Seminar

Community-acquired pneumonia

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This seminar reviews important features and management issues of community-acquired pneumonia (CAP) that are especially relevant to immunocompetent adults in light of new information about cause, clinical course, diagnostic testing, treatment, and prevention. *Streptococcus pneumoniae* remains the most important pathogen; however, emerging resistance of this organism to antimicrobial agents has affected empirical treatment of CAP. Atypical pathogens have been quite commonly identified in several prospective studies. The clinical significance of these pathogens (with the exception of *Legionella* spp) is not clear, partly because of the lack of rapid, standardised tests. Diagnostic evaluation of CAP is important for appropriate assessment of severity of illness and for establishment of the causative agent in the disease. Until better rapid diagnostic methods are developed, most patients will be treated empirically. Antimicrobials continue to be the mainstay of treatment, and decisions about specific agents are guided by several considerations that include spectrum of activity, and pharmacokinetic and pharmacodynamic principles. Several factors have been shown to be associated with a beneficial clinical outcome in patients with CAP. These factors include administration of antimicrobials in a timely manner, choice of antibiotic therapy, and the use of a critical pneumonia pathway. The appropriate use of vaccines against pneumococcal disease and influenza should be encouraged. Several guidelines for management of CAP have recently been published, the recommendations of which are reviewed.

Community-acquired pneumonia (CAP) is a common disorder that is potentially life threatening, especially in older adults and those with comorbid disease. Since 1998, when CAP was last featured as a Seminar in *The Lancet*,[1] new information on cause, clinical course, diagnostic testing, and management has been published. This seminar is a review of important clinical features and management issues for immunocompetent adults with CAP in light of recent information and guidelines.[2–15]

Causes

Although many pathogens have been associated with CAP, it is a small range of key pathogens that cause most cases. The emergence of newly recognised pathogens, such as the novel coronavirus associated with (SARS), increases the challenge for appropriate management of these infections.

The predominant pathogen in CAP is *Streptococcus pneumoniae* (pneumococcus), which accounts for about two-thirds of all cases of bacteraemic pneumonia.[16] Cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease in immunocompetent, non-elderly adults.[17]

Other causative agents include, but are not limited to *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae (Chlamydia pneumoniae), Legionella* spp, *Chlamydophila psittaci (Chlamydia psittaci), Coxiella burnetii,* enteric gram-negative bacteria (enterobacteriaceae), *Pseudomonas aeruginosa*, *Staphylococcus aureus*, anaerobes (aspiration pneumonia), and respiratory viruses (influenza virus, adenovirus, respiratory syncytial virus, parainfluenza virus, coronavirus).[6–9,15,16,18–22] Gram-negative bacilli (Enterobacteriaceae and pseudomonadas) are the cause of CAP in some patients (those who have had previous antimicrobial treatment or who have pulmonary comorbidities).[23] The frequency of other causes, such as *Mycobacterium tuberculosis, C psittaci* (psittacosis), *C burnetii* (Q fever), *Francisella tularensis* (tularaemia), and endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis) vary between epidemiological settings.

Table 1[18,24–30] shows the causes of CAP in adults in hospital as reported by workers from several prospective studies in several worldwide locations who used comprehensive diagnostic approaches. The incidence of specific pathogens varied in accordance with the completeness of testing and specificity of diagnostic criteria (ie, definite *vs* presumptive diagnosis [table 1]). Collectively, *S pneumoniae* was the most frequently isolated organism, with the highest incidence of this pathogen reported in studies that included detection by a urinary antigen test.[28,29] Relative to other pathogens, *M pneumoniae*, *C pneumoniae*, and *L pneumophila* were also common. These organisms (along with other *Chlamydia* spp and *C burnetii*) are often referred to as "atypicals", a label of contended scientific merit. Nevertheless, the term remains popular with clinicians and is in widespread use in recent scientific reports.[31] These atypical pathogens are not often identified in clinical practice, however, because (with the exception of *L pneumophila*) there is not a specific, rapid, or standardised test for their detection; as such, the frequency of these pathogens is probably underreported.[31]

Search strategy and selection criteria

This seminar relies on articles retrieved from a search of MEDLINE to identify pertinent articles about CAP published since 1997, and consensus statements of guidelines for the management of CAP in adults.[2–15] A preference was given to published articles that were evidenced-based, extensively reviewed with a grading of studies in the literature, and supported by expert opinion.

Lancet 2003; **362:** 1991–2001

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	USA[18] (n=2776)	USA[24] (n=410) excludes HIV infected patients	Japan[25] (n=200)	Spain[26] (n=90)	Argentina[27] (n=343)	Thailand[30] (n=147)	UK[29] (n=267)	Kenya[28] (n=281)
Diagnostic methods	BC, SC, LC, Ser, LUA,	BC, SC, VC, Ser	BC, SC, MpC, ClC, LC, LUA, Ser	BC, SC, LC, VC, LUA, PCR, Ser, PTNA	BC, SC, Ser, NPVA, LUA	BC, SC, LUA, SpUA, Ser	BC,SC,LC, Ser, LUA, SpUA, Sp CIE	BC,SC, NAC, Ser, SpUA
S pneumoniae	12·6% (5·5%)†	11% (6%)	20·5%	30%	10% (3%)	22·4% (17%)	48%	46%
M pneumoniae	32·5% (5·4%)	7% (0·5%)	9·5%	22%	5% (5%)	6·8% (4·1%)	3%	2·5%
C pneumoniae	8·9% (2·4%)	6 % (1·0%)*	7·5%	13%	3 (3%)	16·3 (14%)	13%	0%
H influenzae	6·6% (0·4%)	5% (0·25%)	11%	7%	5% (0·3%)	2·7% (0%)	7%	3·6%
Staph aureus	3·4% (0·4%)	2% (1%)	5·0%		2% (0·6%)	3·4% (3·4%)	1·5%	1·4%
Moraxella catarrhalis	0·76% (0%)	0·2% (0%)	3·0%		1% (0%)	NR	NR	0%
Legionella spp	3·0% (2·4%)	8% (4%)	1·0%		1% (0·5%)	5·4% (3·4%)	3%	0%
Enterobacteriaceae	2·8% (0·7%)	1% (0·5%)	2·5%	1%	3% (2%)	11% (6·8%)	<1·4%	2·5%
Pseudomonas spp	1·7% (0·1%)	0%	2·0%	0%	2% (0%)	0·7% (0·7%)	1%	0·4%
Anaerobes	NR	16%†	4·0%		10%	2% (2)	1·1%	NR
Virus	12·7%[5]	1% (1%)	3%	6%	7% (3%)	NR	23%	5·7%
Pneumocystis spp	1·4%	0%	NR	8%	0·3% (0·3%)	NR	NR	NR
M tuberculosis	1·4%	5% (5%)	NR	4%	2% (2%)	NR	Excluded	8·9%
C psittaci	NR	NR	1·0%	1%	<1% (0%)	NR	NR	0%
C burnetii	NR	NR	0·5%	1%	<1% (0·3%)	NR	0·7%	0%
Other agents	05%	0·7% (0·7%)	2·0% *(S Milleri)*	3%	3%	6·1%	2%	
Mixed infection	2%	8%	NR	NR	6%	6·1%	NR	11%
Unknown		46%	41·5%	17%	48%	28·6%	25%	35%

BC=blood cultures. SC=routine sputum culture and test for tuberculosis. MpC=*M pneumoniae* culture. ClC=*Chlamydia* spp culture. LC=*Legionella* spp culture. VC=viral culture; PTNA=percutaneous transthoracic needle aspirate culture. NVA=nasopharyngeal viral antigen detection. Ser=Serological detection. LgUA=*Legionella* spp urinary antigen. SpUA=*Strep pneumoniae* urinary antigen. Sp CIE=counter immune electrophoresis for *S pneumoniae*. NR=not reported. *Listed as *Chlamydia* spp. †Listed as "aspiration". Data are total proportion of cases, ie, both definitive and presumptive diagnoses; number in parentheses is proportion of definitive diagnoses. Definitive diagnosis assigned by one of the following criteria: CAP pathogen cultured from a normally sterile site; a noncommensal organism (eg, *Mycobacterium tuberculosis*, *Legionella* spp) was identified from any site; a positive urinary antigen, a positive PCR test, or when paired serological testing revealed a significant increase in antibody titre. A presumptive diagnosis was assigned when growth of a pathogen in sputum culture was accompanied by a gram stain showing a compatible organism or when one high serum antibody titre was noted for a pathogen. Although Ruiz-Gonzales[26] did not specifically define the status of diagnostic criteria as definite or presumptive, the methods used can be accepted as representing definite diagnosis criteria.

Table 1: **Causative agent in community-acquired pneumonia that necessitated admission**

The proportion of cases in recent studies with a defined cause ranged from 52 to 83%. By contrast, in an observational study that assessed the 'real-world' practice from several centres in the USA, only 6% of outpatients and a quarter of inpatients with CAP had the cause of their disease defined.[32] In a study of consecutive patients with CAP, Ruiz-Gonzales and colleagues[26] used microbiological analysis and PCR to test for respiratory pathogens in lung aspirate specimens obtained by transthoracic needle aspiration. Their results showed that use of these tests increased the proportion of cases of CAP for which a cause could be established to 83%, from 50% reported when conventional tests—ie, sputum and blood cultures and serological tests—were used. Their results also changed the ranking of pathogens established by conventional testing from *M pneumoniae* (35%), *C pneumoniae* (17%), *S pneumoniae* (17%) to *S pneumoniae* (30%), *M pneumoniae* (22%), *C pneumoniae* (13%).[26] Importantly, *S pneumoniae* represented one third of all causes not documented by conventional testing.

Legionella spp are still a common cause of severe CAP. A review of nine studies of CAP that resulted in admission to an intensive care unit (seven from Europe and one each from USA and South Africa) noted that *Legionella* spp were the second most commonly identified pathogens, with *S pneumoniae* being most often detected.[33] Aerobic gram-negative bacilli, *H influenzae*, and *S aureus* were also identified, although few of these cases could be judged as definite (ie, confirmed bacteraemia or isolation from pleural fluid or lung tissue). In an international collaborative survey of 508 patients with culture-positive legionellosis, 92% of the isolates with serogroup 1 were *L pneumophila*, accounting for 84% of the total. *L pneumophila* serogroup 1 accounted for 88% of isolates in America and Europe but for only 46% in Australia and New Zealand where *L longbeachae* accounted for 30% of cases.[34]

The most common pathogens identified from recent studies of mild (ie, in ambulatory patients) CAP were *S pneumoniae, M pneumoniae, Chlamydia* spp, and viruses (mostly influenza virus).[35,36] *Mycoplasma* spp were most common in patients younger than 50 years and without important comorbid conditions or abnormality of vital signs, whereas *S pneumoniae* was the most common pathogen for older patients or those with significant underlying disease.[36]

An awareness of the likely cause of CAP in different settings is important to allow the start of appropriate antimicrobial treatment. Table 2 shows the most common pathogens associated with CAP as derived from collective results of various studies.[18,19,24–30, 33, 35, 36] Severity of illness is judged by site of care (outpatient *vs* inpatient).

Although objective confirmation is often difficult, multiple organisms that infect a patient concurrently or sequentially can cause CAP.[37,38] For example, influenza A or *C pneumoniae* infection might be followed by a secondary infection with *S pneumoniae*. In one study of patients admitted with serologically diagnosed *C pneumoniae* pneumonia, 45% of patients were infected with other pathogens, the most common copathogen being *S pneumoniae*.[38] The incidence of mixed infection varied from 2 to 11% (table 1). The importance of treating multiple infecting organisms has not been established; however, identification of one pathogen should not preclude tests for other causes when a patient is not responding to treatment.

Outpatients (mild)	Non-ICU inpatients	ICU (severe)
S pneumoniae	*S pneumoniae*	*S pneumoniae*
M pneumoniae	*M pneumoniae*	*Legionella* spp
H influenzae	*C pneumoniae*	*H influenzae*
C pneumoniae	*H influenzae*	Gram-negative bacilli
Respiratory viruses*	*Legionella* spp	*S aureus*
	Aspiration respiratory viruses*	

ICU=Intensive care unit. *Influenza A and B, adenovirus, RSV, parainfluenza. Based on collective data.[18,19,24–30,33,35,36]

Table 2: **Most common causative factor in community-acquired pneumonia by site of care**

Clinical course

In a study of ambulatory patients with CAP, median time to resolution of fever was 3 days; 5 days for myalgia, 6 days for dyspnoea, and 14 days for both cough and fatigue.[39] Symptoms can last even longer in seriously ill patients. Fine and colleagues[32] have noted that 86% of patients had at least one persisting pneumonia-related symptom at 30 days. Patients should be informed that symptoms can last for this long to allow them a better awareness of their illness and expected clinical course.

Death rates associated with CAP have not changed greatly over the past two decades—in part because of the increased number of patients at risk of the disease, such as elderly people and patients with multiple comorbid conditions. In a prospective study[40] of prognostic factors of CAP caused by bacteraemic pneumococcal disease in five countries, death rates ranged from 6% in Canada to 20% in the USA and Spain (13% in the UK and 8% in Sweden). Independent predictors of death were age greater than 65 years, residence in a nursing home, presence of chronic lung disease, high acute physiology and chronic health evaluation (APACHE) score, and need for mechanical ventilation. Disease severity and frequency of underlying conditions were factors that affected outcome. Mortensen and colleagues[41] noted that about half of deaths in patients with CAP were attributable to the worsening of pre-existing conditions.

Diagnosis

Diagnostic evaluation of patients with symptoms suggestive of pneumonia is important for several reasons: the accurate diagnosis of CAP, appropriate assessment of severity of illness, and appropriate use of microbiological analyses to establish the cause of the illness.

Accurate diagnosis of CAP

Adult patients who are immunocompetent should be assessed for pneumonia if they present with symptoms that include cough, sputum production, laboured breathing (including altered breath sounds and rales), or fever. These symptoms are non-specific and might also be present in patients with upper respiratory-tract infections, other lower respiratory-tract infections such as acute bronchitis and chronic bronchitis, and non-infectious diseases—eg, reactive airways disease, atelectasis, congestive heart failure, vasculitis, pulmonary embolism, and malignant disease.

Although guidelines vary with respect to the emphasis placed on obtaining a chest radiograph for ambulatory patients, this study is usually necessary to establish the diagnosis of CAP and to differentiate it from other respiratory illnesses.[42,43] A CAP diagnosis is important to ensure appropriate use of antimicrobial agents, especially since most cases of upper respiratory-tract infection and acute bronchitis are of viral origin and do not merit treatment with antibacterial agents. Spiral CT scans are much more sensitive in detecting pulmonary infiltrates in patients admitted with CAP, but the clinical significance of this finding is unclear.[44]

Illness severity and site of care

A key decision for a clinician is whether to admit a patient with CAP to hospital.[45] The general consensus is that most patients can be safely treated as outpatients.[6] However, selected patients should be admitted if they have special requirements such as the need for close observation, respiratory support, intravenous antibiotics, or other concerns. This decision about whether or not a patient should be admitted might have an effect on the extent of diagnostic testing as well as the choice of empirical antimicrobial treament. The advantages of not admitting patients for CAP are great and include decreased cost, patient preference, and avoidance of iatrogenic complications in hospital.[46,47] For elderly patients in particular, a reduction in immobilisation time (ie, time in a hospital bed) can facilitate better convalescence.

The decision to admit a patient with CAP depends on many variables, including the severity of illness, associated disease, adequacy of home support, and probability of adherence to treatment. Recognised risk factors for increased mortality of patients with CAP include extremes of age, comorbid illnesses such as malignant disease, congestive heart failure, coronary artery disease, alcoholism, abnormality of vital signs, and several laboratory and radiographic findings.[16] The admission decision relies on a clinician's judgment; however, prognostic scoring rules have been developed that provide support for this decision.[15,48,54]

A pneumonia severity of index score, the "pneumonia prediction rule", has been developed from studies of the pneumonia Patient Outcomes Research Team (PORT).[48] The prediction rule stratifies patients to one of five categories with a point system based on several variables after an initial evaluation of three factors: age, presence of comorbid conditions, and vital signs and mental status. This process has been validated as a method for identifying patients at risk of death, which is low for risk classes I–III (0·1–2·8%), intermediate for class IV (8·2–9·3%), and high for class V (27–31%). It is also an effective method for triaging patients and, in particular, for identifying low-risk patients who can be safely treated as outpatients.[49–52] Subsequent recommendations by the pneumonia PORT are that, before calculation of the severity of index score, patients should first be assessed for any pre-existing condition that might compromise the safety of home care, including haemodynamic instability, active co-existing conditions that would necessitate admission, acute hypoxaemia, social or psychiatric problems compromising home care, or the inability to take oral medication.[53]

By contrast, the British Thoracic Society guidelines recommend an assessment of severity based on the presence of "adverse prognostic features".[15] Such adverse features include, age greater than 50 years, coexisting disease, and four additional specific core features, remembered by the acronym CURB: mental Confusion, elevated Urea nitrogen, Respiratory rate greater or equal to 30 breaths per min, and low Blood pressure. Additional adverse prognostic features include hypoxaemia and bilateral or multilobar pulmonary infiltrates on chest radiographs. Patients who have none of the features listed are at low risk of death and do not usually require inpatient care, whereas those who display two or more core adverse prognostic features should be admitted. A scoring method based on this British Thoracic Society assessment has been developed; this system was assessed with use of a compilation of data from three prospective studies of CAP done in the UK, New Zealand, and the Netherlands.[54] A six point score (one point for any of confusion, urea >7 mmol/L, respiratory rate >30, low blood pressure, and age >65 years) enabled patients to be stratified in accordance with risk of death (score 0=0·7% increase in risk of death; 1=2·1%; 2=9·2%; 3=14·5%; ⩾4=40%). This simple scoring system can be used to stratify patients with CAP into different groups for management purposes.

Prediction rules might oversimplify the interpretation of important variables, and, therefore, these scoring systems

and guidelines are meant to contribute to, rather than supersede, clinicians' judgment. Additional limitations of the severity of illness scoring systems include a potential overemphasis on age and the perception by some health-care workers that the systems are not practical for every-day routine patient management.

There are no universally accepted criteria for severe CAP requiring admission to an intensive care unit. One set of variables that has been proposed as a reliable predictor defines severe CAP as the presence of two out of three possible minor criteria (systolic BP <90 mm Hg, multilobar disease, PaO_2/FiO_2 <250), or one of two major criteria (need for mechanical ventilation or septic shock).[9,55] However, an assessment by the pneumonia PORT study group noted that these criteria had only a modest predictive value.[56]

Identification of the causative agent

The use of diagnostic studies to establish the causative agents of CAP is controversial because there is not a rapid, easily done, accurate, cost-effective method to allow immediate results for most patients at the point of service (ie, the initial assessment by a clinician in an office or acute-care setting).[6–9,15,57–60] Nevertheless, there is a good rationale for establishing the causative agent in the disease to allow the selection of antibiotics that permit optimum selection of agents against a specific pathogen and limit the misuse of antibiotics and its consequences, and to identify pathogens associated with notifiable diseases such as Legionnaires' disease or tuberculosis.[6] Despite these good reasons, there is an absence of solid, documented benefit with respect to establishing the causative agent.

Routine microbiological tests are not recommended by most guidelines for patients managed in the community. However, if a patient has purulent sputum, it is reasonable to send a sample to the laboratory for gram stain and culture on the basis that the information could be of use in directing specific treatment if the patient fails to respond to initial empirical treatment.[6]

Investigations that are recommended for patients who require admission include: blood cultures, sputum gram stain and culture, and thoracentesis if pleural fluid is present. About 11% of patients with CAP will have positive blood cultures, more commonly associated with severe illness.[6] Although the usefulness of blood cultures for all patients admitted to hospital is questioned,[61–63] investigators in one study[64] noted that if results of blood cultures were obtained within 24 h of admission, survival rates were improved. The yield of clinically useful information is greater if the culture specimen is collected before antibiotics are administered.[62] The value of routinely doing a sputum gram stain and culture has long been debated.[6–9,15,57,58,65] These tests are limited by the fact that many patients cannot produce a good specimen, patients often receive antimicrobial agents before assessment, and many specimens yield inconclusive results. The validity of the gram stain is related directly to the experience of the interpreter. Indeed, some discrepant findings about the sputum gram stain are presumably explained by the quality of specimens and technical expertise; and when stringent criteria are applied, although the sensitivity drops, the specificity for pneumococcal pneumonia can approach 90%.[65] Sputum culture for other pathogens (ie, *Legionella* spp, fungi, viruses, *Mycobacterium* spp) should be considered to identify unusual pathogens or notifiable diseases. However, because the early administration of treatment is important for the outcome of CAP, an attempt to obtain expectorated sputum should never delay the prompt start of antimicrobial treatment.

Other tests that might be useful in patients admitted to hospital include the urinary antigen assays for *Legionella* spp and *S pneumoniae* and a direct stain (ie, acid-fast) for detection of mycobacterial infections in patients who are in high-risk categories for tuberculosis. The urine antigen assays for *L pneumophila* serogroup 1 (LgUA) and for pneumococcus (SpUA) can be done easily and rapidly. The LgUA has a sensitivity of 70% and a specificity greater than 90% for infections caused by serogroup 1 and should be especially useful in the USA and Europe since about 85% of isolates are serogroup 1.[66,67] Since *Legionella* spp are a common cause of severe CAP, this test should be routinely considered for patients requiring admission to an intensive care unit. An assay approved by the Food and Drug Administration (FDA) for pneumococcal urinary antigen has been assessed in several studies.[68–71] The sensitivity in defining invasive pneumococcal disease in adults is 60–90% with a specificity close to 100%. In one of the largest published studies to date, Gutierrez and colleagues[71] used this assay on concentrated urine samples obtained from 452 adults with CAP. Pneumococcal antigen was detected in 19 (70%) of 27 patients with proven pneumococcal pneumonia. Of the 269 patients who had pneumonia with no pathogen identified, antigen was detected in 69 (26%), which suggests that an important proportion of cases that are presently undiagnosed by standard tests can be identified with this assay. However, 16 (10%) of 156 samples from patients with pneumonia caused by other agents were positive, indicating potential problems with specificity.

Many rapid diagnostic tests such as nucleic acid amplification tests (ie, PCR) assays are still in early stages of development, or are not commonly available, or are not sufficiently accurate.[72–74] The role of these new tools is under investigation and they are not yet in routine use; however, they could offer the potential for rapid diagnosis and have been shown to be useful in clinical situations.[72,74] Serological tests are not usually helpful in the early management of CAP since acute and convalescent concentrations are needed before ascribing the cause of the disease to a specific pathogen.

Percutaneous transthoracic needle aspiration (PTNA) has been advocated as a valuable, safe method to increase the chance of establishing the causative agent in the disease.[75–76] Nevertheless, PTNA or other invasive testing (including bronchoscopy and biopsy) are not routinely recommended for the assessment of patients with CAP.[6] Clinical settings that might warrant the use of such tests include pneumonia in immunocompromised hosts, suspected tuberculosis in the absence of productive cough, selected cases of chronic pneumonia, pneumonia associated with suspected neoplasm or foreign body, suspected *Pneumocystis carinii* pneumonia, some cases in which intubation is required, and suspected conditions which necessitate lung biopsy.

Factors affecting treatment choice

Antimicrobials are the mainstay of treatment for most patients with CAP.[6] Decisions about antimicrobial treatment are guided by factors such as spectrum of activity, pharmacokinetics, efficacy, safety profile, cost, and whether or not a specific pathogen is identified (ie, empirical *vs* pathogen-directed treatment). The emergence of resistant respiratory pathogens, especially drug-resistant strains of *S pneumoniae*, is becoming an important concern that has complicated initial empirical management of CAP.

Drug resistant *S pneumoniae*

Surveillance studies indicate that the prevalence of drug resistant *S pneumoniae* continues to increase worldwide.[77–81] In two recent multinational studies, the worldwide prevalence of penicillin-resistant and macrolide-resistant *S pneumoniae* ranged from 18·2 to 22·1% and from 24·6% to 31·8%, respectively.[80,81] The dominant factor in the emergence of drug resistant *S pneumoniae* in one US study has been human-to-human spread of only a few clonal groups that harbour resistance determinants to multiple classes of antibiotics (including cephalosporins, macrolides, doxycycline, trimethoprim/sulfamethoxazole).[82]

Despite the rapid increase in the prevalence of drug resistant *S pneumoniae*, its clinical relevance in the outcome of CAP remains controversial and depends on the class of antimicrobial agent being considered. Most studies suggest that current levels of β lactam resistance do not usually result in treatment failures for patients with CAP.[83–88] While the present breakpoints for *S pneumoniae* susceptibility to penicillin (≤0·06 μg/mL, susceptible; 0·1–1·0 μg/mL, intermediate susceptibility; ≥2·0 μg/mL, resistant) are relevant for meninigitis, they do not reliably predict clinical outcome for CAP.[5,89] On the basis of established pharmacokinetic and pharmacodynamic principles, adequate drug concentrations in serum and tissue should be achieved with appropriate doses of parenteral β lactams or oral amoxicillin to treat effectively many pneumococcal strains that are thought to be non-susceptible to penicillin by the present criteria.[5,89] Furthermore, an analysis of nine controlled trials of a high-dose oral formulation of amoxicillin-clavulanate noted a good clinical response for respiratory infections (mostly outpatients) caused by *S pneumoniae* with penicillin minimal inhibitory concentrations (MIC) up to 8 μg/mL.[90]

Although most studies have not shown an adverse effect of β lactam resistance on the outcome of pneumococcal pneumonia, most clinicians remain concerned that clinical failures will become more frequent if the proportion of resistance strains and their MICs increase. Moreover, in controlled studies of pneumococcal bacteraemia, Feikin and colleagues[91] noted an increased risk of death in patients with high-level resistance (penicillin MIC ≥4 μg/mL) and Metlay and colleagues[92] showed an increase risk of suppurative complications for non-susceptible infections. Risk factors for penicillin-resistant *S pneumoniae* have been identified (ie, age <2 years or >65 years, β lactam treatment within 3 months, alcoholism, medical comorbidities, immunosuppressive illness or treatment, and exposure to a child in a day-care centre.[93]

The clinical relevance of macrolide resistant *S pneumoniae* might be dependent on the type of resistance expressed by a particular strain. The most common mechanisms of resistance include methylation of a ribosomal target encoded by *erm* gene and efflux of the macrolides by cell membrane protein transporter, encoded by *mef* gene.[94] *S pneumoniae* strains with *mef* are resistant at a lower level (with MICs usually 1–16 μg/mL) than *erm*-resistant strains; and it is possible that such strains (especially with MIC<8 μg/mL) might be inhibited if sufficiently high concentrations of macrolide can be obtained within infected tissue (such as could arise with newer macrolides-clarithromycin or azithromycin).[96–99] However, there is recent evidence that the MICs of these strains are increasing and this could affect the effectiveness of these macrolides.[100] The "*mef*-resistant" strains are usually susceptible to clindamycin. Most *erm*-resistant isolates have an MIC greater than 32 μg/mL for erythromycin and are thought to be highly resistant to all macrolides and clindamycin. Until recently, reports of failure of CAP treated with macrolides have been rare, particularly for patients at low risk of drug-resistant strains. However, since 2000, anecdotal reports and one controlled study have documented failures attributable to macrolide-resistant *S pneumoniae* in patients treated with an oral macrolide who have subsequently required admission with *S pneumoniae* bacteraemia.[101–04] Currently, *mef*-associated resistance predominates in North America. *erm*-associated resistance predominates in Europe and is common in Japan.[105]

Although the worldwide prevalence of pneumococcal resistance to the newer fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) remains low (fewer than 2% of cases), in some countries resistance has increased substantially.[106–08] The overall prevalence of fluoroquinolone resistance (levofloxacin >4 μg/mL) in Hong Kong in 2000 had increased to 13·3% because of the dissemination of a fluoroquinolone-resistant clone.[107] Treatment failures have already been reported, most often in patients who have previously been treated with fluoroquinolones.[109,110] Risk factors for levofloxacin resistance were identified as previous exposure to a fluoroquinolone, residence in a nursing home, nosocomial infection, and chronic obstructive pulmonary disease.[111]

In view of the emerging resistance of the pneumococcus to existing drugs, alternative agents need to be considered. Although glycopeptides (ie, vancomycin, teicoplanin) are almost certain to provide antibiotic coverage for drug resistant *S pneumoniae*, they are not active against other key respiratory pathogens (ie, atypicals, *H influenzae*) and there is a strong reason not to use these drugs until needed because of fear of emergence of other resistant organisms such as vancomycin-resistant enterococci, vancomycin resistant *S aureus*. Other agents effective against drug-resistant *S pneumoniae* include quinupristin/dalfopristin, linezolid, and the ketolides. The focus of treatment of quinupristin/dalfopristin and linezolid is more for nosocomial infections (and especially for vancomycin-resistant enterococci or macrolide-resistant *S pneumoniae*). The ketolides (*telithromycin* is the first to be marketed) are a novel addition to the macrolide group of antibacterials and have an efficacy against key respiratory pathogens (including penicillin-resistant and erythromycin-resistant strains).[112]

Empirical antimicrobial treatment

Until rapid diagnostic methods improve, most patients will be treated empirically. Although some authorities propose a syndromic approach to treatment (ie, counting on the predictability of a causative agent based on the presenting clinical manifestations), most data indicate that the presenting clinical features are not specific enough to predict reliably the causative agent of CAP.[6–9,15] Thus, unless there is a specific epidemiological factor (such as an influenza epidemic), the empirical approach to initial therapy is usually based on the likelihood that one of the key pathogens is responsible for disease. Specific recommendations for empirical therapy for CAP as included in recently published guidelines from North America, UK, and Japan are shown in table 3.

Several observational studies have assessed the effect of empirical antimicrobial regimens on patients' outcomes. Although limited by their retrospective design, these studies show that use of macrolides as part of an initial combination treatment (usually with a cephalosporin agent) or monotherapy with a fluoroquinolone for

	Outpatient	Non-ICU inpatient	ICU (severe)
North American Guidelines (synthesis from IDSA, Canadian guidelines,† CDC, 2000; American Thoracic Society 2001)[5–9]	If no significant risks for DRSP*: Macrolide or doxycycline If risks for DRSP*: Antipneumococcal fluoroquinolone§ or High-dose amoxicillin (3 g/day) or amoxicillin/clavulanate plus macrolide (if amoxicillin is used and there is a concern for H influenzae, use agent active for β lactamase producing strains‡	β lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam) plus macrolide‡ (can use doxycycline if macrolide not tolerated) or Antipneumococcal fluoroquinolone§ alone	β lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam, piperacillin/tazobactam) plus macrolide‡ or fluoroquinolone§ (if β lactam allergy, use fluoroquinolone§ plus clindamycin) In the case of structural lung disease: antipseudomonal agent (piperacillin/tazobactam, carbapenem, or cefepime) plus antipseudomonal fluoroquinolone (high dose ciprofloxacin or levofloxacin)
Japanese Respiratory Society (2000)[12]	(Specified as mild or moderate pneumonia) When bacterial pneumonia suspected: a penicillin type (with a β lactamase inhibitor (orally), or penicillin type (injection) Or cepham type drug When atypical pneumonia suspected: macrolide or tetracycline	(Specified as severe pneumonia) For younger patients without underlying illness: injection use fluoroquinolone For elderly or underlying illness: Carbapenem plus [tetracycline or macrolide]; or third generation ceph plus clindamycin plus [tetracycline or macrolide]	Not specified Consider as for other inpatients, for elderly, or underlying illness
British Thoracic Society (2001)[15]	Amoxicillin 500–1000 mg thrice daily (alternatively, erythromycin or clarithromycin)	If admitted for non-clinical reasons or previously untreated in the community: Amoxicillin (macrolide as alternative). If admitted for pneumonia and oral therapy appropriate: amoxicillin plus [erythromycin or clarithromycin]; (alternative–antipneum fluoroquinolone) If parenteral appropriate: (ampicillin or benzylpenicillin) plus (erythromycin or clarithromycin) (alternative–IV levofloxacin)	(Defined as severe) Co-amoxiclav or 2nd/3rd generation cephalosporin plus [iv erythro or clarithro, +/- rifampicin] (Fluoroquinolone with enhanced pneumococcal activity plus benzylpenicillin as alternative)

ICU= intensive care unit. DRSP=drug resistant *S pneumoniae*. *β lactam treatment within the past 3 months, admission within the past month, alcoholism, immune-suppressive illness (including treatment with corticosteroids), medical comorbidities, exposure to a child in a day-care centre. †Canadian Infectious Disease Society and Canadian Thoracic Society. ‡If chronic obstructive pulmonary disease, use a macrolide active against β lactamase producing *H influenzae* (ie, azithromycin, clarithromycin). §Gatifloxacin, levofloxacin, moxifloxacin.

Table 3: **Comparison of recommendations of guidelines for empirical antimicrobial therapy of community-acquired pneumonia in adults**

patients who require admission seems to be associated with decreased risk of death or a shorter hospital stay than with a cephalosporin alone.[113–16] The specific causative agent of infection was not estalished in these studies; however, it is possible that the added coverage for atypical pathogens might, in part, explain this observation. Results of additional retrospective studies suggest that the benefit of combination therapy that includes a macrolide applies not only to CAP in general but also to CAP specifically associated with *S pneumoniae* bacteraemia.[117,118] The possible coexistence of atypical pathogens or the immunomodulating effect of the macrolides might, in part, be responsible for this finding. However, interpretation of these studies is subject to limitations inherent in their retrospective study design; and, since they only assessed empirical treatment, the findings are not necessarily applicable for pathogen-directed treatment that usually is started 24–48 h after initial therapy.[119]

Recommendations for empirical therapy of outpatients

North American guidelines variably recommend macrolides, doxycycline, an antipneumococcal fluoroquinolone (eg, levofloxacin, gatifloxacin, moxifloxacin), or the combination of a β lactam plus macrolide as treatment options for patients who are mildly ill and can be treated as outpatients.[5–9] In general, the North American guidelines recommend a macrolide as first-line treatment for outpatients with no comorbidity or risk factors for drug-resistant *S pneumoniae*. The rationale is that the macrolides provide effective therapy for the most common bacterial pathogens for such patients, primarily *S pneumoniae* (that has, until now, been mostly responsive to macrolide in North America) as well as the atypical organisms (especially *M pneumoniae* and *C pneumoniae*, which are common in outpatients). The positioning of the macrolides as prominent first-line agents in the North American guidelines is partly based on the presumption that the newer macrolides (azithromycin or clarithromycin) can be effective against macrolide-resistant *S pneumoniae* strains in which lower-level resistance results from increased drug efflux with resulting MIC often less than 8 μg/mL. However, because recent data indicate that *mef*-mediated resistance is becoming associated with higher MICs (from a median of 4 μg/mL to 8 μg/mL), it is reasonable to consider alternative treatment (ie, "respiratory fluoroquinolone", or high dose amoxicillin plus macrolide) if risk factors for drug-resistant *S pneumoniae* are present. The Centers for Disease Control and Prevention (CDC) statement emphasises that the fluoroquinolones should be reserved for cases associated with failure, or allergy to other agents, or documented drug-resistant *S pneumoniae*.[5] The rationale is that widespread use would lead to the development of fluoroquinolone resistance in the respiratory pathogens (as well as other pathogens colonising the treated patients).

By contrast, the primary agents recommended in the recently published British Thoracic Society guidelines are β lactams—mostly penicillins—and not macrolides.[15] The rationale is that these agents are effective against *S pneumoniae,* and when given in high doses they are even effective for most strains with decreased sensitivity to penicillin. Since most of the macrolide resistance in Europe is *erm*-mediated, high-level resistance, the macrolides are not regarded as optimum first line empirical agents to treat this pathogen if *S pneumoniae* is

likely. Additionally, the British statement places less importance on the need to treat the atypical pathogens empirically in ambulatory patients (mild disease). Rather, the statement suggests that since *M pneumoniae* exhibits epidemic periodicity every 4–5 years and chiefly affects younger people, a policy for initial empirical treatment that aims always to cover this pathogen was unnecessary.

The two approaches represented by the North American and the British Thoracic Society statements differ because of the greater emphasis in North America to treat routinely the atypical pathogens and the fact that macrolide-resistant *S pneumoniae* in Europe is of higher level resistance than in North America. Future studies are needed to address the issue of whether routine treatment should be able to treat atypical pathogens. The Japanese statement advocates initial therapy based on a syndromic approach (ie, macrolides or tetracycline for likely atypical pneumonia and a penicillin-type agent for bacterial pneumonia).[12]

Recommendations for empirical therapy of inpatients

North American guidelines recommend treatment with a β lactam plus a macrolide or monotherapy with a fluoroquinolone for patients admitted to the general ward (in part, because of results showing that these regimens are associated with a substantial reduction in deaths compared with that noted with cephalosporin alone).[5–9,113–16] Recommendations in the British Thoracic Society guidelines are similar to those from North America. Workers from two recent studies in Europe noted that most patients who were admitted with CAP were successfully treated with penicillin alone.[120–21] The Japanese statement stratifies patients on the basis of age and the presence of underlying illness, with an injected fluoroquinolone being recommended for the first category and a combination regimen for the second category.

For patients with severe CAP who require admission to an intensive care unit, all guidelines recommend comprehensive antimicrobial therapy to cover *S pneumoniae* (including drug-resistant *S pneumoniae*), *Legionella* spp and the possibility of *Pseudomonas* spp. Australian guidelines advocate empirical therapy for *Burkholderia pseudomallei* for patients in tropical areas, acknowledging the relevant local pathogens.[11]

Pathogen-directed therapy

Treatment options are obviously simplified if the causative agent is established or strongly suspected (table 4). Diagnostic procedures that provide identification of a specific cause within 24–72 h can still be useful for guiding continued treatment. If, for example, an appropriate culture shows the isolation of penicillin-susceptible *S pneumoniae*, treatment can be specified by selecting a narrow spectrum agent (such as penicillin or amoxicillin), which will hopefully reduce the selective pressure for resistance. This information is often available at the time for consideration when the patient is switched from parenteral to oral therapy.

Length and route of antimicrobial treatment

There are no controlled trials that have specifically assessed the optimum duration of anitmicrobial treatment in CAP. The decision is usually based on the causative pathogen, response to treatment, comorbid illness, and complications. Until further data are available, it seems reasonable to treat bacterial infections such as those caused by *S pneumoniae* until a patient is afebrile for 72 h.[6] Most randomised clinical trials for the new fluoroquinolones or newer macrolides have shown good outcomes with 7–10 days of treatment, and shorter courses could even be possible with the use of these agents (azithromycin could be used for shorter courses of treatment in ambulatory patients because of its longer half-life in tissue).

For many pathogens, there is no clear advantage of intravenous therapy over oral therapy; however, for most patients admitted to hospital the common practice is to begin therapy with intravenous drugs. Changing from intravenous to oral therapy when the patient is clinically stable or improving and is able to ingest drug is associated

Organism	Preferred antimicrobials	Alternative antimicrobials
S pneumoniae (MIC <2 μg/mL)	Pencillin G; amoxicillin	Macrolide;* telithromycin cephalosporins (oral-cefpodoxime; cefdinir; cefprozil; cefuroxime, cefditoren; parenteral-cefuroxime, ceftriaxone, cefotaxime); clindamycin; doxycyline; fluoroquinolone†
S pneumoniae (MIC ⩾2 μg/mL)	Agents based on susceptibility tests, including cefotaxime, ceftriaxone, fluoroquinolone† telithromycin (orally, for mild infections)	Vancomycin; linezolid; (high dose amoxicillin, 3 g/day,should be effective for strains with MIC 2–4 μg/mL)
H influenzae	Non-β lactamase producing: amoxicillin β lactamase producing: second or third generation cephalosporin; amoxicillin/clavulanate	Fluoroquinolone; doxycycline; azithromycin; clarithromycin‡
M pneumoniae/ C pneumoniae	Macrolide; a tetracycline	Fluoroquinolone†
Legionella spp	Fluoroquinolone;§ azithromycin, clarithromycin	Doxycycline
C psittaci	A tetracycline	Macrolide
Cox burnetii	A tetracycline	Macrolide
Enterobacteriaceae	Third generation cephalosporin; carbapenem	β lactam β lactamase inhibitor¶; fluoroquinolone
P aeruginosa	Aminoglycoside plus antipseudomonal β lactam‖	Aminoglycoside plus ciprofloxacin; ciprofloxacin or high dose levofloxacin** plus antipseudomonal β lactam
Methicillin susceptible *S aureus*	Anti-staph penicillin††	Cefazolin; clindamycin
Methicillin resistant *S aureus*	Vancomycin	Teicoplanin; linezolid
Anaerobe (aspiration)	β lactam β lactamase inhibitor¶; clindamycin	Carbapenem‡‡
Influenza	Amantadine or rimantadine (influenza A); oseltamivir or zanamivir (influenza A or B)	

Based on recommendations from IDSA and British Thoracic Society guidelines (choices should be modified based on susceptibility tests results and advice from local specialists. Refer to local references for appropriate doses). *Strains with reduced susceptibility to penicillin should have verified in-vitro susceptibility. †Levofloxacin, gatifloxacin, moxifloxacin (not a first-line choice for penicillin susceptible strains); ciprofloxacin is appropriate for Legionella, and most gram-negative bacilli (including *H influenza*). ‡Azithromycin more active in vitro than clarithromycin for *H influenza*. §Author's preference. ¶ticarcillin/clavulanate; piperacillin/tazobactam for gram-negative bacilli; ampicillin/sulbactam or amoxicillin/clavulanate appropriate for oral anaerobes. ‖ticarcillin, piperacillin, ceftazidime; cefepime, aztreonam, imipenem, meropenem. **750 mg one daily. ††nafcillin, oxacillin flucloxacillin. ‡‡imipenem/cilastatin; meropenem; ertapenem.

Table 4: **Recommended antimicrobial therapy for specific pathogens**

Process of care	Process-outcome link
Hospital admission decision[47–50,132]	Admission of low-risk patients associated with unnecessary cost and diminished patient satisfaction
Timing of initial antibiotics[64,128]	Earlier administration associated with improved survival
Choice of antibiotic therapy[132–135]	If according to guidelines, associated with better outcome
Switch to oral therapy[124,125,132]	Associated with decrease length of time in hospital and cost. Appropriate even for Strep pneumoniae bacteraemia
Discharge criteria[127,131,132]	Associated with decrease cost and readmission rates
Use of critical pathway[130–134,136]	Decrease number of patients admitted to hospital, duration of admission, and mortality

Modified from Metersky.[122]

Table 5: **Selected CAP processes of care-outcome link**

with several economic, care, and social benefits.[122,123] This approach has been shown to be appropriate, even for patients with pneumococcal bacteraemia.[124] Most patients can be safely discharged without inhospital observation after switch to oral treatment.[125,126] Ideally, parenteral drugs should be given in an oral formulation with adequate bioavailability; if no oral formulation is available, then an oral agent with a similar spectrum of activity should be selected on the basis of in vitro or predicted susceptibility patterns of the established or probable pathogen.

Processes of care (quality indicators)

Many studies have assessed processes of care—ie, interventions undertaken to assess, diagnose, or treat—with the clinical outcome of patients (table 5). In a meta-analysis from a structured review of 4531 published reports, Rhew[127] identified several quality indicators that were judged to be valid on the basis of published evidence or professional consensus and that were associated with a beneficial effect on outcome in elderly patients with CAP. These indicators were: use of pneumococcal and influenza vaccines (for prevention of CAP); administration of antimicrobials in a timely matter (within 8 h of arrival at the hospital); advice to cease smoking for patients who smoke; drainage of a pleural empyema; conversion from parenteral to oral antimicrobial treatment when the patient is improving, haemodynamically stable, and able to take oral medications; and use of appropriate discharge criteria (ensuring that patients are clinically stable at the time of release from hospital).[127] Whereas the studies reviewed by Rhew supported 8 h as the target time for appropriate initiation of antimicrobial agents, more recent data have shown that starting therapy within 4 h was associated with better outcomes for patients who needed to be admitted.[128] Although one study of CAP patients who were admitted to academic medical centers did not show a benefit of many of these indicators, implementation of a pneumonia practice guideline that promote some or all of these quality indicators has been shown in many other studies to be associated with better outcomes (including a reduced risk of death).[129—34]

Prevention of CAP

Despite controversies over efficacy of the polysaccharide pneumococcal vaccine (PPV), both this vaccine and the influenza vaccines are recommended in current guidelines by the CDC.[137,138] In a meta-analysis of 14 trials that included more than 48 000 patients, polysaccharide pneumococcal vaccine prevented definite pneumonia by 71% and mortality by 32% (but not all-cause death).[139] However, this vaccine has not been consistently effective in controlled trials in elderly patients. An important advance has been the development and licensure of the pneumococcal conjugate vaccine in infants which not only reduces serious pneumococcal infections in children but also the colonisation of vaccine strains.[140,141] Although the benefits of this vaccine have yet to be directly proven in clinical trials in adults, its use in children has been shown to reduce the rate of pneumococcal disease in adults.[140] This reduction is probably due to decreased transmission of pneumococci from children; and thus could provide an effective method for reducing disease caused by drug-resistant strains.

Future challenges

CAP will continue to represent an important threat to patients in the future as the number of patients at risk (elderly people and those with comorbid conditions) increase. Accucrate and rapid diagnostic methods to define causative pathogens are needed to allow more specific, directed therapy. If the specific causative pathogen is known, it seems reasonable to presume that patients will respond better and that antibiotics could be used more appropriately; but studies to assess this approach are needed. Although not discussed in this review, a greater understanding of the pathogenesis and host response should lead to new approaches to treatment. As the complexities of the host response are revealed, therapeutic benefits are likely to be realised. The optimum approach to management will need to be constantly reassessed as new information is generated.

Conflict of interest statement

T M File has received research grants from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, GlaxoSmithKline, Merck, Ortho-McNeil, and Pfizer; he has served as a consultant for Abbott, Aventis, Bayer, Glaxo Smith Kline, Merck, Ortho-McNeil, Pfizer, and Wyeth.

Acknowledgments

I thank James Tan for his critical review of the manuscript.

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