Recent changes in the management of community acquired pneumonia in adults

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In 1901 William Osler described pneumonia as the “captain of the men of death.”¹ Mortality has altered little since penicillin became routinely available, and community acquired pneumonia remains a leading cause of mortality worldwide.² Here, we review studies published in the past two years and focus on changes in the aetiology, stratification of severity, and antimicrobial management of community acquired pneumonia in adults.

What is community acquired pneumonia and how is it diagnosed?

The British Thoracic Society (BTS) defines community acquired pneumonia as the presence of symptoms and signs consistent with acute lower respiratory tract infection, in association with new radiographic shadowing (figure) for which there is no alternative explanation, which is managed as pneumonia and is the main reason for seeking healthcare advice.³ This definition may not be useful, however, when radiology is not easily accessible. A review of studies that used clinical definitions based on symptoms and signs found these alternative definitions to be inferior to radiography in detecting pneumonia.³

How common is community acquired pneumonia?

The annual incidence of community acquired pneumonia in the United Kingdom is 5-11 cases per 1000 adult population.⁴ Incidence data cannot be extrapolated to other populations because health care varies greatly worldwide. The incidence of the disease varies

with age, being higher in very young children and elderly people.⁵

What organisms cause community acquired pneumonia?

Data from a prospective observational study in a UK teaching hospital show that a microbiological diagnosis can be made in 75% of cases.⁶ In real life practice, outside clinical trials, the rate of microbiological diagnosis is much lower, around 10-20%. The most common causative organism worldwide is *Streptococcus pneumoniae*. The incidence of less common organisms is variable and depends upon geography, healthcare setting, and the availability of suitable diagnostic tests. Box 1 shows the most common organisms in order of incidence and this subject has been extensively reviewed elsewhere.⁷

Atypical pneumonia refers to pneumonia caused by organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. A recent retrospective observational study based on data obtained as part of drug trials from 4337 patients in 21 countries found that the organism was an atypical one in 22% of cases of community acquired pneumonia where an organism was identified, which suggests that these organisms may be more common than previously thought.⁸

How has the aetiology of community acquired pneumonia changed?

Although no evidence of major changes in the aetiology of community acquired pneumonia has been seen worldwide, new strains of previously identified organisms have emerged that may, in future, have global implications.

Pneumococcal vaccination

In 2000, a heptavalent conjugate pneumococcus vaccine was licensed in the United States. The vaccine was recommended for all children under 2 years and some older children with “high risk” conditions. Take-up of the vaccine in the US by 2004 was around 73%.⁹

Sources and selection criteria

We searched Medline with the phrase “((community acquired pneumonia [title]) not (infant* or neonat* or child*))” and restricted the search to articles published in English in the previous two years. We identified 149 articles, the titles of which we reviewed to identify major themes. Where necessary we made additional searches based on the themes highlighted by the initial search. We then used this information to prepare a brief review of the sections with which we were most familiar.

Box 1 Common causes of community acquired pneumonia treated in different healthcare settings in order of incidence⁷**Outpatients**

Streptococcus pneumoniae
Mycoplasma pneumoniae
Haemophilus influenzae
Chlamydia pneumoniae
 Respiratory viruses

Inpatients

Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydia pneumoniae
Haemophilus influenzae
Legionella spp
 Respiratory viruses

Intensive care unit

Streptococcus pneumoniae
Legionella spp
Haemophilus influenzae
 Gram negative bacilli
Staphylococcus aureus

Invasive pneumococcal disease in vaccinated and unvaccinated children and adults decreased between 1999 and 2004 (from 3485 cases in 1999 to 1930 in 2004). The decrease in unvaccinated people suggested that children were a major reservoir for the disease and that herd immunity may be important in this condition. Rates of non-sensitivity to antibiotics in serotypes covered by the vaccine also fell, but the incidence of non-vaccine serotypes increased (“disease replacement”), particularly penicillin non-sensitive strains, which rose by 312%.⁹ Furthermore, new “vaccine escape recombinants” have been reported since the introduction of immunisation.¹⁰ The increase in the incidence of non-vaccine strains, their increased antibiotic resistance, and the emergence of recombinants may mean that the heptavalent vaccine is little more than a holding mechanisms in our fight against this deadly infection. It remains to be seen whether these experiences will be replicated in other countries where the vaccine has been introduced, such as the UK, which

introduced routine vaccination of all children under 2 years in 2006. The incidence of pneumococcal penicillin non-sensitivity in the UK peaked in 2000 at 6.7%; rates have declined since and are currently relatively static at around 3%.¹¹

Community acquired MRSA

The emergence of community acquired methicillin resistant *Staphylococcus aureus* (MRSA)—as distinct from hospital strains—has been reported in Australasia, Europe, and North America.¹² Community acquired MRSA is a rare cause of pneumonia but a more common cause of skin and soft tissue infection. Most strains produce the Paton-Valentine leucocidin, which probably confers the ability to cause severe necrotising pneumonia. In the 2003-4 influenza season, the Centers for Disease Control and Prevention (CDC) received reports of 15 cases of pneumonia as a result of community acquired MRSA associated with influenza. The median age of the patients, four of whom died, was 21 years, and most of them had no comorbidities or risk factors for MRSA.¹² Few such cases were reported during the next two influenza seasons, but in December 2006 and January 2007 the CDC received reports of 10 cases of pneumonia caused by community acquired

Table 1 | Guidelines for initial empirical treatment of adults with community acquired pneumonia treated in the community

Preferred treatment	Alternative treatment
British Thoracic Society guidelines	
Oral amoxicillin	Oral erythromycin or clarithromycin
American Thoracic Society guidelines	
No comorbidities:	
Oral azithromycin, clarithromycin, or erythromycin	Oral doxycycline
Comorbidities present:	
Oral moxifloxacin, gemifloxacin, or levofloxacin	Oral amoxicillin plus a macrolide

Posterior-anterior (top) and lateral (bottom) chest radiographs showing right upper lobe consolidation in a patient with community acquired pneumonia

UNANSWERED QUESTIONS

Should antibiotics be given within four hours of the patient's admission to hospital or once a diagnosis has been confirmed?

Could severity scores help determine which patients should be treated early and empirically and which could be treated later once a definitive diagnosis has been made?

What is the optimal length of antibiotic treatment in community acquired pneumonia?

Does stratifying patients into "at risk" groups actually improve patient outcome?

Have non-vaccine pneumococcal serotypes increase in the UK, as in the US, since the introduction of the pneumococcal vaccine?

How effective is the CRB-65 score (measuring confusion, respiratory rate, and blood pressure) in general practice?

MRSA in Louisiana and Georgia; six of the patients died. On this occasion a short interval occurred between the development of respiratory symptoms and the detection of disease. Four of the patients died within four days of symptoms starting; this suggests that rather than pneumonia occurring after infection with influenza, concomitant infection was more likely.¹³

Although community acquired MRSA is rare in Europe, with the exception of certain geographical hotspots, close attention should be paid to the emergence of this pathogen, especially because rates of colonisation and infection with community acquired MRSA, particularly soft tissue infections, seem to be increasing.¹²

Which antibiotics should be used to treat community acquired pneumonia?

Existing guidelines cover the most common organisms that cause pneumonia and their antibiotic susceptibility, in the community and in hospital.^{14,15} Because confirmation of the organism responsible is often delayed, antibiotics are started empirically. BTS guidelines for hospital patients with non-severe community acquired pneumonia suggest using amoxicillin and a macrolide to cover both "typical" and "atypical" organisms; the American Thoracic Society (ATS) suggests the use of a fluoroquinolone (tables 1 and 2). However, a recent worldwide meta-analysis of patients with non-severe

community acquired pneumonia found no evidence for the empirical use of antibiotics active against atypical pathogens and recommended sole use of beta-lactam antibiotics in non-severe pneumonia.¹⁶ The authors suggest that the incidence of *Legionella* pneumonia is less than 3%, but a more recent retrospective epidemiological study suggests that the incidence in Europe is much higher (9%), supporting the BTS policy of covering atypical organisms in non-severe community acquired pneumonia treated in hospital.⁸ ATS guidelines also suggest the addition of vancomycin or linezolid for community acquired MRSA.¹⁵

Local antibiotic policies are usually based on an interpretation of the national guidelines, taking into account local pathogen prevalences, local resistance rates, and local incidences of side effects, such as infection with *Clostridium difficile*.

How quickly should we give antibiotics?

It seems logical that antibiotics should be given early—and guidelines recommend this—^{14,15} but there has been recent controversy over whether this may reduce diagnostic accuracy. Evidence in favour of the rapid delivery of antibiotics comes from a review of the US Medicare database in 2004.¹⁷ This showed reduced in-hospital mortality, 30 day mortality, and length of hospital stay in patients (>65 years old) given their first dose of antibiotics within four hours. Although a prospective cohort study from the US also found that a delay in giving the first dose of antibiotic of more than four hours was associated with increased mortality, it also found however that altered mental state, absence of fever and hypoxia, and increasing age were independently associated with such a delay.¹⁸ After adjusting for these factors, the association between delayed time to first dose of antibiotic and mortality was no longer statistically significant. This suggests that time to first dose of antibiotic is a marker of comorbidities associated with confounding factors linked to an atypical presentation and increased risk of mortality, rather than being a direct contributor to outcome.

An audit of patients before and after implementation of guidelines to give the first dose of antibiotic within four hours of admission in patients with community acquired pneumonia found that significantly more patients were given an admission diagnosis of community acquired pneumonia and their first antibiotic within four hours of admission after implementation.¹⁹ However, a large proportion of these patients were not classified as having pneumonia at discharge, suggesting that guideline implementation led to more patients being incorrectly diagnosed with pneumonia and receiving antibiotics inappropriately. This is a problem given concerns about the side effects of antibiotics and increasing resistance rates. The earlier BTS recommendation was that, if a patient is admitted to hospital with community acquired pneumonia, the first dose of antibiotic should be given within two hours of admission, or immediately by the general practitioner if the condition is life threatening or delays in treatment are anticipated.¹⁴ The ATS advocated that the first dose

Table 2 | Guidelines for initial empirical treatment of adults with community acquired pneumonia treated in hospital

Preferred treatment	Alternative treatment
British Thoracic Society guidelines	
Non-severe disease:	
Oral amoxicillin plus erythromycin or clarithromycin	Oral moxifloxacin or levofloxacin
Severe disease:	
Intravenous co-amoxiclav or cefuroxime or cefotaxime plus erythromycin or clarithromycin	Intravenous levofloxacin plus benzylpenicillin
American Thoracic Society guidelines	
Non-intensive care unit:	
Oral or intravenous fluoroquinolone	Oral or intravenous cefotaxime, ceftriaxone, or ampicillin plus erythromycin or clarithromycin
Intensive care unit:	
Intravenous cefotaxime, ceftriaxone, or ampicillin-sulbactam plus either azithromycin or fluoroquinolone	

Box 2 CURB-65 severity score¹⁴**Method**

Score 1 point for each of following features that are present:

- Confusion (mental test score ≤ 8 new disorientation in person, place or time)
- Urea > 7 mmol/l
- Respiratory rate ≥ 30 breaths/min
- Blood pressure (systolic < 90 mm Hg, or diastolic ≤ 60 mm Hg)
- Age ≥ 65 years

Interpretation of CURB-65 score

- 0-1: Probably suitable for home treatment; low risk of death
- 2: Consider hospital supervised treatment
- ≥ 3 : Manage in hospital as severe pneumonia; high risk of death

should be given while the patient is still in the emergency department.¹⁵ It will be interesting to see whether future BTS and ATS guidelines will advocate more diagnostic certainty before the first dose of antibiotic is given.

Length of antibiotic treatment

With increasing rates of antibiotic resistance attention has turned to reducing the length of antibiotic courses. ATS guidelines suggest a minimum of five days for uncomplicated community acquired pneumonia, whereas BTS guidelines suggest at least seven days for patients managed in the community and 10 days for patients with severe disease.^{14,15} A recent meta-analysis of randomised controlled trials comparing short course regimen (< 7 days) with extended course regimens (> 7 days) found no significant difference between the two approaches in mild to moderate pneumonia with regard to clinical success, mortality, bacteriological success, and adverse events.²⁰ In addition, a randomised double blind controlled trial in adults admitted to hospital with mild-moderate pneumonia found that stopping amoxicillin after three days in patients who had greatly improved was not inferior to continuing treatment for eight days.²¹ Furthermore, a multicentre, randomised controlled trial from the Netherlands found that an early (after three days) switch from intravenous to oral antibiotics in patients with severe community acquired pneumonia was safe and reduced length of hospital stay by two days.²² Although recent studies suggest that short course therapy is as efficacious as the longer courses currently recommended by guidelines, ultimately the decision to stop antibiotics should depend upon clinical judgment and the patient's response to treatment.

Severity scores

A prospective cohort study has shown that clinicians overestimate the risk of death in patients with community acquired pneumonia and this leads to unnecessary admissions to hospital.²³ Severity scoring systems were designed to stratify patients in terms of mortality and to aid decisions about hospital admission. Major differences exist between the severity scoring systems recommended in Europe (CURB-65)²⁴ and in the US

(pneumonia severity index).^{24,25} The BTS advocates the use of the CURB-65 score,¹⁴ which was designed to identify patients with severe pneumonia, whereas the pneumonia severity index identifies patients at low risk.

CURB-65 is a simple six point scale—one point for each of confusion, urea > 7 mmol/l, respiratory rate ≥ 30 /min, low systolic (≤ 90 mm Hg) or diastolic (≤ 60 mm Hg) blood pressure, and age ≥ 65 years (box 2). Patients are stratified into three groups. Those with a score ≥ 3 are at high risk of death and should be managed as having severe pneumonia. Those with a score of 2 should be considered for hospital admission or supervised outpatient care, and those with a score of 0 or 1 are at low risk of death and may be suitable for home treatment. Notably, this severity score does not take into account comorbidities or the extent of the pneumonia. Although the score is easy to calculate, the CRB-65 score might be more useful in the community because blood urea does not need to be measured. In a large, prospective observational study conducted in Hong Kong, CRB-65 performed as well as CURB-65 in terms of predicting 30 day mortality in patients admitted to hospital.²⁶ A large multicentre prospective study of inpatients and outpatients with community acquired pneumonia also concluded that both severity scores were equally good at predicting death.²⁷ Future studies should take place solely in the community, where such a severity score could have a major effect on the management of patients with community acquired pneumonia.

The Infectious Diseases Society and ATS consensus guidelines on the management of community acquired pneumonia advocate the use of the pneumonia severity index over CURB-65, because this index is more extensively validated. The pneumonia severity index is difficult to calculate, however, because it is based on more than 20 variables including laboratory and radiological tests. Patients are assigned into five risk classes. Patients in classes 1 and 2 are defined as low risk and potential candidates for outpatient treatment. Patients in class 3 should be admitted to hospital for a short while and be treated on an observation unit, and patients in high risk groups 4 and 5 should be treated in hospital. The index is heavily weighted towards age and comorbidities, and it can underestimate the severity of illness in young otherwise healthy patients. Recently, two prospective studies, from Australia and Hong Kong, compared the ability of CURB-65 and the pneumonia severity index to predict the severity of community

Tips for non-specialists

Keep up to date with your local policy on antibiotics because it may change to reflect variations in disease susceptibility in the local population

Consider MRSA community acquired pneumonia during the influenza season and in cases of severe bilateral cavitating pneumonia

Severity scores—although helpful—are not a substitute for clinical acumen, and all cases that cause concern should be referred for further investigation

SUMMARY POINTS

Mortality from community acquired pneumonia has altered little since penicillin became routinely available

Ongoing vigilance for emerging pathogens is of key importance

Policies on the use of antibiotics should reflect the prevalence of pathogens in the local area, rates of antibiotic resistance, and the incidence of side effects of antibiotics (such as infection with *Clostridium difficile*)

acquired pneumonia and found no significant difference between the two scoring systems.^{26,28} However, a prospective study from the US found that the pneumonia severity index had a significantly higher discriminatory power for predicting 30 day mortality than CURB-65.²⁹

Although the two sets of scores were primarily developed to predict mortality in patients with community acquired pneumonia, recent studies have looked at outcome measures such as admission to the intensive care unit. In general, both scores perform less well in predicting the need for admission to intensive care than in predicting mortality,^{26,28} perhaps because admission to intensive care is governed by local availability.

A major question that has yet to be answered is whether stratifying patients with community acquired pneumonia into severity classes actually improves patient outcome.

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ADDITIONAL EDUCATIONAL RESOURCES

Information for healthcare professionals

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British Thoracic Society (www.brit-thoracic.org.uk/ClinicalInformation/Pneumonia/PneumoniaGuidelines/tabid/136/Default.aspx)—Guidelines for the management of community acquired pneumonia in adults

American Thoracic Society (www.thoracic.org/sections/publications/statements/pages/mtpi/idsaats-cap.html)—Infectious Diseases Society of America/American Thoracic Society guidelines on community acquired pneumonia

INFORMATION RESOURCES FOR PATIENTS

British Lung Foundation (www.lunguk.org/you-and-your-lungs/conditions-and-diseases/pneumonia.htm)—Information on the causes, treatment and prevention of pneumonia