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Epidemiology and etiology of community-acquired pneumonia

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The seriousness of community-acquired pneumonia (CAP), despite being a reasonably common and potentially lethal disease, often is underestimated by physicians and patients alike. Terms such as the "old man's friend" have been used to describe CAP, even though such a term could not be farther from the truth. A more appropriate appellation is "the captain of the men of death," a description coined by Sir William Osler almost a century ago. To appreciate how serious CAP can be, one can examine the yearly impact of this disease in the United States. Because CAP is not a reportable disease, however, data on its incidence and epidemiology represent an educated guess rather than an exact representation. It has been estimated that approximately 4 million cases occur annually, but it also has been suggested that as many as 5 to 6 million cases actually may occur [1,2].

CAP results in more than 10 million visits to physicians, 64 million days of restricted activity, and 600,000 hospitalizations [3,4]. Approximately 80% of patients with CAP are treated as outpatients, and the mortality rate for these patients is usually less than 1%. The remaining 20% of patients require inpatient management, and the overall mortality rate is approximately 12%. This figure can vary substantially with different patient groups, such as the elderly who are admitted to an ICU from a nursing home [5–7]. The mortality rate for a 75-year-old patient who is transferred from a nursing home to an ICU and requires mechanical ventilation can exceed 50%.

I limit the discussion of the epidemiology and cause of CAP to bacteria and the severe acute respiratory syndrome (SARS) coronavirus and only discuss CAP cases involving immunocompetent adults.

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Epidemiology

Attack rates

Like the attack rates for many other infections, the attack rates for CAP are greatest among the oldest and youngest members of the population. Figures may vary from study to study and among different ethnic populations. One study in the United States showed that the highest rate was in children aged 0 to 4 years, and there were 12 to 18 cases per 1000 persons despite an overall attack rate of 12 cases per 1000 persons per year [8]. A study involving Finish patients aged 60 years or older found attack rates of 20 cases per 1000 persons annually [9].

Risk factors

Risk factors may be considered from general and specific points of view. There are risk factors for CAP itself and for specific pathogens such as *Streptococcus pneumoniae*, drug-resistant *S pneumoniae* (DRSP), gram-negative rods such as the Enterobacteriaceae, and *Pseudomonas aeruginosa* (Table 1).

Data on attack rates presented earlier show that the elderly are at increased risk for CAP, but older age is not a risk factor for a specific pathogen, with the sole exception of DRSP [10,11].

In addition to older age, other risk factors for CAP include coexisting illnesses such as chronic obstructive pulmonary disease (COPD), renal insufficiency, congestive heart disease, coronary artery disease, diabetes mellitus, malignancy, chronic neurologic disease, and chronic liver disease [6,12].

Another study involving patients aged 60 years or older found that the independent risk factors for CAP include asthma, alcoholism, immunosuppression, institutionalization, and age greater than 70 years (compared with patients aged 60–69 years) [13].

Because *S pneumoniae* is the most common bacterial cause of CAP, it is appropriate to begin with this bacterium to address risk factors for specific pathogens. Factors that increase the risk for infection with the pneumococcus are dementia, seizures, congestive heart failure, COPD, cerebrovascular disease, and overcrowding in institutions [14,15]. DRSP is a different matter and is part of the larger issue of the increasing rates of resistance that *S pneumoniae* and other pathogens have against β-lactams, macrolides, and fluoroquinolones. Although there are reports in the literature of increasing antimicrobial resistance among respiratory pathogens, why are there no matching reports of increasing clinical failures with antibiotics?

There are three possible answers to this question: (1) Mortality may be a relatively insensitive measure of the impact of resistance; (2) there is a poor correlation between in vitro susceptibility results and clinical outcomes; and (3) detection of clinical failure with an antimicrobial agent requires the use

Table 1
Risk factors for community-acquired penumonia and for specific pathogens

Entity	Risk factors
CAP	Increasing age Coexisting illness (COPD, renal insufficiency, congestive heart failure, coronary artery disease, diabetes mellitus, malignancy, chronic neurologic disease, chronic liver disease)
CAP (patient age >60 y)	Asthma Alcohol Immunosuppression Institutionalization Age >70 y
S pneumoniae	Dementia Seizures Congestive heart failure COPD Cerebrovascular disease Overcrowding in institutions
DRSP	Age >65 y Alcohol β-lactams within 3 mo Presence of more than one coexisting disease Immunosuppressive illness Exposure to kids in day care centers
Legionnaires' disease	AIDS Hematologic malignancy End-stage renal disease
P aeruginosa	Severe structural lung disease Steroids Broad-spectrum antibiotics Immunosuppression (e.g., malnutrition) Undiagnosed HIV infection Neutropenia

of the drug alone (ie, monotherapy) to treat an infection caused by a bacterial pathogen that is resistant to that drug. The latter is something that most investigators would be reluctant to study.

A number of controlled studies have assessed mortality as the main outcome measure in patients with pneumonia caused by penicillin-sensitive or penicillin-resistant pneumococci [16–22]. Some studies failed to show any effect of resistance on patient mortality [17–19,21], whereas other studies demonstrated a significant impact on patient mortality; however, these latter studies had methodologic or design flaws or assessed immunocompromised patients (who are not discussed in this article) [16,20,22].

Risk factors for DRSP are age greater than 65 years, alcoholism, use of β-lactam antibiotics within the previous 3 months, presence of more than one coexisting disease, immunosuppressive illness, and exposure to children in day care centers [11,23].

Risk factors for Legionnaire's disease are AIDS, hematologic malignancy, and end-stage renal disease. The rate ratios (ie, the observed prevalence in the legionella cases/expected prevalence in the population) were 41.9, 22.4, and 21.4 respectively [24].

Haemophilus influenzae commonly is seen with *S pneumoniae* and *Moraxella catarrhalis* in patients with chronic bronchitis who have a mild-to-moderate acute exacerbation of chronic bronchitis. *H influenzae* is also likely to be seen in patients with CAP who smoke. Gram-negative rods other than *H influenzae* are not common causes of CAP, but on report found that they are responsible for mortality rates of approximately 33% [25]. They account for approximately 8% to 10% of CAP cases that are admitted to a medical ward; these hospitalized cases represent 18% of all CAP cases. The most common gram-negative rod is *Pseudomona aeruginosa*. Considerable controversy was generated by the first suggestion of a treatment regimen for *P aeruginosa* infection in the original 1993 Canadian CAP Guidelines [26]. Some investigators insisted that such infection was seen only in nosocomial settings, whereas others countered that it could cause community- and hospital-acquired disease.

Gram-negative rods, such as the Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella* sp), typically are encountered in patients with coexistent disease, such as cardiac or pulmonary illness, particularly COPD, renal insufficiency, chronic neurologic disease, liver disease, diabetes mellitus, or a malignancy that was active in the past year [6]. Other risk factors for such pathogens are residence in a nursing home and immunosuppression [6,27].

P aeruginosa can be an aggressive and virulent pathogen. It may occur in patients with CAP, especially in those who are severely ill. The risk factors for *P aeruginosa* infection include severe structural lung disease such as bronchiectasis; treatment with steroids or broad-spectrum antibiotics; and immunosuppression in the form of malnutrition, which tends to result from T-cell-type deficiency, undiagnosed HIV infection, and neutropenia [6,27,28].

Why is there such a fundamental difference between the etiologic pathogens seen with CAP and with hospital-acquired pneumonia (HAP)? In CAP, *S pneumoniae* and the atypical pathogens occur more frequently, while in HAP, gram-negative rods are the most common pathogens as a group and *Staphylococcus aureus* represents is the most common microorganism.

To understand these differences and the predisposition for infection with aerobic gram-negative rods in HAP, the pathogenesis of nosocomial pneumonia should be considered. For certain infections, inhalation of an infected aerosol is the most important route of infection. For aerobic gram-negative rods, however, silent aspiration or microaspiration of oropharyngeal secretions is the most important route. Valenti et al [29] and Johanson et al [30] have shown that although oropharyngeal colonization by gram-negative rods is unusual in healthy individuals, such colonization occurs with increasing frequency in individuals with an underlying disease of significant severity. This finding was demonstrated in a quantitative animal

study in which the subjects were made increasingly ill by progressively infarcting more renal tissue [31].

It has been postulated that as the underlying disease progresses, cell-surface fibronectin is lost from the cells lining the oropharynx. As a result, receptors that usually are covered by fibronectin in the healthy state are exposed to gram-negative rods [32,33]. This loss is believed to occur as a result of the increased concentration of protease in the saliva [34].

The resultant exposure of receptors to gram-negative rods on host oropharyngeal cells provides a foothold for pathogens which otherwise would have been washed into the gut. Once oropharyngeal colonization by the pathogens is established, the subsequent silent aspiration of these virulent bacteria eventually results in the overwhelming of local host defenses in the lung and the development of pneumonia.

Anaerobic pulmonary infection is seen primarily in humans and may occur in patients with poor oral hygiene (the anaerobes arise in the gingiva and between the teeth). The anaerobes gain access to the distal airways if the airways are unprotected because of a swallowing disorder, neurologic illness, or impaired consciousness. Aspiration then occurs.

As mentioned earlier, *S aureus* is the most common cause of HAP but is seen occasionally in CAP (usually in severe CAP). The frequency of *S aureus* infection ranges from 1% to more than 22% in severe CAP cases and is up to 5% in all CAP cases. Risk factors include intravenous drug use, diabetes mellitus, renal failure, and recent infection with viral influenza [35].

SARS is the first important new infectious disease of the millennium. Reports of a new respiratory disease began appearing from Guangdong province in Southern China in late 2002. It was recognized as a distinct entity in February 2003 by Carlo Urbani of the Word Health Organization (WHO), who subsequently died of this infection. An explosive outbreak was described in Hong Kong in March 2003. Between November 2002 to August 2003, 8422 cases and 916 deaths occurred, and an overall fatality rate among cases in Hong Kong, China, Taiwan, Singapore, Canada, and the United States was 11%. The fatality rates among different age groups were as follows: 0 to 24 years, less than 1%; 25 to 44 years, 6%; 45 to 64 years, 15%; and greater than 65 years, 50%.

The SARS pathogen is a coronavirus that was identified by the WHO laboratory network in April 2003 [36]. A coronavirus is an RNA virus that first was isolated from chickens in 1937, and 15 species are known to infect humans, cattle, pigs, rodents, cats, dogs, and birds. Coronaviruses infect the epithelial cells of the respiratory or enteric tracts, but based on nucleotide and amino acid similarities, the SARS coronavirus (SARS-CoV) is only distantly related to previously sequenced coronaviruses and is not believed to have circulated in humans previously [37].

It has been postulated that SARS-CoV is a previously unknown animal coronavirus that mutated and developed the ability to infect humans. The virus can survive on paper or plaster walls for 36 hours, on plastic surfaces

and stainless steel for 72 hours, and on glass slides for 96 hours. The primary mode of transmission is direct mucus membrane (eyes, nose, mouth) contact with infectious respiratory droplets or through exposure to fomites. High-risk transmission settings include healthcare settings and households. Transmission to a casual or social contact occasionally may occur if there is intense exposure to a patient with SARS (eg, at the workplace or in airplanes and taxis).

The risk for transmission is greatest with healthcare workers, especially when aerosol-generating procedures are performed. Other risk factors are increased age, male sex, presence of comorbid conditions, and household contact with a probable case of SARS. Individuals with underlying chronic heart or lung disease also seem to be at increased risk for severe disease, although previously healthy young adults also have died.

Patient with SARS who are super spreaders have infected at least 10 contacts, including healthcare workers, family and social contacts, and visitors to healthcare facilities where the patient was hospitalized. Such a concept is not unique to SARS but has been seen in other infection settings, including Ebola virus infection, rubella, and laryngeal tuberculosis. In Singapore, five super spreaders are believed to have been responsible for 170 probable and suspect cases of SARS.

Cause

S pneumoniae is an encapsulated gram-positive diplococcus that, like *H influenzae*, colonizes the nasopharynx, which provides the organism with its ecologic niche. This site is the key reservoir for invasive infections by *S pneumoniae* in the host or for person-to-person transmission. Such spread occurs from one person to another by close contact, such as at day care centers, homeless shelters, or prisons [38–40].

Once the pneumococcus adheres to the appropriate nasopharyngeal cell, it may colonize or cause active infection. The latter occurs if the bacteria gain access to areas from which they are not removed easily. Such sites are the Eustachian tubes, distal airways, or sinuses, and infection can range from mild to severe.

The pneumococcus has a number of constituents that can serve as virulence factors, such as pneumolysin, autolysin, or capsular polysaccharide. Pneumolysin can activate complement, and capsular polysaccharide can activate complement or interfere with phagocytosis [41].

In addition to its ability to cause infection and avoid host defense mechanisms, the pneumococcus also can acquire free DNA that has been released from other nasopharyngeal pathogens. It then incorporates this DNA into its genetic makeup and accepts conjugative transposons, which carry genes. These mechanisms allow the pneumococcus to become resistant to one or more antimicrobial drugs [42,43].

S pneumoniae is the most commonly encountered cause of CAP that requires hospitalization. Among all patients with CAP, approximately 20% are hospitalized, 18% are admitted to medical wards, and 2% are admitted to the ICU. In a review of nine articles examining the cause of CAP, the isolation rate of *S pneumoniae* in hospitalized patients varied from 9% to 55% [5,44]. In a review of studies focusing on outpatients with CAP, *S pneumoniae* was not the most common pathogen, and its prevalence ranged from 5% to 9% [44]. Selected features of certain CAP pathogens are listed in Table 2.

The term "atypical pathogen" has lead to some confusion and controversy, and not all investigators believe that its use should be continued. The term usually includes *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydophilia pneumoniae*, and *Legionella* spp, but some investigators also include other microorganisms such as viruses, *Coxiella* spp, and *Chlamydia psittaci*. Reiman coined the term "atypical pneumonia" in 1938 after a number of cases

Table 2
Selected features of certain community-acquired pneumonia pathogens

Pathogen	Selected features
S pneumoniae	Gram-negative diplococcus Nasopharynx is key reservoir for invasive infection or person-to-person spread Has number of virulence factors Can acquire free DNA
M pneumoniae	Person-to-person transmission by respiratory droplets Invade as extracellular parasites Cases can be individual, small outbreaks, or mini-epidemics
C pneumoniae	Obligate intracellular parasites Dependent on host for energy production 50% of people are seropositive by age 20 y *C pneumoniae* has highest prevalence in elderly, and *M pneumoniae* has highest prevalence in the young
L pneumophila	Aerobic gram-negative unencapsulated bacilli Responsible for 95% of *Legionella* spp infections Has number of virulence factors Main reservoir in environment is water (freshwater, reservoirs, air conditioners) No person-to-person spread
H influenzae	Nonspore-forming gram-negative coccobacilli Humans are only host Person-to-person spread by droplet spread or direct contact Nontypeable *H influenzae* main *Hemophilus* spp CAP pathogen in adults
SARS-CoV	Hopefully a unique outbreak RNA virus Coronaviruses first found in cattle, pigs, rodents, cats, dogs, birds Presumably a previously unknown coronavirus that mutated and began to infect humans

of pneumonia were seen without any obvious etiologic agent and somewhat unusual or atypical signs and symptoms of pneumonia that failed to respond to standard treatments of the time, such as sulfonamides or penicillins [45].

Mycoplasmas are the smallest free-living forms and are prokaryotes that have a tri-layered cell membrane instead of a cell wall. Most mycoplasmas are aerobes and exhibit fastidious growth requirements. They have their own class, Mollicutes, and a human pathogen belongs to the family Mycoplasmataceae [46].

The mycoplasma that causes pneumonia in humans is *M pneumoniae*, which is transmitted from person to person by respiratory droplets generated by coughing. These pathogens generally invade as extracellular parasites, and after they adhere to target epithelial cells, they can cause damage by direct mechanisms (eg, hydrogen peroxide) or indirect mechanisms by an inflammatory response generated by their presence [47].

Cases of mycoplasma pneumonia can occur as individual cases, small outbreaks (eg, in families), or mini-epidemics (eg, in military barracks or boarding schools) [48]. U.S. data from suggest that the yearly incidence of *M pneumoniae* pneumonia is 1 case per 1000 persons [49]. Although all age groups may be affected, the highest attack rates are in individuals aged 5 to 20 years [50]. The nature of infection, however, seems to be age related. Infection tends to manifest as an upper respiratory tract infection in patients younger than 3 years and as bronchitis and pneumonia in patients older than 5 years [51,52].

Although *M pneumoniae* can cause outpatient and inpatient cases of CAP, the former is more common. Of the various etiologic agents that cause CAP in general and outpatient CAP in particular, *M pneumoniae* is the most common (prevalence, 17%–37%) [53–56].

The chlamydiae are obligate intracellular parasites. *C pneumoniae* differs from *Chlamydia trachomatis* and *Chlamydia psittaci* in that it is spread by respiratory secretions, person-to-person spread has not been reported, and it has a human reservoir. The chlamydiae have cell walls, and although they can synthesize some proteins, they must depend on the host to produce their own energy. The chlamydiae contain elementary bodies that are the infectious form of the parasite. Once engulfed by a host cell, the elementary bodies differentiate into reticulate bodies, which in turn divide to become a chlamydial inclusion.

Seroprevalence studies have been shown that infection with *C pneumoniae* is common and that approximately one half of the adults in Asia, North America, and parts of Western Europe have been infected [57–60]. Seropositivity of 50% usually is reached by age 20 years, and in the elderly it has reached almost 75%. The persistence of seropositive responses is likely caused by re-infection over time [61].

C pneumoniae is important in ambulatory and hospitalized patients. In the former, it has been documented as a causative pathogen in 8% of cases (incidence, 100 cases per 100,000 persons) [62]. *C pneumoniae* differs from

M pneumoniae in that *C pneumoniae* infection has the highest prevalence in the elderly, whereas *M pneumoniae* infection has the highest prevalence in the young. In hospitalized patients, *C pneumoniae* was found to be the second most common cause of CAP (peak incidence, 43%) [63].

An outbreak of pneumonia in 1976 at the American Legion Convention in Philadelphia lead to the discovery of the pathogen *Legionella pneumophila*. The subsequent study of stored sera showed that similar outbreaks occurred at the same hotel 2 years earlier, and outbreaks also occurred in Washington, D.C., and Minnesota in 1995 and 1957, respectively.

The Legionellaceae family has more than 40 species and a total of 64 serogroups. *L pneumophila*, which contains 15 serogroups, is responsible for approximately 95% of *Legionella* spp infections. The pathogens are aerobic gram-negative unencapsulated bacilli ranging from 2 to 20 μm in length. Although its role in the pathogenesis of infection is still unclear, *L pneumophila* produces a number of potential virulence factors in the form of hemolysins, proteases, and esterases [64].

The main reservoir for legionellae in the environment is water, including freshwater, moist soils from freshwater sources, and manmade water systems such as reservoirs and air conditioners. Increased numbers of legionellae are seen with increased temperatures (32°C–45°C), stagnant water, and the presence of amoebae and biofilms in the water.

Transmission from person to person has not been documented, and infection occurs solely by acquiring the pathogen from the environment. This situation typically occurs when water that contains the pathogen is aerosolized into appropriately sized droplets (1–5 μm in diameter) and is inhaled or aspirated by a susceptible host [65,66]. Devices capable of producing aerosols include respiratory therapy equipment, showers and faucets, ultrasonic mist machines, cooling towers, and evaporative condensers [67,68].

Generally, one does not associate Legionnaires' disease with outpatient CAP, because infections caused by *Legionella* spp tend to be more severe than most infections caused by *M pneumoniae* and *C pneumoniae*. *Legionella* spp can cause CAP cases that require hospitalization or admission to an ICU, and it is estimated that *L pneumophila* accounts for up to 6% of cases requiring in hospital management [69]. The overall mortality rate in CAP attributed to Legionnaires' disease is 14% [70].

H influenzae are fastidious, nonspore-forming, gram-negative coccobacilli that frequently colonize the upper respiratory tracts of individuals with predisposing conditions, such as COPD. When stained, the bacterium stained can vary in appearance from a small coccobacillary form to long filaments; this variety results in occasional errors of interpretation of the organism. *H influenzae* has no host other than humans, and nontypeable *H influenzae* may be found in the pharynx of as many as 80% of healthy persons.

Transmission from person to person is by droplet spread or direct contact. In approximately 20% of pediatric cases, the clinical infection resulting in pneumonia is caused by *H influenzae* B, whereas in adults, the infection usually

is caused by nontypeable *H influenzae*. This pathogen can cause outpatient and inpatient cases of pneumonia, and it is the third most frequently encountered pathogen in hospitalized cases.

Gram-negative rods other than *H influenzae*, which have been discussed previously in this article, are significant not because of the number of infections they cause but because of the morbidity and mortality associated with them. These rods include the enterobacteriaceae and the nonfermenters, such as *P aeruginosa*. The former are gram-negative facultative anaerobes that are distributed widely in nature and are found in soil, plants, and water. *Escherichia coli* and *Klebsiella* spp have been associated with CAP. These bacteria grow well on MacConkey agar, ferment D glucose, are cytochrome negative, and reduce nitrate to nitrite [71]. As the family name indicates, they are found primarily in the intestine of humans and animals and also are referred to as coliforms.

E coli is a motile, lactose-fermenting coliform that frequently is isolated in the microbiology laboratory. It is identified by its appearance on MacConkey agar and key biochemical reactions.

Klebsiella spp are nonmotile, lactose-fermenting coliforms that form mucoid colonies on agar media because of the presence of a large capsule. This capsule serves to impair neutrophil phagocytosis and interfere with leukocyte migration.

In CAP cases that required ICU admission, two studies showed prevalences of 6.3% and 11.0% for aerobic gram-negative rods [72,73]. No available data show whether gram-negative rods cause mild, ambulatory, outpatient cases of CAP. Gram-negative rods seem to be primarily associated with hospitalized CAP cases.

The nonfermentative gram-negative bacilli, such as *P aeruginosa*, are aerobic, nonspore-forming organisms that do not use carbohydrates as a source of energy or degrade carbohydrates by way of metabolic pathways other than fermentation. In contrast to the enterobacteriaceae, some members of this group may be oxidase positive, whereas others may fail to grow on MacConkey agar. Many of these bacteria are environmental organisms that can survive in an aqueous environment.

P aeruginosa is a straight or slightly curved oxidase-positive aerobic rod that produces pyocyanin, the water-soluble pigment that gives it its green color. Attachment of *P aeruginosa* is facilitated by fimbriae, which serve to anchor the organism to the host's cells. The virulence of pseudomonas and the pathogenesis of pseuodmonal infections is caused by a combination of bacterial invasiveness and various toxins associated with this pathogen. Examples of the latter include exotoxin A, which inhibits protein synthesis by a mechanism identical to that of diphtheria toxin [74]; proteolytic enzymes; lecithinase; collagenase; hemolysins; leukocidin; and elastase. The latter can digest elastin found in the lung and arterial walls. Like other gram-negative bacilli, *P aeruginosa* also contains endotoxin. Although *P aeruginosa* is a well-known nosocomial pathogen, it also can be seen in severe cases of CAP [26].

Anaerobes are a diverse group of microorganisms that are made up of bacteria that require reduced concentration of oxygen for growth (obligate aerobes) or that tolerate oxygen but grow better under anaerobic conditions (aerotolerant anaerobes). They may be gram positive or gram negative, cocci or bacilli, and typically are seen in patients predisposed to aspiration because of an unprotected airway or decreased level of consciousness. Microaerophils and anaerobes from the mouth flora are the anticipated pathogens in bacterial infections that are associated with aspiration, such as aspiration pneumonia and lung abscess. The prevalence of anaerobic infection in ambulatory patients with CAP is unknown, but aspiration is suspected in 5% to 10% of patients requiring in hospital management [75].

S aureus is an aerobic gram-positive coccus that is catalase and coagulase positive, and its major reservoir in humans is the anterior nares. From the nares, the skin, groin, axillae, and perineal region may become colonized [76]. Staphylococci appear in grape-like clusters when viewed by gram stain. They possess a typical gram-positive cell wall consisting of a thick layer of peptidoglycan, and they are nonflatulate, nonmotile, and nonspore forming. The organism grows best aerobically and is classified as a facultative anaerobe. Although 12 species of staphylococci colonize humans, the three of significant medical importance are *S aureus*, *S epidermidis*, and *S saprophyticus*.

S aureus can be a virulent pathogen and is associated with a number of infectious diseases. It can produce a number of enzymes and toxins that may have roles as pathogenic factors. Examples of enzymes include catalase, coagulase, hyaluronidase, and β-lactamases. Examples of toxins include α-, β-, γ-, and δ-toxin; and leukocidin. There are also epidermolytic toxins that are responsible for the findings of scalded skin syndrome, toxic shock syndrome toxin 1, and enterotoxins.

S aureus is not associated with outpatient cases of CAP, but it has been described as a potential pathogen in hospitalized cases (rate, 1%–3.7%) [77,78].

SARS represents what it is hoped will remain a unique outbreak of a respiratory illness. Various SARS risk factors and a description of the pathogen have been discussed earlier. As of August 2004, only one outbreak, involving eight cases, has occurred as a result of a laboratory-based accident in China, and no outbreaks have occurred as a result of community spread.

Infections in the elderly

In the United States, CAP is the fifth leading cause of death in individuals older than 65 years, and it is estimated that 60,000 persons in this age group die from CAP annually [79]. For patients who reside in long-term care facilities, who represent an important subset of the elderly, the risk for pneumonia is particularly high [80]. Despite these facts, data on the cause and epidemiology of CAP in the elderly are neither plentiful nor robust.

An observational CAP study showed that in the "elderly elderly" (ie, patients aged 80 years or older), the pneumococcus was the most important pathogen and was detected in almost one quarter (23%) of patients [81]. A Finnish study showed that in patients aged 60 years or older, the prevalences of select etiologic pathogens were 49% for *S pneumoniae*, 12% for *C pneumoniae*, 10% for *M pneumoniae*, 4% for *H influenzae*, and 10% for various respiratory viruses [82]. The atypical pathogens (*M pneumoniae*, *C pneumoniae*, *Legionnella* spp) were found in 7% of patients younger than 80 years but in only 1% of patients older than 80 years [81]. In the elderly with comorbid conditions (cardiopulmonary, renal, hepatic, or central nervous system disease; diabetes; malignancy), infection with a gram-negative rod, such as an enterobacteriaceae or *P aeruginosa*, was more likely to occur and was more severe [83].

Pneumonia acquired in a nursing home is important for a number of reasons. It is the second most common cause of infection in this setting, has the highest mortality rate for any nursing-home–acquired infection, and frequently results in the transfer of cases to the hospital for management. The overall incidence of nursing-home–acquired pneumonia varies from 0.3 to 2.5 episodes per 1000 days of resident care [84,85]. In a study by Muder [84], the most common etiologic agent in cases of nursing-home–acquired pneumonia were *S pneumoniae*, followed by *H influenzae* (nontypeable) and *M catarrhalis*. The risk for invasive pneumococcal disease was fourfold higher for patients with nursing-home–acquired pneumonia compared with patients with CAP [86]. With increasing age, the rate of oropharyngeal colonization by gram-negative rods increases. The incidence of aspiration also is higher in the nursing-home setting than in the community. It seems reasonable to assume that gram-negative rods would be important pathogens in nursing-home–acquired pneumonia; however, a significant drawback to the study of such pneumonias is the fact that there is too much reliance on sputum cultures to establish the diagnosis. More carefully done studies are needed to define the cause and epidemiology of pneumonia in the elderly and in the nursing-home setting.

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