zinc supplementation in addition to standard antibiotic therapy was not shown to have significant benefit on clinical recovery of severe or nonsevere pneumonia in children 2 to 59 months of age [89].

Duration of Therapy

Most studies have evaluated 10-day therapy, and this duration is associated with good outcomes. However, a shorter duration may be equally as effective, especially for mild disease treated on an outpatient basis [30].

Benefits of Guideline Adherence

Because the PIDS/IDSA guideline for management of CAP in children is relatively recent, data are lacking on the benefits of guideline-adherent treatment in the pediatric population. One study did show that more children received appropriate antibiotics after the development of a clinical practice guideline based on the PIDS/IDSA guideline and an antimicrobial stewardship program [14]. It is assumed that more data will become available over time.

Late Complications

Data on the long-term effects of pneumonia during childhood are lacking. A systematic review demonstrated that severe pneumonia in children younger than 5 years of age is associated with long-term sequelae, with restrictive lung disease being the most common sequela [95]. Overall, major respiratory sequelae (e.g., restrictive lung disease, obstructive lung disease, bronchiectasis) occurred in 5.5% of children treated on an outpatient basis and in 13.6% of children hospitalized for treatment [95]. Sequelae occurred in approximately 54% of children who had pneumonia caused by adenovirus.

PREVENTION OF PNEUMONIA

IMMUNIZATION

The primary preventive strategy for pneumonia is immunization with pneumococcal and influenza vaccines, especially for older individuals (older than 65 years of age), young children, and groups at high risk (***Table 9***) [91]. Other strategies include improved hand hygiene compliance and adherence to healthy lifestyle behaviors.

HIGH-PRIORITY AND HIGH-RISK GROUPS FOR VACCINATION	
Vaccination	**Priority Groups**
Annual influenza vaccination	Adults 65 years of age and older Children 6 to 59 months of age Residents of long-term care facilities Adults and children with chronic medical conditions Women who are pregnant during the influenza season
Pneumococcal vaccination	Adults 65 years of age and older with no history of pneumococcal vaccination Adults younger than 65 years of age with at least one of the following: • Chronic disease (e.g., lung, cardiovascular, or liver disease or diabetes) • Compromised immune system • Alcoholism • Cochlear implants • Cerebrospinal fluid leaks • Functional or anatomic asplenia • Resident of nursing home or long-term care facility • Current or recent past history of smoking
Source: [28; 91]	*Table 9*

Pneumococcal Vaccination

Pneumococcal vaccines have been improved over time by broadening the coverage of serotypes in the vaccine to include those that are causing the most common invasive infections. In the past, a single agent, PPSV23, has been recommended for use in selected adults with conditions of impaired immunity, and for all adults older than 65 years of age [96]. This vaccine provides some protection against 85% to 90% of the pneumococcal serotypes that cause invasive disease in these populations [97]. Pneumococcal conjugate vaccines are used for younger children, as polysaccharide vaccines are not effective in children younger than 2 or 3 years of age. In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) replaced the 7-valent vaccine (PCV7) previously in use since 2000 [97].

The use of pneumococcal conjugate vaccines in the pediatric age group has been followed by a reduction in the incidence of pneumococcal disease among children, and, indirectly, among adults as well. By 2013, the incidence of invasive pneumococcal disease caused by serotypes represented in the PCV13 vaccine had declined in the adult population older than 65 years of age by approximately 50% compared with 2010 [227]. In 2012, upon approval by the FDA, the ACIP recommended the use of PCV13 for adults with immune deficits and other conditions that impose a heightened risk for invasive pneumococcal infection. After reviewing additional data in 2014, the ACIP extended its recommendation for PCV13 use to all adults older than 65 years age [227].

The ACIP now recommends that both PCV13 and PPSV23 be administered routinely in series to all adults older than 65 years of age (***Table 10***) [227]. Only a single dose of PCV13 is recommended for adults. No additional dose of PPSV23 is indicated for adults who have previously received this vaccine at or after age 65 years. Pneumococcal vaccine-naïve older adults or those for whom the vaccine history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23 in 6 to 12 months. Current information, schedules, and guidance for adult immunizations is maintained at the CDC/ACIP website at https://www.cdc.gov/vaccines/schedules.

IMMUNIZATION SCHEDULE RECOMMENDED BY THE ACIP	
Vaccination	**Recommended Recipients**
Influenza vaccination (annually)[a]	Adults and children 6 months of age and older
Pneumococcal vaccination (PCV13 and PPSV23, in series 6 to 12 months apart)[b]	Adults 65 years of age and older
	High-risk children and adults (2 to 64 years of age)
Haemophilus influenzae b (series of 4)	Infants at 2, 4, 6, and 12 to 15 months of age
Pneumococcal conjugate vaccine (series of 4)	Infants at 2, 4, 6, and 12 to 15 months of age
[a]In its 2012 immunization schedule for adults, the ACIP notes that the trivalent inactivated vaccine (TIV) may be used for all adults, including pregnant women. Adults older than 65 years of age may receive either standard-dose or high-dose TIV. The live, attenuated influenza vaccine (LAIV) may be used in healthy, nonpregnant adults who are younger than 50 years of age and have no high-risk medical conditions. Healthcare staff who care for severely immunocompromised patients should receive TIV rather than LAIV. [b]Both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered routinely in series to all adults older than 65 years of age. The dose of PPSV23 should be given 6 to 12 months after a dose of PCV13.	
Source: [91; 92; 227]	*Table 10*

Influenza Vaccination

The influenza vaccine is developed each year to contain the three virus strains that are expected in the upcoming influenza season. The vaccine has traditionally been a trivalent inactivated vaccine (TIV), but in 2003, a trivalent live, attenuated influenza vaccine (LAIV) was introduced in the United States [97]. In 2010, a new high-dose formulation of TIV became available. The LAIV, which contains four times the amount of influenza antigens as other TIVs, is designed to induce a higher immune response in older people [97]. The LAIV is administered as a nasal spray.

The ACIP once recommended a risk-stratified approach to influenza vaccination, but it updated its recommendations to universal vaccination beginning in the 2010–2011 influenza season ***(Table 10***) [91]. The ACIP's immunization schedule also notes which types of vaccines should be used according to age and other factors. In their guideline for the management of CAP, the IDSA/ATS make the following strong recommendations for prevention based on the ACIP recommendations [47]:

- All persons 50 years of age and older, others at risk for influenza complications, household contacts of high-risk persons, and healthcare workers should receive inactivated influenza vaccine as recommended by the ACIP (level I evidence).
- The intranasally administered LAIV is an alternative vaccine formulation for some persons 5 to 49 years of age without chronic underlying diseases, including immunodeficiency, asthma, or chronic medical conditions (level I evidence).
- Pneumococcal vaccines are recommended for persons 65 years of age and older and for those with selected high-risk concurrent diseases, according to the current ACIP guideline (level II evidence).

The IDSA/ATS guideline for management of CAP also states that vaccination status should be assessed at the time of hospital admission for all patients, especially those with medical illnesses [47]. If vaccination is needed, it may be done either at hospital discharge or during outpatient treatment. The Joint Commission developed measures for influenza and pneumococcal vaccination, as appropriate, for inpatients, which became effective for discharges on and after January 1, 2012 [94].

The PIDS and the IDSA also echo the ACIP recommendations in their guideline [30]:

- Children should be immunized with vaccines for bacterial pathogens, including *S. pneumoniae*, *H. influenzae* type b, and pertussis (strong recommendation, high-quality evidence).
- All infants 6 months of age or older and all children and adolescents should be immunized annually with vaccines for influenza virus (strong recommendation, high-quality evidence).
- Parents and caretakers of infants younger than 6 months of age, including pregnant adolescents, should be immunized with vaccines for influenza virus and pertussis to protect the infants from exposure (strong recommendation, weak-quality evidence).
- High-risk infants should be provided immune prophylaxis with RSV-specific monoclonal antibody to decrease the risk of severe pneumonia and hospitalization caused by RSV (strong recommendation, high-quality evidence).

Vaccine Efficacy

Declining rates of pneumonia and pneumonia-related deaths are thought to represent the effectiveness of influenza and pneumococcal vaccination [40; 98; 99]. In a study of a community-dwelling older population, influenza vaccination decreased the risk of hospitalization for pneumonia or influenza, as well as the risk of death, across 10 influenza seasons [7]. Systematic reviews and meta-analyses have shown that pneumococcal vaccination reduces the incidence of invasive pneumococcal disease in both older adults and children, although the findings are unclear for adults with chronic illness [100; 101]. Other studies of adults have shown that pneumococcal vaccination is associated with benefit in terms of a lower risk of adverse outcomes associated with the disease. For example, in a study of nearly 3,500 older people (median age: 75 years) who were hospitalized for CAP, the rate of mortality or ICU admission was 40% lower among those who had received prior PPSV23 vaccination [8].

Among children, the introduction of the PCV7, and later PCV13, has led to a substantial decrease in the rate of invasive pneumococcal disease, but the decrease in the rate of CAP has been less dramatic. Early studies showed substantial improvements in the hospitalization rate for CAP only among young children. In one study, the hospitalization rate decreased 39% for children younger than 2 years of age [98]. In another study, the decrease was substantial only for children younger than 1 year of age (22%) and was minimal for children 1 to 5 years of age; the rate increased for adolescents and children older than 5 years of age [4]. The rate of outpatient CAP visits has not changed significantly for this population [5; 10].

Vaccination Rates

Despite the wide distribution of the ACIP immunization schedule and public campaigns about the importance of vaccination, rates of both pneumococcal and influenza vaccination remain relatively low. According to National Center for Health Statistics data collated for 2016, the estimated rate of influenza vaccination is 49.9% for children, 31.8% for adults 18 to 49 years of age, 45.2% for adults 50 to 64 years of age, and 67.2% for adults 65 years of age and older [103].

According to the CDC, influenza vaccination coverage for the 2014–2015 season among adults 19 years of age or older was 44.8%, an increase of 1.6% from the 2013–2014 season [102]. Coverage among white adults was higher (48.5%) than that for blacks (37.7%) and Hispanics (33.0%). Influenza coverage was 32.5% among adults 19 to 49 years of age and 48.7% among adults 50 to 64 years of age. Coverage among adults 65 years of age or older (73.5%) was higher compared with younger age groups. Among healthcare personnel , influenza vaccination coverage overall was 68.6%. Among healthcare personnel with and without direct patient care responsibilities, influenza vaccination coverage was 68.9% and 67.9%, respectively.

RATE OF INFLUENZA VACCINATION AMONG ADULTS ACCORDING TO AGE AND RACE/ETHNICITY, FIVE-YEAR INTERVALS, 2005–2015			
Age/Ethnicity	**Rate**		
	2005	**2010**	**2015**
18 to 44 years of age	10.1%	24.6%	30.9%
45 to 64 years of age	20.2%	37.8%	45.1%
65 years of age and older	59.7%	63.9%	69.1%
White	22.5%	36.9%	44.2%
Black	15.5%	28.1%	36.7%
Hispanic	12.0%	26.5%	31.2%
Source: [113]			*Table 11*

RATE OF PNEUMOCOCCAL VACCINATION AMONG ADULTS 19 YEARS OF AGE AND OLDER, 2015		
Race/Ethnicity	**High-Risk Adults 19 to 64 Years**	**Adults 65 Years and Older**
All races	23.0%	63.6%
White (non-Hispanic)	24.0%	68.1%
Black (non-Hispanic)	24.0%	50.2%
Hispanic or Latino	19.4%	41.7%
Asian	24.0%	49.0%
Based on data from the National Health Interview Survey, United States, 2015.		
Source: [102]		*Table 12*

The national rate of influenza vaccination among all adults has improved over the past decade, yet racial disparities persist. Comparing rates at five-year intervals from 2005 to 2015, the rate of vaccination has more than doubled for adults younger than 65 years of age and for each ethnic category (***Table 11***) [113]. The rate disparity between white adults (44.2%) and that observed for black (36.7%) and Hispanics (31.2%) remains evident. Previous studies have also shown higher rates of vaccination for white older adults compared with black and Hispanic older adults [104; 105; 106; 107]. Racial disparities have also been found when rates of pneumococcal and influenza vaccination for residents of long-term care facilities were compared, with substantially lower rates for black residents [108; 109; 110].

Data on influenza vaccination readiness among children and adults comes from national survey for the 2017–2018 influenza season. Only approximately two of every five persons in the United States had received an influenza vaccination by early November 2017. The rate was 38.6% for all persons 6 months of age and older. Among children, influenza vaccination coverage was somewhat higher for Hispanic children (41.3%) than for non-Hispanic white (38.0%) and non-Hispanic black (34.6%) children.

According to national surveys, the overall rate of pneumococcal vaccination is approximately 64% for adults 65 years and older, and the rate is substantially lower (approximately 23%) for younger adults in high-risk groups. The CDC report on pneumococcal vaccination coverage (PPSV23 and PCV13) for 2015 is summarized in ***Table 12*** [102].

RATE OF VACCINATION WITH AT LEAST FOUR PCV DOSES AMONG CHILDREN 19 TO 35 MONTHS OF AGE	
Race/Ethnicity	**Rate**
White (non-Hispanic)	84.1%
Black (non-Hispanic)	74.5%
Hispanic	81.4%
American Indian/Alaska Native	80.1%
Asian	81.0%
Multiracial	83.6%
Total	83.3%
PCV = pneumococcal conjugate vaccine.	
Source: [112]	*Table 13*

In addition, adherence to the recommendation for pneumococcal and influenza vaccinations for older adults admitted to the hospital has been low. In a study of nearly 105,000 patients 65 years of age and older who had not received either vaccination before admission to the hospital, 99.4% did not receive the pneumococcal vaccine and 97.3% did not receive the influenza vaccine before hospital discharge [111].

Rates of both pneumococcal and influenza vaccination are higher among children than adults. Overall, approximately 83% of children 19 to 35 months of age have received at least four PCV13 doses [112]. The rate varies according to race/ethnicity, with the lowest rates among Asian and black children (***Table 13***) [112].

Barriers to Vaccine Use

In its Healthy People 2020 initiative, the U.S. Department of Health and Human Services has set objectives for improving pneumococcal and influenza vaccination rates among adults and children, with targets of 80% to 90% (***Table 14***) [114]. To reach these targets, healthcare providers must address documented barriers to recommended vaccinations and gain a better understanding of other challenges to vaccination. Unequal access to health care appears to account for a low percent of racial disparities [105]. Rather, lack of awareness of the need for vaccination and misconceptions about vaccines have been reported as the primary barriers in several studies [104; 105; 106; 115; 116; 117].

Among adults, misconceptions about vaccines range from the belief that healthy people do not need vaccinations to a fear of side effects [104; 106; 116]. Beliefs about vaccines vary by race/ethnicity, age, education, and gender. For example, in a survey of more than 6,700 older adults, lack of awareness that influenza vaccination was needed was more common among Hispanic (33%) and black individuals (25%) than among white individuals (21%) [105]. In contrast, concern about side effects was more common among white individuals (15%) than among black and Hispanic individuals (10% and 6%, respectively) [105]. The belief that vaccination would not prevent illness was consistent across the racial/ethnic groups. In other studies, lower rates of influenza vaccination among older black adults have been significantly associated with lower rates of positive attitudes about vaccination [105; 118]. It is unclear whether the negative attitude represents mistrust of the vaccine itself or of healthcare/healthcare providers in general [105]. The findings of one study showed that, compared with white adults, more black and Hispanic adults believed that they had become sick from a previous influenza vaccination [106]. Language proficiency and level of acculturation have been associated with lower vaccination rates among older Hispanic adults [107; 119].

Parental attitudes about vaccines are an important factor in vaccination rates among children. The primary attitude is concern about the safety and efficacy of the vaccine, including fear of adverse events, the discomfort associated with vaccination, distrust of advocates of vaccination, and belief that the vaccine should not be given when a child has a minor illness [117; 120; 121; 122]. Difficulty remembering or confusion about the vaccination schedule for children is also a major challenge [120; 122]. Changes in access to health care have been noted as a factor in the low rate of influenza vaccination among teenagers [117].

HEALTHY PEOPLE 2020 TARGETS FOR PNEUMOCOCCAL AND INFLUENZA VACCINATION RATES		
Target Population	**Target Rate**	**Baseline Rate for Improvement (Year)**
Pneumococcal vaccination		
Four doses of PCV by 19 to 35 months of age	90%	80% (2008)
Adults 65 years of age and older	90%	60% (2008)
High-risk adults 16 to 64 years of age	60%	17% (2008)
Institutionalized adults 18 years of age and older[a]	90%	66% (2006)
Annual influenza vaccination		
Three doses of Hib vaccine by 19 to 35 months of age	90%	57% (2009)
Children 2 to 4 years of age	80%	40% (2008)
Children 5 to 12 years of age	80%	26% (2008)
Children 13 to 17 years of age	80%	10% (2008)
Adults 18 to 64 years of age	80%	25% (2008)
Adults 65 years of age and older	90%	67% (2008)
High-risk adults 18 to 64 years of age	90%	39% (2008)
Institutionalized adults 18 years of age and older	90%	62% (2006)
[a]Adults residing in long-term care facilities and nursing homes. PCV = pneumococcal conjugate vaccine; Hib = *Haemophilus influenzae* type b.		
Source: [114]		*Table 14*

Healthcare provider-related factors should also be addressed. Slightly more than half of older adults have said that their healthcare provider did not recommend influenza vaccination, and this percentage has been consistent across races/ethnicities [105; 106]. The lack of provider recommendation may be a misperception or may be a reality. It has been noted that nearly half of providers do not follow the ACIP recommendations for vaccination [116]. Provider recommendation is essential, as it has been found to be the strongest predictor of whether a person will receive vaccination, even among those who have negative attitudes toward vaccines [104; 106; 115; 116; 123]. Providers have said that the lack of an effective reminder system is a factor in low vaccination rates [116; 123].

Strategies to improve rates of vaccination and other preventive measures rely on effective patient-clinician communication. Among the most important factors for effective communication across all healthcare settings are knowledge of the language preference of the patient and family; an awareness of the patient's and family's health literacy levels; and an understanding of and respect for the patient's and family's cultural values, beliefs, and practices [124; 125; 126]. These issues are significant, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2013, more than 60.3 million Americans speak a language other than English in the home, with more than 25.1 million of them (8.6% of the population) reporting that they speak English less than "very well" [127]. Clinicians should ask their patients what language is spoken at home and what language they prefer for their medical care information, as some patients prefer their native language even though they have said they can understand and discuss medical information in English [128].

BARRIERS TO OPTIMAL VACCINATION AND POSSIBLE SOLUTIONS	
Barriers	**Solutions**
Decreased knowledge about pneumonia and its seriousness	Provide education resources (language-specific, as appropriate) that highlight the potential severity of disease and the consequences of not receiving protection through vaccination.
Belief that vaccines are unsafe or will cause illness	Refer patient (or parent) to objective information about vaccines.
Lack of awareness for the need of vaccination	Take advantage of all visits (well and acute) to remind patients (or parents) about the need for vaccination, to administer vaccination, or to schedule appointment for vaccination.
Lack of provider recommendations	Identify high-risk patients and encourage them to receive vaccination.
Lack of effective practice systems	Implement effective reminder systems and standing orders.
Source: Compiled by Author	*Table 15*

When the healthcare professional and the patient speak different languages, a professional interpreter should be used. Studies have demonstrated that the use of professional interpreters rather than "ad hoc" interpreters (e.g., untrained staff members, family members, friends) facilitates a broader understanding, leads to better outcomes, and is better aligned with patient preferences [129; 130; 131].

Studies have indicated that as many as 26% of patients have inadequate health literacy, which means they lack the ability to understand health information and make informed health decisions; an additional 20% have marginal health literacy [132; 133; 134]. Health literacy varies widely according to race/ethnicity, level of education, and gender. Clinicians are often unaware of the literacy level of their patients and family, but several instruments are available to test the health literacy level [126; 135]. These instruments vary in the amount of time needed to administer and the reliability in identifying low literacy. Among the most recent tools is the Newest Vital Sign (NVS), an instrument named to promote the assessment of health literacy as part of the overall routine patient evaluation [136]. The NVS takes fewer than three minutes to administer, has correlated well with more extensive literacy tests, and has performed moderately well at identifying limited literacy [126; 135]. Two questions have also been found to perform moderately well in identifying patients with inadequate or marginal literacy: "How confident are you in filling out medical forms by yourself?" and "How often do you have someone help you read health information?" [126]. Clinicians should adapt their discussions and educational resources to the patient's and family's identified health literacy level and degree of language proficiency and should also provide culturally appropriate and translated educational materials when possible.

Cultural competency is essential for addressing healthcare disparities among minority groups [124]. Clinicians should ask the patient about his or her cultural beliefs, especially those related to health, and should be sensitive to those beliefs.

Targeted evidence-based strategies can help clinicians improve vaccination rates (***Table 15***). Education about the importance of vaccination is the cornerstone of most strategies. Messages should be clear and emphasize the benefits of vaccination and the risks of not receiving vaccination. Acknowledging the risks of vaccines can help enhance patient trust [117]. Clinicians should give their patients a list of online resources that provide balanced information on vaccines (***Table 16***). Differences in beliefs about vaccines across racial/ethnic groups indicate that targeted messages developed for specific demographic subgroups may be useful [219]. In addition, language-specific educational resources may also help increase vaccination rates by enabling patients to better understand the need for vaccination and its safety.

RESOURCES ABOUT VACCINATIONS FOR PATIENTS AND PARENTS
American Academy of Pediatrics https://www.aap.org
American Academy of Family Physicians https://www.aafp.org
U.S. Department of Health and Human Services Vaccines https://www.vaccines.gov
The History of Vaccines https://www.historyofvaccines.org
Immunization Action Coalition http://www.vaccineinformation.org
Centers for Disease Control and Prevention Vaccines for Children (VFC) Program https://www.cdc.gov/vaccines/programs/vfc
Source: Compiled by Author *Table 16*

Education and provider recommendation are particularly important for high-risk people, as the lowest vaccination rates are reported for this population [102; 103]. One survey showed that provider recommendations for pneumococcal and influenza vaccination were low for this population; the rate of recommendation was lowest for people with a weakened immune system and those receiving radiation therapy or chemotherapy (***Table 17***) [116]. Clinicians should identify high-risk patients in their practice and take special steps to ensure that these patients receive appropriate vaccinations.

HEALTHCARE PROVIDER RECOMMENDATIONS FOR INFLUENZA AND PNEUMOCOCCAL VACCINATIONS BY PATIENT TYPE

Patient Type	Influenza Vaccine		Pneumococcal Vaccine	
	Physicians	PA/NP/RNs	Physicians	PA/NP/RNs
All adults	39%	59%[a]	—	—
Aged ≥50 years	28%[a]	15%	4%	18%[a]
Aged ≥65 years	37%	28%	65%	55%
Chronic lung disease	45%	40%	68%	55%
Diabetes mellitus	31%	25%	44%[a]	26%
Heart disease	20%	11%	29%[a]	12%
Chronic liver disease	22%	16%	27%	20%
Chronic kidney disease	22%	12%	25%	17%
Weak immune system	17%	20%	24%	29%
Radiation/chemotherapy	14%	9%	17%	10%
Asplenia	—	—	27%[a]	8%
Complications or risk from other illness	25%	17%	28%	23%
Smoker	—	—	13%	11%
Close contact with someone at high risk	24%	22%	11%	10%

[a]Significantly greater (P <0.05) than other provider group.
NP = nurse practitioner; PA = physician assistant; RN = registered nurse.

Source: Reprinted with permission from Johnson D, Nichol KL, Lipczynski K. Barriers to adult immunization. Am J Med. 2008;121:S28-S35. *Table 17*

Missed opportunities represent another practice-related area in which clinicians can improve vaccination rates. Although many clinicians check immunization status during well visits, most do not check the status during acute visits, nor do they take advantage of the visit to administer the vaccination [105; 115]. Healthcare providers can close the gap on missed opportunities for vaccination by taking advantage of every office visit to administer vaccinations, reminding their patients about the need for vaccination, or scheduling a future appointment for vaccination [105; 115; 117]. Educational fliers and pamphlets in the waiting room and examination rooms can engage patients and parents and help prompt discussions about vaccination [116].

Patient reminder and recall systems in primary care settings have been effective in improving vaccination rates. A meta-analysis found that rates among both children and adults increased up to 20% with several types of reminders, including postcards, letters, and phone calls [137]. The most effective reminder system was phone calls, but it was also the most expensive. Given that about 25% of primary care physicians currently use reminder systems, increasing the number of physicians who use such systems can in turn increase vaccination rates [123]. Standing orders for vaccinations have been shown to substantially increase vaccination rates, yet are used by only 20% to 33% of physicians [123; 138]. Again, adopting this system results in improved vaccination rates.

Many people have turned to facilities outside of their primary healthcare provider to receive vaccinations. Health fairs, pharmacies, grocery stores, senior centers, and workplaces have become more common settings for vaccination because of their convenience and lower cost [123; 138]. Clinicians can also help increase vaccination rates by participating in community events that provide vaccinations and by promoting these settings as alternative options.

Programs to provide vaccinations to high-risk patients in the emergency room have been successful at increasing vaccination rates [139; 140]. In a three-week intervention program at one inner city emergency department, participants were provided appropriate immunizations when they were at high risk for specific diseases [139]. During the study period, rates of influenza and pneumococcal vaccinations increased from 16% to 83% and from 18% to 84%, respectively. Such programs can help healthcare systems adhere to guideline recommendations for vaccinating hospitalized patients.

PNEUMONIA ASSOCIATED WITH HEALTHCARE FACILITIES

Pneumonia associated with healthcare facilities encompasses the broad category of cases that arise in persons who reside in, or have had significant recent exposure to, facilities such as hospitals, nursing homes, dialysis clinics, and transfusion centers. Despite advances in clinical care and prevention, this category of pneumonia remains a serious cause of morbidity and mortality and a challenging, costly public health issue. The IDSA and the ATS subdivide and defines this category of pneumonia as follows:

- HAP is hospital-acquired pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.
- VAP is a separate type of HAP that develops more than 48 hours after endotracheal intubation.
- HCAP is defined as pneumonia that occurs in a nonhospitalized patient with extensive healthcare contact, as defined by one or more of the following:
  - Intravenous therapy/chemotherapy or wound care within the prior 30 days
  - Residence in a nursing home or other long-term care facility

- Discharge from an acute care hospital or chronic care facility within the prior 90 days
- Attendance at a hospital or hemodialysis clinic within the prior 30 days

HAP and VAP have been studied most often, and the bulk of data on causative pathogens comes from studies of VAP. All three categories of pneumonia carry an increased risk for drug-resistant infection, though the risk of multidrug-resistant infection has been more consistently applicable to HAP and VAP [28]. Within the category of HCAP, nursing home-acquired pneumonia is the type with the most published data and will be discussed in this course. The ATS and the IDSA have collaborated to provide evidence-based recommendations, updated in 2016, for the diagnosis and treatment of HAP and VAP [28].

EPIDEMIOLOGY

Approximately 3 to 10 cases of HAP occur per 1,000 hospital admissions [26]. Pneumonia as a complication of hospitalization increases length of stay (by more than one week), increases mortality risk, and adds an additional cost of care that can reach $40,000 per case [26].

The rate of VAP is higher than that for HAP, with a reported rate of 1 to 4 cases per 1,000 ventilator-days, and rates as high as 10 cases per 1,000 in some neonatal and surgical populations [12; 28; 141]. An estimated 10% of patients requiring mechanical ventilation will develop VAP, and the mortality rate directly attributable to VAP is estimated at 13% [28]. Excess cost of care resulting from prolongation of hospital stay is estimated to be range from $30,000 to $40,000 per patient [28]. Pediatric VAP has not been as well studied as in adults. It occurs most commonly in children 2 to 12 months of age [142].

Pneumonia develops in approximately 2.3% of nursing home residents [1]. The mortality rate attributed to nursing home-acquired pneumonia is 10% to 30% [143].

RISK FACTORS

Illness and injury requiring admission to a healthcare facility often confers an increased risk for infection. Multiple factors account for this, including weakness and debility, use of indwelling catheters, compromised immune function, and poor nutrition [26; 144]. To these may be added sedating medication intended to promote sleep or permit invasive procedures; this in turn increases the risk for aspiration of nasopharyngeal secretions colonized with nosocomial bacterial pathogens.

The nasopharynx tends to become colonized by enteric gram-negative bacilli within a few days after admission to a hospital. Risk factors for colonization by multidrug-resistant pathogens include exposure to critical care units, prolonged hospital stay, prior antibiotic therapy, history of cigarette smoking, major surgery, multiple organ-system failure, and foreign bodies such as nasogastric and endotracheal tubes [26; 144].

Hospital-Acquired Pneumonia

In a systematic review, the American College of Physicians found several patient-related and surgery-related factors that increased the risk of postoperative pulmonary complications. The most common patient-related factors were the presence of COPD and an age older than 60 years [145]. Other significant factors were an American Society of Anesthesiologists (ASA) class of 2 (defined as a patient with mild systemic disease) or higher, functional dependence, and congestive heart failure. Cigarette use was associated with a modest increase in risk, and obesity and mild or moderate asthma were not found to increase risk [145]. Use of a PPI or histamine2 receptor antagonist is also thought to be a risk factor [45]. Surgery-related factors included prolonged duration of surgery (i.e., more than three to four hours), emergency surgery, and surgical site, with abdominal surgery, thoracic surgery, neurosurgery, head and neck surgery, vascular surgery, and aortic aneurysm repair being associated with the greatest risks [145].

Ventilator-Associated Pneumonia

The risk for VAP appears to be greatest during the first week after intubation. In one study, the risk was estimated to be 3% per day during the five-day period following intubation, decreasing to 2% per day for days 5 through 10, and to 1% per day for longer durations [147]. In a population of children who had cardiothoracic surgery, pneumonia risk correlated with mechanical ventilation for longer than three days [144]. Nearly half of all cases of VAP develop within the first four days of mechanical ventilation [148].

Other identified risk factors among adults include prolonged placement of the patient's head in the supine position; use of a nasogastric tube, paralytic agents, or PPI or histamine2 receptor antagonist; advanced age; chronic lung disease; and head trauma [45; 149]. Among children, VAP has been significantly associated with subglottic/tracheal stenosis, trauma, and tracheostomy [150]. In one study, VAP was most frequently associated with ICU admission diagnoses of postoperative care, neurologic conditions, sepsis, and cardiac complications [151].

Nursing Home-Acquired Pneumonia

The risk factors reported to be associated with nursing home-acquired pneumonia include profound disability, immobility, urinary incontinence, deteriorating health status, difficulty swallowing, and inability to take oral medications [42]. Older age, male gender, and antipsychotic and anticholinergic medications have also been reported to increase risk [23; 42].

ETIOLOGY

Gram-negative enteric bacilli and *Pseudomonas* spp. rarely colonize the upper respiratory tract of healthy individuals, but often do so in persons with an underlying disease, such as alcohol use disorder, and in those who are hospitalized or reside in nursing homes. Therefore, a history of recent hospitalization or nursing home residency should heighten suspicion for a gram-negative pathogen when such a patient presents with clinical signs of infection.

Most cases of pneumonia that develop in a healthcare facility are caused by aspiration of oropharyngeal or gastric secretions colonized with hospital bacterial flora [26; 28]. Consequently, the prevalent causation as well as the antibiotic sensitivity pattern of resident pathogens will vary from region to region in relation to the type of facility and burden of antimicrobial usage. The selection of initial antibiotic therapy in these cases is based on the patient's risk factors for infection with a multidrug-resistant organism, such as MRSA, *P. aeruginosa*, *K. pneumoniae*, or *Acinetobacter*. The ATS/IDSA lists the following risk factors for multidrug-resistant pathogens in patients presenting with HAP or VAP [233; 28]:

- Prior intravenous antibiotic use within 90 days
- Septic shock at time of VAP
- ARDS prior to onset of VAP
- High frequency of antibiotic resistance in the community of residence or the hospital unit of residence
- Five or more days of hospitalization prior to onset of pneumonia
- Home infusion therapy
- Chronic dialysis within 30 days
- Family member with multidrug-resistant infection
- Immunosuppression

Viral and fungal pathogens are rare causes of HAP, VAP, and nursing home-acquired pneumonia in immunocompetent adults. Outbreaks of viral pneumonia may occur during influenza season, and influenza, parainfluenza, adenovirus, and RSV are involved in about 70% of those cases [28]. *Candida* spp. and *Aspergillus fumigatus* may cause pneumonia in patients who have had organ transplantation or who have a compromised immune system and neutropenia.

Hospital-Acquired Pneumonia

Among adults with no previous antibiotic exposure, the most common bacterial causes of HAP are *S. pneumoniae*, *H. influenzae*, *Escherichia coli*, *K. pneumoniae*, and *S. aureus* [26; 28; 35; 148]. Gram-negative bacilli resistant to first-generation cephalosporins also frequently develop in late-onset HAP. For up to 40% of adults with previous antibiotic exposure, late-onset HAP is caused by potentially multidrug-resistant pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and MRSA [26]. In a study of more than 3,600 patients admitted to an ICU, *Pseudomonas* spp. was the cause of pneumonia in 25% of patients; MRSA in 18%; and *Acinetobacter* spp. in 6% [35]. Other studies have shown that *S. aureus* is common among patients who are in a coma or have diabetes or renal failure. *P. aeruginosa* is common among patients who have had a prolonged stay in the ICU, have received prior antibiotics or corticosteroids, or who have structural lung disease. *Legionella* is usually found in patients who have compromised immune systems [35].

The causes of HAP in children have not been well studied. However, outbreaks of pneumonia caused by RSV have been common in pediatric wards [28].

Ventilator-Associated Pneumonia

The most common pathogens associated with VAP in adults are *S. aureus* and *P. aeruginosa*, followed by *Enterobacter* spp., *A. baumannii*, and *K. pneumoniae* [26; 148; 152; 153]. These bacteria are among those that have become resistant to antibiotics, and the frequency of infection with MRSA is increasing. Almost half of all cases are caused by infection with more than one pathogen [148]. Although bacteria are the primary causative agents, viruses and saprophytic fungi have also been implicated as well [154].

As with HAP, few data are available on the etiology of VAP in children. In one report, *P. aeruginosa* was the most common cause, accounting for 22% of cases [142].

Nursing Home-Acquired Pneumonia

The bacterial pathogens that cause pneumonia in residents of nursing homes (and other long-term care facilities) differ according to the severity of disease. *S. pneumoniae* and *H. influenzae* are the most common causes of mild-to-moderate pneumonia in long-term care facilities [155]. In cases requiring hospitalization, *C. pneumoniae*, *S. aureus*, and influenza virus are frequently observed as well. Patients with severe illness commonly are infected with methicillin-sensitive *S. aureus* or MRSA, gram-negative enteric pathogens, or *P. aeruginosa* [23; 155].

DIAGNOSIS

The difficulty in recognizing HAP, VAP, or nursing home-acquired pneumonia has been well documented [28; 147; 156]. The clinical signs often resemble other, noninfectious conditions, and the specificity of clinical criteria is low [148]. According to the CDC definition, the diagnosis in adults is made on the basis of clinical signs and results of laboratory testing or imaging and must meet one of two criteria [157].

Criterion 1 is rales or dullness to percussion on physical examination of the chest and at least one of the following:

- New onset of purulent sputum or change in character of sputum
- Organisms cultured from blood
- Isolation of an etiologic agent from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

Criterion 2 is chest radiograph that shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion and at least one of the following:

- New onset of purulent sputum or change in character of sputum
- Organisms cultured from blood
- Isolation of an etiologic agent from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

- Isolation of virus from or detection of viral antigen in respiratory secretions
- Diagnostic single antibody titer immune globulin M or fourfold increase in paired sera immune globulin G for pathogen
- Histopathologic evidence of pneumonia

A set of clinical diagnostic criteria for HCAP includes the presence of a new and persistent (more than 48 hours) infiltrate in addition to one of the following [148]:

- Radiographic evidence of cavitation or necrosis
- Histopathologic evidence of pneumonia
- Positive pleural or blood culture for the same micro-organism as that found in respiratory secretions

Plus two of the following signs:

- Core temperature >38.3°C (100.94°F)
- WBC count >10,000 cells/mm^3
- Purulent tracheal secretions

There are no compelling data to recommend a specific approach to diagnosing HAP and VAP. For patients who are not receiving mechanical ventilation, collection of a sputum specimen should be attempted before antibiotic therapy is begun [35; 158]. Specimens for culture can be obtained by bronchoscopy with a protected specimen brush to limit contamination or by bronchoalveolar lavage. The latter method has been found to lead to higher rates of treatment than diagnosis based on the CDC definition, and one study showed that preferential sampling of the right lung (rather than the left) improved the diagnostic accuracy of bronchoalveolar lavage [35; 159; 160]. However, the invasive procedure has disadvantages, including high cost, need for technical expertise, and the potential for false-negative results [35; 159].

The ATS/IDSA guideline recommends collecting specimens from the lower respiratory tract for culture, preferably by noninvasive techniques, and reliance on semiquantitative culture technique [28]. Noninvasive methods to obtain respiratory samples in patients with HAP (non-VAP) include spontaneous expectoration, sputum induction, nasotracheal suctioning (in a patient unable to produce a sample), and endotracheal aspiration in a patient with HAP who subsequently requires mechanical ventilation [28]. A 2012 meta-analysis found no evidence that the use of quantitative cultures of respiratory secretions resulted in decreased mortality, reduced time in ICU and on mechanical ventilation, or higher rates of antibiotic change compared with qualitative cultures in patients with VAP [161]. In addition, there was no difference in mortality whether invasive or noninvasive methods were used to obtain specimens.

TREATMENT

The treatment of HAP and VAP is complicated by two divergent needs: the need for empiric therapy with a broad-spectrum antibiotic, to aid in reducing mortality rates, and the need to avoid the indiscriminate use of antibiotics, to avoid the development of resistance. To address this complex issue, the strategy of de-escalation therapy was developed. With this treatment approach, a broad-spectrum antibiotic targeted to likely pathogens is administered, and the antibiotic regimen is modified after the results of cultures are known [154; 162]. This strategy has reduced the mortality rate while achieving an overall objective of a more judicious use of antibiotics [154; 163]. In one study, de-escalation led to a significantly lower mortality rate compared with either escalation therapy or therapy that was neither escalated nor de-escalated (17% vs. 43% and 24%, respectively) [151].

RECOMMENDED ANTIBIOTIC THERAPY FOR HEALTH FACILITY-ASSOCIATED PNEUMONIA ACCORDING TO SITE OF CARE	
Site of Care	**Recommended Regimen**
Nursing home	Antipneumococcal fluoroquinolone or either a high-dose ß-lactam/ß-lactamase inhibitor or a second- or third-generation cephalosporin in combination with azithromycin
Hospital	Antipseudomonal cephalosporin, antipseudomonal carbapenem, or extended-spectrum ß-lactam/ß-lactamase inhibitor and antipseudomonal fluoroquinolone or aminoglycoside and anti-MRSA agent (vancomycin or linezolid)
Intensive care unit	Empiric MRSA and double coverage of *Pseudomonas* pneumonia
Source: [28]	*Table 18*

The empiric treatment of nosocomial pneumonia in general, requires knowledge of the infection history (hospital flora) of the healthcare facility and of individual patient units [35; 148; 164]. The selection of an empiric antibiotic regimen for HAP and VAP should be guided by local antibiotic-resistance data. The ATS/IDSA recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population(s), if possible [28].

In managing a case of HAP and VAP, the clinician should review in detail the guidance provided by the ATS/IDSA, and consider consultation with appropriate subspecialty colleagues [28]. Recommendations governing selected issues of initial management emphasize the following principles [28]:

- Obtain sputum samples from the lower respiratory tract for culture before beginning antibiotic therapy. Do not delay initiation of therapy for critically ill patients in order to obtain specimens.
- Begin treatment promptly, selecting an empiric antibiotic regimen that covers *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli.
- In selecting coverage for *S. aureus*, choose an agent active against MRSA (vancomycin or linezolid) for patients with risk factor(s) for antimicrobial resistance, treatment in hospital or units where >10% of isolates are methicillin-resistant, and patients in settings where the prevalence of MRSA is unknown.
- In selecting coverage for *P. aeruginosa*, one antibiotic active against this pathogen is satisfactory if the patient has no risk factors for antimicrobial resistance and <10% of gram-negative isolates from the patient's unit are resistant to the agent chosen; otherwise, prescribe two antipseudomonal antibiotics from different classes.
- Consider de-escalation of antibiotics after the results of cultures and sensitivities are known and the clinical response is satisfactory.
- After an optimal antibiotic regimen is confirmed, a seven-day course of therapy is recommended, provided the rate of improvement of clinical, radiographic, and laboratory parameter is satisfactory.
- For patients with HAP/VAP, it is suggested to use serum procalcitonin levels plus clinical criteria to guide discontinuation of antibiotic therapy, rather than clinical criteria alone.

Selection of specific antimicrobial therapy is influenced by the timing of onset of clinical signs, as well as the presence or absence of risk factors for infection with multidrug-resistant organisms. For early-onset pneumonia and/or patients with no such risk factors, limited-spectrum antibiotic therapy is recommended (***Table 18***) [28]. For late-onset pneumonia and/or patients at increased risk for multidrug-resistant organisms, a broad-spectrum antibiotic regimen is recommended.

Ventilator-Associated Pneumonia and Multi-Drug Resistant Pathogens

VAP is often caused by MRSA and gram-negative bacilli such as *Acinetobacter* spp. and *Pseudomonas*. Vancomycin has been considered the first choice for treatment of MRSA infections [154]. However, the ATS/IDSA guidelines note that linezolid may have advantages over vancomycin for pneumonia caused by MRSA [28]. Linezolid has been compared with vancomycin for the treatment of pneumonia caused by MRSA in many studies, and linezolid has been found to improve survival and to be more cost-effective [147; 165; 166; 167; 168]. In a 2008 study, the rate of early microbiologic cure was not significantly higher for linezolid than for vancomycin, although there were trends favoring linezolid in several secondary clinical outcomes, such as clinical cure; duration of ventilation, hospitalization, and stay in ICU; survival time not on a ventilator; and overall survival [169]. The findings led the authors to suggest that the benefit of linezolid may be related to factors other than bacterial clearance.

For healthcare-associated or community-acquired MRSA pneumonia, the IDSA recommends IV vancomycin or linezolid 600 mg PO/IV twice daily, if the strain is susceptible, for 7 to 21 days, depending on the extent of infection.

(https://academic.oup.com/cid/article/52/3/e18/306145. Last accessed August 22, 2018.)

Level of Evidence: A-II (Good evidence from one or more 1 well-designed clinical trial, without randomization to support a recommendation for use)

Role of Inhaled Antibiotic Therapy

For cases of VAP caused by gram-negative bacilli that are susceptible only to aminoglycosides or polymyxins, the ATS/IDSA suggests both inhaled and systemic antibiotics, rather than systemic antibiotics alone [28]. It is also reasonable to consider adjunctive inhaled antibiotic treatment as a last resort for patients who are not responding to intravenous antibiotics alone, whether or not the infecting organism is multi-drug resistant.

According to a meta-analysis, a short fixed-course (7 or 8 days) of antibiotic therapy may be more appropriate than a prolonged course (10 to 15 days) for patients with VAP not caused by non-fermenting gram-negative bacilli [170]. The short course reduced recurrence of pneumonia caused by multiresistant organisms without adversely affecting other outcomes. Among patients with nonfermenting gram-negative bacilli, recurrence was greater after the short course.

Nursing Home-Acquired Pneumonia

The ATS/IDSA guideline provides some direction for choice of antibiotic therapy but do not specify a distinct management protocol for nursing home-acquired pneumonia. This is expected to be addressed in the forthcoming updated guidelines for management of CAP.

Adherence to Guideline-Directed Treatment

The lack of adherence to guideline-directed treatment of pneumonia cases associated with healthcare facilities is evidenced by wide variations in practice. For example, one study showed that more than 100 different antibiotic regimens had been prescribed as initial treatment and that de-escalation therapy was used for only 22% of patients [151]. Adherence rates for pneumonia associated with healthcare facilities have been reported to be lower than rates of adherence to guidelines for treatment of CAP. In one survey, guideline-recommended antibiotics were used 78% of the time for CAP, compared with 9% for HCAP [18]. This lack of adherence was not due to unfamiliarity or disagreement with the guidelines; 71% of the survey respondents said they were aware of the guidelines, and 79% said they agreed with and practiced according to them. In contrast, another survey showed that fewer than half of physicians were familiar with the ATS/IDSA guideline for treatment of nursing home-associated pneumonia [23]. It is reasonable to expect that strategies used to enhance adherence to guidelines in the setting of CAP would also be beneficial in the setting of pneumonia associated with healthcare facilities. Thus, feedback on performance, reminder systems, standardized order sets, and education emphasizing outcomes and cost-effectiveness would be valuable.

PREVENTION

The CDC has published a guideline for the prevention of HAP and VAP, with a focus on strategies to decrease or eliminate modifiable risk factors for pneumonia associated with healthcare facilities [93]. These strategies are related to preoperative and postoperative care and measures to reduce the risk of transmission of etiologic pathogens. In addition, steps to prevent the spread of influenza virus are essential, especially during influenza season.

Hospital-Acquired Pneumonia

The prevention of postoperative pneumonia has long been a part of initiatives to decrease complications among patients undergoing surgery. The Respiratory Risk Index was developed to classify patients as being at low, medium, or high risk for postoperative respiratory failure [26]. The factors in the index include the complexity of the surgery, the ASA status, and comorbidities.

Smoking triples the risk for pulmonary complications after surgery, and smoking cessation for at least eight weeks before surgery, when possible, is recommended for current smokers [26]. The risk for complications in patients with respiratory disease or congestive heart failure can be ameliorated by optimum treatment before surgery (e.g., treatment with steroids for patients with COPD or asthma) [26].

Effective pain management after surgery also helps to decrease the risk of pulmonary complications. For postoperative patients who are not mechanically intubated, the ability to cough and clear secretions is important for preventing pulmonary complications [26]. The use of incentive spirometry and deep breathing exercises are recommended, especially for people at high risk for pulmonary complications, as are frequent coughing and early movement (in bed and/or walking) [26; 93; 145]. Fair evidence supports the selective (rather than routine) use of a nasogastric tube after abdominal surgery [145].

Ventilator-Associated Pneumonia

Two guidelines were developed to focus specifically on the prevention of VAP; one was jointly developed by the Society for Healthcare Epidemiology of America (SHEA) and IDSA, and the other was jointly developed by the Canadian Critical Care Trials Group and the Canadian Critical Care Society [149; 171]. In addition, the CDC guideline addresses the prevention of HAP and VAP [93].

PRACTICAL STEPS IN FOLLOWING GUIDELINES TO PREVENT VENTILATOR-ASSOCIATED PNEUMONIA
Assessment of Readiness to Extubate and Sedative Interruptions
• Implement a protocol to lighten sedation daily at an appropriate time to assess for neurologic readiness to extubate. Include precautions to prevent self-extubation, such as monitoring and vigilance, during the trial. • Include a sedative interruption strategy in the overall plan to wean the patient from the ventilator; add the strategy to the weaning protocol, if available. • Assess compliance each day on multidisciplinary rounds. • Consider implementation of a sedation scale, such as the Riker scale, to avoid oversedation.
Elevation of the Head of the Bed
• Include the intervention on nursing flow sheets and discuss at multidisciplinary rounds. • Encourage respiratory therapy staff to notify nursing staff if the head of the bed is not elevated or empower respiratory therapy staff to place the bed in this position with the help of nursing staff. • Include the intervention on order sets for initiation and weaning of mechanical ventilation, delivery of tube feedings, and provision of oral care.
Oral Care with Chlorhexidine
• Include the intervention as part of the intensive care unit admission order set and ventilator order set. Make application of prophylaxis the default value on the form. • Include intervention as an item for discussion on daily multidisciplinary rounds. • Post compliance with the intervention in a prominent place to encourage change and motivate staff. • Develop a comprehensive oral care process that includes the use of 0.12% chlorhexidine oral rinse. • Schedule chlorhexidine as a medication, which then provides a reminder for nursing staff and triggers the oral care process delivery.
Prophylaxis of Peptic Ulcer Disease
• Include intervention as part of the intensive care unit admission order set and ventilation order set. Make application of prophylaxis the default value on the form. • Include intervention as an item for discussion on daily multidisciplinary rounds. • Empower pharmacy staff to review orders for patients in the intensive care unit to ensure that some form of prophylaxis is in place at all times for patients.
Prophylaxis of Deep Venous Thrombosis
• Include intervention as part of the intensive care unit admission order set and ventilation order set. Make application of prophylaxis the default value on the form. • Include intervention as an item for discussion on daily multidisciplinary rounds. • Empower pharmacy staff to review orders for patients in the intensive care unit to ensure that some form of prophylaxis is in place at all times for patients.
Source: [174] *Table 19*

All of these agencies suggest a multicomponent strategy for prevention of pneumonia. Compliance with guidelines, however, has been slow; nursing surveys demonstrate rates of adherence to specific preventive measures ranging from 15% to 50% [12; 172]. Education is beneficial, and training sessions are a proven means to enhance knowledge and practice among healthcare professionals caring for intubated patients [173].

The Institute for Healthcare Improvement (IHI) found that implementation of its ventilator bundle, a collection of five prevention strategies drawn from these guidelines, led to a 45% reduction in the incidence of VAP [174]. The bundle includes the following interventions [174]:

- Assessment of readiness to extubate and daily interruptions of sedation
- Elevation of the head of the bed

- Daily oral care with chlorhexidine
- Prophylaxis of peptic ulcer disease
- Prophylaxis of deep venous thrombosis

The IHI how-to guide on preventing VAP provides several practical recommendations, and posting compliance with the ventilator bundle in a prominent place in the ICU can encourage and motivate staff (***Table 19***) [174].

Assessment of Readiness to Extubate

Because of the increasing risk of infection as the duration of ventilation increases, the primary goal is to extubate patients as early as possible. Thus, assessment of the readiness for extubation and weaning protocols are key aspects in the preventive approach [28; 35]. Daily interruption of sedation until the patient is awake has been shown to significantly decrease the number of days on mechanical ventilation, from 7.3 days to 4.9 days in one study [175]. There are risks to this approach, including the potential for increased pain, anxiety, and desaturation [174]. However, sedation interruption has been further demonstrated to reduce the complications of prolonged mechanical ventilation [176]. The SHEA/IDSA guideline recommends daily assessment of the readiness to wean and the use of weaning protocols [171]. For children, daily assessment of readiness to extubate should be carried out, but sedation interruption is not recommended because of the high risk of unplanned extubation [177].

Elevation of the Head of the Bed

Reducing the risk of aspiration and contamination with gastric secretions also helps to prevent the development of pneumonia. Positioning the head of the bed at an angle of 30 to 45 degrees reduces the risk of aspiration significantly [149; 178; 179]. In one randomized, controlled trial, there were 18% fewer cases of VAP among intubated patients in the group assigned to the recumbent position (45 degrees) compared with the group assigned to the supine position [179]. In another study, elevation of the head of the bed to 30 degrees was the most effective measure among a group of preventive interventions, resulting in a 52% variance in the rate of VAP [180]. Both the ATS/IDSA and SHEA/IDSA guidelines recommend maintaining the head of the bed at a 30- to 45-degree angle [28; 171]. An angle of 30 to 45 degrees is also recommended for infants and children, but a lower angle (15 to 30 degrees) should be used for neonates [177].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Institute for Clinical Systems Improvement recommends that, in the absence of medical contraindications, the head of the bed should be elevated at an angle of 30–45 degrees for patients at high risk for aspiration.

(https://www.icsi.org/_asset/y24ruh/VAP-Interactive1111.pdf. Last accessed August 22, 2018.)

Strength of Recommendation/Level of Evidence: A (Randomized, controlled trial) and R (Consensus statement)

Daily Oral Care with Chlorhexidine

Oral care interventions have been suggested by some, in part because of an association between a high level of dental plaque and a high rate of colonization with aerobic pathogens, including *S. aureus*, gram-negative bacilli, and *P. aeruginosa* [181]. Research has shown that oral decontamination with chlorhexidine leads to a significant reduction in the colonization of pathogens in the oropharynx. In most studies, the intervention has not had a significant effect on the rate of VAP or associated mortality, but more recent studies have shown a significant decrease in the rate of pneumonia [180; 182; 183; 184; 185; 186]. Brushing the teeth with chlorhexidine does not seem to add benefit [183]. Regular oral care with an antiseptic solution or chlorhexidine is recommended in the ATS/IDSA and SHEA/IDSA guidelines [28; 171].

Prophylaxis of Peptic Ulcer Disease

Prophylaxis of peptic ulcer disease has evolved with some conflicting views. Antacids, histamine2 receptor antagonists, and sucralfate have been traditionally given to patients receiving mechanical ventilation to prevent the formation of stress ulcers. However, reducing the amount of gastric acid can increase the risk of colonization of gram-negative bacilli in the stomach. As a result, the WHO recommends avoiding the use of these agents [187]. The CDC notes that there was insufficient evidence on the use of peptic ulcer prophylaxis and includes no recommendations in this regard in its guideline [93]. The ATS/IDSA guideline states that the risks and benefits of prophylaxis should be weighed carefully [28]. The most recent guideline, developed by SHEA/IDSA, notes that histamine2 receptor antagonists and PPIs should be avoided in patients who are not at high risk for developing a stress ulcer or stress gastritis [171]. However, peptic ulcer prophylaxis is recommended for children, as appropriate for age and health status [177].

Prophylaxis of Deep Venous Thrombosis

There is no clear relation between prophylaxis of deep vein thrombosis and VAP pneumonia, but the ACCP reported a decrease in the rate of VAP when such prophylaxis was implemented as part of a package of interventions and included this measure in its clinical practice guideline [188]. This recommendation also applies to children, as appropriate for age and health status [177].

Other Measures

In addition to the interventions in the ventilator bundle, other measures have been recommended to help prevent VAP. One such measure is selective decontamination of the digestive tract, which involves the use of either topical antiseptic, oral antibiotics, or a brief course of systemic antibiotics [26]. A meta-analysis of 28 studies showed that selective decontamination of the digestive or respiratory tract with use of topical antiseptic or antimicrobial agents helped reduce the frequency of VAP in the ICU [146]. The estimate of efficacy in prevention was 27% for antiseptics and 36% for antibiotics. Neither had an effect on mortality. This intervention is recommended in the SHEA/IDSA guideline [171].

Other preventive measures are targeted primarily to the care and use of ventilator equipment and practices in direct patient care. Meticulous attention to aseptic care of the equipment is necessary, and all reusable components, such as nebulizers, should be disinfected or sterilized. Tubing circuits should be replaced after 48 hours or earlier if there are signs of malfunction or contamination [93]. Changes in the design of the endotracheal tube have also been evaluated; for example, a tube with a suction port above the cuff allows for continuous aspiration of subglottic secretions. Use of this specially designed endotracheal tube has led to significantly lower rates of VAP as well as shorter durations of ventilation and shorter stays in the ICU [189; 190]. Among patients who had major cardiac surgery, the greatest benefit was found for patients who received ventilation for more than 48 hours [190]. Although the cost of the tube is higher than traditional tubes, the overall cost savings in preventing VAP more than compensates [189]. In one meta-analysis, subglottic secretion drainage was significantly associated with a decreased incidence of VAP, shorter time on mechanical ventilation, and longer time to the development of pneumonia [191]. The CDC, the ATS/IDSA, and the SHEA/IDSA guidelines recommend subglottic secretion drainage with this tube when possible [28; 93; 171].

The use of noninvasive ventilation is another measure that has reduced the incidence of VAP [93; 192; 193; 194]. In one study, the incidence decreased from 20% to 8% when noninvasive techniques were used routinely for critically ill patients with acute exacerbation of COPD or severe cardiogenic pulmonary edema [192]. Again, the CDC, the ATS/IDSA, and the SHEA/IDSA guidelines recommend the use of noninvasive ventilation when possible [28; 93; 171].

Quality Improvement Initiatives and Enhanced Infection Control Strategies

Quality improvement and infection control initiatives and strategies have led to a substantial decrease in the rates of VAP since the early 2000s [195]. The use of physician-led multidisciplinary rounds with team decision-making, checklists, and a focus on the ventilator bundle has led to significant reductions in the risk for pneumonia [196; 197; 198]. Strong downward trends were also found for the average length of stay in the ICU and the financial costs per patient [196].

Nursing Home-Acquired Pneumonia

As with HAP, strategies to decrease or eliminate modifiable risk factors for nursing home-acquired pneumonia should be implemented. In a guideline developed by a multidisciplinary panel, three recommendations were made for preventing pneumonia among nursing home residents [199]:

- Pneumococcal vaccination of patients at admission, if indicated
- Annual influenza vaccination for residents
- Annual influenza vaccination for nursing facility staff

Influenza Outbreaks

The vaccination status of healthcare workers has been found to have a direct effect on transmission of influenza virus to patients. Outbreaks of influenza in healthcare settings have been associated with low rates of vaccination among healthcare workers, and lower rates of nosocomial influenza have been related to higher vaccination rates among healthcare workers [200; 201]. Because of these findings, the ACIP recommends annual influenza vaccination for all healthcare workers, and the IDSA/ATS guideline endorses this recommendation [47]. The ACIP notes that the TIV is preferred over LAIV for workers who are in close contact with severely immunosuppressed people requiring protective isolation [112]. In addition, the Joint Commission began including vaccination programs in its accreditation standards in 2007 [123].

Despite these recommendations, only 29% to 69% of healthcare workers receive the influenza vaccination each year [202; 203; 204]. Healthcare workers have given many reasons for not being vaccinated, and the reasons vary among professions. Across all categories, shortage of the vaccine is the primary reason for not being vaccinated; other reasons include concern about side effects, inconvenience, and forgetfulness [204].

Efforts to increase the vaccination rate among healthcare workers are ongoing. A CDC guideline includes four level I recommendations to help increase rates of vaccination [205]:

- Offer influenza vaccine annually to all eligible healthcare workers
- Provide influenza vaccination to healthcare workers at the work site and at no cost as one component of employee health programs. Use strategies that have been demonstrated to increase influenza vaccine acceptance, including vaccination clinics, mobile carts, vaccination access during all work shifts, and modeling and support by institutional leaders.

- Monitor influenza vaccination coverage and declination of healthcare workers at regular intervals during influenza season and provide feedback of ward-, unit-, and specialty-specific rates to staff and administration.
- Educate healthcare workers about the benefits of influenza vaccination and the potential health consequences of influenza illness for themselves and their patients, the epidemiology and modes of transmission, diagnosis, treatment, and non-vaccine infection control strategies, in accordance with their level of responsibility in preventing healthcare-associated influenza.

Hand Hygiene

Hand hygiene is the most important preventive measure in hospitals, and the Joint Commission mandates that hospitals and other healthcare facilities comply with the Level I recommendations in the CDC guideline for hand hygiene [206]. The CDC guideline states the specific indications for washing hands, the recommended hand hygiene techniques, and recommendations about fingernails and the use of gloves [207]. The guideline also provides recommendations for surgical hand antisepsis, selection of hand-hygiene agents, skin care, educational and motivational programs for healthcare workers, and administrative measures.

Despite the simplicity of the intervention, its substantial impact, and wide dissemination of the guideline, compliance with recommended hand hygiene has ranged from 16% to 81%, with an average of 30% to 50% [207; 208; 209; 210; 211; 212]. Among the reasons given for the lack of compliance are inconvenience, understaffing, and damage to skin [207; 210; 213]. The development of effective alcohol-based handrub solutions addresses these concerns, and studies have demonstrated that these solutions have increased compliance [211; 214; 215]. The CDC guideline recommends the use of such solutions on the basis of several advantages, including [207]:

- Better efficacy against both gram-negative and gram-positive bacteria, mycobacteria, fungi, and viruses than either soap and water or antimicrobial soaps (such as chlorhexidine)
- More rapid disinfection than other hand-hygiene techniques
- Less damaging to skin
- Time savings (18 minutes compared with 56 minutes per eight-hour shift)

The guideline suggests that healthcare facilities promote compliance by making the handrub solution available in dispensers in convenient locations (such as the entrance to patients' room or at the bedside) and provide individual pocket-sized containers [207]. The handrub solution may be used in all clinical situations except for when hands are visibly dirty or are contaminated with blood or body fluids. In such instances, soap (either antimicrobial or nonantimicrobial) and water must be used.

However, there are many other reasons for lack of adherence to appropriate hand hygiene, including denial about risks, forgetfulness, and belief that gloves provide sufficient protection [207; 210; 213]. These reasons demand education for healthcare professionals to emphasize the importance of hand hygiene. Also necessary is research to determine which interventions are most likely to improve hand-hygiene practices, as no studies have demonstrated the superiority of any intervention [216]. Single interventions are unlikely to be effective.

ILLUSTRATIVE CASE

A man, 73 years of age, with a history of coronary disease, COPD, benign prostatic hyperplasia, and type 2 diabetes is hospitalized on transfer from an assisted-living facility because of weakness, loss of appetite, and low-grade fever. He had been admitted elsewhere for similar symptoms six months earlier and was diagnosed with urinary tract infection and treated with an unknown antibiotic. On evaluation, the patient's temperature is 37.6°C (99.8°F) and his other vital signs are stable; his exam is unremarkable. The WBC is normal, and the urinalysis shows pyuria. The admission chest x-ray shows hyperlucent lung fields and flattened diaphragms indicative of emphysema, but no infiltrate. Empiric treatment with a first-generation cephalosporin is begun for presumed urinary tract infection. The patient has no further fever, and his appetite and strength improve over the next 48 hours. He does have periods of mild agitation and insomnia, which are treated with a benzodiazepine at bedtime.

On the fourth day, as plans for discharge were in place, the patient appears worse, with a cough and a temperature of 38°C (100.4°F). A repeat chest x-ray shows a small focal opacity in the left upper lobe, thought to represent "aspiration." No change in antibiotics is made, and he is observed. Over the next 36 hours, the patient's condition worsens; he now has a cough productive of purulent sputum, fever (102°F to 103°F), shortness of breath, and tachypnea. A follow-up chest x-ray now shows an extensive opacification/infiltrate in the left upper lobe, with signs suggestive of either central cavitation or consolidation high-lighting emphysematous blebs.

In this elderly, somewhat debilitated man with chronic lung disease, who may be at risk of aspiration, a rapidly progressive, necrotizing (hospital-acquired) pneumonia developed while he was being treated with an oral cephalosporin for urinary tract infection, and receiving a nightly sedative medication for sleep.

What are the etiologic considerations and how should the patient be managed? Within days of admission to a hospital, and especially if treated with antibiotics, many patients develop nasopharyngeal colonization by hospital flora (e.g. gram-negative bacilli and occasionally S. aureus). When pneumonia supervenes, it reflects this colonization; moreover, prior antibiotic therapy tends to select out resistant pathogens. Therefore, the selection of empiric antibiotic treatment for this patient is based on the presumption of hospital-acquired bacterial infection in the lung caused by one or more pathogens resistant to first-generation cephalosporins. Cultures of blood and sputum should be obtained; gram stain of the sputum is often helpful in cases such as this, as it may demonstrate a predominate pathogen and whether it is gram-positive or gram-negative. Empiric antibiotic therapy, following ATS/IDSA recommendations for HAP, should be started promptly. A good choice here would be either an extended-spectrum ß-lactam/ß-lactamase inhibitor or a carbapenem with activity against Pseudomonas, combined with a fluoroquinolone and vancomycin, pending culture results.

Gram stain of the patient's sputum shows many polys and gram-negative bacilli; the culture is positive for *K. pneumoniae* and *P. aeruginosa*. His management, including empiric antibiotic therapy followed by de-escalation (of vancomycin) after culture data are available, conforms to ATS/IDSA recommendations. The patient is treated for 10 days and recovers following a brief period in the ICU.

This case illustrates that the pathogenesis of adult bacterial HAP is essentially the same as for CAP; namely, nasopharyngeal and upper respiratory colonization by virulent bacteria combined with aspiration of infected secretions during a period of impaired host pulmonary defenses. The difference lies in the burden of vulnerability imposed by hospitalization, including the propensity for colonization by gram-negative bacilli and the likelihood of antimicrobial resistance—so uncommon in healthy individuals outside of healthcare facilities, but so prevalent among patients hospitalized longer than 48 hours.

SUMMARY

Pneumonia-related mortality and morbidity have decreased since the late 1990s, but the disease still represents a substantial healthcare concern, especially for high-risk adults and children. Pneumonia is primarily classified according to the setting in which it develops, and the epidemiology, etiology, and risk factors vary according to setting. Diagnosis can be challenging because of differences in presentation and the lack of reliable, cost-effective, and rapidly available diagnostic testing methods. Specialty society guidelines for prevention, diagnosis, and treatment are available for CAP, HAP, and VAP. Guideline-directed treatment has been shown to improve the care of patients while promoting good antibiotic stewardship, minimizing exposure to inappropriate antibiotic treatment and reducing the emergence of antibiotic-resistant pathogens.

For CAP and nursing home-acquired pneumonia, determining the site of care is an important initial decision point. Guidelines from the IDSA/ATS, the PIDS/IDSA, and the ATS outline useful criteria for determining need for hospitalization and ICU care. These objective criteria are important factors in decision-making, but clinical judgment is also necessary for selecting the most appropriate site of care. Initial antibiotic treatment of all types of pneumonia is empirical. The selection is best made in relation to the most likely pathogens in a given clinical setting and to patient variables, such as comorbidities, recent exposure to antibiotics, and immunization status (for children). The timeliness of antibiotic treatment is also important; treatment should begin as soon as possible after diagnosis is made, administering the first dose promptly at the originating site of care.

Guideline-directed therapy of pneumonia has been shown to decrease morbidity and mortality, but adherence varies across settings and specialties and has been suboptimal. Physician practices and healthcare systems can improve adherence by implementing evidence-based strategies, such as standardized order sets, reminders, performance feedback, and easy-to-carry resources.

The incidence of pneumonia and its associated morbidity and mortality can be reduced further by adherence to effective preventive measures. Several guidelines are available for preventing specific types of pneumonia. The primary preventive strategy for CAP is immunization with influenza and pneumococcal vaccines, especially for individuals at high risk. These vaccinations have been shown to decrease the incidence and severity of pneumococcal pneumonia, as well as the risk of long-term morbidity and mortality. However, rates of vaccination vary across age, race/ethnicity, and risk. Two target populations with the lowest immunization rates are high-risk adults in need of pneumococcal vaccination and teenagers in need of influenza vaccination. Rates of vaccination among healthcare professionals are also low. Clinicians and healthcare systems should encourage vaccination and offer convenient access, especially during influenza season.

Lack of awareness about the need for vaccination, misconceptions about vaccines, and low level of knowledge about pneumonia have been reported to be the primary barriers to vaccination, especially among minority populations. Clinicians should promote practice strategies and public health efforts designed to target these barriers and address the populations in greatest need. Several strategies have been shown to increase vaccination rates, and education is the cornerstone. Clinicians should emphasize to patients the need and benefit of immunization, address concerns about the safety of vaccines, and incorporate routine immunization protocols into their practices. Provider recommendation is essential, as it is the strongest predictor of vaccination. System-related strategies such as automatic reminders and standing orders have also been effective.

Guidelines for prevention of HAP focus on measures to reduce pulmonary complications after surgery. Prevention of VAP relies on strategies to reduce the risk of transmission of etiologic agents. Use of a ventilator "bundle" (a set of interventions) has been shown to markedly reduce VAP. Although adherence to guidelines is suboptimal, healthcare facilities are increasingly implementing initiatives to help enhance adherence.

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