

# 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

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## Introduction

Community-acquired pneumonia (CAP) remains a serious illness with a significant impact not only on individual patients but also on society as a whole. Guidelines for the initial antibiotic management of CAP were developed in Canada in 1993 and subsequently by the American Thoracic Society (ATS) that same year and by the Infectious Diseases Society of America (IDSA) in 1998 [1–3]. Each of these sets of guidelines has its own strengths and weaknesses, but individually and collectively they have helped to organize and codify our approach to the patient with CAP. Perhaps most important, they have highlighted the weaknesses and deficiencies in this area and have raised important questions for present and future research.

As a result of developments in the past several years, it became clear that our guidelines should be updated and revised. This document is a joint effort by the Canadian Infectious Disease Society (CIDS) and the Canadian Thoracic Society (CTS) and we hope that it will be the first of many such collaborations.

## Methods

A committee was established that was composed of members from both the CIDS and CTS, plus additional colleagues from the United States with strong interests in CAP. The members were divided into 3 teams, each of which was responsible for 1 of 3 sections. These were (1) epidemiology, risk factors, and etiology; (2) diagnosis; and (3) treatment. The committee met for 2 days in Toronto in January 1999, and then each team proceeded to develop a draft of its section. These drafts were then circulated among the committee members, and a revised version was sent to colleagues in the United States, Europe, and Israel for review. This document was then finalized on the basis of their input.

Relevant articles published during 1966 to the present were retrieved from MEDLINE with use of the MeSH terms “exp pneumonia/,” “community-acquired,” “nursing home,” “human,” “random,” “clinical trial,” “exp antibiotics/,” and “English language.” In addition, abstracts from the annual International Conference on Antimicrobial Agents and Chemotherapy and IDSA meetings held in 1997, 1998, and 1999 were reviewed. For the section on epidemiology and etiology, we searched the terms “community-acquired pneumonia” and “etiology” (simultaneously) and found 968 citations.

We applied a hierarchical evaluation of the strength of evidence modified from the Canadian Task Force on the Periodic Health Examination [4]. Well-conducted randomized, controlled trials constitute strong or level I evidence; well-designed controlled trials without randomization (including cohort and case-control studies) constitute level II or fair evidence; and expert opinion, case studies, and before-and-after studies are level III (weak) evidence. Throughout these guidelines, ratings appear as roman numerals in parentheses after each recommendation.

None of these categories are readily applied to studies of the etiology of pneumonia. Instead, we applied the categories defined by Marston et al. [5] to indicate the degree of certainty that a given etiologic agent has caused the pneumonia: definite, probable, or possible. Unfortunately, most of the studies examined for this document were reported before publication of Marston’s article.

An examination of the articles on etiology of pneumonia led to a decision to use a small number of articles (for the group of patients requiring admission to the hospital—the largest group) in which the authors used comprehensive methods to try to establish an etiologic diagnosis. It was felt to be important to present the data in tables that allow the reader to see the range of various pathogens identified in each study rather than to use a summary table. Searches of the subsets of patients treated on an ambulatory basis, in nursing homes, or in intensive care units (ICUs) yielded small numbers of studies, which are reported in their entirety.

For the section on diagnosis, a set of explicit criteria for inclusion and exclusion were applied for selecting articles used for the evidence-based portion of this section. Inclusion criteria required that each article report original research on patients with CAP and that the information obtained regarding a particular aspect in the workup of CAP be considered in the original hypothesis of the article. Excluded articles dealt predominantly with patients aged <18 years, the immunosuppressed, or individual case studies or reviews. Most studies cited in this section were performed either in the emergency department or in a physician’s office.

For the treatment section, 585 published articles or abstracts on

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clinical trials concerning CAP were identified. It was decided that recommendations regarding choice of antibiotics that were based solely on in vitro susceptibility data and the generalization of experience from another clinical condition involving similar organisms would be considered to be based on level III evidence.

## Epidemiology, Risk Factors, and Etiology

### Epidemiology

Pneumonia (together with influenza) is the sixth leading cause of death in the United States, and an estimated 4 million cases occur annually. It accounts for 600,000 hospital admissions and 64 million patient-days of restricted activity each year [6, 7].

The attack rates for pneumonia are highest at the extremes of age. In one study, the overall annual rate of pneumonia was 12 cases per 1000 persons per year [8]. Rates were highest in the group aged 0–4 years, at 12–18 cases per 1000 persons. In the group aged 5–60 years, the rate was 1–5 cases per 1000 persons. In a detailed population-based study of 47,000 persons in 4 Finnish communities, Jokinen et al. [9] reported that the incidence of pneumonia increased rapidly for each year of age >50, and the rate was as high as 20 cases per 1000 persons per year among patients age  $\geq 60$  years. It was also noted in this study that in years with influenza A epidemics, pneumonia rates for adults exceeded those in nonepidemic years. In 2 Ohio counties in 1991, Marston et al. [5] found that the incidence of CAP requiring hospitalization among adults was 2.66 per 1000 persons. The incidence was higher among blacks than whites (3.37 per 1000 persons vs. 2.53 per 1000) and higher among males than females (2.91 vs. 2.44 per 1000 persons). The rate was 0.91 per 1000 for persons aged <45 years, 2.77 per 1000 for persons 45–64 years of age, and 10.12 per 1000 for persons aged  $\geq 65$  years ( $P < .001$ ).

In a study of all residents aged  $\geq 60$  years in a Finnish township, Koivula et al. found that pneumonia occurred at an annual rate of 14.6 per 1000 (185 of the 4175 residents developed pneumonia over a 3-year period). Most of the cases of pneumonia were community-acquired (145 [71%] of 185); 39% of those were treated at home, with a 2.8% mortality rate, and 49 cases (29%) were nosocomial [10].

Many investigators have focused on the rates of bacteremic pneumococcal pneumonia in population-based studies. During the period 1983–1992, Sankilampi et al. [11] found that 9.1 per 100,000 adults per year developed pneumococcal bacteremia in Finland, whereas in Denmark the annual rate was 18 per 100,000 for all age groups [12]. Similar population-based studies of pneumococcal bacteremia in Southern California and Israel showed rates of 12.5 per 100,000 adults and 14.5 per 100,000 adults, respectively [13, 14].

### Risk Factors for Pneumonia

Koivula's study [10] found several independent risk factors for pneumonia in all persons aged  $\geq 60$  years in a Finnish township: alcoholism (RR, 9), asthma (RR, 4.2), immunosuppression (RR, 1.9), institutionalization (RR, 1.8), and age >70 years compared with age 60–69 years (RR, 1.5).

A study that specifically examined risk factors for pneumococcal infections found that dementia, seizure disorders, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) were risk factors for this infection [15]. A number of these risk factors increase the likelihood of aspiration, which is a key factor in the pathogenesis of pneumonia. More recent studies of invasive pneumococcal disease in the United States have added new risk factors: HIV infection (OR, 41.8) and black race (OR, 1.36) [16]. Other investigators have confirmed the high attack rates of pneumococcal pneumonia among patients with HIV infection [17, 18].

Additional risk factors for pneumococcal pneumonia include overcrowding in institutions [19–21]. Forty-six cases of pneumonia occurred over 4 weeks in a Houston jail designed to house 3500 prisoners but housing 6700 [19]. An outbreak of pneumococcal disease occurred in a shelter for the homeless [21], and 3 nursing homes in the United States reported attack rates of 12%–15% for pneumococcal pneumonia in unvaccinated elderly patients [20].

Using data from the passive surveillance system of the Centers for Disease Control and Prevention (CDC), Marston et al. [22] defined some of the risk factors for acquiring legionnaires' disease. They did this by comparing 3254 patients diagnosed with legionnaires' disease who were reported to the CDC from 1980 to 1989 with the population of the United States with respect to demographic characteristics and rates of underlying disease. Rates of legionnaires' disease were higher in the northeastern states and during the summer. A markedly elevated risk of acquiring legionnaires' disease was identified for persons with AIDS (RR, 41.9) or hematologic malignancy (RR, 22.4). RR for the other variables were as follows: male sex, 1.46; smoking, 1.83; diabetes, 1.89; all types of cancer, 3.87; and end-stage renal disease, 21.4.

For the practicing physician, answers to questions about occupation and recent travels are key in the evaluation of the individual patient, and the answers may lead to the correct etiologic diagnosis. We all remember some of the medical trivia that we memorized for exams but never thought would be helpful in our day-to-day work. However, not infrequently the epidemiological evaluation of a patient with pneumonia may provide important information, not only for the management of that patient's condition but also for the public health of the community in which the person resides. Table 1 gives a partial list of epidemiological tidbits that one should remember when assessing a patient with pneumonia.

One of the most fascinating aspects of the epidemiology of

**Table 1.** Clues to the epidemiology and etiology of pneumonia, based on the medical history.

Feature	Possible etiologic agent or associated condition
<b>Environmental</b>	
Exposure to contaminated air-conditioning cooling towers; hot tub; recent travel and stay in a hotel; grocery store mist machine; visit to or recent stay in a hospital with drinking water contaminated by <i>L. pneumophila</i>	<i>Legionella pneumophila</i>
Exposure to infected parturient cats, cattle, sheep, or goats	<i>Coxiella burnetii</i>
Pneumonia develops after windstorm in an area of endemicity	<i>Coccidioides immitis</i>
Outbreak of pneumonia in shelter for homeless men or jail	<i>Streptococcus pneumoniae</i> , <i>Mycobacterium tuberculosis</i>
Outbreak of pneumonia in military training camp	<i>S. pneumoniae</i> , <i>Chlamydia pneumoniae</i> , adenovirus, <i>M. pneumoniae</i>
Outbreak of pneumonia in a nursing home	<i>C. pneumoniae</i> , <i>S. pneumoniae</i> , respiratory syncytial virus, influenza A virus
Exposure to contaminated bat caves; excavation in areas of endemicity	<i>Histoplasma capsulatum</i>
Exposure to turkeys, chickens, ducks, or psittacine birds	<i>Chlamydia psittaci</i>
Exposure to mice or mice droppings	Hantavirus
Exposure to rabbits	<i>Francisella tularensis</i>
<b>Travel history</b>	
Travel to Thailand or other countries in Southeast Asia	<i>Burkholderia pseudomallei</i> (melioidosis)
Immigration from countries with high endemic prevalences of tuberculosis	<i>M. tuberculosis</i>
<b>Occupational history</b>	
Health care work	<i>M. tuberculosis</i> , acute HIV seroconversion with pneumonia
Tick bite ( <i>Dermacentor variabilis</i> or <i>Ixodes dommini</i> [scapularis])	Rocky Mountain spotted fever (rarely complicated by pneumonia), <i>Ehrlichia</i> species
<b>Host factor</b>	
Diabetic ketoacidosis	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i>
Alcoholism	<i>S. pneumoniae</i> , <i>Klebsiella pneumoniae</i> , <i>S. aureus</i> , anaerobes
Chronic obstructive lung disease	<i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>
Solid organ transplantation (pneumonia occurring >3 mo after transplantation)	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Legionella</i> species, <i>Pneumocystis carinii</i> (rarely CMV), <i>Strongyloides stercoralis</i>
Sickle cell disease	<i>S. pneumoniae</i>
HIV infection and CD4 cell count <200/ $\mu$ L	<i>P. carinii</i> , <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Cryptococcus neoformans</i> , <i>M. tuberculosis</i> , <i>Rhodococcus equi</i>
B cell defects (e.g., multiple myeloma, Hodgkin's disease)	<i>S. pneumoniae</i>
Granulocytopenia	Aerobic gram-negative rod-like bacteria such as <i>Escherichia coli</i> or <i>K. pneumoniae</i>

pneumonia is its constant change. It is now necessary for the physician to know not only the epidemiology of pneumonia itself but also the epidemiology of local antimicrobial susceptibility patterns. The physician must be aware of the rate of occurrence of penicillin- and macrolide-resistant *Streptococcus pneumoniae* in the community and the factors that predispose to such resistance in the patient.

### The Etiology of Pneumonia

An evidence-based approach to the etiology of pneumonia is difficult. There are >100 microbial causes of pneumonia, and almost all have been isolated from pulmonary tissue at least once. The problem is that one cannot obtain pulmonary tissue routinely. Therefore, the physician must rely on results of blood, sputum, or pleural fluid cultures and the results of serological tests to make an etiologic diagnosis. Blood cultures are positive for only 6%–10% of patients with pneumonia, and pleural fluid is obtained only from patients in whom a complicated pleural effusion is noted. Sputum is obtained for culture from about one-third of patients with pneumonia [23], and since sputum passes through a heavily colonized oral cavity, any pathogen isolated from this specimen can at best only be presumed to be a possible cause of pneumonia. In recent years investigators

have recognized these limitations and have categorized the etiology of pneumonia as definite, probable, or possible [5].

Marston et al. [5] defined these categories as follows. Definite infection was defined as isolation of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, enterobacteriaceae, or *Pseudomonas aeruginosa* from blood or pleural fluid cultures; a  $\geq 4$ -fold increase in titers of antibodies to *Legionella pneumophila* (to  $\geq 1:128$ ), *Mycoplasma pneumoniae* (to  $\geq 1:64$ ), or *Chlamydia pneumoniae* or a increase in respiratory syncytial virus (RSV) or influenza virus antigens (to  $\geq 1:32$ ); isolation of influenza virus or *Legionella* species from respiratory secretions; or an ELISA for *L. pneumophila* serogroup 1 urinary antigen with a sample-to-control ratio of  $\geq 3$ .

Probable infection was defined as isolation of *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, enterobacteriaceae, or *P. aeruginosa* from purulent sputum (sputum with moderate or large numbers of neutrophils seen on Gram stain) in which a compatible organism was seen in moderate or large amounts on sputum Gram stain.

Possible infection was defined as isolation of pneumonia-causing pathogens other than *Legionella* species in a culture of purulent sputum that, on Gram stain, demonstrated a predominance of (1) gram-positive cocci (possible diagnosis of infection

**Table 2.** Studies of the etiology of community-acquired pneumonia (CAP) treated on an ambulatory basis.

Reference	Location of study	Dates or duration of study	n	Etiology of CAP, no. (%) of patients				
				<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Mycoplasma pneumoniae</i>	<i>Chlamydia pneumoniae</i>	Unknown
[215]	Goteberg, Sweden	3 y	54	5 (9)	6 (12)	20 (37)	ND	(41)
[169]	Halifax, Nova Scotia	Nov 1991–Mar 1994	149	1	1	34 (22.8)	16 (10.7)	(48)
[216]	Neuchatel, Switzerland	4 y	161 <sup>a</sup>	17 (11)	3 (2)	28 (17.4)	ND	(47)
[217]	Amherst, Nova Scotia	July 1989–June 1990	75 <sup>b</sup>	—	—	22 (29)	1 (5.3) <sup>c</sup>	(55)
Total			439	23 (5)	10 (2.3)	104 (24)	—	211 (48)
95% CI				–3.7% to 14%	–5% to 1%	11% to 38%		38.6% to 56%

NOTE. ND, not determined.

<sup>a</sup> 8.7% required hospitalization.<sup>b</sup> 35% required hospitalization.<sup>c</sup> Of 19 tested.

with *S. pneumoniae* assigned), (2) gram-positive cocci in clusters (possible diagnosis of infection with *S. aureus* assigned), or (3) gram-negative coccobacilli (possible diagnosis of infection with *H. influenzae* assigned); a titer  $\geq 1:1024$  of antibodies to *L. pneumophila* in either the acute-phase or convalescent-phase serum specimen; a titer  $\geq 1:64$  of antibodies to *M. pneumoniae*; or an IgG antibody titer  $\geq 1:512$  or an IgM antibody titer  $\geq 1:16$  to *C. pneumoniae*. These criteria for assignment of the etiology of pneumonia (with the exception of possible infection by serological criteria) should be adopted in future studies.

CAP is not one homogeneous entity. One way to consider the etiology of CAP is to group patients according to the following categories.

1. Site of care. This category would include (a) outpatients; (b) inpatients in hospital wards; (c) inpatients in intensive care units; and (d) nursing home residents.
2. Site of acquisition of pneumonia. Included in this category would be (a) the community at large and (b) a nursing home.
3. Immune status. This category would include (a) immune-suppressing illness (e.g., HIV infection), and (b) exogenous immunosuppression.
4. Specific comorbid illnesses. Included in this category would be (a) chronic obstructive lung disease and (b) predisposition to aspiration.

In this discussion of the etiology of CAP, it is important to remember that the type and extent of diagnostic tests used in the various studies that form the basis for our conclusions about the etiology of pneumonia differed considerably. Some pathogens, such as *C. pneumoniae*, are recent discoveries and have not been included in all studies. Although it is not a microbial etiologic category, macroaspiration pneumonia defines a definite subset of pneumonia that may be due to chemical injury or to polymicrobial infection. It is unfortunate that many study reports have not specified whether or not the investigators included macroaspiration as a cause of pneumonia.

Before discussing the etiology of pneumonia under specific categories, it is worth noting that Fine et al. [24], in a meta-analysis, reported on 33,148 patients from 127 study cohorts. *S. pneumoniae* accounted for 4432 (13.3%) of these patients.

The second most common etiology was *H. influenzae*, accounting for 833 (2.5%) of the patients. Other etiologies were *M. pneumoniae* (507 patients [1.5%]), mixed bacterial species (301 [0.91%]), *Coxiella burnetii* (182 [0.5%]), and *S. aureus* (157 [0.47%]). Even in this meta-analysis, most patients had pneumonia of unknown etiology.

*Etiology of pneumonia treated on an ambulatory basis.* Up to 80% of patients with pneumonia are treated on an ambulatory basis. Unfortunately, the etiology of pneumonia in this group of patients has not been well studied. Table 2 gives a summary of the studies that have examined the etiology of pneumonia in outpatients. *M. pneumoniae* is more common in ambulatory patients than in patients who require admission to the hospital. Indeed, in all 4 studies cited in table 2, *M. pneumoniae* was the most common etiology, accounting for 17%–37% of the patients. In these studies the importance of bacterial pathogens is understated because many of the outpatients did not have sputum specimens collected.

*Etiology of community-acquired pneumonia that requires admission to the hospital.* Table 3 gives detailed information on 10 studies of CAP that requires hospitalization. These studies were carried out from 1981 through 1992 in the United States, Canada, France, Finland, Sweden, Israel, and the Netherlands. The methods used to make an etiologic diagnosis varied somewhat from study to study, but all were reasonably comprehensive. Several conclusions can be drawn from these studies: the most common cause of CAP that requires hospitalization is *S. pneumoniae* (table 3), and the frequency with which *S. pneumoniae* causes CAP ranges from 5% to 55% [25, 26].

The 3 studies that used various methods to detect antibodies to pneumolysin or its immune complexes showed very high rates of pneumococcal pneumonia [25–27]. In these studies *S. pneumoniae* accounted for 55%, 32%, and 42.8% of the cases of pneumonia. If the pneumolysin data are correct, then about half of all cases of CAP are due to *S. pneumoniae*. Mundy et al. found that *S. pneumoniae* accounted for 15.1% of the cases of pneumonia among immunocompetent adults hospitalized with CAP at Johns Hopkins Hospital in Baltimore [28].

At the same hospital, there had been 3 previous studies of CAP. In the first study, carried out during 1965–1966, *S. pneu-*

**Table 3.** Selected studies defining the etiology of community-acquired pneumonia (CAP) that requires hospitalization.

Reference	Location of study	Date(s) of study	n	Etiology of CAP, no. (%) of patients						AGNRs
				<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenza</i>	<i>Staphylococcus aureus</i>	<i>Legionella pneumophila</i>	<i>Mycoplasma pneumoniae</i>	<i>Chlamydia pneumoniae</i>	
[23]	Halifax, Nova Scotia	Nov 1981–Mar 1987	588	52 (8.8)	26 (4.4)	22 (3.7)	14 (2.3)	39 (6.6)	—	19 (3.2)
[44]	Pittsburgh, PA	Jul 1986–Jun 1987	359	55 (15.3)	39 (10.9)	12 (3.3)	22 (6)	7 (2)	22 (6.1)	21 (5.9)
[25]	Columbes, France	Feb 1983–Jan 1984	116	30 (26)	13 (12)	3 (2.5)	5 (4)	4 (3.5)	—	8 (7)
[26] <sup>a</sup>	Oulu, Finland	May 1986–May 1987	125	69 (55)	14 (11)	—	—	6 (5)	54 (43)	1 (1)
[218] <sup>a</sup>	Umea, Sweden	Dec 1982–Nov 1984	196	63 (32)	8 (4)	3 (1.5)	3 (1.5)	13 (6.6)	—	1 (0.5)
[28]	Baltimore, MD	Nov 1991–Nov 1992	385	69 (17.9)	28 (7.3)	14 (3.6)	13 (3.4)	3 (0.8)	14 (3.6)	26 (6.8)
[32] <sup>a</sup>	Southern Israel	Nov 1991–Nov 1992	346	148 (42.8)	19 (5.5)	—	—	101 (29.2)	62 (17.9)	—
[5]	Ohio	1991	2776	351 (12.6)	184 (6.6)	94 (3.4)	—	404/1244 <sup>b</sup> (32.5)	172/1923 <sup>b</sup> (8.9)	124 (4.5)
[48]	Leiden, Netherlands	1985	334	90 (27)	26 (8)	4 (1)	8 (2)	19 (6)	—	11 (3.2)
[27]	Arkansas	1985	154	8 (5)	2 (1)	7 (5)	6 (4)	3 (2)	8 (5)	7 (5)
Total			5379	935 (17.3)	359 (6.6)	159 (2.9)	70 (1.3)	598/4361 <sup>b</sup> (13.7)	332/3292 <sup>b</sup> (10.1)	218 (4.05)
95% CI				12.9% to 35.4%	4.5% to 9.5%	1.1% to 3.6%	0.8% to 3.7%	1.2% to 17.6%	−1.2% to 17.6%	1.8% to 5.5%

NOTE. AGNRs, aerobic gram-negative rods.

<sup>a</sup> Serological tests (usually for antibodies to pneumolysin) were used to diagnose pneumococcal pneumonia, in addition to blood culture and in some cases sputum culture.

<sup>b</sup> No. of patients with etiology/no. tested.

*moniae* was isolated from the sputum of 62% of the 100 patients studied [29]. During 1971–1972, 154 patients were studied and 42% had pneumococcal pneumonia [30]. In the 1979–1980 study of 147 patients, 34% had pneumococcal pneumonia diagnosed [31]. There are several possible explanations for the decreasing rate of isolation of *S. pneumoniae* from sputum at Johns Hopkins (and at other centers). Twenty-three percent of the patients in the study of Mundy et al. [28] had received antibiotic therapy before admission. It is well known that after only 1 or 238 doses of an antibiotic to which *S. pneumoniae* is susceptible, the organism can no longer be recovered from sputum.

Bedside inoculation of sputum for culture (done in earlier studies but not done now) results in higher *S. pneumoniae* recovery rates. It is noteworthy that in all 9 studies shown in table 3, *S. pneumoniae* was the most common cause of bacteremic pneumonia, occurring in 6%–10% of all cases of pneumonia. Indeed, *S. pneumoniae* accounts for 60% of cases of bacteremic pneumonia [23]. This is supporting evidence that *S. pneumoniae* is the most common cause of CAP.

The second most common cause of pneumonia, ranging from 3.4% [31] to 43% [26] in various studies of CAP that requires hospitalization, is probably *C. pneumoniae* (table 3). The study by Kauppinen et al. [26], in which 43% of the cases were due to *C. pneumoniae*, was carried out during an epidemic of *C. pneumoniae*, so it is probably not representative of the frequency of this agent as part of the etiology of CAP. Mundy et al. [28] isolated *C. pneumoniae* from 1 of 385 patients with CAP, and PCR-EIA was positive for 13 others (3.6%); an additional 46 met the investigators' serological criteria for diagnosis of *C. pneumoniae*, although these are not included in their data. If these 46 patients are included, then the rate of isolation of *C. pneumoniae* in the study of Mundy et al. [28] was 15.5% (60 of 385 patients). Other studies have relied exclusively on serological methods for diagnosis of *C. pneumoniae* pneumonia [23, 26, 32].

*H. influenzae* is the third most common cause of CAP that requires hospitalization (table 3). Most studies have shown a higher prevalence of *H. influenzae* pneumonia among patients with COPD. However, the recent study by Torres et al. [33], which focused specifically on patients with COPD and pneumonia, found that *H. influenzae* was the third most common cause of pneumonia in this group of patients, accounting for 9% of the cases.

*L. pneumophila* accounts for 2%–6% of cases of CAP that requires hospitalization. About 55% of these cases are due to *L. pneumophila* serogroup 1 [22], and *Legionella micdadei*, *Legionella feeleyi*, *Legionella bozemanii*, *Legionella dumoffii*, and *Legionella longbeachae* account for most of the rest of the cases of legionnaires' disease. The development ELISA for the detection of soluble *Legionella* serogroup 1 antigen in urine will probably improve recognition of the number of cases due to *Legionella*, but probably not much beyond 6% of the total cases

of CAP. This assay will make the detection of outbreaks much easier. The use of this assay has indicated that a previously used diagnostic criterion for legionnaires' disease, that of a single or stable antibody titer  $\geq 1:256$ , should not be used to diagnose legionnaires' disease [34].

Aerobic gram-negative rods (AGNRs) such as *Escherichia coli* and *Klebsiella* species are relatively uncommon causes of CAP overall, but they are still important pathogens in those patients who are ill enough to require admission to an ICU. Colonization of the upper airway with AGNRs increases with increasing age and with illness. These agents are often recovered from sputum specimens of elderly patients with pneumonia; the problem is to differentiate colonization from infection. Riquelme et al. [35] studied 101 patients aged  $>65$  years with CAP. They diagnosed *P. aeruginosa* pneumonia in 1 patient. Rello et al. [36] studied 95 patients aged  $\geq 65$  years with severe CAP who were admitted to the ICU, 83 of whom required mechanical ventilation. Six (6.3%) had AGNR pneumonia: 3 cases were due to *P. aeruginosa*, 1 was due to *Citrobacter freundii*, 1 was due to *Klebsiella pneumoniae*, and 1 was due to a nonfermentative gram-negative bacillus. However, Moine et al. [37] found that 11% of 132 patients with CAP who were admitted to the ICU had AGNR pneumonia.

*M. pneumoniae* is a more common cause of ambulatory CAP (table 2) than it is of CAP that requires hospitalization (table 3). However, *M. pneumoniae* can cause severe pneumonia, even to the extent that ventilatory assistance is required.

A variety of respiratory tract viruses occur in association with CAP that requires hospitalization. Most of the time, the viral infection probably precedes the pneumonia and undoubtedly plays a role in the pathogenesis of pneumonia. The markedly increased rates of pneumonia during influenza season is an example. This also explains why influenza vaccine reduces both the number of cases of influenza and the number of cases of pneumonia during influenza outbreaks [38]. RSV, a well known pathogen of children, is emerging as an important respiratory pathogen in adults. The data in table 3 show a trend in this direction. In recent years there have been many outbreaks of RSV in nursing homes [39, 40], and the number of cases involving the elderly living at home is increasing [41].

*M. catarrhalis* was an infrequent cause of pneumonia in the studies shown in table 3.

Macroaspiration is an important cause of pneumonia, accounting for 3.3%–14.1% of cases. Unfortunately, this entity is often not documented in many studies of the epidemiology of pneumonia. Most of these patients probably have a chemical pneumonitis, but polymicrobial pneumonia with both aerobic and anaerobic components of the oral flora does occur [42].

About 2% of cases of CAP that require hospitalization are due to pneumonia distal to an obstructed bronchus. Liaw et al. [43] performed needle aspiration to obtain specimens distal to the obstructed bronchus in 26 patients with this form of pneumonia. Microorganisms were recovered from 7 of 9 febrile

patients and 2 of 17 afebrile patients. Five cases were monomicrobial. Microorganisms isolated included *P. aeruginosa*, *K. pneumoniae*, viridans streptococci, *Bacteroides fragilis*, *Peptostreptococcus* species, *Mycobacterium tuberculosis*, *Pseudomonas (Stenotrophomonas) maltophilia*, *Streptococcus sanguis*, *S. aureus*, *Bacteroides* species, *Veillonella* species, and *E. coli*.

*M. tuberculosis* must always be remembered as a cause of CAP. Its importance is that undiagnosed tuberculous pneumonia can result in many secondary cases. From the data reported in table 3 it is evident that *M. tuberculosis* accounted for 1.4%–10% of cases of CAP that requires hospitalization.

*Pneumocystis carinii* must also be included in any discussion of the etiology of CAP. The data in table 3 indicate that *P. carinii* caused 2% of cases of CAP that requires hospitalization early in the HIV epidemic [23, 44]. Mundy et al. [28] divided the study patients into 2 groups: the 205 who were not infected with HIV (data given in table 3) and the 180 who were infected with HIV. Forty-eight (26.7%) of the HIV-infected group had *P. carinii* pneumonia.

Sputum cannot be processed for culture for anaerobes because it is expectorated through the oral cavity, which has a rich endogenous anaerobic flora. Patients who have pneumonia that is likely to be caused by anaerobes can be identified on the basis of their history and physical examination [45]. These patients are usually prone to aspiration during episodes of decreased consciousness (due to seizures, neurological diseases affecting the swallowing mechanism, drug overdoses, alcohol, etc.). Periodontal disease or dental caries (which increase the inoculum of anaerobes aspirated) increase the risk of pleuropulmonary anaerobic infection [46]. Foul-smelling sputum, lung abscess, and empyema are common manifestations of pulmonary infection with anaerobes [47].

Fungi are not commonly considered as a cause of CAP, except in areas where *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* are endemic, where these fungi can be important causes of endemic and epidemic CAP. When these agents occur sporadically outside areas of endemicity, they cause diagnostic problems because clinicians do not include them in their differential diagnosis. In this regard it is noteworthy that 3 (1.5%) of the 206 patients in the study of Mundy et al. [28] had pneumonia caused by fungi. This emphasizes the importance of inquiring about travel to areas with endemic fungi.

*Coxiella burnetii* is the etiologic agent of the zoonosis Q fever. Cattle, sheep, and goats are the usual animal reservoirs for this microbe. In these animals *C. burnetii* localizes to the mammary glands and to the endometrium. *C. burnetii* is activated during pregnancy, reaching high concentrations in the placenta, and at the time of parturition the organism is aerosolized. When susceptible humans inhale the contaminated aerosols, Q fever pneumonia results. Cats and dogs can also become infected with *C. burnetii*, which can spread to humans at the time of parturition. Characteristically, a household outbreak of pneu-

monia occurs 2 weeks following delivery of newborn kittens or puppies from an infected animal. *C. burnetii* is endemic in most countries, except New Zealand. In the studies cited in table 3, *C. burnetii* accounted for 3% of the cases of pneumonia in Nova Scotia [23], 5.8% of those in an Israeli study [32], and 1 of 324 cases in the Netherlands [48]. *C. burnetii* is more likely to cause pneumonia in rural than in urban areas.

*Cryptococcus neoformans* can cause pneumonia in both immunocompetent and immunocompromised hosts. Among immunocompetent hosts with pulmonary cryptococcal infection, only ~50% are symptomatic. In contrast, immunocompromised patients with pulmonary cryptococcal infection are symptomatic with fever and cough, and ~80% develop meningoencephalitis. The radiographic pattern includes single or multiple nodules, diffuse interstitial infiltrates, or widespread alveolar consolidation with respiratory failure. This latter pattern is more commonly seen in patients who are severely immunosuppressed.

Despite extensive investigation there is always a subset of patients with pneumonia of unknown etiology. Thus, even in a study in which bronchoscopy was performed on 40 patients with CAP in order to obtain specimens for culture [49], an etiologic diagnosis could be made for only 70% of the patients. It is likely that some of these cases of unknown etiology are due to undiscovered pathogens. Recently, Hall's coccus, an amoebal pathogen, has been found to cause pneumonia [50].

In most studies of CAP, a small percentage of patients have  $\geq 2$  agents identified as the cause of the pneumonia. Among the studies listed in table 3, this ranged from 2.8% in the Pittsburgh study [44] to 10.3% in the Halifax study [23]. Mundy et al. [28] and Bates et al. [27] reported that 6.2% and 6.4%, respectively, of their patients had pneumonia of mixed etiology. In such cases it is not clear whether both pathogens actively cause disease concurrently or whether infection occurs sequentially (i.e., 1 of the organisms causes infection first, which then allows the second agent to cause disease).

**Etiology of nursing home-acquired pneumonia.** Table 4 summarizes studies of the etiology of nursing home-acquired pneumonia. *S. pneumoniae* is the most commonly isolated pathogen. With increasing age, the rate of colonization of the oropharynx by AGNRs increases [51]. However, an important question is what percentage of pneumonia in nursing home patients is caused by these bacteria. Since macroaspiration is common in nursing home patients, it is likely that this group of organisms is important in nursing home-acquired pneumonia. A major limitation of studies of nursing home-acquired pneumonia is reliance on sputum culture to make an etiologic diagnosis, as evidenced by the 40% rate of *K. pneumoniae* infection in the study of Garb et al. [52]. This seems very high when compared with the findings in other studies cited in table 4 and exemplifies the problem of relying on sputum cultures to make an etiologic diagnosis.

**Etiology of pneumonia in patients with COPD.** From October 1992 to December 1994, Torres et al. [33] studied 124

**Table 4.** Etiology of nursing home-acquired pneumonia.

Reference	n	Etiology of pneumonia, no. (%) of patients							
		<i>Streptococcus pneumoniae</i>	<i>Chlamydia pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Staphylococcus aureus</i>	<i>Moraxella catarrhalis</i>	<i>Klebsiella pneumoniae</i>	Other AGNRs	Unknown
[52]	35	9 (26)	—	2 (6)	9 (26)	—	14 (40)	—	—
[23]	131	9 (6.8)	—	1	7 (5.3)	—	—	7 (5.3)	77 (59)
[219]	104	31 (29.8)	—	20 (19)	11 (10.5)	4 (3.8)	—	24 (23)	14 (13)
[220]	56	5 (8.9)	—	4 (7.1)	1 (1.8)	3 (5.5)	—	—	43 (77)
[221]	115	7 (6)	—	3 (2.5)	2 (1.7)	—	7 (16)	20 (17)	83 (72.8)
[222] <sup>a</sup>	30	—	2 (6.6)	—	—	—	—	—	23 (76.7)
Total	471	61 (12.9)	2 (0.4)	30 (6.4)	30 (6.4)	7 (1.5)	21 (4.4)	51 (10.8)	240 (51)
95% CI		1.2%–29.7%		0%–15%	0%–21%				13.6%–85%

NOTE. AGNRs, aerobic gram-negative rods such as *Escherichia coli*.

<sup>a</sup> This serological study found 3 patients who had dual infections with *C. pneumoniae* and one of the following: RSV-1, parainfluenza virus 3; and influenza virus type A; it also found 1 patient infected with parainfluenza virus type 3 and 1 patient infected with influenza virus type A.

patients with COPD and pneumonia. There were 115 males and 9 females, with a mean age of 67 years. An etiologic diagnosis was made for 64%. The most common etiologies were *S. pneumoniae*, 43% of patients; *C. pneumoniae*, 12%; *H. influenzae*, 9%; *Legionella* species, 9%; viridans streptococci, 4%; *C. burnetii*, 4%; *M. pneumoniae*, 3%; and *Nocardia asteroides*, 3%. There was 1 isolate each of 10 other microbial agents, one of which was *S. aureus*. The enterobacteriaceae as a group accounted for 4% of the isolates.

**Severe CAP.** The majority of cases of CAP are managed on an outpatient basis. However, the minority of patients who require hospitalization account for a significant mortality rate [24] and for the majority of health care expenses for CAP [53]. Both cost and risk of death are considerably greater for those patients with severe CAP that requires management in the ICU [24]. The mortality rate was 36.5% for 788 ICU patients with CAP in 13 study cohorts included in the meta-analysis by Fine et al. [24].

Identification of the causative organism(s) allows for appropriate therapy, but in one study it did not result in an improvement in survival rate among patients who require admission to the ICU [54]. *S. pneumoniae* is the most commonly identified causative organism in patients treated in an ICU (table 5). The other commonly identified bacterial pathogens are *L. pneumophila*, *H. influenzae*, and *S. aureus*. However, any agent that causes pneumonia can cause infection severe enough to require intensive care. Both aerobic gram-negative bacilli and *Legionella* occur more frequently in patients treated in the intensive care setting than in those treated elsewhere (table 5).

Although a causative organism is more commonly identified in CAP patients treated in an ICU than elsewhere, an etiologic agent is identified for only ~60% of the patients, despite the more intensive diagnostic testing. Aspiration of tracheal secretions and bronchoscopy with either bronchoalveolar lavage or protected-brush sampling, followed by quantitative culture of the collected specimens, are commonly performed for intubated patients [54]. Transthoracic needle aspiration has also been used diagnostically in patients with severe CAP [54].

## Diagnosis

The subject of diagnostic testing of patients with CAP has generated considerable debate among pulmonologists and infectious disease specialists. The range of recommendations extends from the relatively limited testing recommended by the ATS guidelines and the European Study on Community-Acquired Pneumonia (ESOCAP) Committee to the more extensive testing recommended by the IDSA [2, 3, 55]. We will make recommendations for investigations based upon the severity of illness of the patients. Since the severity of illness is reflected by the site of care selected by the physician, these recommendations will be site-specific as well.

### Site-Based Investigation (Office vs. Emergency Department vs. ICU)

A diagnosis of CAP is often entertained on the basis of the initial presentation of a constellation of symptoms and signs. Once these are considered, the physician then frequently orders radiographic and laboratory studies. Although a number of criteria for clinical, radiographic, and laboratory findings have been proposed to identify CAP, it is known that no criteria are perfectly reliable for diagnosis [56]. Furthermore, recommendations for patients deemed well enough to be treated on an ambulatory basis are different from recommendations for patients ill enough to require hospitalization, either in a general ward or in the ICU (figure 1).

At the outset, it should be noted that although the importance of the history, physical examination, chest radiography, and certain laboratory tests for assessment of patients suspected of having CAP has been stressed, it is surprising how few studies have examined the relative value of this approach. Furthermore, the few studies reported to date are limited in that none used autopsy as a reference standard to determine if pneumonia was in fact present; instead, these studies relied on chest radiography or clinical suspicion to determine the presence or absence of CAP.



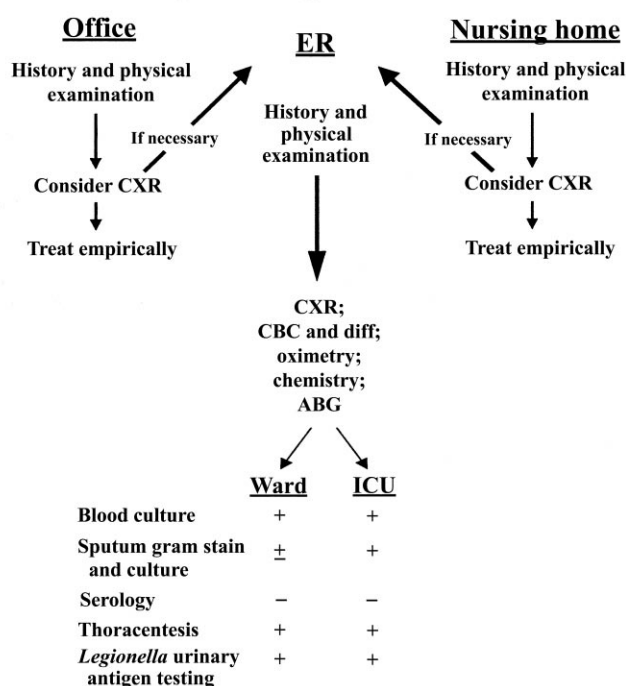
### Clinical Findings in CAP

Patients who present with fever and new cough, purulent tracheobronchial secretions, and focal respiratory abnormalities on physical examination should be suspected of having pneumonia. An important variable in the workup of this disease is the reliability of a physician eliciting information relevant to the diagnosis of CAP, but to date it has not been investigated. Even studies of interobserver variation in identifying the presence of symptoms in patients with CAP have not been reported [57], although significant variation between observers has been noted in several epidemiological studies of other respiratory diseases [58–60]. Such variation has resulted in the development of standardized questionnaires for certain respiratory diseases, but no such questionnaires are presently available for documenting symptoms in acute respiratory infections.

The reliability of physical signs in the diagnosis of CAP is also unknown, but interobserver variation in recognizing certain findings has been studied and seen to vary dramatically [61–63]. In one study investigating interobserver variability, 24 physicians performed physical examinations on 24 patients with respiratory disease, 4 of whom had pneumonia. Agreement varied, depending upon the physical finding sought. Agreement was more likely with regard to the presence or absence of increased tactile fremitus (85%) and wheezes (79%) than with regard to crackles (72%) and tachypnea (63%) [57, 62]. Based upon the physical examination findings alone, the diagnosis of pneumonia was correctly made by fewer than 40% of the examiners. In another study designed to investigate the ability of physicians to detect abnormal auscultatory findings on the basis of radiographic abnormalities, interobserver agreement was noted in only 41.5% of cases, and this decreased to 25% when the presence of crepitant rales was investigated [63].

Use of physical examination findings at presentation to determine which patients can be treated as outpatients and which need to be hospitalized also has not been systematically studied. The one study investigating the importance of physical ex-

### Diagnostic algorithm for CAP



**Figure 1.** Site-based algorithm for the investigation of community-acquired pneumonia (CAP). ABG, arterial blood gas determination; CBC and diff, complete blood cell and differential counts; CXR, chest radiography; ER, emergency department; ICU, intensive care unit; +, recommended; ±, recommended in certain specific circumstances; -, not recommended.

amination findings was reported by Fine et al. [64]. It was designed to identify CAP patients who were at low risk of dying within 30 days of presentation; that is, low-risk patients who would be good candidates for outpatient treatment. This large study included both derivation and validation cohorts.

In the derivation arm, a number of values were identified by

**Table 5.** Etiology of community-acquired pneumonia that requires admission to an intensive care unit (ICU).

Reference	Location of study	Dates of study	n	Etiology of pneumonia, no. (%) of patients					Ventilated, %	Mortality, %
				<i>Streptococcus pneumoniae</i>	<i>Legionella pneumophila</i>	AGNRs	<i>Staphylococcus aureus</i>	Unknown		
[105]	Spain	1988–1990	58	13 (37)	8 (22.8)	4 (11.4)	—	23 (39.6)	72	22.4
[223]	UK (25 hosp)	1987	60	11 (18)	7 (12)	—	2 (3)	18 (30)	88	48
[37] <sup>a</sup>	France	1987–1989	132	43 (32)	4 (3)	14 (11)	5 (4)	37 (28)	37	24
[224]	Spain (26 ICUs)	1991–1992	262	30 (11)	21 (8)	8 (3)	10 (4)	108 (41.2)	NS	NS
[225]	Sweden	1977–1981	53	15 (28)	—	—	2 (4)	13 (25)	58	25
[54]	Seville, Spain	1985–1987	67	12 (37.5)	7 (21.8)	8 (25)	—	35 (52.3)	—	20.8
[226] <sup>a</sup>	Barcelona, Spain	1984–1987	92	13 (14)	13 (14)	5 (5) <sup>b</sup>	—	28 (30)	61	20
[83]	Lille, France	1987–1991	299	80 (26.7)	—	52 (17.3)	57 (18) <sup>c</sup>	102 (34.1)	50	28.5
Total			1023	217 (21)	60 (5.8)	91 (8.8)	76 (7.4)	364 (35.6)		
95% CI				17% to 34%	2.6% to 17.7%	3.3% to 17.8%	–0.28% to 13.7%	27.5% to 42.9%		

NOTE. AGNRs, aerobic gram-negative rods; hosp, hospitals; NS, not stated; UK, United Kingdom.

<sup>a</sup> Immunosuppressed patients excluded.

<sup>b</sup> Five patients infected with *P. aeruginosa* had bronchiectasis.

<sup>c</sup> *Staphylococcus* species.

**Table 6.** Interobserver variability in interpretations of chest radiographs for patients with community-acquired pneumonia.

Reference	Type of study	Description of population	Were investigators unaware of other investigators' results?	Were test methods adequately described?	Criteria used to assess quality of sample
[72]	Prospective	Ambulatory and hospitalized; age, >17 y; $\geq 1$ clinical sign of CAP	Yes	Yes	Graded quality of chest radiograph
[73]	Prospective	Ambulatory; age, >17 y; CAP or evidence of lower respiratory tract infection and ERS of >20 mm/h or CRP of >20 mg/L	Yes	No	NS
[74]	Prospective	Adults with symptoms and radiographic evidence of CAP	Yes	Yes	NS

NOTE. CRP, C-reactive protein level; ERS, erythrocyte sedimentation; NS, not stated.

multivariate analysis, and on the basis of these findings, points were given for age, sex, the presence of comorbid illness, and abnormalities noted on physical examination and laboratory and radiographic studies. On the basis of this score, patients were stratified into 1 of 5 severity-of-illness categories, and factors such as length of stay, need for ICU admission, and subsequent hospitalization were compared. The physical examination abnormalities used in this scoring system were as follows: systolic blood pressure <90 mm Hg; heart rate  $\geq 125$  beats per minute; spontaneous respiratory rate  $\geq 30$  breaths per minute; an oral temperature <35°C or >40°C; and altered mental status. The scoring system was then validated in another large set of CAP patients. The utility of such a scoring system for determining who should be admitted remains to be determined, but one recent study suggested that although the number of low-risk patients hospitalized for CAP could be reduced, the incidence of subsequent admissions for CAP was greater than that among control patients [65].

**Recommendation.** The clinical assessment (history and physical examination) is the foundation upon which further assessment is based and therefore is mandatory for all patients, despite these limitations (III).

### Chest Radiographs

Chest radiographs are frequently ordered when patients are suspected of having pneumonia. Finding new or progressive

infiltrates in conjunction with other clinical and laboratory abnormalities has been suggested as a method to identify patients with pneumonia. A chest radiograph is occasionally helpful in identifying a specific etiology, and it can also identify markers for a more complicated course of illness (multilobar infiltrates, parapneumonic effusions) or suggest alternative etiologies (e.g., bronchogenic carcinoma). However, it is appreciated that a number of infectious and noninfectious etiologies may present with a radiographic picture indistinguishable from the picture for pneumonia. Expert opinion has varied regarding the use of posteroanterior and lateral chest radiography for patients with clinically suspected CAP; some consensus statements suggest that a chest radiograph be obtained for all patients suspected of having CAP, but other statements are not so definitive [2, 3].

Although the use of chest radiographs to diagnose pneumonia has been studied with regard to patients receiving mechanical ventilation [66–70], only one study has evaluated its ability to detect pulmonary infiltrates in patients suspected of having CAP [71]. This study enrolled 47 patients who were treated in the hospital or as outpatients and presented with clinical symptoms of CAP. The gold standard was the finding of infiltrates on high-resolution CT (HRCT). Chest radiography was performed with either an AMBER (Oldelft, The Netherlands) or a digital Fuji FCR 9501 chest radiographic unit (Fuji, Tokyo). The chest radiographs revealed pulmonary infiltrates in 18 patients (38.3%), whereas HRCT detected infiltrates in these 18 patients and in an additional 8 patients (4

**Table 7.** Interobserver variability in interpretations of chest radiographs of patients with community-acquired pneumonia (CAP).

Reference standard observer, other observer	Sensitivity, %	Specificity, %	Patients with CAP; control subjects	Study design	Antibiotics used	Reference
2 radiologists	85.4	84.6	282; 10	Cohort	NS	[72]
Interobserver variability			21; 30	Selected cohort	No	[73]
Pulmonologist	59	96				
Radiologist	56	96				
Resident	36	94.5				
3 radiologists			15	Consecutive	NS	[74]
Radiologist	87	ND				
Staff	72	ND				
Resident	66	ND				
4th-y student	55	ND				
1st-y student	59	ND				

NOTE. ND, not determined; NS, not stated.

**Table 8.** Prediction rules for when *not* to order chest radiographs (development of low-yield criteria) for patients with community-acquired pneumonia (CAP).

Reference	Type of study	Description of population	Were investigators unaware of other investigators' results?	Were test methods adequately described?	Criteria used to assess quality of sample
[77]	Retrospective	>18 y old with fever or respiratory complaints and no CHF	NS	No	NS
[78]	Prospective	Adults who presented with cough; temp. $\leq 40^{\circ}\text{C}$ ; pulse $\leq 160$ ; SBP $\geq 90$ mm Hg	Yes	Yes	NS
[81]	Prospective	Ambulatory adults with probable CAP	Yes	Yes	NS
[80]	Prospective	Ambulatory adults with fever or respiratory symptoms	Yes	Yes	Yes
[79]	Prospective	Ambulatory adults with suspected CAP	Yes	Yes	Yes
[76]	Prospective/ retrospective <sup>a</sup>	Emergency department or outpatient clinics	Yes	Yes	Yes

NOTE. CHF, congestive heart failure; SBP, systolic blood pressure.

<sup>a</sup> Retrospective application of 4 criteria.

inpatients and 4 outpatients; 55.3%). Even among the 18 patients in whom infiltrates were noted on chest radiographs, HRCT detected additional infiltrates in all. HRCT was almost twice as likely as chest radiography to detect infiltrates in the upper lobes, lower lobes, and lingula. Unfortunately, the significance of the improved sensitivity of the HRCT was not studied; whether this improved sensitivity made a difference in the management or outcome of the cases remains to be determined.

Aside from how sensitive chest radiography is in detecting an infiltrate, there are at least 2 additional questions regarding the role of chest radiographs in the investigation of patients suspected of having CAP: how accurate are interpretations of chest radiographs, and when should chest radiography be ordered?

The accuracy of interpretations of chest radiographs of patients presenting with symptoms of CAP has been addressed by 3 studies (tables 6 and 7) [72–74]. Patients were enrolled in studies of various designs, and the reference standard was either an “expert panel” or simply direct comparison. These studies revealed that the overall sensitivity of radiologists’ detection of infiltrates ranged from 56% to 85.4%, but sensitivity decreased when residents or medical students read the same chest radiographs. The only study comparing the interpretations of radiologists and chest physicians found that the sensitivity was similar: 56% and 59%, respectively. In only 2 studies was specificity investigated, and it was reported as 84.6% and 96%, regardless of experience. These results are similar to those of other studies [75].

In an attempt to reduce the use of unnecessary chest radiography, several authors have developed prediction rules for ordering chest radiographs for patients with respiratory symptoms [76–81]. In the 1 retrospective study and 4 prospective studies that have been reported, the presence of infiltrates in patients who presented with clinical symptoms was felt to confirm CAP (tables 8 and 9). The criteria employed varied dramatically among the studies, but 2 studies [78, 80] included a derivation and a validation arm (tables 8, 9, and 10). In 4 of the studies, prediction rules were developed with good sensi-

tivity but usually reduced specificity (table 9). In one derivation/validation study, Singal et al. showed that clinical judgement was at least as good as the prediction rules [81].

The success of using decision rules developed by the 4 prospective studies versus clinical judgment alone was reported by Emerman et al. [76]. In this study, Emerman et al. compared the accuracy of each of the 4 prediction rules with a cohort of patients presenting to an emergency department or outpatient setting. Overall, the prevalence of pneumonia in this study was 7%. The sensitivities of the 4 decision rules ranged from 62% to 76%, and specificity ranged from 55% to 76%, whereas clinical judgment was 83% sensitive and 57% specific.

**Recommendation.** Under most circumstances, chest radiography is recommended for the routine evaluation of a patient suspected of having pneumonia (II). The advantage of chest radiography is that the diagnosis of pneumonia is strengthened (but not confirmed) by the presence of an infiltrate. Occasionally, information regarding etiology and prognosis may be obtained and alternative diagnoses may be entertained. However, the panel realizes that in some instances a chest radiograph might not be obtained; for example, when the patient is in a nursing home or when access to radiographic equipment is limited. The panel recognizes that under these circumstances a trial of empirical therapy without radiographic confirmation of the diagnosis is a reasonable approach (III).

Although the chest radiograph is the standard means of confirming pneumonia, it is less sensitive than HRCT scans in detecting pulmonary infiltrates, but the significance of this observation remains to be determined [71] (II). Interobserver variability in sensitivity among radiologists’ interpretations of chest radiographs ranges from 56% to 87% but improves in relation to training. Although several prediction rules have been developed to assist physicians in reducing orders for chest radiographs, these rules appear to be no better than clinical judgement [76] (II).

### Laboratory Testing

No studies to date have prospectively identified which laboratory tests to order for patients presenting with CAP. The

**Table 9.** Sensitivity and specificity of prediction rules for when *not* to order chest radiographs (development of low-yield criteria) for patients with community-acquired pneumonia (CAP).

Reference, criterion <sup>a</sup>	Sensitivity, %	Specificity, %	ROC curves	Patients with (without) CAP, <i>n</i>	Study design	Use of antibiotics
[77]	93	96.4		129 (335)	Case study	NS
[78]				48 (435)	Case series (d/v)	NS
Score -1	74	70				
Score 0	59	88				
[81]				45 (220)	Case series	NS
Clinical judgement			0.75			
Prediction rules			0.73			
[80]				1420 total	Case series (d/v)	NS
Derivation			0.82			
1st validation	93	43	0.82			
2d validation	90	35	0.76			
[79]	98	18		118 (190)	Case series	NS
[76]				21 (269)	Case series	NS
Prediction rules of:						
[78]	67	67				
[80]	71	67				
[79]	62	76				
[81]	76	55				
Clinical impression of:						
Attending physician	83	57				
House staff	89	58				

NOTE. D/v, derivation/validation; NS, not stated; ROC, relative operating characteristic.

<sup>a</sup> Prediction rules used by these studies are summarized in table 10.

only large derivation/validation study of the relative importance of laboratory tests was reported by Fine et al. [64]. The abnormal laboratory values noted in this study were as follows: hematocrit, <30%; glucose,  $\geq 250$  mg/dL; sodium, <130 mmol/L; blood urea nitrogen,  $\geq 30$  mg/dL; and arterial pH, <7.35.

**Recommendations.** Unless clinical or radiographic findings suggest risk factors for poor outcome, *routine* laboratory assessment of ambulatory patients suspected of having CAP is unnecessary (III). Once a patient has been directed to the emergency department for further assessment (on the basis of initial clinical and radiographic findings), determinations of the complete blood cell count, electrolyte levels, liver function, renal function, and O<sub>2</sub> saturation are recommended (II) (figure 1). Significant abnormalities identified by these laboratory investigations have been noted as risk factors for a complicated hospital course or death. They have been used in the prediction rule developed by Fine et al. and have been prospectively validated for mortality risk [82].

The panel recommends that these tests be routinely performed for all patients referred to the emergency department as a means of assessing the severity of illness (II) and the need for hospitalization. There is no evidence to suggest that these investigations are useful in the routine assessment of patients in any other clinical setting (i.e., a physician's office or a nursing home). In addition, the panel recommends that arterial blood gas levels be considered for patients with chronic obstructive lung disease, since an O<sub>2</sub> saturation assessment will not inform the physician of hypercapnic respiratory failure (III). If a patient does not have specific risk factors for a complicated course or death and there are no other reasons for hospital admission,

the physician will probably select empirical therapy and discharge the patient from the emergency department.

### Microbiological Investigations

There are many advantages to determining a specific etiological pathogen, including the ability to select the optimal drug; to reduce antibiotic abuse in terms of cost, resistance, and adverse drug reactions; and to identify organisms that have potential epidemiological significance such as *M. tuberculosis*, *Legionella* species, and drug-resistant *S. pneumoniae* [3]. Unfortunately, the reality of current clinical practice is that despite extensive and exhaustive diagnostic testing, even when conducted in medical centers interested in the epidemiology of pneumonia, a specific etiologic agent will not be found in one-third to one-half of cases [27, 44, 23]. With the possible exception of sputum Gram stain findings, the information obtained becomes available only after the most significant decisions regarding antimicrobial therapy have already been made.

Although studies assessing the direct impact of diagnostic testing on clinical outcomes have not been performed, a body of evidence is emerging that knowledge of the pathogen may not affect clinical outcome [54]. Antibiotics found to be initially effective against the target pathogen(s) are associated with better outcomes, but the identification of the pathogen(s) has no beneficial effect on outcome [25]. Identification of the organism after the initial incorrect choice of empirical therapy and subsequent correction of treatment to cover the offending pathogen does not appear to affect outcome [83]. Woodhead et al. found that in routine clinical practice (as opposed to carefully con-

**Table 10.** Prediction rules for ordering a chest radiograph for patients with community-acquired pneumonia (CAP).

Reference	Prediction rule
[77]	Do not order chest radiograph if (1) patient is asthmatic, (2) auscultation is normal, or (3) patient is not demented
[78]	Use scoring system: rhinorrhea, -2 points; sore throat, -1; night sweats, +1; myalgia, +1; sputum all day, +1; respiratory rate >25 breaths/min, +2; temp $\geq 37.8^{\circ}\text{C}$ , +2
[81]	Use logistic regression for predicting infiltrate: $P = 1/(1-e^Y)$ , where $Y = -3.095 + 1.214 (\text{cough}) + 1.007 (\text{fever}) + 0.823 (\text{crackles}) + .030 (\text{clinical pretest probability for CAP})$
[80]	Determine the number of abnormal clinical findings: absence of asthma, temp. $>37.8^{\circ}\text{C}$ , heart rate of $>100$ beats/min, decreased breath sounds, crackles
[79]	Order chest radiography when any variable is present: temp. $>37.8^{\circ}\text{C}$ , pulse of $>100$ beats/min, or respirations $>20$ breaths/min

NOTE. See table 9 for sensitivity and specificity findings. e, exponential value; P, probability of an infiltrate on chest radiograph; temp, temperature.

ducted prospective diagnostic investigations), causative pathogens are found in ~25% of cases, and the results of these investigations lead to a change in therapy in <10% of cases [84]. They concluded that routine microbiological investigation of all adults admitted to the hospital was not helpful and probably was unnecessary.

**Sputum Gram stain and culture.** Several potential difficulties arise when sputum is examined routinely for the presence of pathogenic organisms. In many instances, a sample simply cannot be obtained, especially from the elderly. Even if a sample can be obtained, the quality of the specimen is frequently inadequate, especially if taken routinely by nursing staff. Prompt transport to the laboratory is necessary, and identification of an adequate sample (<25 squamous epithelial cells per low-power field [SECs/lpf]) requires properly trained staff [85]. There is considerable interobserver variability in the assessment of sputum Gram stains [86], and although many clinicians have promoted the value of Gram stains, the role of this test remains controversial [2]. Even its supporters have recommended that treatment of acutely ill patients not be delayed if there is difficulty in obtaining specimens [3].

A recent meta-analysis evaluated the sensitivity and specificity of Gram staining of sputum in cases of community-acquired pneumococcal pneumonia [87]. The investigators found 12 articles that met predetermined criteria for eligibility [31, 86, 88–97]. They included the ability to create a  $2 \times 2$  table of true-positives, true-negatives, false-positives, and false-negatives. Other characteristics that were sought included whether inclusion and exclusion criteria were explicit; whether interobserver and intraobserver variability were assessed; whether the result of Gram staining was the primary outcome variable; and general clarity of the study. They concluded that the sensitivity of sputum Gram staining ranged from 15% to 100%, keeping in mind that sputum culture was the reference standard for the majority of studies. Specificity ranged from 11% to 100%.

The test characteristics varied widely among studies and depended on the test's interpreter as well as the study population. No single estimate of sensitivity or specificity could be reached,

and the authors cautioned that its use in general clinical practice might be hazardous.

Our own review of the literature, including the meta-analysis referred to above, supports these findings (tables 11 and 12). In 5 instances the values for sensitivity and specificity could not be reproduced from the published data. According to the meta-analysis, additional data were obtained from the authors of these 5 studies when sensitivity and specificity could not be calculated from the data in the original articles. These values were used in table 12.

Of the 12 studies included in the meta-analysis, 11 were prospective. Most investigators studied consecutive patients admitted over a specified time period to a single institution. In many cases the institution was a veterans' or county hospital, suggesting that the patient population was relatively uniform but perhaps not representative of the entire population at risk of CAP. In slightly more than half the studies, the investigators did not control for the prior administration of antibiotics. In 9 of the 12 studies the Gram stain interpreter was blinded to the reference standard results. In most instances, the reference standard was a sputum culture, although occasionally, the standard was a culture of transtracheal aspirate, culture of bronchial aspirate, or a combination. Blood culture was the reference standard in only 1 study, in which all patients had bacteremic pneumococcal pneumonia. A clear definition of a positive Gram stain was given in only half of the studies.

In 7 of the 12 studies, the sputum Gram stain had a sensitivity of <70%, indicating that nearly one-third of patients had a false-negative Gram stain. When only a laboratory technician reviewed the smear, the sensitivity was less, ranging from 15% to 69%. The 2 studies that revealed sensitivity and specificity of >80% used infectious disease or pulmonary specialists as interpreters.

Rein et al. examined sputum Gram stains of consecutive patients with pneumonia and found that different interpretive criteria for a positive Gram stain altered the test characteristics quite dramatically [92] (table 13). The sensitivity ranged from 48% to 100%, depending on the definitions used. For example,

**Table 11.** Characteristics of studies of the value of sputum Gram staining for patients with community-acquired pneumonia (CAP).

Ref.	Enrollment	Description of population	Were test results and reference standard assessed blindly?	Were test methods adequately described?	Criterion or criteria used to assess the quality of the sample
[227]	Prospective	Adults aged 15–74 y with abnormal chest radiographs	No	No	NS
[31]	Retrospective	All admitted patients with diagnosis of CAP, 1971–1972, 1979–1980	No	No	NS
[90]	Prospective	All adult patients admitted Sept 1978–May 1979	No	Yes	≥10 bacteria per OIF
[91]	Prospective	Adults admitted to VA hospital; no antibiotic treatment	No	No	NS
[88]	Prospective	All patients with CAP admitted to VA hospital in 1 y	Yes	Yes	More PMNLs than squamous epithelial cells; >50% of organisms of one morphology
[89]	Prospective	Bacteremic patients with CAP admitted Jan 1982–July 1987	Yes	Yes	>10 organisms per OIF
[92]	Prospective	Consecutive patients in winter months	Yes	Yes	>50% organisms of one morphology or >10 organisms per OIF
[93]	Retrospective	Patients with positive cultures and pneumonia	No	Yes	NS
[94]	Prospective	NS	Yes	No	NS
[95]	Prospective	CAP patients admitted to Changzheng Hospital, 1 Dec 1986–28 Feb 1987	Yes	Yes	>10 organisms per OIF
[96]	Prospective	Consecutive CAP patients for 1 y	Yes	No	NS
[97]	Prospective	All CAP patients admitted July 1986–Mar 1987	Yes	Yes	>50% organisms of one morphology

NOTE. NS, not stated; OIF, oil-immersion field; ref., reference; VA, Veterans' Administration.

if the presence of any gram-positive diplococci of any shape defined the presence of *S. pneumoniae*, then the Gram stain was 100% sensitive for the diagnosis. On the other hand, if lancet-shaped diplococci within a flora of predominantly gram-positive organisms were found, the sensitivity dropped to 48%. The specificity ranged from zero to 100%, depending on the definition of a "gold standard." As in most diagnostic tests, as the sensitivity increased, the specificity declined.

Perhaps the best-designed and conducted study is that of Fine et al. [97]. In a prospective multicenter study, house staff and microbiology personnel prepared a Gram stain for each of 99 cases of pneumonia involving 97 patients. Two senior staff microbiologists, blinded to the clinical cases, evaluated the stains. The senior staff's determination of the etiologic agent (on the basis of their interpretation of the Gram stain and/or the subsequently identified pathogen from sputum culture, blood culture, or serology) was the "gold standard." House officers' detections of pneumococci had 90% sensitivity (with the staff microbiologist's interpretation of the Gram stain as the reference standard) but only 58% in terms of detection of *H. influenzae*. With microbiological evaluation as the reference standard, the sensitivity fell to 86%. There was a 50% false-positivity rate for detecting pneumococci. The size of the study precluded any conclusions regarding the performance of house officers in identifying other organisms, especially gram-negative bacteria.

Among the initial cohort of patients evaluated, 19% could not produce sputum, and 25% did not have a specimen prepared by the house officers. Despite the careful nature of this study, a sputum Gram stain was prepared for <80% of patients and was properly implemented for fewer than half. Moreover, even when only 1 organism was identified, the house officers still selected >1 antibiotic in almost half the cases, suggesting a lack

of confidence in their own interpretation. Although the investigators concluded that more rigorous training of house officers is required to better use this test, perhaps a more realistic conclusion would be that the test characteristics of Gram staining preclude increasing its use.

These studies have examined the test characteristics of Gram stains for patients suspected of having pneumococcal pneumonia. The very nature of the Gram stain would favor the identification of pneumococci over any other organisms because of the strong staining characteristics of these bacteria. The studies examined in this document, for the most part, did not even attempt to examine the role of Gram staining in identifying other organisms. In particular, the sensitivity of Gram stains for the identification of gram-negative organisms is unknown but almost certainly is lower than that for identification of *S. pneumoniae*. It is important to note that a satisfactory reference standard such as bronchoalveolar lavage, protected-specimen-brush sampling, or transtracheal aspiration was not used in the vast majority of studies. In most studies, a proper definition of a positive Gram stain was not given. Finally, the clinical and financial implications of an incorrect diagnosis based upon Gram stain findings have not been examined.

**Blood cultures.** Blood culture specimens are drawn from most patients with CAP who are admitted to the hospital, and the literature dealing with their use focuses on 3 questions: (1) What percentage of patients with CAP have bacteremia? (2) When bacteremia is present, what organisms are most commonly identified? (3) Does the presence of bacteremia have clinical relevance for either modifying antibiotic therapy or predicting outcome (prognosis)?

First, what percentage of CAP patients have bacteremia? Almost every report on a large series of patients with CAP describes the diagnostic value of blood cultures. In a review of

**Table 12.** Characteristics of studies of the value of sputum Gram staining for patients with community-acquired pneumonia (CAP).

Reference, interpreter	n	Patients who received antibiotics, %	Reference standard	Sensitivity, %	Specificity, %	Likelihood ratio
[227] Laboratory technician	404	45	Combination	15	98	7.5
[31] House officer or student	154	93	Sputum culture	52	88	4.3
House officer or student	147	94	Sputum culture	63	80	3.1
[90] ID specialist	151 <sup>a</sup>	57	Sputum culture	84	85	5.6
[91] Unknown	16	0	Sputum culture	100	67	3.0
[88] House officer	76	22	Sputum culture	94	64	2.6
[89] Laboratory technician	59	0	Blood culture	69 <sup>b</sup>	83	4.1
[92] Fellow	28	NS	Sputum	60	61	3.5
Fellow	42		Combination <sup>c</sup>	62	85	1.6
[93] Fellow	40	NS	Sputum culture	55	94	9.2
[94] House officer or student	53	0	Sputum culture	96	11	1.1
Laboratory technician	30	0	Sputum culture	43	88	3.6
[95] Pulmonary fellow	95	48	Sputum culture	88	85	5.9
[96] Fellow	40	53	Combination	67	100	?
[97] House officer	36	NS	Combination	86	72	3.1

NOTE. ID, infectious disease; NS, not stated.

<sup>a</sup> Of 266 samples obtained, 76% were purulent; atypical infections were excluded.<sup>b</sup> Thirty-eight of 59 patients.<sup>c</sup> Sputum, mouse inoculation, pneumococcal/Quellung.

CAP, Marrie stated that 8%–10% of all admitted patients will have positive blood culture results and that a pneumococcus accounts for 60% of the cases of bacteremia [98]. Similarly, Bartlett and Mundy reviewed 12 series of CAP and reported that 330 (11%) of 2935 patients admitted to the hospital had bacteremia, with pneumococci accounting for 67% of the positive cultures [99]. Other studies, reviewed below (table 14), revealed similar percentages, although the percentage of those whose cultures are positive is higher among more severely ill patients and patients who did not receive antibiotics before hospitalization.

In one large retrospective study, the specific diagnostic yield of blood cultures was examined for all patients who had blood cultures performed within 48 h of admission for CAP that was confirmed by radiography, in the absence of recent risk factors such as hospitalization, nursing home residence, or immune suppression (e.g., HIV-related illness, steroid therapy, or recent chemotherapy) [100]. Of the 517 eligible patients, 11.4% had positive blood cultures, but in only 6.6% of the population were the organisms not thought to be contaminants. Of the 34 with these true-positive results, *S. pneumoniae* was recovered from 29 and *H. influenzae* from 3; the results of blood cultures lead to an alteration in antibiotic therapy for only 7 of the 34 patients.

Very few studies have examined the incidence of bacteremia among outpatients with CAP, but the number of patients with this condition is generally low. In one study of 1350 patients presenting to an emergency department, the incidence of bacteremia (due to all causes) among nonadmitted patients was 1.8%, and only 7 of 24 patients with positive results had their medical management altered by the culture data [101].

Among admitted patients, the results vary depending upon the population studied and the frequency of prior antibiotic administration. In one series of 719 patients, including 18% in nursing homes and 18% who needed mechanical ventilation, there were 48 cases of bacteremia (6.7%), and *S. pneumoniae* accounted for 58% of these [23]. The same senior investigator reported a series of 1118 patients, with bacteremia occurring in 76 (6.7%) [102]. One of the largest CAP studies was the Ohio evaluation of 2776 CAP patients admitted to all hospitals in 2 Ohio counties over a 1-year period [5]. Patients of all ages and with disease of any severity were included. The overall number of patients with bacteremia was 207 (7.4%), although only 2102 of the studied patients had blood cultures performed, yielding a 9.8% positivity rate. The incidence of pneumococcal bacteremia was 6.4% among those not taking antibiotics before admission and 2.7% among those who had taken antibiotics prior to admission.

**Table 13.** Test characteristics of sputum Gram staining for patients with community-acquired pneumonia (CAP), according to different diagnostic criteria.

Diagnostic criterion	Sensitivity, %	Specificity, %
Any gram-positive diplococci, any shape	100	0
Any gram-positive lancet-shaped diplococci	83	38
>10 gram-positive diplococci per OIF, any shape	83	31
Preponderance of gram-positive cocci, any shape	86	31
Preponderance of gram-positive diplococci, any shape	86	46
>10 gram-positive lancet-shaped diplococci per OIF	55	85
Preponderance of >10 gram-positive lancet-shaped diplococci per OIF	62	85
Preponderance of gram-positive lancet-shaped diplococci	48	100

NOTE. Table is modified from [92]. OIF, oil-immersion field.

Similarly, in an Israeli study of 346 admitted patients, the incidence of bacteremia was 9.5%, but it rose to 13% among those not taking antibiotics before admission and was only 4.5% among those taking antibiotics at the time of admission [32]. In a United States study of 359 patients, the incidence of bacteremia was 7.8%, with pneumococci accounting for 16 of 28 patients (57.1%) with positive blood cultures [44]. Another United States study showed a positive blood culture result for 59 of 385 patients with CAP admitted to the hospital, who included both HIV-positive and HIV-negative patients. In each group the incidence of bacteremia was the same (15.1% for HIV-negative and 15.6% for HIV-positive patients) [28]. In both groups, *S. pneumoniae* accounted for ~40% of the positive blood cultures, but 8 (13.6%) of 59 yielded gram-negative organisms.

In 2 other European studies, the incidence of bacteremia was slightly higher. In one study of 236 hospitalized patients, 193 had admission blood cultures performed, and 34 (17.6%) if these patients were found to have bacteremia; a pneumococcus was found in 16 (47.1%) of these 34 patients [103]. In another study, of 93 episodes of CAP in Germany, 50 patients had blood cultures performed, and 7 (14%) were positive [104].

When CAP patients admitted to the ICU have been evaluated, the incidence of bacteremia has generally been higher. For example, in a group of 299 such patients, 46 had bacteremia (15.3%), with pneumococci present in 25 (54%) of these 46 patients, staphylococci in 12, and gram-negative organisms in 6 [83]. In another series, of 132 patients with ICU-admitted CAP, blood cultures were performed for 127, and 34 (27%) were positive, with the pneumococcus accounting for 22 and gram-negative organisms for 7 positive results [37]. In another series of severe CAP, 6 of 58 patients (10.3%) had bacteremia, with the pneumococcus accounting for 5 of 6 episodes [105].

When bacteremia is present, what organisms are most commonly identified? From the preceding discussion, it is clear that the most commonly identified organism in patients with bacteremic CAP is pneumococcus, but rates of gram-negative bacteremia can be significant in severely ill patients admitted to the ICU. The high incidence of pneumococci in bacteremic patients could reflect 2 possibilities: (1) pneumococcus is the most common agent associated with CAP (and thus bacteremia

with this organism should also be common) or (2) possibly, a higher percentage of CAP patients with pneumococcal infection are bacteremic than patients with CAP due to other organisms. The latter possibility is difficult to be sure of, since there are ways other than blood culture (such as sputum culture) to diagnose pneumococcal infection, but for other organisms, sputum cultures are not always considered reliable (as with gram-negative organisms).

In general, most studies have found that a larger percentage of patients with pneumococcal pneumonia have bacteremia than do patients with CAP caused by other pathogens (table 15). In the study of Marston et al. [5] there were 351 patients with either probable or possible pneumococcal pneumonia, and 154 (43.9%) were bacteremic; in comparison, bacteremia was noted in 5.4% of patients infected with *H. influenzae*, 19.3% of patients infected with gram-negative organisms, and 12.7% of patients infected with *S. aureus*. Fang et al. reported that bacteremia occurred in 29% of patients with pneumococcal pneumonia, a proportion significantly higher than related to other bacterial etiologies [44]. Mundy et al. found bacteremia to accompany pneumococcal infection in 38.7% of HIV-negative patients and in 42.1% of HIV-positive patients [28]; on the other hand, only 8 (30.7%) of 26 patients with gram-negative infection were bacteremic. In an Israeli study, pneumococcal pneumonia was diagnosed by serology as well as by other means, and in this group only 7.5% of patients with pneumococcal infection had positive blood cultures [106].

In severely ill patients, the findings are similar: a greater percentage of patients with pneumococcal pneumonia have bacteremia than do patients with CAP of other etiologies. In one study, 25 (31.2%) of 80 patients with pneumococcal infection were bacteremic, whereas 12 (21%) of 57 infected with *S. aureus* and 6 (14.6%) of 41 infected with enteric gram-negative organisms were bacteremic [83]. In another large series, bacteremia was present in 22 (51.2%) of 43 patients with pneumococcal pneumonia and in 13 (30.9%) of 42 with CAP caused by other organisms [37].

Although pneumococcus is the dominant bacteremic organism, one study reported a high incidence of *K. pneumoniae* bacteremia in alcoholic patients, among whom this organism surpassed the pneumococcus in incidence [107]. In that study,



**Table 14.** Yield of blood cultures (BCs) in studies of community-acquired pneumonia (CAP).

Reference	Characteristics of patients	No. of patients (no. with BCs)	BCs positive, %	Comments
[99]	Mixed population of admitted patients	2935	11	Retrospective compilation of 12 studies
[100]	All with radiographically evident pneumonia; BCs done within 48 h of admission	517	11.4	Only 6.6% of isolates considered noncontaminants
[101]	Outpatients (ER) with all types of infection	1350	1.8	Not specific to pneumonia
[23]	Admitted with all forms of CAP, including patients on mechanical ventilation and those in nursing homes	719	6.7	
[102]	All CAP patients admitted over 8 y	1118	6.7	
[5]	All CAP patients admitted during 1 y in 2 Ohio counties	2776 (2102)	9.8 <sup>a</sup>	
[32]	All CAP patients hospitalized during 1 y, many with mild disease	346	9.5	Cultures positive for 13% of nonrecipients of anti- biotics at time of admission and 4.5% of antibi- otic recipients
[44]	All patients with radiographically evident CAP admitted over 1 y	359	7.8	
[28]	All patients admitted during 1 y	385	15.1/15.6 <sup>b</sup>	
[103]	All patients admitted during 1 y	236 (193)	17.6	
[104]	Admitted CAP patients	93 (50)	14	
[83]	CAP patients admitted to ICU during 5 y	299	15.3	3 additional positive cultures were considered to be due to contaminants
[37]	CAP patients admitted to ICU during 18 mo	132 (127)	27	
[105]	CAP patients admitted to ICU during 3 y	58 (58)	10.3	

NOTE. ER, emergency department.

<sup>a</sup> Blood cultures were positive for 7.4% of the total population studied ( $n = 2776$ ).<sup>b</sup> Blood cultures were positive for 15.1% of HIV-negative and 15.6% of HIV-positive patients.

28 alcoholics with CAP were evaluated and 46% had positive blood cultures, with 11 of 13 due to *K. pneumoniae* and the remaining 2 to pneumococcus. The patients with *K. pneumoniae* bacteremia all died, generally quite rapidly, despite intensive care.

Does bacteremia have clinical relevance? One study reported a mortality rate of 19% in a mixed population of 499 patients with pneumococcal bacteremia [16], and another reported a rate of 11.5% among patients needing intensive care [108]. In the study involving 499 patients, mortality was 11% among those aged <65 years, 22% among those aged 65–84 years, and 38% among those aged >84 years [16]. In a series of 108 patients with pneumococcal bacteremia, the mortality rate was 24.1% and increased with advancing age [109]. These reported mortality rates are higher than those generally seen among all patients with CAP, implying that bacteremia negatively affects the prognosis. When studies have examined prognostic factors for patients with CAP, bacteremia has not always emerged by itself as a factor. It is likely that the systemic response to bacteremia, and not merely the positivity of blood culture, is a more important determinant of outcome. One exception to this conclusion may be the patient with recurrent pneumococcal bacteremia. In one study, the mortality rate associated with a second episode of this infection in 15 patients was 47%, generally because recurrent bacteremia was often a sign of immune suppression [110]. Similarly, among HIV-positive patients with pneumococcal bacteremia, mortality was 57%, compared with 25% among those without HIV infection [111].

**Diagnostic testing for *S. pneumoniae*.** In the pre-penicillin era, *S. pneumoniae* was implicated in ~80% of patients with

CAP sufficiently severe to require hospitalization [112]. It accounted for ~66% of cases reported in 122 publications dealing with CAP from 1966 to 1995 and for ~66% of all bacteremic pneumonia cases [113]. Nevertheless, the yield of *S. pneumoniae* from respiratory secretions has been relatively low in recent years, for reasons that have not been fully identified. In general, many authorities conclude that the major problem with pneumococcal pneumonia is false-negative rather than false-positive findings.

**Diagnosis ratings.** The etiologic diagnosis of CAP caused by *S. pneumoniae* can be categorized as definite, probable, or possible, according to the criteria described by Marston et al. [5]. The diagnosis is considered definite if a patient has a compatible clinical syndrome and *S. pneumoniae* is recovered from an uncontaminated specimen of blood, pleural fluid, a transthoracic aspirate, a transtracheal aspirate, or from a metastatic infection site.

The diagnosis of pneumococcal pneumonia is considered probable if there is a compatible clinical syndrome, along with (1) the detection of typical organisms in combination with polymorphonuclear leukocytes by a Gram stain of respiratory secretions and/or (2) the recovery of *S. pneumoniae* in at least moderate growth (>5 colonies in the secondary streak) in a specimen deemed appropriate for culture by cytological screening. The Gram stain evidence depends on recognition of lancet-shaped gram-positive diplococci as the predominant organisms, preferably in a field showing large numbers of PMNs [31, 88, 89, 99, 113, 114]. The specificity of this finding is increased with a positive Quellung test [31] and/or a positive culture for this organism.

**Table 15.** Organisms present in patients with cases of bacteremic community-acquired pneumonia.

Reference	Proportion (%) of cultures positive for pneumococcus	Other prominent bacteria	% of patients with pneumococcal pneumonia and bacteremia	Comment
[5]	154/207 (74.3)	Gram-negatives, <i>H. influenzae</i> , <i>S. aureus</i> , others	43.9	Bacteremia more common with pneumococcus than with other etiologies; yield of pneumococcal blood cultures declined with antibiotic therapy before admission
[44]	16/28 (57.1)	<i>S. aureus</i>	29	Bacteremia more frequent with pneumococcus than with other etiologies
[28]	28/59 (47.4)	<i>H. influenzae</i> , gram-negatives	38.7/42.1 <sup>a</sup>	Pneumococcal infection also diagnosed with serology
[106]	26/33 (78.8)		7.5	
[83]	25/49 (51)	<i>S. aureus</i> , gram-negatives	31.2	Bacteremia more common with pneumococcus than with other etiologies
[37]	22/34 (64.7)	Gram-negatives	51.2	Bacteremia more common with pneumococcus than with other etiologies

<sup>a</sup> Percent of HIV-negative/HIV-positive negative patients.

Culture of *S. pneumoniae* from expectorated sputum should be attempted only when specimens satisfy (admittedly arbitrary) criteria by cytological screening; the best result according to correlation with transtracheal aspiration is <25 SECs/lpf. The threshold for "significance" with quantitative cultures is 10<sup>6</sup> organisms/mL for expectorated sputum, 10<sup>3</sup> organisms/mL for bronchoscopic and protected-brush specimens, and 10<sup>4</sup> organisms/mL for bronchoalveolar lavage specimens [115–117].

The diagnosis of pneumococcal pneumonia is considered possible if the above conditions for probable infection are not completely met. Numerous centers have used various methods to detect pneumococcal polysaccharide in respiratory secretions and other body fluids to support the diagnosis of pneumococcal pneumonia. These methods include counterimmunoelectrophoresis, latex agglutination, immunofluorescence, and EIA. Although these techniques are sometimes favored, their cost, time requirements, and relative lack of sensitivity and specificity are major limitations.

#### Recommendations for Microbiological Investigation of CAP

**Sputum Gram stain and culture.** For the majority of patients treated on an outpatient basis, no specific microbiological investigations are recommended (II). Direct staining of sputum may be diagnostic for infections caused by *Mycobacterium* species, *Legionella* species, *P. carinii*, and endemic fungi. Clinical circumstances would dictate the use of these tests for individual patients (risk of exposure, residence in area of endemicity, compatible clinical picture). Suspicion of pneumococcal infection and use of Gram stain as a rapid diagnostic tool may be particularly helpful in regions where there is significant pneumococcal resistance, and the initial empirical therapeutic choices may change.

For patients admitted to a hospital ward, the panel recommends that sputum Gram staining and culture be performed before administration of an antibiotic, if it can be ensured that there is an adequate sample (<25 SECs/lpf on cytological

screening), rapid assessment within 1–2 h of production of the sample, and interpretation by a properly trained staff (II). Therapy should not be delayed for acutely ill patients if there is difficulty in obtaining an adequate specimen.

For patients admitted to the ICU, a more concerted effort to obtain lower-respiratory-tract secretions is recommended (III). Since these patients are monitored closely and may be intubated, it is more likely that an interpretable sample will be obtained.

**Blood cultures.** The panel recommends that 2 blood cultures be performed for all hospitalized patients (II).

**Serology.** The panel recommends that serology not be performed as part of the routine management of CAP (II). These tests are usually not helpful in the early management of CAP since the determination of acute and convalescent titers is required before ascribing clinical illness to these pathogens. Cold agglutinin tests are neither sensitive nor specific for determination of infection with *M. pneumoniae* and are not recommended [118] (II). Serological response to *Mycoplasma*, *Chlamydia*, and *Legionella* species usually takes weeks after symptoms occur, which reduces the value of these investigations, except for epidemiological purposes.

**Legionella urinary antigen test.** The panel recommends the *Legionella* urinary antigen test as part of the routine management of severe CAP, especially when patients are admitted to an ICU (II). This test identifies only *Legionella pneumophila* serogroup I, which is the most common serogroup causing clinical illness. The test has a sensitivity of 70% and specificity of 100% and is easily and rapidly performed [119]. A negative urinary antigen test does not exclude the diagnosis, particularly if it is caused by organisms other than *L. pneumophila* serogroup I, but a positive test is diagnostic of infection.

**DNA probes and amplification.** These tools are being rapidly developed to assist clinicians with the rapid and accurate diagnosis of problem pathogens such as *C. pneumoniae* and *M. pneumoniae*. These organisms can be identified from a single

throat swab rapidly [120]. However, the role of these new tools is under investigation, and recommendations cannot be made until the test properties of these new tools have been clarified.

### Thoracentesis

The panel recommends diagnostic thoracentesis for any patient suspected of having CAP in whom a significant collection (>10 mm in thickness on the lateral decubitus view) [121] of pleural fluid is noted (II). The incidence of pleural effusion associated with pneumonia ranges from 36% to 57%, and it is commonest in patients with pneumococcal pneumonia [122]. Patients who present later in the course of pneumonia and those who are bacteremic are more likely to have a parapneumonic effusion [123]. Anaerobes are the most common cause of frank empyema, occurring either alone or in conjunction with aerobes [124]. Patients with pneumococcal pneumonia and parapneumonic effusions, even with positive pleural fluid bacteriology, have a relatively good response to antimicrobial therapy and may not require pleural fluid drainage [121].

### Invasive Procedures

The panel does not recommend the routine use of invasive testing for patients suspected of having CAP (II). There may be unique circumstances when bronchoscopy, bronchoalveolar lavage, protected-specimen brushing, or percutaneous lung needle aspiration may be useful, such as in patients with fulminant pneumonia or among those unresponsive to a standard course of antimicrobial therapy, but this is exceptional [125].

### Treatment

The most recent Canadian guidelines for the treatment of CAP in immunocompetent adults were published in 1993 [1]. These and similar documents adopted by the ATS and IDSA focused on treatment recommendations that were based upon the presence or absence of comorbid conditions, severity of illness at the time of clinical presentation, and whether treatment is to be given on an outpatient or inpatient basis [2, 3]. These guidelines were well received because they provided the practicing physician with a rational and manageable approach to the initial selection of antimicrobials for the empirical treatment of this common condition. However, a number of important developments that have transpired since these earlier publications have had a great impact on our decisions regarding the management of CAP.

In the current update, the impact of 5 such developments are considered: (1) decision analysis for hospitalization or intensive care; (2) clinical relevance of emerging resistance among respiratory pathogens, especially penicillin-resistant and macrolide-resistant *S. pneumoniae*; (3) the availability of new-generation macrolides and (4) new-generation fluoroquinolone an-

tibiotics; and (5) the desirability and feasibility of iv-to-oral sequential antimicrobial therapy.

### Decision to Hospitalize

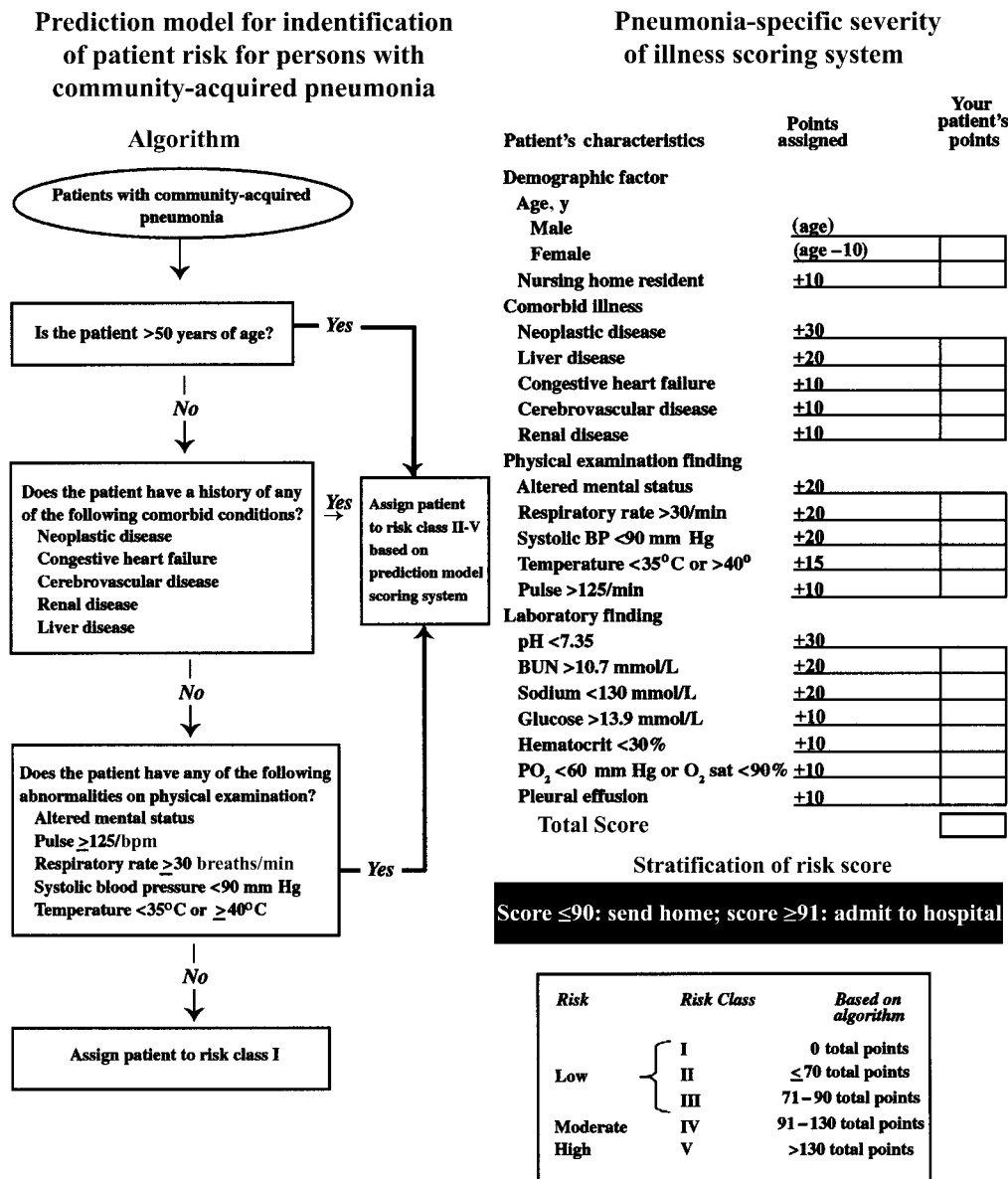
The decision to hospitalize a patient with CAP depends on many variables, including the severity of illness, associated diseases and other prognostic factors, adequacy of home support, and probability of compliance. Several scoring systems and prediction rules have been tested for CAP to see whether they have adequate positive and negative predictive values to determine the optimal site of patient care or the need for intensive care. The acute physiological and chronic health evaluation (APACHE II) is the most widely accepted scoring index for estimating the risk of death in intensive care patients. It scores the severity of a dozen physical examination and laboratory indices, age, and underlying health problems, and the total score correlates with the risk of death in a wide range of disease categories, including respiratory failure due to infection.

Other similar scoring systems have also been tested for severe CAP, including the acute physiological score (APS) and the simplified acute physiological score (SAPS) [126]. Although they correlate with mortality and are useful for comparing the severity of illness and treatment outcome among different patient cohorts, they are somewhat difficult to use, and their sensitivity and specificity are not adequate to help in the decision-making for individual patients.

Fine et al. [82] devised a scoring system for predicting the risk of death for patients with CAP (figure 2). This clinical prediction rule, based on age, comorbid disease, clinical findings, and laboratory investigations, was derived from data on 14,199 patients and was validated with data from 38,039 patients with CAP. These indices are valuable for estimating mortality for groups of patients and have been useful for identifying patients with CAP who should be hospitalized [127] or who may be safely discharged from the hospital [128]. Such prediction rules have also facilitated the development of critical pathways for the management of CAP in the institutional setting [129, 130].

Auble et al. [131] reviewed 13 studies in the past 10 years that have used multivariate analyses to identify independent predictors of adverse outcomes for patients presenting with CAP. Among these, only the Pneumonia Patient Outcome Research Team (PORT) clinical prediction rule of Fine et al. [82] fulfilled the stringent quality standards. It is the only rule that has been tested in an independent cohort of patients [65]. In this latter study, 166 consecutively enrolled low-risk patients with pneumonia who presented to an emergency department during the intervention period were compared with 147 consecutive retrospective control subjects who were identified during the previous year. There were no significant baseline differences between these 2 groups of patients.

The percentage of patients initially treated as outpatients in-



**Figure 2.** A pneumonia-specific severity-of-illness scoring system and factors associated with the decision to admit a patient with community-acquired pneumonia to the hospital (modified from [82]).

creased from 42% in the control period to 57% in the intervention period (36% relative increase; 95% CI, 8%–72%;  $P = .01$ ). However, more outpatients during the intervention period were subsequently admitted to the study hospital (9% vs. 0%). When any admission to the study hospital within 4 weeks of presentation was considered, there was a trend toward more patients receiving all their care as outpatients in the intervention group (42% vs. 52%; 25% relative increase; 95% CI, –2% to 59%;  $P = .07$ ). No patient in the intervention group died in the 4-week follow-up period. Thus, use of a risk-based algorithm effectively identified low-risk patients with CAP who could be safely treated initially

as outpatients (II; figure 2). Recently, the IDSA has endorsed this pneumonia prediction rule to assist physicians with initial site-of-care decisions for adult patients presenting with CAP in ambulatory care settings [3].

It should be noted that although the clinical prediction rules developed by Fine et al. [82] are useful for predicting mortality for groups of patients, they are not always sensitive enough to help in the decision-making process for individual patients. Fine et al. also pointed out that their scoring system has limitations because it excludes social and some medical conditions that may interfere with therapy or have an impact on mortality [82].

Moreover, their study was not designed to predict which patients require intensive care.

The decision to admit patients with CAP to an ICU is usually dictated by the need for mechanical ventilation or hemodynamic support and closer monitoring of the patient. The presence of some clinical or laboratory findings are predictive of the need for intensive care. The most commonly reported include tachypnea ( $\geq 30$  breaths/minute), arterial hypoxemia despite oxygen supplementation, need for mechanical ventilation, and shock (diastolic blood pressure  $< 60$  mm Hg or systolic blood pressure  $< 90$  mm Hg). The sensitivity and specificity of various clinical and laboratory findings for defining severe CAP that requires admission to the ICU were defined in a study by Ewig et al. [132]. A respiratory rate of  $> 32$  breaths/min, for example, has a sensitivity of 64% and a specificity of 57%.

Of note, the current criteria for severe pneumonia, as defined by the ATS, had a high sensitivity (98%) and negative predictive value (99%) but low specificity (32%) and positive predictive value (24%) [132].

#### Clinical Impact of Emerging Resistance

**Penicillin resistance in *S. pneumoniae*.** Penicillin-susceptible *S. pneumoniae* is defined by an MIC of  $< 0.1$  mg/L [133]. Intermediate penicillin resistance is defined by an MIC of 0.1–1.0 mg/L, and high-level penicillin resistance is defined by an MIC  $\geq 2.0$  mg/L. *S. pneumoniae* isolates with reduced susceptibility to penicillin are often referred to as penicillin-nonsusceptible pneumococci (MIC,  $\geq 0.1$  mg/L) or penicillin-resistant pneumococci (MIC,  $\geq 2.0$  mg/L) [134]. *S. pneumoniae* isolates resistant to  $\geq 2$  classes of antimicrobials with different mechanisms of action are considered multidrug-resistant [135].

In 1965 a Boston laboratory reported that 2 of 200 clinical isolates were resistant to penicillin [136]. The first reported case of clinically significant infection caused by a penicillin-resistant strain of *S. pneumoniae* was reported from Australia in 1967 [137]. Multidrug-resistant strains of *S. pneumoniae* were first reported from South Africa in 1977 [137]. Since then, the isolation of penicillin-nonsusceptible pneumococci has been reported worldwide, although there is considerable variation in incidence from country to country, with the highest rate reported from Korea (70%) [138]. The reasons for these variations are not well understood but could include regional differences in patterns of antibiotic use.

The emergence of antimicrobial-resistant *S. pneumoniae* may occur rapidly within a country. This has been well documented in the United States, where the prevalence of pneumococci non-susceptible to penicillin increased from 5% in 1987 to 8% by 1992 and to 25% by 1995 (7%–10% penicillin-resistant pneumococci) [134, 139, 140]. A national survey during 1997 found that among 845 clinical isolates of *S. pneumoniae* from 34 different medical centers, 27.8% (range, 10.5%–50.0%) had intermediate penicillin

susceptibility, whereas 16% (range, 0%–36.8%) were highly resistant to penicillin [141].

Until recently, surveys have found the incidence of penicillin-nonsusceptible pneumococci in different areas of Canada to be  $\leq 3\%$ . However, since 1994, increased resistance has been reported in different provinces [142, 143]. A Canada-wide survey carried out between September 1994 and May 1995 and between September and December 1996 found an increase in highly penicillin-resistant *S. pneumoniae*, from 2.1% to 4.4%, and an increase in intermediate-resistant strains, from 6.4% to 8.9% (table 16) [144]. A subsequent smaller survey in 1997 revealed a rate of 21.8% for intermediate-resistant strains (range, 15.0%–33.3%) and 8.4% for highly resistant strains (range, 2.5%–17.2%) [141]. The most recent Canada-wide study reported the prevalence of penicillin-resistant *S. pneumoniae* from respiratory sites to be 21.2% (14.8% with intermediate and 6.4% with high-level resistance) [145]. Therefore, Canada appears to be experiencing a period of rapid increase in incidence of penicillin-nonsusceptible pneumococci, as occurred earlier in the United States and elsewhere.

Although penicillin resistance in *H. influenzae* and *M. catarrhalis* is due to  $\beta$ -lactamase production, high-level resistance to penicillin in *S. pneumoniae* is due to altered  $\beta$ -lactam target sites (penicillin-binding proteins) and hence cannot be overcome by the addition of a  $\beta$ -lactamase inhibitor. Furthermore, penicillin resistance in *S. pneumoniae* is often a marker for a multidrug-resistant (MDR) phenotype [146]. Thus, *S. pneumoniae* isolates with intermediate or high-level penicillin resistance often exhibit reduced susceptibility to oral cephalosporins and, in many instances, to macrolides, trimethoprim-sulfamethoxazole, and tetracyclines (table 17).

The only antibiotics equally active against both penicillin-susceptible and penicillin-resistant strains of *S. pneumoniae* are vancomycin and the “respiratory” fluoroquinolones such as levofloxacin, grepafloxacin, gatifloxacin, gemifloxacin, trovafloxacin, and moxifloxacin (table 17) [145–147]. Grepafloxacin has been withdrawn from the market because of concerns about cardiac toxicity, and trovafloxacin is restricted because of concerns about severe liver toxicity. Moxifloxacin has been launched in the United States and will be launched in Canada shortly.

Whether penicillin-nonsusceptible pneumococcal strains are more or less virulent than their penicillin-susceptible counterparts is controversial [148]. Einarsson et al. [149] reported a lower rate of bacteremia associated with penicillin-resistant *S. pneumoniae* infections than with penicillin-susceptible *S. pneumoniae* infections (8% vs. 29%, respectively). Ewig et al. [150] reported similar findings. Furthermore, although failure of penicillin therapy for meningitis caused by penicillin-resistant *S. pneumoniae* has been well documented, it is not at all clear whether nonmeningeal infections with penicillin-resistant *S. pneumoniae* have a worse outcome than infections with penicillin-susceptible *S. pneumoniae* when treated with high-dose iv penicillin [150–153].

**Table 16.** Penicillin susceptibility of 1320 isolates of *Streptococcus pneumoniae* collected from across Canada from September 1994 through May 1995 and of 1044 isolates collected from September through December 1996.

Province	No. (%) of isolates susceptible to penicillin			
	Intermediately susceptible		Resistant	
	1994-95	1996	1994-95	1996
Alberta and BC	8 (5.9)	18 (16)	1 (0.7)	4 (3.5)
NW Territories	8 (9.6)	6 (10.5)	3 (3.6)	2 (3.5)
Saskatchewan	25 (18)	12 (14)	3 (2.2)	6 (7.1)
Manitoba	4 (5.3)	12 (7.1)	1 (1.3)	9 (5.4)
Ontario	30 (4.6)	39 (8.4)	15 (2.3)	21 (4.5)
Quebec	5 (6.5)	2 (2.1)	4 (5.2)	3 (3.2)
Maritimes <sup>a</sup>	5 (3.2)	4 (6.3)	1 (0.6)	1 (1.6)
Total	85 (6.4)	93 (8.9)	28 (2.1)	46 (4.4)

NOTE. Intermediately susceptible, MIC, 0.1–1.0 mg/L; resistant, MIC, >2.0 mg/L. Table is modified from [144]; reprinted with permission. BC, British Columbia; NW, northwest.

<sup>a</sup> Newfoundland, Nova Scotia, Prince Edward Island, New Brunswick, Labrador.

Among clinical penicillin-nonsusceptible pneumococcal isolates from Canada and the United States, over two-thirds are only intermediately resistant [141, 145]. Even among those with high-level resistance, nearly all have MICs of  $\leq 4$  mg/L. On the other hand, the peak serum concentrations of penicillin G with a dosage of 40,000 U/kg iv every 4 h are  $\sim 40$  mg/L, and those of amoxicillin after oral administration of 500 mg range from 5.5 mg/L to 11.0 mg/L. Thus, the current laboratory definitions of penicillin resistance for non-CSF isolates of *S. pneumoniae* may not be clinically relevant, and this issue is being reexamined by the National Committee for Clinical Laboratory Standards.

In the opinion of the consensus group, there is substantial evidence that penicillins remain effective in the treatment of nonmeningitic pneumococcal infections caused by strains for which MICs are  $\leq 4$  mg/L. For intermediately resistant strains, either amoxicillin (500 mg t.i.d.) or cefuroxime (500 mg twice daily) remains effective as oral therapy [147]. For highly resistant strains for which MICs are  $\geq 2$  mg/L, high-dose iv penicillin (2 MU q6h) remains appropriate (II). Administration of "respiratory" fluoroquinolones and parenteral treatment with a third-generation cephalosporin (e.g., cefotaxime [1 g q8h] or ceftriaxone [1 g q24h] are alternative choices), but there is little evidence that these regimens are superior to high-dose iv penicillin for nonmeningitic infections with penicillin-resistant *S. pneumoniae* strains for which MICs are  $\leq 4$  mg/L [147] (III).

**Macrolide and fluoroquinolone resistance of *S. pneumoniae*.** In Canada, >11% of *S. pneumoniae* isolates are resistant to macrolides [147]. The mechanism of resistance is either target-site modification that is mediated by  $\geq 1$  methylase genes (*erm*), or an efflux pump mechanism that is mediated by the *mef* gene [147]. In sharp contrast to penicillin resistance in *S. pneumoniae*, in which the MIC increases incrementally over time, the increase in MIC of macrolides is abrupt and of greater magnitude (MICs >10 mg/L). Furthermore, among penicillin-nonsuscep-

tible pneumococci isolates from Canada, 38% are resistant to erythromycin and >20% are resistant to either azithromycin or clarithromycin [145]. Despite this, very few cases have been reported in which the presence of macrolide resistance in vitro in isolates from patients with *S. pneumoniae* pneumonia has led to clinical failure or breakthrough bacteremia during macrolide therapy [154, 155]. This is in part due to the fact that the etiology of CAP is not identified in >50% of cases, and any association of treatment failure with macrolide-resistant *S. pneumoniae* may be difficult to detect or confirm clinically.

Another possible explanation is that since macrolides are highly concentrated in alveolar macrophages, achieving concentrations that are several-fold higher than those possible in serum, in vitro susceptibility results may not accurately predict in vivo activity [156].

In a Canada-wide survey of *S. pneumoniae* susceptibility, Matsumura et al. [157] found no increase in fluoroquinolone resistance between 1988 and 1995. However, there has been a notable increase in fluoroquinolone resistance among *S. pneumoniae* isolates in Canada, from 0% in 1993 to 1.7% during 1997 and 1998 [158]. The prevalence of fluoroquinolone resistance was higher among isolates from older patients (2.6% of isolates from persons aged  $\geq 65$  years vs. 1.0% of isolates from persons aged 15–64 years;  $P < .001$ ), and among isolates from Ontario (1.5% of isolates, vs. 0.4% of isolates from the rest of Canada;  $P < .001$ ). Wise et al. [159] also found 2 of 29 clinical isolates to be highly resistant to ciprofloxacin and newer fluoroquinolones with enhanced gram-positive activity. This raises concerns that if the new fluoroquinolones are targeted for the empirical treatment of CAP, including that caused by *S. pneu-*

**Table 17.** Resistance to 16 antimicrobial agents among *Streptococcus pneumoniae* isolates recovered at 18 Canadian medical centers during 1997–1998.

Antimicrobial agent	% of isolates resistant, grouped by susceptibility to penicillin		
	Susceptible (n = 929)	Intermediately susceptible (n = 175)	Highly resistant (n = 76)
Cefaclor	12.1	52.3	97.3
Cefixime	0.3	31.0	96.8
Cefuroxime	0.6	26.3	96.1
Cefprozil	0.0	9.9	93.5
Cefotaxime	0.1	1.7	6.4
Erythromycin	3.8	17.7	38.2
Azithromycin	2.2	14.1	21.0
Clarithromycin	3.0	14.1	22.6
Chloramphenicol	1.1	0.0	30.6
Tetracycline	3.9	24.6	42.1
TMP-SMZ	4.7	34.3	77.6
Vancomycin	0.0	0.0	0.0
Levofloxacin	0.2	0.0	0.0
Grepafloxacin	0.3	0.5	0.0
Trovafoxacin	0.0	0.0	0.0
Moxifloxacin	0.0	0.0	0.0

NOTE. Susceptible: MIC, 0.12–1 mg/L; high-level resistance: MIC,  $\geq 2$  mg/L; susceptible: MIC,  $\leq 0.06$  mg/L. TMP-SMZ, trimethoprim-sulfamethoxazole. Table is modified from [145].

*moniae*, then fluoroquinolone-resistant strains may become prevalent. The mechanism of fluoroquinolone resistance is either changes in the target topoisomerases (*gyrA* and/or *parC*) or an efflux pump [147].

**$\beta$ -lactamase production in *H. influenzae*, *M. catarrhalis*, and enterobacteriaceae.** Currently >30% of *H. influenzae* isolates in Canada (the percentage varies by region and province) have aminopenicillin resistance due to  $\beta$ -lactamase production [160]. Nearly all strains are susceptible to ceftriaxone and cefuroxime, but >50% of  $\beta$ -lactamase-producing *H. influenzae* isolates display either intermediate or high-level resistance to clarithromycin [139]. Aminopenicillin resistance in *M. catarrhalis* is stable at ~90%, but second- or third-generation cephalosporins and amoxicillin/clavulanate remain active against these organisms.  $\beta$ -lactamase production by enterobacteriaceae is mediated either chromosomally or by plasmids. Enterobacteriaceae species that produce type I chromosomal  $\beta$ -lactamases are resistant to  $\beta$ -lactamase inhibitors (clavulanate, sulbactam, tazobactam), and  $\beta$ -lactam treatment against these organisms is limited to use of a carbapenem (e.g., imipenem or meropenem) or fourth-generation cephalosporin (e.g. cefepime or ceftazidime) [161].

Plasmid-mediated  $\beta$ -lactamases include the TEM and SHV families, as well as extended-spectrum  $\beta$ -lactamases (ESBLs) that are either TEM and SHV mutants or cephalosporinases unrelated to TEM and SHV enzymes [160, 162]. Organisms that produce low levels of TEM-1 or SHV-1 may be variably susceptible to second-generation cephalosporins (e.g., cefaclor, cefuroxime, cefprozil, cefamandole, cefonicid, and loracarbef), third-generation cephalosporins (e.g., cefotaxime, ceftizoxime, cefoperazone, ceftriaxone, ceftazidime, cefixime, cefpodoxime, and ceftibuten), or  $\beta$ -lactamase inhibitors. However, hyper-producers of TEM-1 or SHV-1 are resistant to these agents but may be treated with cephamycins (cefoxitin, cefotetan, and cefmetazole), carbapenems, or fourth-generation cephalosporins (e.g., cefepime or ceftazidime).

More recently, a novel class of TEM-1-derived  $\beta$ -lactamases resistant to  $\beta$ -lactamase inhibitors (inhibitor-resistant TEM-derived or IRT  $\beta$ -lactamases) has been described; these have been found mostly in clinical isolates of *E. coli* [163]. Gram-negative bacilli that express ESBLs can degrade fourth-generation cephalosporins and are often resistant to other classes of drugs such as aminoglycosides and fluoroquinolones. As many as 50% of *K. pneumoniae* strains that express ESBLs may also be resistant to fluoroquinolones [164]. Infections with these organisms are best treated with a carbapenem [161]. The emergence of these different  $\beta$ -lactamases has caused several dilemmas with regard to the initial management of life-threatening infections with CAP, particularly for persons with chronic obstructive lung disease who may have been treated with numerous antimicrobial courses and who may harbor multidrug-resistant gram-negative bacilli. First, the substrate profile of the  $\beta$ -lactamases expressed by different gram-negative rods may be quite variable and difficult to predict without elaborate testing

in the clinical laboratory. Second, even when in vitro testing suggests susceptibility to a  $\beta$ -lactam/ $\beta$ -lactamase-inhibitor, the inoculum effect may negate its usefulness clinically. Finally, multidrug resistance is relatively common among  $\beta$ -lactamase-producing enterobacteriaceae isolates [147].

#### Evidence for the Use of Macrolide Antimicrobial Regimens

The previous Canadian and ATS guidelines for the treatment of CAP emphasized the role of macrolides in initial therapy, primarily because of their in vitro activity against "atypical" respiratory pathogens (e.g., *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*) as well as *S. pneumoniae*. However, erythromycin is poorly tolerated, and the newer macrolides, clarithromycin and azithromycin, are substantially more expensive. Furthermore, the emergence and clinical impact of penicillin-resistant and macrolide-resistant *S. pneumoniae* and of multidrug resistance among many respiratory pathogens require careful consideration.

Macrolides are attractive agents for the treatment of CAP because of their spectrum of antimicrobial activity. Of the 6 pathogens that cause most CAP (*S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* species, *H. influenzae*, and influenza A virus), all but influenza virus are usually susceptible to macrolides, including erythromycin. Macrolides are concentrated intracellularly and are uniformly active against the intracellular organisms such as *M. pneumoniae*, *C. pneumoniae*, *Legionella* species, and *C. burnetii*, the etiologic agent of Q fever. In Canada, >90% of *S. pneumoniae* strains are susceptible to macrolides in vitro, but most of the macrolide-resistant strains are also less susceptible to penicillin [145]. However, the clinical significance of in vitro macrolide resistance among patients receiving macrolides for the treatment of pneumococcal infections has not been well established, even though sporadic cases of treatment failure or breakthrough bacteremia have been reported [154, 155].

Of the 5 main bacterial causes of CAP, *H. influenzae* is the least susceptible to macrolides. According to current laboratory susceptibility criteria, erythromycin is the least active in vitro, clarithromycin is of intermediate activity, and azithromycin is the most active. Data regarding the clinical outcome of respiratory infections due to *H. influenzae* that have been treated with macrolides nearly exclusively concern infections caused by nonencapsulated, nontypeable strains. Although the results of treatment are generally favorable, the number of well-documented cases reported in the literature has been relatively small.

Several prospective observational cohorts have demonstrated that macrolides are commonly used in the treatment of CAP. In the pneumonia PORT study conducted from 1991 through 1994 at 5 medical institutions in 3 cities, macrolides were prescribed for 73.4% of 927 outpatients and 41% of 1328 inpatients [165, 166]. Similarly, of 1113 consecutive patients with CAP who required admission to 20 Canadian medical centers during 1996–1997, >70% received a macrolide, nearly always in con-

junction with an injectable second- or third-generation cephalosporin [130].

**Outcome studies.** In the PORT study, there were 546 patients under the age of 60 years, without comorbidity, who were treated as outpatients [166]. Of the 339 (62.1%) who were treated with a regimen consistent with the 1993 ATS guidelines for CAP, 89.1% received erythromycin alone, 5% received clarithromycin alone, and 5.9% received a combination of other agents. Two hundred and seven individuals received therapy incongruous with the 1993 ATS guidelines, and very few of these received a macrolide. There were no deaths in either group, and subsequent hospitalization related to pneumonia occurred for fewer than 4% in both groups. These data indicate that macrolide therapy is effective for the outpatient treatment of CAP in patients under the age of 60 years. The data also underscore the excellent prognosis of CAP in this subset of patients, which may be independent of the antibiotic used.

In the same study, 318 patients were either aged >60 years or had at least 1 comorbid illness for which the 1993 ATS guidelines recommended against the use of macrolide monotherapy. Despite this, 67% of 262 individuals whose treatment was inconsistent with ATS guidelines were prescribed macrolide monotherapy. Among these individuals treated with macrolide monotherapy, slightly lower mortality and lower rates of subsequent hospitalization were noted than among the 56 individuals whose treatment was consistent with the ATS guidelines, although these differences did not achieve statistical significance. These data support the use of macrolide monotherapy for ambulatory patients with CAP, even for those who are older than 60 years of age or have comorbid illnesses.

In contrast to the PORT study findings, Mundy et al. [167] reported that macrolides were seldom prescribed among 385 consecutive patients hospitalized with CAP in the Johns Hopkins Hospital during 1990–1991. These authors found that infection with *M. pneumoniae*, *C. pneumoniae*, or *Legionella* species could be documented in only 7.5% of the patients, of whom 55.2% also were infected with a second pathogen. Among the 29 patients in whom infection with *M. pneumoniae*, *C. pneumoniae*, or *Legionella* species was identified, only 4 (13.8%) received a macrolide or tetracycline for  $\geq 7$  days. None of these 29 individuals died, including those who did not receive treatment with a macrolide or tetracycline. Mundy et al. [167] argued that because of the infrequent infection caused by “atypical” pathogens in their patient population and the favorable prognosis for this subset of patients even without macrolide treatment, the routine use of macrolides for patients with CAP that requires hospitalization is not indicated. However, the true prevalence of these “atypical” agents in CAP remains controversial.

Several large prospective studies have reported variable prevalence rates, ranging from 7.5% to 63% (median for 7 prospective studies, 22.4%), largely dependent on the criteria used for definite diagnosis [168]. For example, in the study reported by Mundy et al. [167], the diagnosis of *C. pneumoniae* was based

solely on positive culture or PCR. In contrast, Lieberman et al. [106] evaluated 346 patients with CAP in a hospital in southern Israel and reported the presence of either *C. pneumoniae*, *M. pneumoniae*, or *Legionella* species in 63% of their patients. In this study, a large proportion of cases was diagnosed by serological means. In a prospective study of 149 adult patients with CAP in Nova Scotia, Marrie et al. [169] reported an “atypical” agent on the basis of serological diagnosis in 40% of their cases. Thus, “atypical” agents are probably a more frequent cause of CAP than is currently recognized, and the use of a macrolide or a fluoroquinolone for the empirical initial treatment of patients presenting with CAP appears warranted.

**Randomized trials comparing macrolides to other antibiotics.**

There have been several randomized, controlled clinical trials comparing the safety and efficacy of administering a macrolide with either  $\beta$ -lactams [170–173] or a fluoroquinolone [172–179] in the treatment of CAP. Eight of these were double-blind, multicenter trials [172–179] (see table 18).

**Table 18.** Clinical success rates with macrolides in randomized, clinical trials of treatment for community-acquired pneumonia in Canada.

Reference, drug regimen	Trial double-blind?	No. of enrolled recipients	Success rate, % <sup>a</sup>
[170]	No		
Clarithromycin, 500 mg iv b.i.d.		56	86
Amox/Clv, 1.2 g iv q.i.d.		56	84
[171]	No		
Azithromycin, 500 mg po q.d.		54	81
Benzympenicillin, 1 MU po q.i.d.		50	70
[173]	Yes		
Azithromycin, 250 mg po q.d.		53	94
Cefaclor, 500 mg po t.i.d.		66	100
[172]	Yes		
Erythromycin, 1 g po b.i.d.		208	85
Amox/Clv, 500/125 mg po b.i.d.		199	80
Sparfloxacin, 200 mg po q.d.		401	87
[174]	Yes		
Roxithromycin, 150 mg po b.i.d.		150	79 <sup>b</sup>
Sparfloxacin, 200 mg po q.d.		154	94 <sup>b</sup>
[175]	Yes		
Clarithromycin, 250 mg po b.i.d.		175	89
Sparfloxacin, 200 mg po q.d.		167	89
[176]	Yes		
Clarithromycin, 250 mg po b.i.d.		248	89
Grepafloxacin, 600 mg po q.d.		246	83
[177]	Yes		
Clarithromycin, 250 mg po b.i.d.		253	89
Grepafloxacin, 600 mg po q.d.		251	92
[178]	Yes		
Clarithromycin, 500 mg po b.i.d.		180	86
Trovaflaxacin, 200 mg po q.d.		179	89
[179]	Yes		
Clarithromycin, 500 mg po b.i.d.		188	95
Moxifloxacin, 400 mg po q.d.		194	95
[180]	No		
Clarithromycin, 250 mg po b.i.d. (10 d)		101	95
Azithromycin, 500 mg po o.d. (3 d)		102	94

NOTE. Amox/Clv, amoxicillin/clavulanate; po, by mouth.

<sup>a</sup> Based on the percentage of patients clinically evaluable at follow-up.

<sup>b</sup> For this study, 95% CI, 1.9–10.8. For the other studies, 95% CIs were not statistically significant.



*Macrolides versus  $\beta$ -lactams.* Clarithromycin has been compared with amoxicillin–clavulanic acid in the treatment of 112 patients with CAP that requires hospitalization [170]. Clinical cure or improvement was noted in 86% of those treated with clarithromycin and 84% of those treated with amoxicillin–clavulanic acid. Azithromycin was compared with iv benzylpenicillin in patients hospitalized with CAP suspected to be due to *S. pneumoniae* [171]. For the 64 patients with pneumococcal pneumonia, the clinical and radiologic success rate was 83% with azithromycin and 66% with benzylpenicillin (difference not significant).

Lode et al. [172] compared erythromycin to amoxicillin–clavulanic acid for patients with “nonsevere” CAP for which oral therapy was appropriate; 78% of 208 patients assigned to erythromycin and 79% of 199 patients assigned to amoxicillin–clavulanic acid were evaluable for efficacy analysis. At the end of treatment, 85% of the erythromycin regimens and 80% of amoxicillin–clavulanic acid regimens were judged to be successful (difference not significant).

Kinasevitz and Wood [173] compared azithromycin to cefaclor for patients with acute bacterial pneumonia in a double-blind multicenter trial. The overall clinical response rate was 97% among 53 patients treated with azithromycin and 100% among 66 patients treated with cefaclor. The bacteriologic eradication rates were 80.4% and 92.6%, respectively (difference not significant).

*Macrolides versus fluoroquinolones.* In the same study by Lode et al. mentioned above [172], 401 patients were also assigned to sparflaxacin, of whom 324 (81%) were evaluable for efficacy. Of these, 87% were judged to be successfully treated, a clinical response rate which is not significantly different from the 85% success rate among erythromycin-treated individuals.

Örtqvist et al. [174] randomized 304 adults with CAP (75% inpatients; 25% outpatients) to receive either sparflaxacin or roxithromycin. The success rates for sparflaxacin and roxithromycin at the end of follow-up were 82% and 72%, respectively, in the intention-to-treat population and 94% and 79%, respectively, in the evaluable population. The differences in the evaluable patients were statistically significant (95% CI, 1.9%–10.8%). Sparflaxacin was also compared with clarithromycin in the treatment of 342 patients with CAP, with identical success rates of 89% [175]. Whereas abnormal taste was more common with clarithromycin (9.8% vs. 1.7%;  $P < .002$ ), photosensitivity was more common with sparflaxacin (6.0% vs. 0.6%;  $P < .002$ ). Prolongation of the corrected Q-T interval was observed in 4 patients treated with sparflaxacin but in none treated with clarithromycin.

Clarithromycin was compared with grepafloxacin for the treatment of CAP in 494 individuals [176]. The clinical success rate among evaluable patients at 4–6 weeks was 89% for the clarithromycin group, versus 83% in the grepafloxacin group (difference not significant). Similar results were obtained in an independent, double-blind, multicenter international study

[177]. Clarithromycin was also compared with trovafloxacin for the treatment of CAP in 359 ambulatory adults [178]. Clinical success was observed in 94% of clarithromycin-treated and 96% of trovafloxacin-treated subjects at the end of treatment and in 86% of clarithromycin-treated and 89% of trovafloxacin-treated subjects at the end of the study, on day 30 (difference not significant). Finally, clarithromycin was compared with moxifloxacin in a double-blind, multicenter North American trial of 382 outpatients with mild to moderately severe CAP [179]. Similar to previous studies, only 56% of these patients had microbiologically documented infection. Among these, the atypical pathogens *C. pneumoniae* (47%) and *M. pneumoniae* (20%) were the most frequently implicated, followed by *H. influenzae* (18%) and *S. pneumoniae* (17%). The overall response rates were identical in the 2 groups (95%).

*Macrolides versus macrolides.* The efficacy and tolerance of a 3-day, once-daily course of oral azithromycin was compared with those of a 10-day, twice-daily course of oral clarithromycin in a randomized, multicenter study of 203 adults with mild to moderately severe CAP [180] (table 18). The overall clinical response rates (94% vs. 95%) and microbiological eradication rates (97% vs. 91%) were comparable. Both agents were well tolerated, with gastrointestinal complaints being the most frequently reported adverse events (7% vs. 8%, respectively).

*Conclusions.* There is abundant evidence that macrolide monotherapy is highly effective in the treatment of CAP in outpatients with mild to moderately severe disease (I). Data supporting the efficacy of macrolide monotherapy among patients with more severe CAP that requires hospitalization are more limited. Nevertheless, it is common practice, especially in Canada, to add a macrolide to an injectable-cephalosporin regimen to treat CAP in this patient population [130]. There are very few studies regarding the efficacy of macrolide monotherapy for bacteremic pneumococcal pneumonia, a condition that occurs in 3%–5% of patients with CAP that requires hospitalization [23]. A more recent Canada-wide prospective study by Marrie et al. [181] showed bacteremic pneumococcal pneumonia in 6.7% of 855 patients with CAP who required hospitalization at 15 major teaching hospitals during 1998. Among these bacteremic isolates, intermediate penicillin resistance was noted in 4.5%, and the resistance rate to cefuroxime axetil was also 4.5%.

With the exception of trimethoprim-sulfamethoxazole (resistance rate, 16%), the majority of bacteremic *S. pneumoniae* isolates recovered from hospitalized patients with CAP in Canada remain highly susceptible to commonly used antibiotics, including penicillin, doxycycline, and macrolides. The inability of macrolides to enter the CSF in concentrations adequate to inhibit *S. pneumoniae* is of some concern with regard to patients with pneumococcal bacteremia. Consequently, for the subset of obtunded CAP patients who require hospitalization and are suspected of having invasive pneumococcal infection, macrolide monotherapy should be avoided or used cautiously.

### Evidence for the Use of Fluoroquinolones

The development of “respiratory” fluoroquinolones, which have unique antimicrobial activity and favorable pharmacokinetic properties, has also had an impact on the choice of agents for the initial treatment of CAP. Fluorine- and piperazinyl-substituted derivatives of the 4-quinolone (e.g., ciprofloxacin) have enhanced antimicrobial potency against gram-negative bacteria, including *P. aeruginosa*, but have limited gram-positive activity, especially against *S. pneumoniae*. These agents therefore have limited usefulness in the treatment of CAP. However, the new fluoroquinolones are distinguished by their improved activity against gram-positive organisms and in some cases against anaerobes [182]. Quintiliani et al. [183] grouped the fluoroquinolones into 4 generations on the basis of microbiologic activity: those with activity primarily against enterobacteriaceae, typified by nalidixic acid (first generation), those with enhanced gram-negative activity (second generation), those with balanced broad-spectrum activity against both gram-negative and gram-positive bacteria (third generation), and those with further extended activity against anaerobic bacteria (fourth generation; table 19).

Members within the third- and fourth-generation fluoroquinolone groups are also known as “respiratory” fluoroquinolones. These drugs are active against penicillin-susceptible as well as penicillin-resistant *S. pneumoniae*, *H. influenzae*, enteric gram-negative bacilli, and “atypical” respiratory pathogens, including *L. pneumophila*, *C. pneumoniae*, and *M. pneumoniae*. They are generally rapidly bactericidal and have sufficiently long half-lives to allow once-daily dosing. Levofloxacin, trovafloxacin, and gatifloxacin are available for both iv and oral use; the iv formulation of moxifloxacin is currently in development.

**Randomized trials comparing fluoroquinolones to other antibiotics.** To date, there have been at least 14 randomized, double-blind, multicenter trials to evaluate the safety and efficacy of the new fluoroquinolones in the treatment of CAP (table 20). Unfortunately, most of these studies are published only as abstracts at this time, making it difficult to critically evaluate their quality. However, details for 9 of these studies are available in full-length publications: 2 studies of levofloxacin [184, 185], 4 of sparfloxacin [172, 174, 175, 186], and one

each of grepafloxacin [187], trovafloxacin [188], and moxifloxacin [179].

**Fluoroquinolones versus  $\beta$ -lactams.** The study by File et al. [184] was among the first to demonstrate the superior activity of levofloxacin monotherapy for adults with CAP in comparison with control patients who received ceftriaxone and/or cefuroxime with or without erythromycin. Clinical success at 5–7 days post-therapy was achieved in 96% of 226 levofloxacin recipients and 90% of 230 cephalosporin recipients (95% CI, –10.7% to –1.3%; table 20). Among patients with the “typical pathogens” *S. pneumoniae* and *H. influenzae*, the overall microbiological eradication rates were 98% and 85%, respectively (95% CI, –21.6% to –4.8%). The pathogen was eradicated from 100% of the levofloxacin recipients with *H. influenzae* infection, but from only 79% of the cephalosporin recipients (95% CI, –39.2% to –2.5%).

The overall clinical success for patients with “atypical pathogens,” including *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*, was 99% among those given levofloxacin and 94% among those given cephalosporin, with or without erythromycin. Gastrointestinal complaints (nausea, vomiting, diarrhea, or dyspepsia) and central or peripheral nervous system complaints (tremor, speech disorder, or dizziness) were the most common adverse events reported in each treatment group (6%). This study demonstrated that levofloxacin monotherapy can be administered safely and effectively to patients with mild to moderately severe CAP.

Levofloxacin in 2 different dosage regimens was compared with amoxicillin-clavulanate in a double-blind, randomized, multicenter European study [189]. The clinical success rate among 171 patients who received levofloxacin at a dosage of 500 mg once daily was 84%, compared with 80% among 177 patients who received levofloxacin at a dosage of 500 mg b.i.d. and 86% among 168 amoxicillin-clavulanate recipients. Levofloxacin (500 mg b.i.d., either iv or sequential iv-to-oral therapy) was compared with ceftriaxone (4 g iv once daily) in an open, randomized, multicenter European study [185]. The cure rate was 87% among 127 levofloxacin recipients and 86% among 139 ceftriaxone recipients (difference not significant).

The study by O’Doherty et al. [187] assessed the efficacy and safety of grepafloxacin versus amoxicillin in a randomized, dou-

**Table 19.** Classification of the new fluoroquinolones.

Generation	Fluoroquinolones	Antibacterial activity
First	Nalidixic acid, <sup>a</sup> oxolinic acid, cinoxacin	Mainly against enterobacteriaceae
Second	Ciprofloxacin, <sup>a</sup> pefloxacin, norfloxacin, <sup>a</sup> ofloxacin, <sup>a</sup> lomefloxacin	Enhanced, but mainly against gram-negative bacteria; limited against gram-positive bacteria
Third	Levofloxacin, <sup>a</sup> sparfloxacin, temafloxacin, <sup>b</sup> grepafloxacin <sup>b</sup>	Enhanced broad-spectrum activity against both gram-positive and gram-negative bacteria
Fourth	Trovafloxacin <sup>a</sup> (restricted), gatifloxacin, moxifloxacin, clinafloxacin, <sup>b</sup> gemifloxacin (investigational)	Extended activity, including against anaerobes

NOTE. Table is modified from [183]. Third- and fourth-generation are “respiratory” fluoroquinolones.

<sup>a</sup> Available in Canada as of 1 April 2000.

<sup>b</sup> Withdrawn by the manufacturer.

**Table 20.** Clinical success rates with fluoroquinolone monotherapy in randomized, clinical trials of treatment for community-acquired pneumonia in Canada.

Reference, drug regimen	Trial double-blind?	No. of patients enrolled	Success rate, % <sup>a</sup>	95% CI
[184] Levofloxacin, 500 mg po q.d. or iv/po q.d. Ceftriaxone, (1 or 2 g iv) + cefuroxime (500 mg po b.i.d) ± erythromycin or doxycycline	No	226	96	−10.7 to −1.3
[185] Levofloxacin, 500 mg iv/po b.i.d. Ceftriaxone, 4 g iv q.d.	No	127 139	87 86	NS
[189] Levofloxacin, 500 mg po q.d. Levofloxacin, 500 mg po b.i.d. Amoxicillin/clavulanate 500/125 mg po t.i.d.	Yes	171 177 168	84 80 86	NS
[187] Grepafloxacin, 600 mg po q.d. Amoxicillin, 500 mg po t.i.d.	Yes	127 137	76 74	NS
[190] Grepafloxacin, 600 mg po q.d. Cefaclor, 500 mg po t.i.d.	Yes	212 208	73 80	NS
[177] Grepafloxacin, 600 mg po q.d. Clarithromycin, 250 mg po b.i.d.	Yes	251 253	92 89	NS
[176] Grepafloxacin, 600 mg po q.d. Clarithromycin, 250 mg po b.i.d.	Yes	246 248	83 89	NS
[172] Sparfloxacin, 200 mg po q.d. Amoxicillin/clavulanate, 500/125 mg po t.i.d. Erythromycin, 1 g po b.i.d.	Yes	401 199 208	87 80 85	NS
[186] Sparfloxacin, 200 mg po q.d. Amoxicillin, 1 g po t.i.d.	Yes	159 170	89 84	NS
[174] Sparfloxacin, 200 mg po q.d. Roxithromycin, 150 mg po b.i.d.	Yes	154 150	94 79	1.9 to 10.8
[175] Sparfloxacin, 200 mg po q.d. Clarithromycin, 500 mg po b.i.d.	Yes	167 175	89 89	NS
[191] Trovafoxacin, 200 mg iv to po q.d. Ceftriaxone iv to cefpodoxime po ± erythromycin <sup>b</sup>	Yes	218 225	86 82	NS
[188] Trovafoxacin, 200 mg po q.d. Amoxicillin, 1 g po t.i.d.	Yes	152 160	91 81	1.6 to 17.6
[178] Trovafoxacin, 200 mg po q.d. Clarithromycin, 500 mg po b.i.d.	Yes	179 180	89 86	NS
[192] Gatifloxacin, 200 mg po b.i.d. Levofloxacin, 100 mg po t.i.d.	Yes	100 100	98 95	NS
[179] Moxifloxacin, 400 mg po q.d. Clarithromycin, 500 mg po b.i.d.	Yes	194 188	95 95	NS

NOTE. NS, not significant; po, by mouth; ±, with or without.

<sup>a</sup> Based on percentage of patients clinically evaluable at follow-up.<sup>b</sup> Intravenous-to-oral therapy.

ble-blind, multicenter trial. The clinical success rate among evaluable patients at the end of the study was 76% of 114 evaluable grepafloxacin recipients and 74% of 111 amoxicillin recipients (difference not significant). However, in the intention-to-treat population with a documented bacterial pathogen, the clinical success rate in the grepafloxacin group (29 [78%] of 37

patients) was significantly higher than in the amoxicillin group (28 [58%] of 48 patients; 95% CI, 2%–43%). Microbiological eradication with grepafloxacin (32 [89%] of 36 patients) was also superior to that with amoxicillin (32 [71%] of 45 patients; 95% CI, 2%–37%).

This study indicated that oral therapy with grepafloxacin is

equivalent to or better than amoxicillin in achieving a successful clinical and microbiological response in the outpatient treatment of CAP. In another study, oral once-daily grepafloxacin was compared with cefaclor, with similar clinical success rates (73% vs. 80%) [190].

In 2 other double-blind randomized studies, once-daily oral sparflaxacin was compared with either high-dose amoxicillin [186] or amoxicillin-clavulanate [172] (table 20). The clinical success rates with sparflaxacin (89% and 87%, respectively) were equivalent to those with amoxicillin (84%) or amoxicillin-clavulanate (80%).

Similarly, trovafloxacin (iv-to-oral sequential therapy) was compared with ceftriaxone/cefpodoxime, with or without erythromycin, in a double-blind, multicenter international study [191]. The clinical success rate among 180 evaluable trovafloxacin recipients (86%) was comparable to that among 187 ceftriaxone/cefpodoxime recipients (82%). Finally, trovafloxacin (200 mg po once daily) was compared with amoxicillin (1 g t.i.d. po) in a double-blind, multicenter international study [188]. The success rate among 152 evaluable trovafloxacin-treated patients was significantly higher than that among 160 amoxicillin recipients (91% vs. 81%; 95% CI, 1.6%–17.6%). Among patients with known pathogens, the *S. pneumoniae* eradication rate was significantly higher in the trovafloxacin group (20 [100%] of 20) than in the amoxicillin group (17 [81%] of 21; 95% CI, 2.3%–35.8%). All 4 trovafloxacin-treated patients infected with penicillin-resistant *S. pneumoniae* at baseline were clinically cured (with pathogen eradication), whereas treatment clinically failed (with pathogen persistence) for 2 of 5 amoxicillin-treated patients infected with penicillin-resistant *S. pneumoniae* at baseline.

**Fluoroquinolones versus macrolides.** Sparflaxacin was compared with erythromycin [172], roxithromycin [174], or clarithromycin [175] in 3 independent, randomized, double-blind, multicenter trials. The clinical success rates of sparflaxacin (87%, 94%, and 89%, respectively, in the 3 separate studies) were similar to those of erythromycin (85%), roxithromycin (79%), and clarithromycin (89%; table 20). Grepafloxacin was compared with clarithromycin in 2 separate double-blind, multicenter trials [176, 177]. The clinical success rates of grepafloxacin (83% and 92%, respectively, in the 2 trials) were similar to those of clarithromycin (89% and 89%, respectively). Trovafloxacin was also compared with clarithromycin, with equivalent clinical response rates (89% vs. 86%) [178]. Finally, moxifloxacin was compared with clarithromycin in 382 patients with mild to moderately severe CAP, with equivalent clinical response rates (95% for each regimen) [179].

**Fluoroquinolones versus fluoroquinolones.** Oral gatifloxacin (200 mg b.i.d.) was compared with oral levofloxacin (100 mg t.i.d.) in a double-blind, multicenter study conducted in Japan [192]. The clinical success rate among 100 evaluable gatifloxacin recipients was 98%, compared with 95% among 100 evaluable levofloxacin recipients. However, adverse events were relatively

common (10.4% in the gatifloxacin group and 4.6% in the levofloxacin group; difference not significant).

**Conclusions.** There is good evidence that the newer fluoroquinolones are effective and comparable to standard agents such as amoxicillin, amoxicillin-clavulanate, and cephalosporins with or without macrolides in the treatment of mild to moderate CAP in ambulatory patients (I) [193]. Therefore, the “respiratory” fluoroquinolones are a reasonable alternative to macrolides, doxycycline, amoxicillin/clavulanate, or oral cephalosporins for the outpatient management of CAP in otherwise healthy patients, particularly if the first-line agents cannot be tolerated. The availability of once-daily regimens and the feasibility of iv-to-oral sequential therapy are clear advantages of the fluoroquinolones. However, too few well-designed clinical studies have been published to evaluate the role of these fluoroquinolones in the treatment of patients with severe CAP that requires hospitalization and residence in the ICU. Furthermore, the potential for serious adverse effects, such as dizziness, hypoglycemia, prolongation of the corrected Q-T interval, phototoxicity, and hepatotoxicity associated with some fluoroquinolones, is a major concern [194] (table 21).

The potential for rapid development of resistance among *S. pneumoniae* is also problematic [158]. Similar to first- and second-generation fluoroquinolones, the “respiratory” fluoroquinolones are also chelated by antacids containing aluminum, magnesium, or calcium, and by sulcrilate and products containing iron or zinc. Some fluoroquinolones (e.g., ciprofloxacin and grepafloxacin) also competitively inhibit cytochrome P450 enzyme activity to variable degrees, and such agents may result in toxic levels of theophylline or cyclosporin [194].

Among the “respiratory” fluoroquinolones, only levofloxacin, grepafloxacin, and trovafloxacin are currently released in Canada. However, grepafloxacin was recently withdrawn by the manufacturer worldwide because of concerns about cardiac toxicity associated with prolongation of the Q-T interval. In addition, life-threatening hepatotoxicity has been reported with trovafloxacin, and this drug should be reserved only for severe life-threatening infections in hospitalized patients if no other reasonable alternative is available. The frequency of severe hepatotoxicity associated with trovafloxacin is estimated to be <1 per 20,000 cases [194]. The majority of affected patients had preexisting hepatic abnormalities or were receiving concomitant potential hepatotoxins, and the precise role of trovafloxacin in causing or contributing to hepatotoxicity is unknown, although hypersensitivity is suspected.

Sparflaxacin has not been released in Canada. It can cause prolongation of the Q-T interval and severe phototoxicity and should be used with extreme caution [194]. Moxifloxacin and gatifloxacin are released in the United States; however, experience with these agents in the treatment of CAP is relatively sparse. Thus, despite the excellent antimicrobial spectrum and favorable pharmacodynamic properties of these “respiratory” fluoroquinolones for the empirical treatment of CAP, post-

**Table 21.** Frequently occurring adverse effects of the new fluoroquinolones.

Adverse effect	Ciprofloxacin	Clinafloxacin <sup>a</sup>	Gatifloxacin	Grepafloxacin <sup>a</sup>	Levofloxacin	Moxifloxacin	Sparfloxacin	Trovafloxacin <sup>a</sup>
Gastrointestinal								
Nausea	+	ND	+	++	+	++	+	++
Vomiting	+	ND	ND	+	+/-	ND	+	+
Diarrhea	+	++	+	+	+	++	+	+
CNS								
Dizziness	+	ND	+	+	-	+/-	-	+++
Headache	+	ND	+	+	+	+/-	+	+
Allergy								
Rash	+	ND	ND	+	-	ND	+	+/-
Pruritis	+/-	ND	ND	+	-	ND	+/-	+/-
Phototoxicity	+/-	++	+	+	+/-	+	++	+/-
QTc prolongation	-	ND	ND	+	-	ND	+	ND
Taste perversion	-	ND	ND	+++	+/-	ND	-	ND
Injection-site reaction	+	+	NA	NA	+	NA	NA	+/-
Hepatotoxicity	-	ND	ND	ND	-	ND	ND	+/-

NOTE. NA, not applicable; ND, no data available; QTc, heart-rate corrected Q-T interval; -, not observed; +/-, <1%; +, 1-5%; ++, 6%-10%; +++, >10%. Table is modified from [194].

<sup>a</sup> Clinafloxacin was withdrawn by the manufacturer because of concerns about phototoxicity and hypoglycemia; grepafloxacin was withdrawn by the manufacturer because of concerns about QTc prolongation and cardiotoxicity; trovafloxacin is restricted for the treatment of hospitalized patients with severe infections because of the potential for serious hepatotoxicity.

marketing surveillance of their safety profiles will be extremely important before physicians will feel comfortable with their widespread use.

#### Feasibility of Oral or Intravenous-to-Oral Sequential Therapy

In the past 10 years, a large number of new and improved oral antibiotics, including macrolides,  $\beta$ -lactams, and fluoroquinolones, have become available for the treatment of CAP. Most of the innovative antibiotics have greatly improved bioavailability as well as tolerability. Thus, these drugs have become suitable as first-line agents for the treatment of CAP, not only in outpatients but also in hospitalized patients. The past decade has also seen the loss of hospital beds and the expectation by third-party payers of shorter hospital stays. There is constant pressure to reduce expenditures for drugs, including antibiotics. This combination of factors—the availability of newer antimicrobials with improved pharmacokinetic properties and economic constraints in the hospital milieu—has been the major driving force behind the use of oral agents in the treatment of CAP.

At most institutions in Canada and the United States, iv-to-oral sequential therapy has become widely accepted as the standard of practice. More recently, oral agents have been frequently used, either in combination with companion iv antibiotics right from the point of hospitalization or as the sole oral agents. It is interesting that even though the concept of oral antibiotics or iv-to-oral sequential therapy for CAP has become widely accepted, the volume of literature in support of these practices is relatively small. Nevertheless, the available evidence does support the use of iv-to-oral sequential therapy once the patients have demonstrated a satisfactory clinical and laboratory response to the initial course of iv therapy. Limited

evidence also lends support to the use of oral agents for carefully selected CAP patients throughout their hospitalization.

*Intravenous-to-oral sequential antibiotic therapy.* Several clinical studies support the sequential switch from therapy with an iv formulation to therapy with an oral formulation of the same antibiotic, e.g., with a fluoroquinolone such as ciprofloxacin [195] or a cephalosporin such as cefuroxime [196], or the sequential substitution of an iv  $\beta$ -lactam such as ceftriaxone [197, 198] with an oral cephalosporin that has a similar antimicrobial spectrum, such as cefixime, cefpodoxime, or ceftibuten [161]. Among 10 clinical trials designed to evaluate the effectiveness of iv-to-oral sequential antibiotic therapy for the treatment of CAP, 6 were randomized controlled trials [195, 196, 199–202] and the other 4 were nonrandomized [197, 198, 203, 204], although they all had appropriate control groups. Eight of the studies involved adults, accounting for a total of 1051 evaluable patients [197–204]. Two studies targeted the pediatric population, involving a total of 230 patients [203, 204]. All 10 studies demonstrated a favorable outcome in the iv-to-oral sequential therapy group, compared with patients who remained on iv therapy throughout the entire course of treatment. Follow-up data also indicated that there were few relapses necessitating a return to iv therapy.

Not surprisingly, all 10 studies indicated a significant reduction in both the cost of treatment and the length of the hospital stay. Although in some instances the iv-to-oral sequential switch took place after 1 or 2 days of iv therapy, most of the switches occurred on day 3 or 4 of treatment.

On the basis of these available studies, it would appear that the most important considerations in iv-to-oral sequential antibiotic therapy are as follows [205]. (1) Critically ill patients, especially those individuals who are hemodynamically unstable and require intensive care, should be excluded. (2) At the time

**Table 22.** Antimicrobials useful for intravenous-to-oral sequential treatment of patients with community-acquired pneumonia.

Class of agent, preferred iv agent	Preferred oral formulation		Alternative oral formulation	
	Antimicrobial agent	Bioavailability, %	Antimicrobial agent(s) <sup>a</sup>	Bioavailability, %
Fluoroquinolone				
Ciprofloxacin	Ciprofloxacin <sup>b</sup>	70–80	2G fluoroquinolone	≥88
Levofloxacin	Levofloxacin	99	3G fluoroquinolone	≥88
			β-lactam plus macrolide	Variable
Trovaflaxacin	Trovaflaxacin	~88	4G fluoroquinolone	≥88
β-lactam				
Ampicillin	Ampicillin	30–55	Amoxicillin	74–92
			Penicillin V	70–80
			Amoxicillin/clavulanate	74–92
Cefuroxime	Cefuroxime	37–52	Cefaclor	>90
			Cefprozil	>95
			Cefadroxil	>90
			Amoxicillin/clavulanate	74–92
			2-G or 3G fluoroquinolone	≥88
			TMP/SMZ	>90
Ceftriaxone or cefotaxime	Cefuroxime	37–52	3G fluoroquinolone	≥88
			Cefixime	40–50
			Cefpodoxime	50
			Ceftibuten	70–90
				≥88
Ceftazidime, imipenem, or piperacillin/tazobactam	Cefuroxime	37–52	4G fluoroquinolone	
Macrolides				
Erythromycin	Erythromycin	Variable	Clarithromycin	~50
Azithromycin	Azithromycin	~37	3G fluoroquinolone	≥88
			Doxycycline	60–90
Tetracyclines				
Doxycycline	Doxycycline	60–90	Macrolide	Variable
			3G fluoroquinolone	≥88
Lincomycins				
Clindamycin	Clindamycin	90	Metronidazole ± β-lactam	Variable
			4G fluoroquinolone	≥88
Sulfonamide				
TMP/SMZ	TMP/SMZ	70–100 <sup>c</sup>	β-lactam	Variable
			2G fluoroquinolone	≥88

NOTE. 2G, second-generation; 3G, third-generation; 4G, fourth-generation; TMP/SMZ, trimethoprim/sulfamethoxazole.

<sup>a</sup> See table 16 for classification of fluoroquinolones.

<sup>b</sup> Not recommended if *S. pneumoniae* is the suspected pathogen.

<sup>c</sup> Value for SMZ.

of the iv-to-oral sequential switch, the gastrointestinal tract should be functioning normally, especially if the patient is being fed through an orogastric tube. Such patients must be monitored to ensure that they are able to tolerate the oral formulation. (3) The appropriate time for the switch is when the patient has demonstrated a satisfactory clinical and laboratory response to the initial iv therapy. Criteria used in the studies typically included resolution of fever, reduction in cough and respiratory distress, and a significant drop in leukocytosis. (4) At the time of the switch, patients should also be deemed medically stable in other aspects of their physical condition.

The weakness of the available evidence lies in the fact that each study enrolled relatively small numbers of patients. Nevertheless, these studies have consistently demonstrated a favorable outcome, which would be predicted on the basis of the pharmacokinetic profiles of the drugs studied. It is therefore fair to conclude that according to the available evidence, it is highly desirable to implement an iv-to-oral therapy sequential switch

or substitution, as long as the 4 key criteria mentioned above are met and the oral formulation has good bioavailability (II).

Many physicians may feel more comfortable with the iv-to-oral sequential switch if the identical antibiotic is available in an oral formulation. The fact that such a preparation is sometimes unavailable can cause considerable delay in the decision for an iv-to-oral sequential substitution. In such cases, substitution with another oral formulation with a similar spectrum of activity and adequate bioavailability should be considered (table 22) (III). Generally, the iv-to-oral switch can take place after 2–4 days of iv therapy.

**Oral versus intravenous antibiotic therapy.** The availability of newer oral agents with formulations that are highly bioavailable and well-tolerated has raised the possibility of using these oral antibiotics as first-line initial therapy for some hospitalized patients with CAP. There have been 4 clinical studies to evaluate the feasibility of this approach. All 4 were randomized controlled trials in hospitalized patients with CAP that

**Table 23.** Empirical antimicrobial selection for adult patients with community-acquired pneumonia.

Type of patient, factor(s) involved	Treatment regimen	
	First choice	Second choice
Outpatient without modifying factors	Macrolide <sup>a</sup>	Doxycycline
Outpatient with modifying factors		
COLD (no recent antibiotics or po steroids within past 3 mo)	Newer macrolide <sup>b</sup>	Doxycycline
COLD (recent antibiotics or po steroids within past 3 mo); <i>H. influenzae</i> and enteric gram-negative rods implicated	"Respiratory" fluoroquinolone <sup>c</sup>	Amoxicillin/clavulanate + macrolide or 2-G cephalosporin + macrolide
Suspected macroaspiration: oral anaerobes	Amoxicillin/clavulanate ± macrolide	"Respiratory" fluoroquinolone (e.g., levofloxacin) + clindamycin or metronidazole
Nursing home resident		
<i>Streptococcus pneumoniae</i> , enteric gram-negative rods, <i>H. influenzae</i> implicated	"Respiratory" fluoroquinolone alone or amoxicillin/clavulanate + macrolide	2-G cephalosporin + macrolide
Hospitalized	Identical to treatment for other hospitalized patients (see below)	
Hospitalized patient on medical ward		
<i>S. pneumoniae</i> , <i>L. pneumophila</i> , <i>C. pneumoniae</i> implicated	"Respiratory" fluoroquinolone	2G, 3G, or 4G cephalosporin + macrolide
Hospitalized patient in ICU		
<i>P. aeruginosa</i> not suspected; <i>S. pneumoniae</i> , <i>L. pneumophila</i> , <i>C. pneumoniae</i> , enteric gram-force-justifynegative rods implicated	Iv respiratory fluoroquinolone + cefotaxime, ceftriaxone, or β-lactam-β-lactamase inhibitor	Iv macrolide + cefotaxime, ceftriaxone, or β-lactam/β-lactamase inhibitor
<i>P. aeruginosa</i> suspected	Antipseudomonal fluoroquinolone (e.g., ciprofloxacin) + antipseudomonal β-lactam or aminoglycoside	Triple therapy with antipseudomonal β-lactam (e.g., ceftazidime, piperacillin-tazobactam, imipenem, or meropenem) + aminoglycoside (e.g., gentamicin, tobramycin, or amikacin) + macrolide

NOTE. COLD, chronic obstructive lung disease; po, by mouth; 2G, second-generation; 3G, third-generation; 4G, fourth-generation.

<sup>a</sup> Erythromycin, azithromycin, or clarithromycin.

<sup>b</sup> Azithromycin or clarithromycin.

<sup>c</sup> Levofloxacin, gatifloxacin, or moxifloxacin; trovafloxacin is restricted because of potential severe hepatotoxicity.

directly compared the success rates of oral and iv formulations [171, 206–208]. The oral antibiotics included macrolides such as azithromycin [171], β-lactams such as penicillin and cephalosporins [206, 207], and fluoroquinolones such as ofloxacin [208]. The total number of evaluable patients in these 4 studies was 355, including some with bacteremic pneumococcal infection.

Again, the clinical outcomes with the oral treatment strategy were favorable in comparison with outcomes in the iv treatment group, and very few failures were found during follow-up. On the basis of the factors discussed above, it can be recommended that oral formulations of appropriate antibiotics may be considered for the initial treatment of hospitalized patients with CAP, provided that the following criteria are met (II). (1) Patients who are hemodynamically unstable and require intensive care must be excluded. (2) The gastrointestinal tract must be functioning normally, and there should be no history of gastrointestinal intolerance of the class of antibiotic being considered. (3) Close monitoring of the clinical status and tolerability of treatment during the first 48 h is required.

#### Guidelines for Initial Empirical Antimicrobial Therapy

Although many aspects of the previous Canadian guidelines for the treatment of CAP are being revised, the general approach of stratifying patients according to how they can be treated (on an outpatient basis, in a nursing home, or in a

hospital) appears both logical and practical. For the current guidelines to be useful to practicing physicians, a major effort has been made to simplify the recommendations as much as possible in order to emphasize the general principles applicable to the majority of patients with CAP. Accordingly, recommendations for the initial management of CAP in the current guidelines are predicated upon the most likely pathogens in a given population (discussed in the Epidemiology and Etiology section), the general trend of antibiotic resistance among respiratory pathogens across Canada, and the clinical experience with various antibiotic regimens, on the basis of randomized clinical trials (discussed earlier in this section on treatment).

Rather than addressing all possible factors, which may be either of dubious significance or difficult to document in a given patient, the current guidelines address only the most important modifying factors. These factors either affect oropharyngeal colonization by more resistant gram-negative pathogens or may result in antimicrobial selection pressure imposed by previous antibiotic therapy. In addition, unique features of the health care delivery system within Canada, such as the infrastructure support of its health care institutions (including nursing homes), the availability and cost of iv and oral antibiotics in general, and the relative inaccessibility of parenteral antibiotics in the nursing home setting, were taken into consideration. The following updated recommendations are proposed by the consensus group (table 23).

*Site-specific initial treatment of CAP.* Patients with a pneu-

pneumonia-specific risk score of  $>90$  (figure 2) should generally be hospitalized (I). Patients with CAP who do not require hospitalization are categorized separately as outpatients or nursing home residents. For outpatients who do not have modifying factors such as chronic obstructive lung disease or macroaspiration, treatment with a macrolide (erythromycin, azithromycin, or clarithromycin) or doxycycline should suffice to cover pneumococci, *M. pneumoniae*, and *C. pneumoniae*, the most likely pathogens in this setting (II) (table 23).

For the present, macrolides (see Macrolides section) remain effective for patients with mild to moderately severe CAP, on the basis of their pneumonia-specific severity-of-illness score (figure 2). Patients with chronic obstructive lung disease who have not received antibiotics or oral steroids during the previous 3 months can be treated in a manner identical to that of patients without modifying factors, with the caveat that only a newer macrolide (azithromycin or clarithromycin) be used to insure adequate coverage of *H. influenzae*. Patients with chronic obstructive lung disease and a history of use of antibiotics or oral steroids within the past 3 months may have an increased risk for infection with *H. influenzae* and enteric gram-negative bacilli, in addition to *S. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* [33], and for them a "respiratory" fluoroquinolone is recommended.

Among the currently available "respiratory" fluoroquinolones, levofloxacin has a record of safety and effectiveness for the treatment of CAP in a large number of patients, and it has demonstrated substantial cost-savings when included in a critical pathway for the treatment of CAP [130]. On the basis of safety data related to serious liver injury, trovafloxacin should be reserved only for hospitalized patients whose infections are judged to be serious and life-threatening and when the benefit is believed to outweigh the potential risk.

Amoxicillin-clavulanate or a second-generation cephalosporin (e.g., cefuroxime or cefprozil) plus a macrolide is considered a second choice (II). If macroaspiration is suspected, amoxicillin-clavulanate with or without a macrolide or a fourth-generation fluoroquinolone with enhanced activity against anaerobes should be considered (II). An appropriate alternative is use of a third-generation fluoroquinolone (e.g., levofloxacin) plus either clindamycin or metronidazole (III). The choice of initial treatment of CAP for patients with HIV infection is beyond the scope of these guidelines.

Nursing home residents with pneumonia can be evaluated with the same prediction rules for hospitalization used for other patients with CAP (figure 2) [209] (II). For patients who can be treated in the nursing home setting and do not require hospitalization, a "respiratory" fluoroquinolone or amoxicillin-clavulanate plus a macrolide is recommended as the first choice. A second-generation cephalosporin plus a macrolide is an alternative (II) [210].

Patients who require hospitalization, including those transferred from a nursing home, can be categorized according to

whether they can be treated on the general medical ward or require cardioventilatory support in an ICU. Treatment of patients on the general medical ward is directed at bacteremic pneumococcal pneumonia as well as infection with *H. influenzae* or enteric gram-negative bacilli or severe legionella or chlamydia infection. Monotherapy with a "respiratory" fluoroquinolone is the first choice (II). An alternative is a second-, third-, or fourth-generation cephalosporin (e.g., cefuroxime, cefotaxime, ceftriaxone, ceftizoxime, or cefepime) plus a macrolide.

Monotherapy with a fluoroquinolone for hospitalized ward patients offers logistic and financial advantages over combination therapy with a macrolide and a  $\beta$ -lactam. There are also some data suggesting that use of a fluoroquinolone alone may be associated with reduction in mortality [191, 211].

Treatment of patients in the ICU depends upon whether *P. aeruginosa* is a concern, such as for patients with severe structural lung disease or patients who have recently completed a course of antibiotics or steroids. If *P. aeruginosa* is not an issue, broad-spectrum aggressive coverage is still required in the form of an iv macrolide or respiratory fluoroquinolone plus a non-pseudomonal third-generation cephalosporin (e.g., cefotaxime or ceftriaxone) or a  $\beta$ -lactam- $\beta$ -lactamase inhibitor. If *P. aeruginosa* is suspected, an antipseudomonal fluoroquinolone (such as ciprofloxacin) plus an antipseudomonal  $\beta$ -lactam or an aminoglycoside (if antibiotic resistance is not a major concern) should be used (III).

An alternative is triple therapy with an antipseudomonal  $\beta$ -lactam (e.g., ceftazidime, piperacillin-tazobactam, or carbapenem) plus an aminoglycoside (e.g., gentamicin, tobramycin, or amikacin) plus a macrolide (III). It should be noted that whereas synergy between an antipseudomonal  $\beta$ -lactam and an aminoglycoside can frequently be demonstrated against *P. aeruginosa* in vitro, such synergistic interaction is uncommon between a fluoroquinolone and an aminoglycoside [212, 213]. An additive effect can be expected, whereas antagonism is rare. There are insufficient efficacy data to enable recommendation of trovafloxacin, either alone or in combination with an antipseudomonal  $\beta$ -lactam, for initial empirical treatment of serious *P. aeruginosa* infections.

It is important to recognize that these recommendations are derived by the consensus of experts and not entirely based on evidence from randomized clinical trials. Once an etiologic agent has been appropriately identified, the in vitro susceptibility of the pathogen has been confirmed, and infection with a copathogen has been excluded, initial empirical therapy should be modified so that treatment is directed at the specific pathogen(s) involved (table 24).

Unfortunately, there has never been an appropriately designed randomized controlled trial to specifically determine the duration of antibiotic therapy for CAP. Most physicians, including members of this committee, recommend treatment for 1–2 weeks, depending upon the response of the patient.

*Assessment of response to initial treatment.* The rate of clin-



**Table 24.** Specific therapy for selected pathogens in community-acquired pneumonia.

Pathogen	Antimicrobial(s) (dosage)
<i>S. pneumoniae</i>	
Penicillin-susceptible (MIC, <0.1 mg/L)	Oral penicillin G, amoxicillin, cephalosporin, or macrolide
Intermediate resistance (MIC, ≤1 mg/L)	Amoxicillin (500 mg t.i.d. po) or cefuroxime (500 mg b.i.d. po)
High-level resistance (MIC, ≥2 mg/L)	Penicillin G (2 MU q6h iv), cefotaxime (1 g q8h iv), or ceftriaxone (1 g q24h iv), or "respiratory" fluoroquinolone <sup>a</sup>
High-level resistance (in case of CAP and meningitis)	Vancomycin or "respiratory" fluoroquinolone <sup>a</sup>
<i>H. influenzae</i>	3G or 4G cephalosporin or β-lactam/β-lactamase inhibitor
<i>M. catarrhalis</i>	3G or 4G cephalosporin or β-lactam/β-lactamase inhibitor
Respiratory anaeroobe(s)	β-lactam/β-lactamase inhibitor or 3G fluoroquinolone (e.g., levofloxacin) + either clindamycin or metronidazole or 4G fluoroquinolone (e.g., moxifloxacin)
<i>S. aureus</i>	
Methicillin-susceptible	Oxacillin or cloxacillin
Methicillin-resistant	Vancomycin
Enteric gram-negative bacilli	3G or 4G cephalosporin ± aminoglycoside
<i>P. aeruginosa</i>	Ciprofloxacin or aminoglycoside, each plus antipseudomonal β-lactam <sup>b</sup>
<i>Legionella</i> species	Macrolide ± rifampin or fluoroquinolone
<i>C. pneumoniae</i>	Doxycycline or macrolide
<i>M. pneumoniae</i>	Doxycycline or macrolide
<i>C. burnetii</i> (Q fever agent)	Tetracycline

NOTE. Po, by mouth; 2G, second-generation; 3G, third-generation; 4G, fourth-generation; ±, with or without.

<sup>a</sup> Levofloxacin, gatifloxacin, or moxifloxacin.

<sup>b</sup> Ceftazidime, piperacillin-tazobactam, imipenem, or meropenem.

ical response of patients with CAP to antimicrobial therapy depends on the pathogen as well as host factors [214]. However, a subjective response is usually noted within 3–5 days of initiation of treatment. Objective parameters include the resolution of respiratory symptoms (cough or dyspnea), defervescence, improvement in the arterial partial pressure of O<sub>2</sub> and on serial chest radiographs, and normalization of the leukocyte count. The length of hospital stay is often determined by the duration of iv antimicrobial regimens. Intravenous-to-oral sequential therapy is strongly recommended, since this reduces cost and shortens the length of hospital stay, and provides additional psychosocial benefit for the patient (I).

Patients who fail to respond despite what appears to be an appropriate choice of antimicrobial therapy should be reevaluated at 3–5 days after initiation of treatment. Possible reasons for failure include complications of pneumonia such as the presence of an empyema, bronchial obstruction, extrapulmonary spread of infection, superinfections, or misdiagnosis of noninfectious causes (e.g., congestive heart failure, neoplasm, vasculitis, sarcoidosis, drug reaction, alveolitis, pulmonary embolism, or hemorrhage). Additional diagnostic procedures such as CT scanning, bronchoscopy, mediastinoscopy, angiography, or lung biopsy may be required.

### General Measures and Follow-Up

In addition to antimicrobial therapy, certain general principles of management should be implemented. Adequate hydration will help to clear secretions. Cough suppressants may be beneficial for patients with severe paroxysms of coughing that produce respiratory fatigue or pleuritic and chest-wall pain.

Oxygen therapy may be indicated for hypoxemia. Significant pleural effusion (>10 mm on lateral decubitus views) or pleural empyema should be drained either by needle aspiration under CT guidance or surgically. Patients treated in the outpatient setting must be carefully monitored to ensure compliance and clinical improvement. Follow-up by telephone with the patient or a return clinic visit within 48–72 h is strongly suggested. Additional visits and obtaining another chest radiograph within 2–3 weeks of antimicrobial therapy may be beneficial to ensure resolution of the pneumonia.

### Prevention of CAP

The importance of pneumococcal infection in CAP is apparent, but it is also clear that during outbreaks of influenza, the influenza virus has a significant impact on CAP as well. Both of these infections may be prevented by the use of pneumococcal and influenza vaccines. The former is a polyvalent preparation containing purified capsular polysaccharide of the serotypes responsible for most of the invasive pneumococcal infections. The latter vaccine is modified each year to contain antigens of the influenza strains that are anticipated to cause problems in the coming season.

A detailed discussion of these vaccines is beyond the scope of this document, but additional information is available for the interested reader [228–231]. The committee supports the use of the currently available pneumococcal (level II) and influenza vaccines (level I) in unvaccinated patients at risk for infection with either of these pathogens or in those at increased risk of complications from such infections.

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