An Overview of Pneumonia in Community and Hospital Settings

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ABSTRACT

Pneumonia is a common infection among patients both in the community and in the institutional setting and is a leading cause of morbidity and mortality in Canada. In the hospital setting, pneumonia is commonly associated with mechanical ventilation. The impact is significant, with the combined indirect and direct costs of community-acquired pneumonia in the United States estimated at US$12.2 billion and the direct costs of nosocomial pneumonia at US$2.2 billion. Several risk factors, such as altered level of consciousness, immunosuppression, obstruction, and malnutrition, may impair normal pulmonary defences. This article provides an overview of the epidemiology, pathogenesis, risk factors, diagnosis, management, and prevention of community- and hospital-acquired pneumonia, as well as issues related to antimicrobial resistance.

Key words: pneumonia, community-acquired; pneumonia, nosocomial; pneumonia, ventilator-associated; antibiotic resistance

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RÉSUMÉ

La pneumonie est une infection courante chez les patients autant dans la collectivité que dans les établissements de santé et l'une des principales causes de morbidité et de mortalité au Canada. Dans les établissements de santé, la pneumonie est souvent associée à l'utilisation de la ventilation artificielle. Les conséquences sont considérables, comme en témoignent les coûts globaux directs et indirects de la pneumonie extra-hospitalière qui s'élèvent aux États-Unis à environ 12,2 milliards de dollars US et les coûts directs de la pneumonie nosocomiale à 2,2 milliards de dollars US. Plusieurs facteurs de risque, comme une altération de la conscience, l'immunosuppression, une obstruction ou la malnutrition peuvent entraver les défenses naturelles des poumons. Cet article présente un aperçu de l'épidémiologie, de la pathogenèse, des facteurs de risque, du diagnostic, du traitement et de la prévention de la pneumonie extra-hospitalière et nosocomiale, de même que des problèmes liés à la résistance aux antimicrobiens.

Mots clés : pneumonie, extra-hospitalière; pneumonie, nosocomiale; pneumonie, liée à la ventilation artificielle; résistance aux antibiotiques

INTRODUCTION

Pneumonia, an infection of the lungs, is common among patients in both the community and the institutional setting and is a leading cause of morbidity and mortality in Canada. In 2001, combined with influenza, pneumonia was the seventh leading cause of death in the United States, after cardiovascular disease, cancer, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), accidents, and diabetes mellitus.[1] In the community setting, elderly patients account for most admissions to hospital and most deaths due to community-acquired pneumonia (CAP).[2] Nosocomial or hospital-acquired pneumonia (HAP) is the second most common nosocomial infection after urinary tract infection.[3] In the intensive care unit (ICU), ventilator-associated pneumonia (VAP) is common in mechanically ventilated patients, accounting for 86% of HAP.[3,4] Several risk factors such as age and concurrent illnesses may predispose a patient to pneumonia or may affect morbidity and mortality rates. Over the past decade, guidelines have been developed for the management, treatment, and prevention of pneumonia in various settings. This article provides an overview of the epidemiology, pathogenesis, risk factors, diagnosis, management, and prevention of pneumonia, as well as the causative pathogenic organisms and antimicrobial resistance issues.

PATHOGENESIS

Several pulmonary defence mechanisms in the upper airway (e.g., nasopharynx) and the lower airway (e.g., bronchi and alveoli) function to prevent pulmonary infections. Particulate matter and microorganisms are eliminated through anatomic and mechanical barriers, humoral and cell-mediated immunity, and phagocytic activity.[5,6] Details about these defence mechanisms are available in other reviews and will not be presented here. For an invasive infection to occur, the pathogens must gain access to the lungs by direct inoculation, hematogenous spread, inhalation of aerosolized inocula, or aspiration of bacteria that colonize mucosal surfaces.[6] Bacterial colonization of the upper airway followed by aspiration of oropharyngeal contents into the lower respiratory tract is the most common cause of a respiratory tract infection. The bacterial load after colonization of the upper airway may be as high as 10^8 to 10^{10} organisms per millilitre in oropharyngeal secretions in the normal host.[6] It has been estimated that 45% of the population experiences aspiration during sleep.[7] Aspiration of oropharyngeal secretions is more common among patients with altered level of consciousness because of stroke, seizures, alcohol or sedative use, drug intoxication, or underlying diseases.[6]

Other factors that may impair pulmonary host defences include immunosuppression, obstruction, and malnutrition. Exposure to chemical irritants such as tobacco smoke is known to impair mucociliary and macrophage activity, thus interfering with the clearance of particulate matter. Consumption of ethanol may also impair defences by inhibiting cough and epiglottic reflexes. In addition to these mechanisms, some pathogens such as *Mycoplasma pneumoniae* and *Haemophilus influenzae* may impair ciliary function, while viral infections (e.g., influenza) may damage the respiratory epithelium and impair neutrophil and macrophage activity.[6] Furthermore, underlying diseases such as COPD, cystic fibrosis, and malignancy may predispose patients to pneumonia because of structural dysfunction or obstruction.[6]

In contrast, many patients in the ICU undergo intubation with an endotracheal tube and mechanical ventilation. These procedures bypass many of the natural pulmonary defences, placing the patient at greater risk of VAP by facilitating acquisition of and colonization by pathogenic organisms.[8,9] An endotracheal tube, for example, bypasses the cough and mucociliary defences.[9] Inoculation and colonization of the lower respiratory tract may also be facilitated by medical staff and ventilator equipment.[8,9]

SYMPTOMS

The symptoms of pneumonia include fever or hypothermia, rigours, sweats, cough, sputum production, change in sputum colour, pleuritic chest pain, shortness of breath, and tachypnea. Nonspecific symptoms or complaints, such as nausea, vomiting, abdominal pain, loss of appetite, fatigue, myalgias, arthralgias, and headache, occur in approximately 10% to 30% of patients with CAP.[10,11] Among elderly patients, however, fever, cough, and shortness of breath are less commonly reported.[12,13] As a result, the recognition and treatment of pneumonia may be delayed in this age group. In the absence of other complaints, confusion or altered mental status may be more common among elderly patients.[12] Unfortunately, this constellation of symptoms is not useful in determining the specific bacterial cause of pneumonia.[2] In patients with HAP, similar symptoms may be present; in patients with VAP, the symptoms may be less obvious and pneumonia more difficult to diagnose.[3,9]

DIAGNOSIS

In addition to the symptoms described above, several findings consistent with pneumonia can be detected through noninvasive and invasive tests. Auscultatory changes such as altered air exchange, breath sounds, or rales may be detected.[11] Chest radiography may show pulmonary infiltrates consistent with acute pneumonia.[11] Signs of consolidation and tachypnea may also be found.[14] Resolution of such symptoms may be delayed even if the patient receives appropriate antibiotic therapy. In CAP, for example, a majority (64.3% to 86.5%) of patients who have undergone treatment may experience at least one symptom of CAP several weeks after their initial presentation.[15]

Along with history and physical examination, noninvasive tests may include Gram staining, blood culture, sputum culture, and chest radiography, depending on the site of care (outpatient or inpatient). For most ambulatory patients with CAP, microbiologic investigations and chest radiography are not required. In contrast, culture of the sputum, blood, and other body sites, as well as chest radiography, is often performed for hospital inpatients. In conjunction with signs and symptoms, a chest radiograph aids in the diagnosis of pneumonia by characterizing the extent and severity of disease. In the absence of a chest radiograph, the differential diagnosis based on symptoms may include noninfectious causes (e.g., reactive airway disease, congestive heart failure, pulmonary embolism), as well as upper and lower respiratory tract infections.[11] Depending on the severity of illness, invasive tests such as transtracheal or transthoracic aspiration, thoracentesis, open lung biopsy, or bronchoscopy (with protected specimen brush or bronchoalveolar lavage) may also be considered to aid in identifying a causative pathogen.

COMMUNITY-ACQUIRED PNEUMONIA

Epidemiology

CAP is defined as an acute infection of the lung parenchyma occurring in patients residing outside of a hospital or in patients who have been living in a long-term care facility for up to 2 weeks.[11] In the United States, the annual incidence of CAP is estimated at 12 to 18 cases per 1000 population, resulting in 0.6 million to 1.0 million hospital admissions and an estimated 40 000 to 60 000 deaths per year.[11,16] Up to 80% of patients with CAP are treated in the ambulatory outpatient setting.[2] Depending on age and concurrent illnesses, the mortality rate associated with CAP ranges from less than 1% to 30%. The overall economic impact of CAP in the United States was estimated at US$8 billion in 1998, with approximately 60% (US$4.8 billion) attributed to elderly patients (older than 65 years), who are the most vulnerable.[17] In addition, the length of hospital stay was longer for older patients, 7.8 versus 5.8 days for elderly and younger patients, respectively.[17] In a recent study of a US claims database, Colice and others[18] estimated the cost of CAP, including direct and indirect costs, at US$12.2 billion. Similar data are not available for Canada, but given the relative populations of the 2 countries, the number of hospital admissions, the number of deaths, and the associated costs in Canada may be 10% of the US values.

Risk Factors

As described previously, many conditions increase the risk of aspiration of oropharyngeal secretions or impair pulmonary host defences. The independent risk factors for pneumococcal infections identified in one study included dementia, seizure disorders, cigarette smoking, congestive heart failure, cerebrovascular disease, living in an institutional setting, and COPD.[19] In a study of 4175 elderly patients, over 57% of those with pneumonia had one or more of the following factors: heart disease, lung disease, asthma, immunosuppressive therapy, or alcoholism or were living in an institution.[20]

Several independent risk factors for mortality, similar to those predisposing patients to CAP, have been identified, including age (greater than 65 years), immunosuppression, malignancy, congestive heart failure, diabetes mellitus, alcohol consumption, neurologic disorders, and laboratory abnormalities (such as hyponatremia, hyperglycemia, azotemia, hypoalbuminemia, hypoxemia, and abnormalities on liver function testing).[11] The presence of dyspnea, chills, altered mental status, hypothermia or fever, tachypnea, and hypotension have been associated with a higher mortality rate.[11] Radiographic findings (e.g., pleural effusion or pulmonary infiltrate) have also been associated with increased risk of mortality.[11]

Causes

The cause of CAP is unknown in the majority of cases, and a pathogen is recovered in only 40% to 60% of cases. Factors such as alcoholism, COPD, site of care, animal exposure, travel history, aspiration, viral infections, and comorbidities may influence the causative pathogen.[2] The most common bacteria causing CAP include *Streptococcus pneumoniae*, *H. influenzae*, *Staphylococcus aureus*, and atypical pathogens such as *Legionella* spp., *Chlamydia pneumoniae*, and

Mycoplasma spp. (see Table 1).[14] In the ambulatory setting, *M. pneumoniae* appears to be the most common pathogen.[2] Among patients with CAP who require hospital admission, *S. pneumoniae* is the most common cause, followed by *C. pneumoniae*, *H. influenzae*, and *Legionella pneumophila*.[2,14] In 2% to 5% of cases of CAP, multiple pathogens have been identified.[11] Less common causes of CAP include *S. aureus* and gram-negative organisms such as *Klebsiella* spp. and *Pseudomonas aeruginosa*. Nonbacterial causes of CAP include viruses (e.g., respiratory syncytial virus, influenza virus) and fungi. Secondary bacterial infections following respiratory viral infection are relatively common.[16] Recent guidelines have stratified the likely causes of CAP on the basis of patient age, site of acquisition (community or nursing home), site of care (ambulatory, hospital ward, or ICU), and comorbidities.[2,11,16,21]

Table 1. Causes of Community-Acquired Pneumonia*

Cause	Prevalence (%)
Streptococcus pneumoniae	20–60
Haemophilus influenzae	3–10
Staphylococcus aureus	3–5
Gram-negative bacilli	3–10
Miscellaneous†	3–5
Atypical organisms	
Legionella spp.	2–8
Chlamydia pneumoniae	3–6
Mycoplasma pneumoniae	1–6
Viruses	2–15
Aspiration	6–10

*Source: Bartlett and Mundy.[14]
†Includes *Moraxella catarrhalis*, group *A Streptococcus, Neisseria meningitidis.*

Antibiotic Resistance

Of global concern has been the increasing prevalence of antibiotic resistance among CAP pathogens. Bacteria may become resistant to an antibiotic because of a change in target site, production of antibiotic-modifying or antibiotic-inactivating enzymes, decreased penetration of the agent into the bacteria, or presence of an efflux pump.[22] The overuse of antibiotics in humans and agriculture are 2 factors contributing to the rise in antibiotic resistance.[22] This rise in resistance has resulted in significant changes in the management of CAP over the past decade. For example, the emergence of *H. influenzae* and *Moraxella catarrhalis* capable of producing ß-lactamase (an inactivating enzyme) has limited the use of older ß-lactam antibiotics such as penicillin and amoxicillin.[23]

Over the past decade, concern has focused on the emergence of penicillin-resistant *S. pneumoniae* (PRSP). The susceptibility of *S. pneumoniae* is currently defined by the Clinical and Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards) as follows: penicillin-susceptible, minimum inhibitory concentration (MIC) less than 0.06 µg/mL; intermediate susceptibility, MIC 0.12 to 1 µg/mL; and penicillin-resistant, MIC greater than 2 µg/mL.[24] PRSP was first described in the 1960s and remained relatively uncommon in North America until the 1990s.[25] Penicillin resistance in this organism is due to a gene mutation resulting in a change in the penicillin-binding proteins, enzymes in the bacterial cell membrane which are responsible for synthesis of the bacterial cell wall and which are the target sites for penicillin. Selective pressure from the overuse of penicillin and other ß-lactam antibiotics is thought to have been the major contributor to the emergence of PRSP.[25] The prevalence of PRSP in Canada was 2.5% in 1988.[26] More recently, the prevalence of PRSP (intermediate susceptibility and resistant) ranged from 21.2% to 24% among respiratory isolates of *S. pneumoniae* collected between 1997 and 2003.[27] Of particular importance has been the rise in resistant *S. pneumoniae* isolates, from 2.4% in 1999 to 13.8% in 2002.[27] In addition, the proportion of multidrug-resistant (MDR) *S. pneumoniae* increased from 2.7% in 1997 to 8.8% in 2002.[27] Strains of *S. pneumoniae* resistant to antibiotics such as macrolides and fluoroquinolones have been reported globally.

The prevalence of macrolide resistance in Canada is increasing, although its clinical impact remains to be determined. Reports of macrolide treatment failure have been published, although the number of cases remains low (because of low volume of macrolide use).[28] The mechanism for macrolide resistance is an efflux pump (due to the *mefA* gene) or ribosomal methylation (due to the *ermB* gene) blocking the binding of macrolides to the ribosomal target site in *S. pneumoniae*. In North America, the mechanism of resistance is evenly divided between efflux and ribosomal methylation.[29]

The impact of increased fluoroquinolone consumption and the emergence of fluoroquinolone-resistant *S. pneumoniae* in Canada have been described by Chen and others.[30] The annual number of fluoroquinolone prescriptions increased from 0.8 to 5.5 per 100 persons between 1988 and 1997, while the prevalence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones increased from 0% in 1993 to 1.7% in 1997/98.[30] Not surprisingly, treatment failure in patients with CAP receiving respiratory fluoroquinolones

(e.g., levofloxacin), caused by fluoroquinolone-resistant *S. pneumoniae*, has since been reported.[31,32] The mechanism of this resistance is related to changes in *S. pneumoniae* DNA gyrase and topoisomerase (fluoroquinolone target sites) caused by gene mutations or by the presence of an efflux pump. These reports highlight the selective pressure of increasing use of fluoroquinolones and the selection of antibiotic resistance in *S. pneumoniae*. In an update on CAP management, Mandell and others[16] expressed concern about the overuse of fluoroquinolones and the potential loss of this drug class as a treatment for pneumonia.

Management and Treatment

Over the past 10 years, several guidelines have been published in response to evolving knowledge about CAP and antibiotic-resistant pathogens. In 2000, guidelines of the Infectious Diseases Society of America (IDSA)[11] and of the Canadian Infectious Diseases Society (CIDS), in association with the Canadian Thoracic Society (CTS),[2] were published simultaneously. These guidelines reviewed the epidemiology, diagnosis, risk factors, management, and treatment of CAP in depth. A recently published update of CAP management addressed new concerns and treatment approaches developed since 2000.[16] A significant aspect of the more recent guidelines has been support for the use of prognostic scoring to identify patients who should be admitted to hospital. Past surveys have suggested wide variation between hospitals in both Canada and the United States in terms of length of stay for patients with CAP.[33-35] Differences in the length of stay may be attributed to physicians overestimating the risk of death among patients with CAP, which could result in unnecessary hospital admissions. As a result, criteria or prognostic factors have been developed to assist physicians in identifying patients who should be admitted.

The most common method is the Pneumonia Severity Index (PSI), which was developed by Fine and others[36] to identify patients with CAP at low risk of death who can be managed as outpatients (Figure 1). Factors associated with mortality were derived from a database of over 14 000 patients and were validated in over 40 000 patients (Table 2). The PSI allows patients to be classified into 5 risk classes. In the first stage of a 2-step process, patients are screened according to age, comorbidities, and physical findings to identify low-risk patients (class I), who may safely be managed as outpatients. Patients in classes II to V are assigned weighted scores according to age, comorbidities, and physical, radiologic, and laboratory findings. Class I patients have the lowest risk of mortality (0.1%). Patients in classes II and III may also be managed as outpatients since the risk of mortality is less than 1%, although some class III patients may require a brief hospital stay. In contrast, patients in classes IV and V must generally be admitted to hospital because of their high mortality risk (9% to 27%). Use of the PSI in association with treatment guidelines may result in cost savings for institutions treating patients with CAP.[37-39]

Canadian recommendations (from the CIDS and CTS) are presented in Table 3. These recommendations were derived through expert consensus and are not necessarily based on randomized clinical trials.[2] Recommendations for use of antibiotics in the treatment of CAP take into consideration the site of care, probable pathogens, prevalence of antibiotic resistance, and the empiric nature of initial CAP management. ß-Lactam antibiotics, macrolides, respiratory fluoroquinolones, and doxycycline have all been used for empiric treatment of CAP.[2,40] The advantages, disadvantages, and adverse effects of these agents have been presented in recent reviews.[2,40] For outpatient treatment, macrolides (erythromycin, azithromycin, and clarithromycin) are generally recommended.[2] For patients with comorbidities and/or exposure to steroids or antibiotics, respiratory fluoroquinolones (agents with activity against *S. pneumoniae*), such as levofloxacin, gatifloxacin, and moxifloxacin, are recommended.[2] For nursing home residents, a respiratory fluoroquinolone or amoxicillin–clavulanate plus a macrolide may be used.[2] For patients requiring admission to hospital, a respiratory fluoroquinolone is recommended

Table 2. Risk Factors for Death in Patients with Community-Acquired Pneumonia*

Age > 50 years
Male sex
Residence in a nursing home
Concurrent illness (neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease)
Altered mental status
Pulse ≥ 125/min
Respiratory rate ≥ 30/min
Systolic blood pressure < 90 mm Hg
Temperature < 35°C or ≥ 40°C
Blood urea nitrogen ≥ 11 mmol/L
Glucose ≥ 14 mmol/L
Hematocrit < 30%
Sodium < 130 mmol/L
Partial pressure of oxygen < 60 mm Hg
Arterial pH < 7.35
Pleural effusion

*Based on the pneumonia severity index of Fine and others.[36]

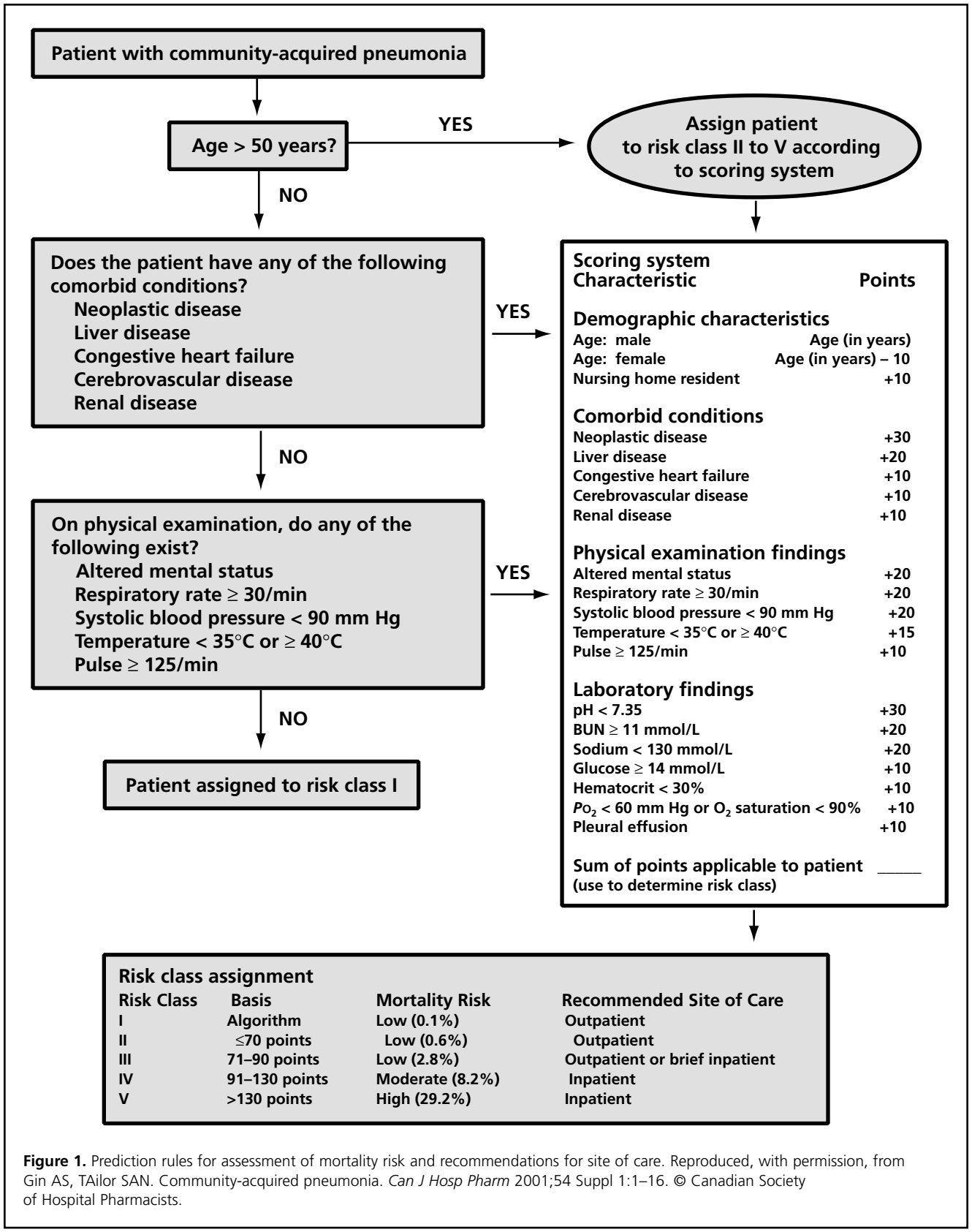

Figure 1. Prediction rules for assessment of mortality risk and recommendations for site of care. Reproduced, with permission, from Gin AS, TAilor SAN. Community-acquired pneumonia. *Can J Hosp Pharm* 2001;54 Suppl 1:1–16. © Canadian Society of Hospital Pharmacists.

Table 3. Antibiotic Recommendations of the Canadian Infectious Diseases Society and the Canadian Thoracic Society for Patients with Community-Acquired Pneumonia*

Site of Care	First-Choice Antibiotic†	Alternative Antibiotic†
Outpatient		
No modifying factors	Macrolide	Doxycycline
COPD, no antibiotics or steroids	New macrolide	Doxycycline
COPD, recent antibiotics or steroids	"Respiratory" fluoroquinolone	Amoxicillin–clavulanate + macrolide OR SGC + macrolide
Suspected macro-aspiration	Amoxicillin–clavulanate + macrolide	"Respiratory" fluoroquinolone + clindamycin or metronidazole
Nursing home	"Respiratory" fluoroquinolone OR amoxicillin–clavulanate + new macrolide	SGC + new macrolide
Medical ward	"Respiratory" fluoroquinolone	Second-generation or higher cephalosporin + macrolide
Intensive care unit	IV "respiratory" fluoroquinolone + cefotaxime, ceftriaxone, or ß-lactam/ß-lactamase inhibitor	IV macrolide + cefotaxime, ceftriaxone, or ß-lactam/ß-lactamase inhibitor
	If *Pseudomonas aeruginosa* is suspected, antipseudomonal fluoroquinolone (e.g., ciprofloxacin) + antipseudomonal ß-lactam or aminoglycoside	Triple therapy: antipseudomonal ß-lactam (e.g., ceftazidime, piperacillin–tazobactam, imipenem, or meropenem) + aminoglycoside (e.g., gentamicin, tobramycin, or amikacin) + macrolide‡

COPD = chronic obstructive pulmonary disease.
*Adapted, with permission, from Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000;31:383-421. © Infectious Diseases Society of America.
†Macrolide = erythromycin, clarithromycin, or azithromycin; new macrolide = clarithromycin or azithromycin; "respiratory" fluoroquinolone = fluoroquinolone with activity against *Streptococcus pneumoniae* (levofloxacin, gatifloxacin, or moxifloxacin), SGC = second-generation cephalosporin (e.g., cefuroxime, cefprozil).
‡For atypical pathogens (e.g., *Legionella*) if required.

as the initial agent for the empiric treatment of CAP.[2] For patients admitted to the ICU, other pathogens such as *P. aeruginosa* or other gram-negative enteric pathogens may need to be considered and therapy adjusted accordingly.[2] For pseudomonal pneumonia, recent guidelines have suggested combining an antipseudomonal ß-lactam with a fluoroquinolone or an aminoglycoside.[2,11,16] In vitro synergy has been demonstrated with the ß-lactam–aminoglycoside combination but not with the ß-lactam– fluoroquinolone combination; the latter exhibited an additive but not antagonistic effect.[2]

The duration of treatment for CAP ranges from 7 to 21 days depending on the severity of illness. As previously indicated, the increasing use of fluoroquinolones has led to concerns that rising fluoroquinolone resistance may negate the usefulness of these agents for CAP within 5 to 10 years.[16] Once the pathogen and antibiotic susceptibilities are known, consideration should be given to streamlining therapy according to results, i.e., use of focused, less broadly active agents. IV administration of penicillin, for example, may be used for nonmeningeal PRSP infections such as CAP with MICs of up to 4 µg/mL.[2]

More recently, however, the IDSA has recommended that cefotaxime and ceftriaxone be the preferred IV agents for treatment of pneumococcal pneumonia (without meningitis) due to strains of *S. pneumoniae* with reduced penicillin susceptibility but with cefotaxime or ceftriaxone MICs less than 2 µg/mL.[16] For cefotaxime and ceftriaxone, use of the new break-points assumes minimal dosing of 1 g q8h in adults or 50 mg/kg q8h in children.[24] These recommendations are based on new interpretative standards for cefotaxime and ceftriaxone defining nonmeningeal and meningeal break-points.[41] Strains of *S. pneumoniae* causing nonmeningeal infection are considered resistant if cefotaxime and ceftriaxone MICs are greater than 4 µg/mL.[41] Changes in the interpretative break-points have been made in recognition of the clinical success observed in patients with PRSP pneumonia.[42,43] As clinicians apply the new interpretative break-points, the use of third-generation cephalosporins may increase. This change highlights the need for adequate susceptibility testing and understanding of local PRSP epidemiology.

Since the publication of the Canadian guidelines, new agents (e.g., telithromycin) and shorter courses of

therapy have been explored for the treatment of CAP. The advantages of short-course therapy include lower costs, better compliance, fewer adverse events, and fewer office visits.[44,45] Short-course therapy with macrolides (e.g., azithromycin), ß-lactam antibiotics, and telithromycin[44-46] has been explored. Telithromycin, a once-daily oral ketolide antibiotic, is a semisynthetic derivative of the macrolides.[47] Although its mechanism of action is similar to that of the macrolides, telithromycin has greater affinity for the ribosomal target site and maintains activity even in the presence of macrolide-resistant *S. pneumoniae* mediated by *mefA* or *ermB*.[47] In comparative studies, telithromycin appears effective in the treatment of CAP, although its use in more severely ill patients requires further study.[48] Tellier and others[48] found that, among ambulatory patients, telithromycin administered for 5 or 7 days was as effective as clarithromycin administered for 10 days. In Canada, telithromcyin has recently been approved for a 7-day course of treatment for CAP.

With respect to the respiratory fluoroquinolones, a higher dose of levofloxacin (750 mg orally or parenterally) was recently approved for the 5-day treatment of CAP. Dunbar and others[49,50] found that levofloxacin 750 mg for 5 days (IV or PO) was as effective as levofloxacin 500 mg for 10 days (IV or PO) for the treatment of patients in PSI classes I to IV. The higher dose takes advantage of the concentration-dependent pharmacodynamic effect of the fluoroquinolones, which shortens the course of treatment. A comprehensive review of the pharmacodynamic activity of antibiotics has been published previously.[51] The pharmacodynamic effect of antibiotics is generally classified as time-dependent (e.g., ß-lactams) or concentration-dependent (e.g., aminoglycosides, fluoroquinolones).[51] For time-dependent antibiotics, maximum bactericidal activity is obtained if the concentration of the antibiotic remains above the MIC of the pathogen for 40% to 60% (or more) of the antibiotic dosing interval.[48] In contrast, for concentration-dependent antibiotics, the higher the concentration, the greater the extent and rate of bactericidal activity.[51]

Prevention

Influenza is known to exacerbate underlying pulmonary and cardiac conditions and to lead to secondary bacterial pneumonia or primary viral pneumonia; in addition, infection with influenza virus may occur concurrently with other pathogens.[49] The use of influenza vaccination in target groups is supported by the Centers for Disease Control and Prevention in the United States[52] and the National Advisory Committee on Immunization (NACI) in Canada.[53] The target groups for whom NACI recommended influenza vaccination for the 2004/05 influenza season are listed in Table 4. In addition to these target groups, vaccination is also encouraged for healthy individuals 2 to 64 years of age.[53] The benefit of vaccination has been reported by Nichol and others, who studied elderly residents living in the community.[54] Influenza vaccination reduced the risk of hospital admission due to pneumonia, cardiac disease, and cerebrovascular disease by 32%, 19%, and 16%, respectively, and the risk of death by 48%.[54] The importance of vaccinating health care workers was demonstrated by Carman and others,[55] who found that the mortality rate due to influenza was lower in hospitals with a high vaccination rate for health care workers than in hospitals with a lower vaccination rate. In a study of influenza vaccination rates in Alberta, under-utilization of vaccination for elderly people was associated with increased utilization of health services for CAP.[56]

Given the prevalence of *S. pneumoniae*, pneumococcal vaccination of at-risk groups is also recommended.[2,11,16] Vaccination with the pneumococcal 23-valent polysaccharide vaccine is recommended for elderly patients and patients with risk factors (Table 5).[57] For patients less than 2 years of age, the 7-valent pneumococcal conjugate vaccine may be used.[58] Pneumococcal antibody levels may decline over 5 to 10 years, although the exact duration of immunity is unknown.[59] Antibody levels may decline more rapidly in

Table 4. Target Groups for Influenza Vaccination (National Advisory Committee on Immunization)[53]

Adults and children with chronic cardiac or pulmonary disease (including bronchopulmonary dysplasia, cystic fibrosis, and asthma) severe enough to require medical follow-up or hospital care
People of any age who are residents of nursing homes or other chronic care facilities
People ≥ 65 years of age
Adults and children with chronic conditions, such as diabetes mellitus and other metabolic diseases, cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy), renal disease, anemia, or hemoglobinopathy
Children and adolescents (6 months to 18 years of age) with conditions treated for long periods with acetylsalicylic acid
People at high risk of influenza complications who are embarking on travel to destinations where influenza is likely to be circulating
People capable of transmitting influenza to those at high risk of influenza-related complications (e.g., health care and other service providers, household members, child care workers)
People who provide essential community services
People in direct contact with poultry infected with avian influenza during culling operations

certain patient groups.[59] The benefits of pneumococcal vaccination have been widely discussed and supported.[2,16,60]

Spanish investigators found a direct correlation between amount of tobacco smoking and incidence of CAP.[61] In a case–control study of patients with CAP, tobacco smoking was identified as an avoidable risk factor for the disease.[62] Because tobacco smoking impairs the normal pulmonary defences, smoking cessation programs should be encouraged.

HOSPITAL-ACQUIRED PNEUMONIA

Epidemiology

HAP is defined as an acute infection of the pulmonary parenchyma occurring in a patient who has been in hospital for at least 48 h that was not present at the time of admission. In 1995 the American Thoracic Society (ATS) classified HAP on the basis of risk factors, severity (mild to moderate or severe), and the time of the pneumonia relative to the patient's admission (early or late).[63] The applicability of these classifications remains controversial and, as such, is beyond the scope of this article.[64,65] In 2005 the ATS and the IDSA revised the guidelines to include healthcare-associated pneumonia (HCAP), as well as simplifying the classification of HAP to early and late regardless of disease severity.[9] Broadly, HCAP includes pneumonia in any patient who was in an acute care hospital for 2 or more days within 90 days preceding the infection; who resided in a nursing home or long-term care facility; who received IV antibiotic therapy, chemotherapy, or wound care within 30 days preceding the current infection; or who attended a hospital or hemodialysis clinic.[9] VAP is defined as pneumonia occurring 2 to 3 days after endotracheal intubation.[9]

HAP accounts for 15% of all nosocomial infections and 27% of hospital-acquired infections in the ICU.[3] The incidence of HAP ranges from 5 to 10 cases per 1000 hospital admissions.[65] The National Nosocomial Infections Surveillance (NNIS) system has reported that the median rate of VAP per 1000 ventilator days among participating hospitals ranged from 2.9 to 15.1 in pediatric and trauma ICUs, respectively.[66] The mortality rate attributed to HAP ranged from 20% to 33%, while VAP, the more serious form of HAP, may account for 60% of deaths due to a nosocomial infection.[3] HAP may prolong patient stay in the ICU by 4.3 to 6.1 days and the total stay in hospital by 4 to 9 days.[3] The cost of the increased length of hospital stay in the United States was estimated at $41 000 per patient, and direct annual costs of US$2 billion have been estimated.[65,67]

Table 5. Patients at Risk of Pneumococcal Disease[57]

Highest risk
People ≥ 2 years of age,* not previously immunized , in the following risk categories, especially those with a recent diagnosis and/or newly entering programs
Sickle cell disease, congenital or acquired asplenia, or splenic dysfunction
Dialysis: upon commencement of dialysis, nephrotic syndrome
Multiple myeloma
Residence in a long-term care facility
Congenital immune deficiencies, specifically IgG, IgG subclass, and IgM deficiencies, and severe combined immunodeficiency†
Chronic cerebrospinal fluid leaks
Induced immunosuppression for organ transplant or post-transplantation (bone marrow or stem cell and solid organ transplants)
Cochlear implants
Moderate to high risk
Age ≥ 75 years
Age 65–74 years of age with any of the following chronic underlying illnesses:
Chronic renal disease, chronic renal insufficiency
Chronic cardiac disease (particularly cyanotic congenital heart disease or cardiac failure)
Chronic pulmonary disease (excluding asthma, except those treated with high-dose oral corticosteroid therapy)
HIV/AIDS
Chronic liver disease with or without ascites (e.g., cirrhosis, alcoholism)
Diseases associated with immunosuppressive therapy or radiation therapy, including autoimmune diseases being treated with high-dose steroids and chemotherapy agent(s)
Malignancy (e.g., leukemia, Hodgkin's or non-Hodgkin's lymphoma)
Poorly controlled diabetes mellitus

*Children from 2 to 5 years of age may receive pneumococcal polysaccharide 23-valent vaccine, but the pneumococcal conjugate vaccine is generally preferred because of the age-dependent response. Polysaccharide vaccine may be used both as a booster dose in this age group and to increase the serotype coverage. Pneumococcal polysaccharide vaccine is not indicated for use in children under 2 years of age, in whom the pneumococcal conjugate vaccine should be used for routine prevention of invasive pneumococcal disease, commencing at 2 months of age.
†People with granulocyte and complement disorders are not at risk.

Risk Factors

The risk factors for HAP and VAP have been grouped into 4 categories: factors that enhance colonization of the oropharynx or stomach, conditions favouring aspiration or reflux from the gastrointestinal tract, conditions requiring mechanical ventilation and exposure to contamination through personnel or respiratory devices, and host factors[3]; the latter include advanced age, malnutrition, and severe underlying conditions such as immunosuppression[3] (see also Table 6).

Table 6. Risk Factors in Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia[68]

Factors Predisposing to Aspiration	Factors Predisposing to Colonization
Witnessed aspiration	Chronic obstructive pulmonary disease
Supine positioning	Antacids or histamine type-2 antagonists
Coma	Tracheostomy
Enteral nutrition	Acute respiratory distress syndrome
Nasogastric tube	Prior exposure to antibiotics
Reintubation	Age > 60 years
Tracheostomy	
Patient transport	
Acute respiratory distress syndrome	
Head trauma	
Monitoring of intracranial pressure	

If colonized by pathogenic organisms, the oropharynx and stomach may serve as reservoirs for those organisms. In HAP and VAP, the oropharynx appears to be the predominant reservoir.[3,68] Factors facilitating bacterial colonization include antibiotic exposure, admission to the ICU, or underlying chronic pulmonary disease.[3,68] In healthy individuals, the corrosive pH of the stomach (below 2) eradicates most bacteria entering the gastric space, which results in an essentially sterile environment. Alterations in stomach flora, resulting from an increase in gastric pH, have been observed in patients receiving an H_2-antagonist or a proton pump inhibitor. Among patients receiving omeprazole, organisms found in the gastric contents were similar to those in the patients' oral cavity.[69] In a study of ICU patients, Donowitz and others[70] noted a predominance of hospital-acquired gram-negative bacteria in the gastric contents of patients receiving cimetidine and antacids (both of which result in a gastric pH above 4). Other factors that may increase gastric pH include advanced age, achlorhydria, ileus or upper gastrointestinal disease, and enteral feeding.[3]

Conditions favouring aspiration or gastrointestinal reflux include endotracheal intubation, insertion of a nasogastric tube, supine position, coma, surgery of the head, neck, or upper torso, and immobilization because of trauma or illness.[3] Prolonged mechanical ventilation increases the probability of exposure to contamination through respiratory devices and the probability of nosocomial spread of pathogens by the health care team (e.g., contaminated or colonized hands).[3] Factors such as more than one intubation, mechanical ventilation for longer than 72 h, prior aspiration of gastric contents, and COPD are associated with an increased risk of VAP in mechanically ventilated patients.[71] In addition to the endotracheal tube providing a direct passage for oropharyngeal organisms into the lungs, bacteria may collect and form a glycocalyx matrix (biofilm) on the tube, which serves as a reservoir for infection.[3] The lung may be inoculated if the biofilm is dislodged as a result of mechanical air flow or manipulation of the endotracheal tube (movement or suctioning).[3]

Causes

The pathogens causing HAP, VAP, and HCAP vary depending on patient population, type of institution, diagnostic methods, and length of the hospital stay. In early pneumonia (occurring up to 4 days after admission), pathogens associated with community-acquired pneumonia (see above), such as *S. pneumoniae* and *H. influenzae*, may be considered.[9] Other potential pathogens include *S. aureus*, *Escherichia coli*, *Klebsiella* spp., *Enterobacter spp.*, *Proteus* spp., and *Serratia* spp.[9] In patients with late-onset HAP (occurring 5 or more days after admission) or with risk factors for antibiotic-resistant organisms, pathogens in addition to those described for early HAP include *P. aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter* spp., extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae, methicillin-resistant *S. aureus* (MRSA), and *Legionella* spp.[9] In the medical ICU setting, common pathogens identified from NNIS surveillance data were *P. aeruginosa* (21%), *S. aureus* (20%), *Enterobacter* spp. (9%), *K. pneumoniae* (8%), *Acinetobacter* spp. (6%), *Candida albicans* (5%), and other Enterobacteriaceae.[72] Overall, gram-negative aerobic pathogens accounted for 64% of isolates collected from ICU patients with HAP.[72] Because pathogens and antibiotic resistance rates may vary considerably from one institution to another, hospitals should be familiar with the local epidemiology of HAP-causing organisms, especially when Canadian and US epidemiologic data are compared. For example, *S. aureus* was reported as the most common cause of nosocomial pneumonia at 2 Canadian tertiary care centres.[73,74]

Antibiotic Resistance

The rising emergence in hospitals of antibiotic-resistant pathogens such as MRSA, vancomycin-resistant enterococci, and MDR gram-negative organisms is of significant concern. Similar to the case for pathogens associated with CAP, the mechanism of antibiotic resistance may include a change in target site, production of antibiotic-modifying or antibiotic-inactivating enzymes, decreased penetration of the antibiotic, or efflux (antibiotic pump). Data from the NNIS indicate that rates

of antibiotic-resistant nosocomial pathogens in the ICU setting continued to rise from 1997–2001 to 2002 (Table 7).[66] The increasing prevalence of ESBL-producing Enterobacteriaceae, such as *K. pneumoniae*, in the ICU is also of concern.[75] The rising rates of MRSA, vancomycin-resistant enterococci, and Enterobacteriaceae resistant to fluoroquinolones or third-generation cephalosporins in the ICU are disturbing. As a result, older agents such as colistin and polymyxin have been used to treat MDR pathogens.[76] As with PRSP, the rising prevalence of antibiotic-resistant HAP pathogens is associated with the volume of antibiotic use. In the United States, the rate of fluoroquinolone-resistant *P. aeruginosa*, for example, was associated with the volume of fluoroquinolone used in the hospital and surrounding community.[77]

Table 7. Rates of Antibiotic Resistance for Pathogens Typically Found in the Intensive Care Unit (National Nosocomial Infections Surveillance System)[66]

Pathogen	% Resistant in 2002	% Change (Compared with 1997–2001)
Vancomycin-resistant enterococci	27.5	+11
Methicillin-resistant *Staphylococcus aureus*	57.1	+12
Methicillin-resistant CNS	89.1	+1
TGC-resistant *Escherichia coli*	6.3	+14
TGC-resistant *Klebsiella pneumoniae*	14	–2
Imipenem-resistant *Pseudomonas aeruginosa*	22.3	+32
Fluoroquinolone-resistant *P. aeruginosa*	32.8	+37
TGC-resistant *P. aeruginosa*	30.2	+22
TGC-resistant *Enterobacter* spp.	32.2	–5

CNS = coagulase negative staphylococci,
TGC = third-generation cephalosporin.

Management and Treatment

For HAP, VAP, and HCAP, clinicians have a wider armamentarium of antibiotic choices to deal with antibiotic-resistant nosocomial pathogens. Initial antibiotic therapy should have broad activity against the most likely pathogens. Inadequate antibiotic therapy and/or a delay in such therapy were identified as important determinants of mortality among ICU patients with a nosocomial infection.[9,78]

In contrast to the 1995 ATS guidelines, the 2005 ATS–IDSA guidelines[9] (Table 8) have placed greater emphasis on initial broad-spectrum therapy and the risk of MDR organisms. Similar to the guidelines for CAP, the 2005 recommendations for HAP were derived through expert consensus and are not necessarily based on randomized clinical trials. For HAP or VAP with early onset and no risk of MDR pathogens, ceftriaxone or a fluoroquinolone (levofloxacin, moxifloxacin, or ciprofloxacin) or a ß-lactam/ß-lactamase inhibitor or ertapenem was recommended. For HAP, VAP, or HCAP of late onset with a risk of MDR pathogens, any one of an antipseudomonal cephalosporin, antipseudomonal carbapenem, ß-lactam/

Table 8. Recommendations of the American Thoracic Society and Infectious Diseases Society of America for Treatment of Hospital-Acquired Pneumonia[9]

Type of Pneumonia	Potential Pathogens	Recommended Therapy
HAP or VAP, early onset (< 5 days since admission), no risk factors for antibiotic resistance, any disease severity	Enteric gram-negative bacilli (*Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Haemophilus influenzae*), methicillin-sensitive *Staphylococcus aureus, Streptococcus pneumoniae*	Ceftriaxone OR levofloxacin, moxifloxacin or ciprofloxacin OR ampicillin–sulbactam OR ertapenem
HAP or VAP or HCAP, late onset (> 5 days since admission), risk factors for antibiotic resistance, any disease severity	*Pseudomonas aeruginosa, Klebsiella pneumoniae,* Acinetobacter* spp.	Antipseudomonal cephalosporin OR antipseudomonal carbapenem OR ß-lactam/ß-lactamase inhibitor OR antipseudomonal fluoroquinolone OR aminoglycoside
	Methicillin-resistant *S. aureus*	Linezolid or vancomycin
	Legionella pneumophila	Macrolide or fluoroquinolone

HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, HCAP = healthcare-associated pneumonia.
*Use a carbapenem for extended-spectrum ß-lactamase strains.

ß-lactamase inhibitor, antipseudomonal fluoroquinolone, or aminoglycoside may be used. If MRSA is suspected, vancomycin or linezolid is recommended. For *L. pneumophila*, a macrolide or fluoroquinolone is preferred. These recent guidelines reflect the rising prevalence of MDR pathogens in the United States, as discussed previously. In Canada, antibiotic therapy should be tailored to the local epidemiology and clinical practice, since the prevalence of MDR pathogens may differ.

Risk factors for the acquisition of MDR organisms causing VAP include duration of ventilation (7 days or more), prior use of antibiotics, and prior use of broad-spectrum antibiotics (third-generation cephalosporins, fluoroquinolones, or imipenem).[79] The risk factors for MDR HAP or VAP identified in the ATS–IDSA guidelines[9] include antibiotic therapy in the preceding 90 days, 5 or more days since admission to hospital, high prevalence of antibiotic resistance in the community or the hospital, and immunosuppression due to disease or therapy. Risk factors for HCAP include a hospital stay of 2 days or more in the preceding 90 days, residence in a long-term care facility, home infusion therapy (including antibiotics), long-term dialysis within 30 days of the infection, home wound care, and exposure to a family member infected with a MDR pathogen.[9]

Successful monotherapy of HAP or VAP with antibiotics such as the fluoroquinolones, imipenem, and meropenem has been documented and is supported in the literature.[80-83] Nonetheless, the respective roles of monotherapy and combination therapy have been actively discussed.[4,84-86] Recent meta-analyses have questioned the role of combination therapy for gram-negative and pseudomonal bacteremia and for febrile neutropenia.[87-92] In one meta-analysis of 64 studies comparing ß-lactam monotherapy with a ß-lactam–aminoglycoside combination in severe infections, no survival benefit was found with the ß-lactam combination.[90] Monotherapy may decrease costs and minimize antibiotic exposure, which may be helpful in decreasing the risk of MDR pathogens and adverse outcomes.[9] For certain pathogens such as *P. aeruginosa*, combination therapy may provide broader activity as well as limiting the emergence of antibiotic resistance.[84,86,89] The current ATS–IDSA guidelines support the use of monotherapy for HAP and VAP if resistant pathogens are absent; conversely, the guidelines recommend that combination therapy be used when MDR pathogens are suspected, despite limited supportive data.[9] Others have advocated a similar approach; for example, Fagon and Chastre[83] suggested that a ß-lactam plus an aminoglycoside or fluoroquinolone be used initially for HAP pending results of microbiologic testing, with monotherapy reserved for when *P. aeruginosa* and other MDR pathogens have been excluded. Nevertheless, antibiotic therapy should be tailored to local epidemiology, prevalence of antibiotic-resistant pathogens, risk factors, severity of illness, and culture and sensitivities.

The recommended duration of therapy for HAP and VAP ranges from 7 to 21 days,[63] although the optimal duration has not been established. A consensus conference on VAP management suggested that therapy be continued for at least 72 h after clinical response, with some clinical improvement expected at about 48 to 72 h of therapy.[9,93] However, antibiotic treatment beyond 14 days may promote colonization with *P. aeruginosa* or other Enterobacteriaceae.[9] De-escalation (also known as streamlining or narrowing) of antibiotic therapy on the basis of culture results, susceptibility, and clinical response is encouraged.[9,83] Therapy may be limited to 7 days if there is a clinical response and *P. aeruginosa* is absent.[9]

To reduce costs in the ICU and to address the overuse of antibiotics (and hence minimize the emergence of antibiotic-resistant pathogens in this setting), shorter courses of antibiotic therapy have been suggested. In a recent trial, which compared 8 and 15 days of antibiotic treatment for VAP, Chastre and others[94] found that mortality rate, rate of recurrence, length of ICU stay, number of days without mechanical ventilation, and number of days of organ failure were similar for the 2 treatment arms. Although the outcomes were similar, VAP patients with nonfermenting gram-negative rods (e.g., *P. aeruginosa*) had higher recurrence and relapse rates with the shorter treatment course.[94] Further investigations are required to define the role of shorter courses of antibiotic treatment in patients with HAP and VAP.

Using a clinical prognostic scoring system (Table 9), Singh and others[95] found that outcome was similar for patients with VAP who received shorter and longer courses of antibiotic treatment in a nonblinded study. The clinical pulmonary infection score (CPIS), developed by Pugin and others,[96] uses 6 clinical variables to determine the presence or absence of pneumonia. Singh and others[95] found that in patients with a low CPIS score (6 or less) on initiation of antibiotics, therapy could be discontinued at 3 days if the CPIS score remained at 6 or less. Similarly, the ATS–IDSA guidelines[9] suggested that a CPIS of 6 or less for 3 days could be used as a criterion for discontinuing therapy in patients at low risk of pneumonia, although further validation is required for severe VAP.[9]

Table 9. Clinical Pulmonary Infection Score (CPIS)*†

Clinical Parameter	Point Value
Temperature (°C)	
≥ 36.5 and ≤ 38.4	0
≥ 38.5 and ≤ 38.9	1
≥ 39 and ≤ 36	2
Blood leukocytes, mL^{-1}	
≥ 4000 and ≤ 11 000	0
< 4000 or > 11 000	1
+ band forms ≥ 50%	1
Tracheal secretions	
Absent	0
Present (nonpurulent)	1
Present (purulent)	2
Oxygenation (Pao_2/Flo_2), mm Hg	
> 240 or ARDS	0
≤ 240 and no ARDS	2
Pulmonary radiography	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2
Progression of pulmonary infiltrate	
No radiographic progression	0
Radiographic progression (after CHF and ARDS excluded)	2
Culture of tracheal aspirate	
Pathogenic bacteria (predominant organism) rare or light in quantity or no growth	0
Pathogenic bacteria moderate or heavy in quantity	1
Same pathogenic bacteria as seen on Gram staining	1

Pao_2/Flo_2 = ratio of arterial oxygen pressure to fraction of inspired oxygen, CHF = congestive heart failure, ARDS = acute respiratory distress syndrome.

*Adapted, with permission, from Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000;162 (2 Pt 1):505–11. © American Thoracic Society.

†CPIS at baseline was assessed on the basis of the first 5 variables (temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate). CPIS at 72 hours was calculated on the basis of all 7 variables. A score > 6 at baseline or at 72 hours is considered suggestive of pneumonia.

Prevention

In 2003 the Centers for Disease Control and Prevision and the Healthcare Infection Control Practices Advisory Committee proposed several recommendations to prevent HAP and VAP,[3] including staff education in preventing infection, infection and microbiologic surveillance, prevention of transmission of organisms (by sterilization or disinfection and by maintenance of equipment and devices), prevention of person to-person transmission of bacteria (through hand hygiene, gloving, wound care, and suctioning of respiratory secretions), modifying host risk for infection through vaccination (for influenza and pneumococcal disease), prevention of aspiration, and prevention of postoperative pneumonia.[3] The details are beyond the scope of this article but may been found at http://www.cdc.gov/ncidod/hip/guide/CDCpneumo_guidelines.pdf. Recommendations for the prevention of VAP were published recently,[97] and they support the CDC recommendations.

The use of prophylactic antibiotics or topical antibiotics to reduce oropharyngeal, tracheal, and gastric colonization or to selectively decontaminate these areas in at-risk patients has been investigated,[3] but the interpretation of results is difficult because of methodological differences among studies. In a recent meta-analysis, the use of topical and systemic agents reduced the number of respiratory tract infections and deaths due to pneumonia in the ICU.[98] Topical agents alone reduced the number of infections but did not change the mortality rate.[98] The use of sucralfate, topical and systemic antibiotics, or topical antiseptics in the ICU setting remains controversial because of concerns about antibiotic resistance and cost-effectiveness.[97] Recent guidelines from the Planning Group of the Canadian Critical Care Society and the Canadian Critical Care Trials Group do not support the use of sucralfate or intratracheal or topical antibiotics, although no recommendations were made regarding IV administration of antibiotics alone or in combination with topical antibiotics.[97] The ATS-IDSA guidelines do not support the routine use of systemic or topical antibiotics to prevent HAP.[9] Further investigations about the role of antibiotics in reducing HAP and VAP infections are required before these strategies can be used routinely.

ROLE OF THE PHARMACIST

Various opportunities exist for pharmacists to participate in the management of CAP and HAP. Depending on practice setting, these activities may range from selecting an appropriate antibiotic to monitoring outcome and performing follow-up.[22,99] In the community setting, pharmacists should encourage patients to complete the full course of antibiotic treatment to ensure clinical success as well as to minimize antibiotic resistance. Because many patients have one or more residual symptoms up to 30 days or more after antibiotic therapy ends, pharmacists should reassure patients if such symptoms persist. If patients indicate worsening symptoms (e.g., fever, chills, shortness of breath), they should seek appropriate medical attention. As previously mentioned, pharmacists should promote and encourage

Table 10. Role of the Pharmacist in the Treatment of Community-Acquired Pneumonia*

Activity	Comments
Assess appropriateness of empiric therapy	Consider most likely pathogens and local resistance patterns. Consider drug route of administration, drug dose, drug interactions, patient allergy status, and cost.
Follow up on patient's progress	Monitor for improvement of clinical signs and symptoms within 3 to 5 days. If patient does not have some indication of clinical response within 3 to 5 days or if patient deteriorates at any time, physician reassessment and alternative drug therapy may be recommended. Assess medication tolerability and adherence. For patients being managed as outpatients, provide telephone follow-up within 48 to 72 h of initiating antimicrobial therapy, to assess efficacy, tolerability, and adherence Streamlining: on day 2 or 3, review culture and sensitivity data; consider narrowing spectrum of therapy if a pathogen is identified. IV to PO step-down: on day 3 to 5, consider switch to PO therapy if patient is improving clinically, is afebrile, is able to ingest oral therapy, and has a normally functioning gastrointestinal tract. Duration: Usually 7 to 14 days, determined by patient's clinical response.
Prevention strategies	Vaccinate for influenza and *Streptococcus pneumoniae*. Encourage smoking cessation.

*Reproduced, with permission, from Gin AS, Tailor SAN. Community-acquired pneumonia. *Can J Hosp Pharm* 2001;54 Suppl 1:1–16. © Canadian Society of Hospital Pharmacists.

smoking cessation programs to decrease the risk of CAP.

Pharmacists should encourage patients at risk of influenza or pneumococcal disease to receive a pneumococcal vaccine and annual influenza vaccination. Informational materials such as patient brochures, posters, and reminders may be used in these efforts. Pharmacists may partner with public health authorities on a seasonal basis to offer "flu shot" clinics in local pharmacies to expand awareness and increase opportunities for the public to receive annual influenza vaccination.

To minimize antibiotic resistance, pharmacists can participate in educational activities to increase awareness about appropriate antibiotic use among prescribers, patients, insurers, and government.[22] Pharmacists can also participate in programs to minimize antibiotic use and to educate the public that antibiotics should not be used for viral infections.[22,84] In partnership with physicians, pharmacists can work to optimize the use of antibiotic therapy.[22] More specific interventions are presented in Table 10.

CONCLUSIONS

Pneumonia is a leading cause of morbidity and mortality in the community and in the hospital setting. Several risk factors may predispose a patient to CAP or HAP. *S. pneumoniae* is the most common cause of CAP, whereas gram-negative pathogens are often associated with nosocomial pneumonia. Antibiotics form part of the core management of CAP and HAP. Several guidelines have been published to assist clinicians in selecting an appropriate empiric regimen. Pharmacists have an important role to play, and they have various opportunities to participate in the prevention and management of pneumonia.

References

1. Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD. Deaths: final data for 2001. *Natl Vital Stat Rep* 2003;52(3):1-116.
2. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. *Clin Infect Dis* 2000;31:383-421.
3. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. Atlanta (GA): Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion; 2004. Available at: http://www.cdc.gov/ncidod/hip/guide/CDCpneumo_guidelines.pdf. Accessed 2005 Aug 12.
4. Mehta RM, Niederman MS. Nosocomial pneumonia in the intensive care unit: controversies and dilemmas. *J Intensive Care Med* 2003;18:175-88.
5. Donowitz LG, Mandell GL. Acute pneumonia. In: Mandell GL, Bennett JE, Dolin R, editors. *Principles and practice of infectious diseases*. 6th ed. Philadelphia (PA): Churchill Livingstone; 2005. p. 819-45.
6. Mason C, Nelson S. Pulmonary host defenses. Implications for therapy. *Clin Chest Med* 1999;20:475-88.
7. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med* 1978;64:564-8.
8. Alcon A, Fabregas N, Torres A. Hospital-acquired pneumonia: etiologic considerations. *Infect Dis Clin North Am* 2003;17:679-95.
9. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.
10. Marrie TJ. Community-acquired pneumonia. *Clin Infect Dis* 1994;18:501-15.

11. Bartlett JG, Dowell SF, Mandell LA, File Jr TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis* 2000;31:411-5.
12. Mylotte JM. Nursing home-acquired pneumonia. *Clin Infect Dis* 2002;35:1205-11.
13. Metlay JP, Schultz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. *Arch Intern Med* 1997;157:1453-9.
14. Bartlett JG, Mundy MD. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618-24.
15. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Feagan BG. Predictors of symptom resolution in patients with community-acquired pneumonia. *Clin Infect Dis* 2000;31:1362-7.
16. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37:1405-33.
17. Neiderman M, McCombs J, Unger A, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. *Clin Ther* 1998;20:820-37.
18. Colice GL, Morley MA, Asche C, Birnbaum HG. Treatment costs of community-acquired pneumonia in an employed population. *Chest* 2004;125:2140-5.
19. Lipsky B, Boyko E, Inue T, Koepsell T. Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 1986;146:2179-85.
20. Koivula I, Sten M, Makela PH. Risk factors for pneumonia in the elderly. *Am J Med* 1994;94:313-20.
21. Neiderman MS, Mandell LA, Anzeuto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163:1730-54.
22. Gin AS, Zhanel GG. Antibiotic resistance: endgame for antibiotics? [continuing education lesson]. *Can Pharm J* 2001 Sep:1-8. Available at: http://www.pharmacists.ca/content/cpjpdfs/CE/CEantimicrobialEnglish.pdf. Accessed 2004 Sep 15.
23. Gin AS, Tailor SAN. Community-acquired pneumonia. *Can J Hosp Pharm* 2001;54 Suppl 1:1-16.
24. Clinical and Laboratory Standards Institute/NCCLS. *Performance standards for antimicrobial susceptibility test.* 15th informational supplement. NCCLS doc M100-S15. Wayne (PA): NCCLS; 2005.
25. Butler JC, Cetron MS. Pneumococcal drug resistance: the new "special enemy of old age". *Clin Infect Dis* 1999;28:730-5.
26. *Streptococcus pneumoniae* resistance data for Canada. Toronto (ON): Canadian Bacterial Surveillance Network; 2004. Available at: http://www.microbiology.mtsinai.on.ca/data/sp/sp_can.shtml. Accessed 2004 Sep 23.
27. Zhanel GG, Palatnick L, Nichol KA, Bellyou T, Low DE, Hoban DJ. Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob Agents Chemother* 2003;47:1867-72.
28. File TM Jr, Garau J, Blasi F, Chidiac C, Klugman K, Lode H, et al. Guidelines for empiric antimicrobial prescribing in community-acquired pneumonia. *Chest* 2004;125:1888-901.
29. Hoban DJ, Wierzbowski AK, Nichol K, Zhanel GG. Macrolide-resistant *Streptococcus pneumoniae* in Canada during 1998-1999: prevalence of mef(A) and erm(B) and susceptibilities to ketolides. *Antimicrob Agents Chemother* 2001;45:2157-50.
30. Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med* 1999;341:233-9.
31. Davidson R, Cavalcanti R, Brunton JL, Bast DJ, de Azavedo JC, Kibsey P, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N Engl J Med* 2002;346:747-50.
32. Pletz MW, McGee L, Jorgensen J, Beall B, Facklam RR, Whitney CG, et al. Levofloxacin-resistant invasive *Streptococcus pneumoniae* in the United States: evidence for clonal spread and the impact of conjugate pneumococcal vaccine. *Antimicrob Agents Chemother* 2004;48:3491-7.
33. Feagan BG, Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK. Treatment and outcomes of community-acquired pneumonia at Canadian hospitals. *CMAJ* 2000;162:1415-20.
34. Fine MJ, Pratt HM, Obrosky DS, Lave JR, McIntosh LJ, Singer DE, et al. Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. *Am J Med* 2000;109:378-85.
35. McCormick D, Fine MJ, Coley CM, Marrie TJ, Lave JR, Obrosky DS, et al. Variation in length of hospital stay in patients with community-acquired pneumonia: Are shorter stays associated with worse medical outcomes? *Am J Med* 1999;107:5-12.
36. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *New Engl J Med* 1997;336:243-50.
37. Orrick JJ, Segal R, Johns TE, Russell W, Wang F, Yin DD. Resource use and cost of care for patients hospitalised with community acquired pneumonia: impact of adherence to Infectious Diseases Society of America guidelines. *Pharmacoeconomics* 2004;22:751-7.
38. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA* 2000;983:749-55.
39. Brown PD. Adherence to guidelines for community-acquired pneumonia: Does it decrease cost of care? *Pharmacoeconomics* 2004;22:413-20.
40. Mandell LA, File TM Jr. Short-course treatment of community-acquired pneumonia. *Clin Infect Dis* 2003;37:761-3.
41. National Committee for Clinical Laboratory Standards (NCCLS). *Performance standards for antimicrobial susceptibility test.* 12th informational supplement. NCCLS doc M100-S12. Wayne (PA): NCCLS; 2002.
42. Pallares R, Linares J, Vadillo M, Cabellos C, Manresa F, Viladrich PF, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995;333:474-80.
43. Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Arch Intern Med* 2000;160:1399-408.
44. Goff DA. Short-duration therapy for respiratory tract infections. *Ann Pharmacother* 2004;38(9 Suppl):S19-23.
45. Guay D. Short-course antimicrobial therapy of respiratory tract infections. *Drugs* 2003;63:2169-84.
46. Stralin K, Sjoberg L, Holmberg H. Short-course beta-lactam treatment for community-acquired pneumonia. *Clin Infect Dis* 2003;38:766-7.
47. Zhanel GG, Walters M, Noreddin A, Vercaigne LM, Wierbowski A, Embil JM, et al. The ketolides: a critical review. *Drugs* 2002;62:1771-804.
48. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *J Antimicrob Chemother* 2004;54:515-23.
49. Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. *Curr Med Res Opin* 2004;20:555-63. Erratum in: *Curr Med Res Opin* 2004;20:967.
50. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003;37:752-60.

51. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998;26:1-12.
52. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB; Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005;54(RR-8):1-40.
53. Orr P; National Advisory Committee on Immunization. Statement on infuenza vaccination for the 2005-2006 season. *Can Commun Dis Rep* 2005;30(ACS-6):1-32.
54. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med* 2003;348: 1322-32.
55. Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;355:93-7.
56. Jin Y, Carriere KC, Predy G, Johnson DH, Marrie TJ. The association between influenza immunization coverage rates and hospitalization for community-acquired pneumonia in Alberta. *Can J Public Health* 2003;94:341-5.
57. National Advisory Committee on Immunization. Recommendations for use of pneumococcal 23-valent polysaccharide vaccine during shortage. *Can Commun Dis Rep* 2004;30(ACS-4):1-4.
58. National Advisory Committee on Immunization. Statement on the recommended use of pneumococcal conjugate vaccine: addendum. *Can Commun Dis Rep* 2003;29(ACS-8):1-16.
59. National Advisory Committee on Immunization. Canadian immunization guide. 6th ed. Ottawa (ON): Canadian Medical Association; 2002. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/pdf/cdn_immuniz_guide-2002-6.pdf. Accessed 2005 May 20.
60. Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997;278:1333-9. Erratum in: *JAMA* 2000;283:341.
61. Almirall J, Gonzalez CA, Balanzo X, Bolibar I. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* 1999;116:375-9.
62. Farr BM, Bartlett CL, Wadsworth J, Miller DL. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. *Respir Med* 2000;94:954-63.
63. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 1996;153:1711-25.
64. Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on Ventilator-Associated Pneumonia. *Eur Respir J* 2001;17:1034-45.
65. McEachern R, Campbell GD Jr. Hospital-acquired pneumonia: epidemiology, etiology, and treatment. *Infect Dis Clin North Am* 1998;12:761-79.
66. NNIS System. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 through June 2003, issued August 2003. *Am J Infect Control* 2003;31:481-98.
67. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002;122:2115-21.
68. Kollef MH. Prevention of hospital-acquired pneumonia and ventilator-associated pneumonia. *Crit Care Med* 2004;32:1396-405.
69. Karmeli Y, Stalnikowitz R, Eliakim R, Rahav G. Conventional dose of omeprazole alters gastric flora. *Dig Dis Sci* 1995;40:2070-3.
70. Donowitz LG, Page MC, Mileur BL, Guenthner SH. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. *Infect Control* 1986;7:23-6.
71. Torres A, Aznar R, Gatell JM, Jimenez P, Gonzalez J, Ferrer A, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990;142:523-8.
72. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. *Crit Care Med* 1999;27:887-92.
73. Greenaway CA, Embil J, Orr PH, McLeod J, Dyck B, Nicolle LE. Nosocomial pneumonia on general medical and surgical wards in a tertiary-care hospital. *Infect Control Hosp Epidemiol* 1997;18:749-56.
74. Taylor GD, Buchanan-Chell M, Kirkland T, McKenzie M, Wiens R. Bacteremic nosocomial pneumonia. A 7-year experience in one institution. *Chest* 1995;108:786-8.
75. Fridkin SK, Gaynes RP. Antimicrobial resistance in intensive care units. *Clin Chest Med* 1999;20:303-16.
76. Leroy O, Jaffre S, D'Escrivan T, Devos P, Georges H, Alfandari S, et al. Hospital-acquired pneumonia: risk factors for antimicrobial-resistant causative pathogens in critically ill patients. *Chest* 2003;123:2034-42.
77. Polk RE, Johnson CK, McClish D, Wenzel RP, Edmond MB. Predicting hospital rates of fluoroquinolone-resistant *Pseudomonas aeruginosa* from fluoroquinolone use in US hospitals and their surrounding communities. *Clin Infect Dis* 2004;39:497-503.
78. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999;115:462-74.
79. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med* 1998;157:531-9.
80. Fink MP, Snydman DR, Niederman MS, Leeper KV Jr, Johnson RH, Heard SO, et al. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrob Agents Chemother* 1994;38:547-57.
81. West M, Boulanger BR, Fogarty C, Tennenberg A, Wiesinger B, Oross M, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003;25:485-506.
82. Sieger B, Berman SJ, Geckler RW, Farkas SA. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. *Crit Care Clin* 1997;25:1663-70. Erratum in: *Crit Care Clin* 1997;25:2067.
83. Fagon JY, Chastre J. Antimicrobial treatment of hospital-acquired pneumonia. *Clin Chest Med* 2005;26:97-104.
84. Chastre JJ. Antimicrobial treatment of hospital-acquired pneumonia. *Infect Dis Clin North Am* 2003;17:727-37.
85. Vincent JL. Ventilator-associated pneumonia. *J Hosp Infect* 2004; 57:272-80.
86. Lynch JP 3rd. Hospital-acquired pneumonia: risk factors, microbiology, and treatment. *Chest* 2001;119(2 Suppl):373S-84S.
87. Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev* 2003;(3):CD003038.
88. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003;326:1111.
89. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004;4:519-27.
90. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004;328:668.

91. Paul M, Leibovici L. Combination antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia [letter]. *Lancet Infect Dis* 2005;5:192-3.
92. Maki DG, Safdar N. Combination antibiotic therapy for *Pseudomonas aeruginosa* bacteraemia — author's reply [letter]. *Lancet Infect Dis* 2005;5:193-4.
93. Rello J, Diaz E. Pneumonia in the intensive care unit. *Crit Care Med* 2003;31:2544-51.
94. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588-98.
95. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. A*m J Respir Crit Care Med* 2000;162 (2 Pt 1):505-11.
96. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew RD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;143:1121-29.
97. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004;141:305-13.
98. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care (Cochrane Review). *Cochrane Database Syst Rev* 2004;(4):CD000022.
99. Dickerson LM, Mainous AG 3rd, Carek PJ. The pharmacist's role in promoting optimal antimicrobial use. *Pharmacotherapy* 2000; 20:711-23.

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