Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines

W S Lim, J T Macfarlane, T C J Boswell, T G Harrison, D Rose, M Leinonen, P Saikku

Abstract

Background—Since the last British study of the microbial aetiology of community acquired pneumonia (CAP) about 20 years ago, new organisms have been identified (for example, *Chlamydia pneumoniae*), new antibiotics introduced, and fresh advances made in microbiological techniques. Pathogens implicated in CAP in adults admitted to hospital in the UK using modern and traditional microbiological investigations are described. Methods—Adults aged 16 years and over admitted to a teaching hospital with CAP over a 12 month period from 4 October 1998 were prospectively studied. Samples of blood, sputum, and urine were collected for microbiological testing by standard culture techniques and new serological and urine antigen detection methods. Results—Of 309 patients admitted with CAP, 267 fulfilled the study criteria; 135 (50.6%) were men and the mean (SD) age was 65.4 (19.6) years. Aetiological agents were identified from 199 (75%) patients (one pathogen in 124 (46%), two in 53 (20%), and three or more in 22 (8%)): *Streptococcus pneumoniae* 129 (48%), influenza A virus 50 (19%), *Chlamydia pneumoniae* 35 (13%), *Haemophilus influenzae* 20 (7%), *Mycoplasma pneumoniae* 9 (3%), *Legionella pneumonia* 9 (3%), other *Chlamydia* spp 7 (2%), *Moraxella catarrhalis* 5 (2%), *Coxiella burnetii* 2 (0.7%), others 8 (3%). Atypical pathogens were less common in patients aged 75 years and over than in younger patients. They should also be covered in all patients with severe pneumonia and younger patients with non-severe infection. Conclusion—*S pneumoniae* remains the most important pathogen to cover by initial antibiotic therapy in adults of all ages admitted to hospital with CAP. Atypical pathogens are more common in younger patients. They should also be covered in all patients with severe pneumonia and younger patients with non-severe infection.

Keywords: adult community acquired pneumonia; pathogens; aetiology; severity assessment

Community acquired pneumonia (CAP) is common in the UK, affecting 250 000 adults per year of whom 83 000 (33%) are admitted to hospital (67% for patients aged 65 years and over). Mortality ranges from 6% to 15%. Initial antibiotic management of CAP is empirical and dependent on a clear understanding of the likely pathogens. In the UK this knowledge is based on studies performed in the 1970s and early 1980s. The largest study, conducted by the British Thoracic Society (BTS) in 1982, excluded adults over 74 years of age, thus missing the group of patients who carry the burden and mortality of CAP.

In the last two decades a number of factors have potentially affected the pattern of adult CAP in the UK. The increasing age of the population, often with co-morbid illnesses or resident in residential and nursing homes, has raised concerns of Gram negative enteric bacterial infection in CAP. Concerns of antibiotic resistance and the emergence of “new” pathogens such as *Chlamydia pneumoniae*, implicated in 3–18% of cases of CAP elsewhere, has led to the promotion of fluoroquinolones and newer macrolides for the treatment of CAP.

The impact of these changes on the microbial aetiology of CAP in the UK and how they should influence new management guidelines is unknown. We have performed a large prospective study of the aetiology of CAP and the outcome in adults admitted to hospital using a wide range of microbiological investigations.

Methods

All adults aged 16 years and over admitted to a large teaching hospital (Nottingham City Hospital) over a 12 month period from 4 October 1998 with CAP were eligible for inclusion in the study. The hospital shares all unslected adult medical admissions on a daily basis equally with the University Hospital in Nottingham, both covering a population of about 700 000.

All patients admitted with a provisional diagnosis of CAP were identified in the admissions unit where standardised clinical data and investigations were obtained. CAP was defined as the presence of an acute illness of 21 days or less duration with:

1. features of a lower respiratory tract infection including:
   a. two or more of: new or increasing cough, sputum production, shortness of breath, wheeze, chest pain, new focal or diffuse signs on chest examination;
and *S pneumoniae* The criteria used to define infection in the 1982 BTS study were followed, updated for new investigations and pathogens.3

<table>
<thead>
<tr>
<th>Table 1 Criteria for microbiological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism</strong></td>
</tr>
<tr>
<td>All bacteria</td>
</tr>
<tr>
<td><em>S pneumoniae, H influenzae</em> or <em>M catarrhalis</em> infection</td>
</tr>
<tr>
<td>Infection with other bacteria including Gram negative enterobacteria (GNEB) and <em>Staph aureus</em></td>
</tr>
<tr>
<td>Atypical and viral pathogens</td>
</tr>
<tr>
<td><em>L pneumophila</em></td>
</tr>
<tr>
<td><em>C pneumoniae</em></td>
</tr>
<tr>
<td><em>M pneumoniae, Chlamydia</em> spp, <em>C burnetti</em>, influenza A and B, respiratory syncytial virus (RSV) and adenoviruses</td>
</tr>
</tbody>
</table>

Serum samples were tested at the National Public Health Institute, Department in Oulu, Finland for antibody responses to *C pneumoniae, H influenzae, M catarrhalis*, and *S pneumoniae*. Urine antigen testing was performed in conjunction with the Central Public Health Laboratory, Coundale, London, UK.

The criteria used to define infection in the 1982 BTS study were followed, updated for new investigations and pathogens.

...radiographs were reviewed by an experienced radiologist (DR) blinded to patient details to confirm the radiographic study entry criteria. All patients were seen regularly in hospital and after discharge until their clinical and radiological features had stabilised. Patients who failed to attend were visited at home. A repeat chest radiographic and blood sample for serological testing were obtained at follow up. The main outcome measure was 30 day mortality.

**LABORATORY INVESTIGATIONS: CRITERIA FOR MICROBIOLOGICAL DIAGNOSIS**

Samples were held at 4°C and transported rapidly to the Nottingham Public Health Laboratory Service (PHLS) laboratory for standard and specialised investigations as previously described and summarised in table 1. The criteria used to define infection in the 1982 BTS study were followed but updated for new techniques (table 1). The pathogens included in the term “atypical” pathogen are specified in table 3. Results for the BINAX-NOW pneumococcal antigen detection kit were read at 60 minutes instead of 15 minutes (as recommended by the manufacturers), based on the increased sensitivity of the 60 minute reading and no apparent difference in specificity (100%) determined in a series of 50 cases of non-pneumococcal proven pneumonias (authors, unpublished data).

**STATISTICAL ANALYSIS**

Data were analysed using SPSS version 8.0 for Windows. χ² or Fisher’s exact tests were used to compare categorical variables. Multivariate analysis was performed by stepwise logistic regression. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CI) and p values, taking p<0.05 as the level of statistical significance.

**Results**

Of 309 patients diagnosed with CAP on admission, eight were unwilling to participate
and 34 were subsequently found not to fulfill study entry criteria, leaving 267 patients in the study cohort, 112 (41%) of whom were elderly (table 2). Of the 267 patients, 190 (71%) were admitted from nursing home and 34 were subsequently found not to fulfill the admission criteria for having severe infection in seven and serological testing in eight). Of the four cases who fulfilled our criteria for aerobic Gram negative enterobacterial infection, both Klebsiella spp and Escherichia coli were isolated from blood culture in one patient. Pseudomonas aeruginosa was identified by Gram stain and culture from sputum in three patients with chronic lung disease and prior antibiotic use, two of whom recovered without receiving antipseudomonal therapy which strongly suggests that, in these cases, Pseudomonas was not an aetiological agent. Details of the three patients with anaerobic infection are given in table 3.

**SPECIMEN COLLECTION**

Specimens obtained included blood cultures prior to antibiotics in hospital from 225 (84%) patients, acute serum from 250 (94%) and follow-up serum from 204 (90%) survivors, urine from 214 (80%) patients, and sputum within 24 hours of admission from 155 (58%) patients, 128 of whom were tested for pneumococcal antigen.

**AETIOLOGICAL AGENTS IDENTIFIED**

Aetiological agents were found in 199 (75%) patients: one pathogen in 124 (46%), two in 53 (20%), and three or more in 22 (8%). Altogether, 144 (54%) bacterial, 62 (23%) viral, and 60 (22%) atypical pathogens were detected (table 3).

**Bacterial pathogens**

The methods of diagnosing the 129 (48%) pneumococcal cases are shown in detail in table 4. Only one penicillin resistant strain was isolated from blood culture of one patient. Pneumococcal infection was diagnosed in 90 of 163 patients (55%) who had not received any antibiotics before admission compared with 39 of 104 (37%) who had been treated with antibiotics (OR 2, 95% CI 1.3 to 3.4, p=0.004). Staphylococcus aureus was isolated from the blood of two of these patients, both of whom had influenza A infection and required treatment in the intensive care unit within 24 hours of admission. Haemophilus influenzae and Moraxella catarrhalis were diagnosed by sputum culture in 11 (40%) pneumococcal cases who were isolated from blood culture of one patient. Pseudomonas aeruginosa was identified by Gram stain and culture from sputum in three patients with chronic lung disease and prior antibiotic use, two of whom recovered without receiving antipseudomonal therapy which strongly suggests that, in these cases, Pseudomonas was not an aetiological agent. Details of the three patients with anaerobic infection are given in table 3.

**Atypical and viral pathogens**

Chlamydia pneumoniae was identified serologically in 35 (13%) cases, more commonly in the winter (31 of 190 patients) than in the summer (four of 77; p=0.015). Legionella pneumophila infection was diagnosed in nine patients (by urine antigen detection in seven and serological testing in eight). Three cases were associated with travel. There was no seasonal variation. Only two patients fulfilled the admission criteria for having severe pneumonia and both survived.

Atypical pathogens were found less often in elderly than in younger patients (16% vs 27%; OR 0.5, 95% CI 0.3 to 0.9, p=0.03) both in the group as a whole and when divided into those with severe and non-severe infection (table 5). Their identification was not influenced by prior infection.
Table 4 Value of pneumococcal diagnostic tests for the 129 patients diagnosed as having pneumococcal infection

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Sensitivity (%)</th>
<th>No (%) positive</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>9/114 (8)</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine antigen</td>
<td>69/114 (61)</td>
<td>31</td>
<td>0.005</td>
</tr>
<tr>
<td>Serology</td>
<td>78/123 (63)</td>
<td>36</td>
<td>0.19</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>9/73 (12)</td>
<td>3</td>
<td>0.08</td>
</tr>
<tr>
<td>Sputum CIE</td>
<td>15/66 (23)</td>
<td>3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CIE = countercurrent electrophoresis.

*Sensitivity = proportion of patients with one or more positive pneumococcal test.
†49 were positive at 15 minutes. Of the remaining 20, seven had pneumococcal infection diagnosed by other tests.

Table 5 Relationship between infection and atypical pathogen, age, and severity

<table>
<thead>
<tr>
<th>Number with atypical pathogen detected</th>
<th>Total (n=60)</th>
<th>Age &lt;75 years (n=42)</th>
<th>Age ≥75 years (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of patients</td>
<td>267</td>
<td>155</td>
<td>112</td>
</tr>
<tr>
<td>Total with atypical pathogen</td>
<td>60 (22%)</td>
<td>42 (27%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Proportion with severe infection</td>
<td>22/103 (21%)</td>
<td>11/41 (27%)</td>
<td>11/62 (18%)</td>
</tr>
<tr>
<td>who had an atypical infection</td>
<td>38/164 (23%)</td>
<td>31/114 (27%)</td>
<td>7/50 (14%)</td>
</tr>
<tr>
<td>Proportion with non-severe infection</td>
<td>22 (2%)</td>
<td>11 (0)</td>
<td>11 (2)*</td>
</tr>
<tr>
<td>Severe CAP (died)</td>
<td>3 (1)</td>
<td>31 (1)†</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Non-severe CAP (died)</td>
<td>1 (0)</td>
<td>3 (1)†</td>
<td>7 (0)</td>
</tr>
</tbody>
</table>

*Both patients had C pneumoniae as the sole pathogen detected. One man aged 90 died 7 days after hospital admission and another aged 78 died at home on day 29 having been previously discharged well.
†Travel associated L pneumophila infection.

Discussion

This is the first UK study to employ a wide range of diagnostic tools to identify the aetiological agents in adult CAP, including C pneumoniae, and to include patients aged 75 years and above. The high pathogen detection rate (75% of cases) reassuringly found no substantial shift in the causes of CAP or antibiotic sensitivity in the UK over the last 20 years, with penicillin sensitive S pneumoniae still the predominant causative agent in nearly half of cases. This is an important finding when reviewing management guidelines for this common condition, particularly as perceived changes in the pattern of CAP have led to changes in national antibiotic guidelines elsewhere.

Pneumococcal infection was diagnosed less commonly in patients who had received antibiotics before admission, presumably due to decreased sensitivity of microbiological tests in this circumstance. None of the bacteremic patients had received prior antibiotics. If prior antibiotic use is taken into account, then the true estimate of pneumococcal incidence is 55%, similar to the 1982 BTS study.

This is the first UK report on C pneumoniae infection in adult CAP and it was identified as the second most common pathogen. However, C pneumoniae was frequently found in mixed infections, in over half of the cases with S pneumoniae, as reported in other countries. Pathogens such as C pneumoniae may play a role in promoting other bacterial infection through their effect on ciliated epithelial cells. The evidence regarding the importance of C pneumoniae as a pathogen is conflicting. Some studies report that outcome is not affected when beta-lactam antibiotics alone are used for patients with evidence of C pneumoniae infection. By contrast, studies from Finland have shown that mixed pneumococcal and C pneumoniae infections cause more severe CAP than that associated with either pathogen alone. Our study did not find this (data not shown). The number of patients fulfilling the criteria for severe infection were similar for these three groupings. The overall mortality in patients with pneumococcal infection was much higher than in those infected with C pneumoniae (14% vs 6%) antibiotic use. Only three of the 60 patients (5%) with infection by an atypical pathogen died, two of whom had C pneumoniae infection and one Legionella.

Of the 50 cases with influenza A virus infection, 38 (76%) occurred in December and January. Respiratory syncytial virus (RSV) was the second most common viral pathogen identified. Of the 11 RSV cases, at least one other pathogen was identified in nine (a bacterial pathogen in eight and influenza A virus in one).

**Mixed infections**

In infections in which Streptococcus pneumoniae was identified, co-pathogens were diagnosed in 60 (47%) patients (influenza A virus in 25, C pneumoniae in 20, H influenzae in nine, other atypical pathogens in four, and other viral pathogens in 11). Where C pneumoniae infection was detected, a co-pathogen was diagnosed in 26 (74%) cases (S pneumoniae in 20, influenza A virus in six, H influenzae in four, other bacterial pathogens in four, and other viral pathogens in one). Overall, of 144 patients in whom infection with a bacterial pathogen was diagnosed, an atypical pathogen was also identified in 30 (21%) cases and a viral pathogen in 41 (28%) cases.

**CLINICAL OUTCOME**

Thirty day mortality was 15% (40 patients); 35 patients died during hospital admission, seven within the first 24 hours, 12 within the first 2 days, and 22 within the first 4 days. The median length of stay in survivors was 7 days (1st and 3rd quartile values 4 and 11 days, respectively). Of 17 (6%) patients admitted to the intensive care unit, five (30%) died. The median time to admission to the intensive care unit was 1 day; 12 (71%) were admitted within the first 24 hours of admission.

The mBTS severity prediction rule was 78% sensitive and 68% specific (negative predictive value (NPV) 95%) at predicting death in comparison with the BTS original prediction rule which was 60% sensitive and 73% specific (NPV 91%). For elderly patients aged 75 years or over the sensitivity (77%) and NPV (86%) of the mBTS rule remained high, although specificity was reduced to 53%. Seven of 90 patients (8%) with one of the four features in the mBTS rule died compared with 14 of 61 (23%) with two features, 12 of 36 (33%) with three features, five of six (83%) with four features, and two of seven (27%) with no features present (χ² test for trend: odds ratio 3.6, 95% CI 1.4 to 9.1, p<0.001).
and no patients with mixed pneumococcal and
C pneumoniae infection died. However, two
elderly patients with C pneumoniae infection
alone died. Outbreaks associated with signifi-
cant mortality have been reported in homes
for the elderly in the USA.15
Our study supports the view that, unlike
other atypical infections, C pneumoniae infec-
tion affects adults of all ages, usually as a
coopathogen, and can be associated with severe
infection and occasionally death. This provides
support to the recommendations to include an
antibiotic effective against atypical pathogens
for patients of all ages with severe CAP.9
The frequency of L pneumophila infection
was lower than the 15% we reported 17 years
ago, a trend seen in other countries.16
Although yearly variation may partly explain
these findings,17 increased use of macrolides in
the community may also be relevant.16 Most of
our cases had non-severe CAP, contrary to the
view that Legionella infection is usually severe.18
All our cases received an early macrolide as
part of their hospital treatment, possibly influ-
encing our low mortality. Delayed treatment
for Legionella infection relates to increased
mortality.19 Furthermore, the report of a
positive Legionella urine antigen test within 3
days of admission positively influenced early
management in seven of nine patients, empha-
sising the likely value of urine antigen detection
as a rapid diagnostic tool for patients admitted
to hospital with CAP.
Infection with M pneumoniae was uncom-
mon which is probably explained by the four
yearly cycle of mycoplasma epidemics in
Europe; our study coincided with the tail end of
a national epidemic.1 Our mycoplasmal
pneumonia rate of 3% is similar to the 2%
reported in 1982, contrasting with the 14%
and 18% rates reported in UK studies during
epidemic years.14 Ready access to current epi-
demiological trends, as is available on the
PHLS website (www.phls.co.uk), could be use-
f ul to clinicians for planning empirical anti-
biotic management.
Most of the cases of influenza were compli-
cated by bacterial co-infections, emphasising
the importance of influenza prevention. Only
68 of 175 eligible patients (39%) had received
the influenza vaccine in the preceding 12
months, higher than the estimated 23% vaccine
uptake among high risk patients in England
and Wales in 1996/7 but still an area that can be
improved.20 Similarly, pneumococcal vaccina-
tion in the last 10 years was reported in only 29
(25%) of 114 eligible patients.

IMPLICATIONS FOR THE MANAGEMENT OF CAP
How does this study contribute to the develop-
ment of an up to date management strategy for
patients hospitalised with CAP?
Nearly all hospitals in the UK now operate
an integrated emergency admission policy for
adults of all ages, many of whom are elderly.
Our patient cohort is typical of the pattern of
CAP in the UK with half aged 65 years and
above and about 40% over 75 years.121 We have
demonstrated that penicillin resistant
S pneumoniae remains the most important pathogen in adults

We would like to thank Hoechst Marion Roussel for supporting
this study through a research grant and Binx for providing the
Streptococcus pneumoniae Binx-NOW antigen detection kits
free. We are grateful to all who contributed in different ways to
this study: Robert Cave, Joanne Palfryman and the team of
technical and medical staff at Nottingham Public Health Labo-
atory for their dedication to the study, Anne Jaskola in
Finland who coordinated the microbiology specimens, and phy-
sicians at Nottingham City Hospital for allowing us to study
their patients.
Conflicts of interest: TR has received research funding from Eisai Ltd and support for attending conferences from Wyeth. WSL has received research funding from Hoechst Marion Roussel (this study) and Bayer and support for attending conferences from Bayer. JTM has received consultancy fees from Pfizer, Abbott, Hoechst Marion Roussel, Trinty, Gliaxa Wellcome, research funding from Hoechst Marion Roussel (this study), Rhone Poulenc Rorer and Bayer, lecture fees from AstraZeneca, Hoechst Marion Roussel and Pfizer and support for attending conferences from Astra, Pfizer, Allen and Hanbury and 3M.


Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines

W S Lim, J T Macfarlane, T C J Boswell, T G Harrison, D Rose, M Leinonen and P Saikku

*Thorax* 2001 56: 296-301
doi: 10.1136/thorax.56.4.296

Updated information and services can be found at:
http://thorax.bmj.com/content/56/4/296

These include:

**References**
This article cites 22 articles, 6 of which you can access for free at:
http://thorax.bmj.com/content/56/4/296#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Pneumonia (infectious disease) (579)
- Pneumonia (respiratory medicine) (562)
- TB and other respiratory infections (1273)
- Drugs: infectious diseases (968)
- Epidemiologic studies (1829)
- Influenza (106)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/