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 pneumonai*)e), 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 pneumonai*ae 35 (13%), *Haemophilus influenzae* 20 (7%), *Mycoplasma pneumonai*ae 9 (3%), *Legionella pneumonai*ae 9 (3%), other *Chlamydia* spp 7 (2%), *Moraxella catarrhalis* 5 (2%), *Coxiella burnettii* 2 (0.7%), others 8 (3%). Atypical pathogens were less common in patients aged 75 years and over than in younger patients (16% v 27%; OR 0.5, 95% CI 0.3 to 0.9). The 30 day mortality was 14.9%. Mortality risk could be stratified by the presence of four "core" adverse features. Three of 60 patients (5%) infected with an atypical pathogen died.

Conclusion—*S pneumonai*ae 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.

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. fever
2. tachypnoea
3. hypoxia
4. chest symptoms
5. focal chest signs

(i) two or more of: new or increasing cough, sputum production, shortness of breath, wheeze, chest pain, new focal or diffuse signs on chest examination;
Table 1  Criteria for microbiological diagnosis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bacteria</td>
<td>Isolation from blood processed in BacTec 9240 system or from pleural fluid, bronchoscopic aspirates, or post mortem lung aspirates</td>
</tr>
</tbody>
</table>
| S pneumoniae, H influenzae or M catarrhalis infection | (a) Isolation from washed and diluted sputum in significant numbers by semiquantitative culture or (b) for S pneumoniae:  
  • Pneumococcal antigen (PCA) detected in urine (BINAX-NOW kit, results read at 60 minutes)  
  or in sputum by countercurrent immunoelectrophoresis (CIE) or (c) Serological criteria for S pneumoniae:  
  • ≥3-fold rise in antibody titre against C-polysaccharide (CPS) or ≥2-fold rise against pneumolysin (PLY), pneumococcal surface antigen A (PsaA)64 or PLY2, PsaA- or CPS-specific immune complexes detected23  
  (d) Serological criteria for H influenzae or M catarrhalis:  
  • ≥3-fold rise in antibody titre66 |
| Infection with other bacteria including Gram negative enterobacteria (GNEB) and Staph aureus | The predominant organism in the sputum Gram stain in addition to isolation from washed and diluted sputum in significant numbers by semiquantitative culture |
| Atypical and viral pathogens     |                                                                                                                                                      |
| C pneumoniae                    | (a) at least 3-fold rise in IgG or IgA antibodies or (b) presence of IgM antibody, using EIA kit (Labsystems, Helsinki, Finland)                  |
| L pneumophila                   | Isolation of organism from respiratory samples or Legionella antigen detected in urine by Biotest kit25 26 or 4-fold or greater rise in immunofluorescent antibody titre to ≥84 using formalised yolk sac antigen to L pneumophila serogroup 1 |
| M pneumoniae, Chlamydia spp, C burnetti, influenza A and B, respiratory syncytial virus (RSV) and adenoviruses | 4-fold or greater antibody rise or a single titre of ≥128, by complement fixation test                                                                   |

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, Colindale, London, UK.

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

Patients were seen within 24 hours of admission by a study investigator to confirm study entry criteria and informed consent. All chest 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 pneumonia (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 fulfil 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 a nursing home.

## Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong> Mean (SD)</td>
<td>65.4 (19.6)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>18–97</td>
</tr>
</tbody>
</table>

### Age groups (years)

- 18–44: 49 (18)
- 45–64: 59 (22)
- 65–74: 47 (18)
- 75–84: 68 (25)
- 85+: 44 (16)

### Smoking status

- Current: 73 (27)
- Ex-smoker (>6 months): 100 (37)
- Never: 80 (30)
- Not known: 14 (5)

### Alcohol consumed

- None: 158 (59)
- <21 units/week: 76
- ≥21 units/week: 15 (6)
- Not known: 18

### Vaccination status

- Influenza vaccine (in last 12 months): 76 (28)
- Pneumococcal vaccine (in last 10 years): 39 (14.6)

### Comorbid illnesses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (% in n=267)</th>
<th>Age &lt;75 years (% in n=155)</th>
<th>Age ≥75 years (% in n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>83 (31)</td>
<td>72 (46.4)</td>
<td>11 (63.6)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>82 (31)</td>
<td>71 (45.7)</td>
<td>11 (63.6)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>33 (12)</td>
<td>20 (13)</td>
<td>13 (11.6)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>12 (5)</td>
<td>11 (7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>30 (11)</td>
<td>25 (16)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (8)</td>
<td>20 (13)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Dementia</td>
<td>22 (8)</td>
<td>19 (12.2)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Cancer</td>
<td>15 (6)</td>
<td>14 (9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>8 (3)</td>
<td>6 (4)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

### Antibiotics prior to hospital admission

- Total (%): 184 (69)
- >21 units/week: 15 (6)
- ≤21 units/week: 169 (63)

### Pathogen detection

- **Bacterial pathogens**: 144 (54%)
- **Atypical pathogens**: 60 (22%)
- **Viral pathogens**: 35 (13%)

### 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 6.4, p<0.004).

### 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

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

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...
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>Sole means of diagnosis (no of patients)</th>
<th>Prior antibiotics (n=104)</th>
<th>No prior antibiotics (n=163)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>9/114 (8)</td>
<td>3</td>
<td>0</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine antigen</td>
<td>69/114 (61)</td>
<td>31</td>
<td>17 (16)</td>
<td>52 (32)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serology</td>
<td>78/123 (63)</td>
<td>36</td>
<td>26 (25)</td>
<td>53 (33)</td>
<td>0.19</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>9/73 (12)</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>0.08</td>
</tr>
<tr>
<td>Sputum CIE</td>
<td>15/66 (23)</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CIE = countercurrent electrophoresis.
*Sensitivity = proportion of patients with one or more positive pneumococcal test.
†Travel associated L pneumophila infection.

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

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

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 bacteraemic 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% v 6%).

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 four (2%) with no features present (χ² test for trend: odds ratio 2.8, 95% CI 1.96 to 4.0, p<0.001).

Mixed infections
In infections in which Strepococcus 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 (5 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.
and no patients with mixed pneumococcal and \(C\) pneumoniae infection died. However, two elderly patients with \(C\) pneumoniae infection alone died. Outbreaks associated with significant mortality have been reported in homes for the elderly in the USA.\(^{16}\)

Our study supports the view that, unlike other atypical infections, \(C\) pneumoniae infection affects adults of all ages, usually as a co-pathogen, 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.\(^{3}\)

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 \(L\) pneumophila infection is usually severe.\(^{18}\) All our cases received an early macrolide as part of their hospital treatment, possibly influencing our low mortality. Delayed treatment for \(L\) pneumophila infection relates to increased mortality.\(^{19}\) Furthermore, the report of a positive \(L\) pneumophila urine antigen test within 3 days of admission positively influenced early management in seven of nine patients, emphasising the likely value of urine antigen detection as a rapid diagnostic tool for patients admitted to hospital with CAP.

Infection with \(M\) pneumoniae was uncommon 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 epidemiological trends, as is available on the PHLS website (www.phls.co.uk), could be useful to clinicians for planning empirical antibiotic management.

Most of the cases of influenza were complicated 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 vaccination 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 development 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 all patients hospitalised with CAP.

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.\(^{11-21}\) We have shown that penicillin sensitive \(S\) pneumoniae remains the most important pathogen in adults of all ages admitted with CAP and this should be covered effectively by the chosen empirical antibiotic. Ampicillin resistant bacteria are uncommon and concerns regarding Gram negative enterobacterial infections in the elderly seem unfounded.

Our study confirmed that pneumococcal, \(H\) aemophilus, and staphylococcal infections are the usual bacterial pathogens implicated in fatal CAP and such pathogens should always be covered by initial antibiotic therapy for severe pneumonia. We also recommend that empirical cover for atypical pathogens should be offered to all patients with severe CAP as 21% of our patients with atypical infection had features of severe pneumonia and three died.

This is also important as several previous studies have found \(L\) pneumophila infection to be the second most common cause of CAP requiring intensive care.\(^{5,18}\) The high proportion of patients who died or needed admission to the intensive care unit within the first few days of hospital admission emphasises the need for early identification of patients with severe pneumonia. The modified BTS rule performs better than the BTS rule in this regard, with sensitivity and NPV values being high, even in the elderly population. We found that patients could be stratified into increasing mortality risk groups using the four individual “core” features of the mBTS rule (CURB: Confusion, Urea, Respiratory rate, Blood pressure)—a strategy which may be more useful in management than just two categories of severe and non-severe. The “post-take” ward round is recommended as a good time to review patients and to decide on step up or step down of treatment options.

For non-severe CAP our study supports the use of empirical antibiotic cover for atypical pathogens for younger patients admitted to hospital but not for elderly patients. Atypical pathogens were twice as common in younger patients and led to no deaths in elderly patients presenting with features of non-severe pneumonia. Avoidance of early routine combination antibiotics, including a macrolide, in younger patients to prevent a pathogen group would probably be of net advantage in view of the complications of multiple antibiotic use in the elderly.

Overall, this study supports the current UK recommendations for covering the range of pathogens found in the management of CAP, stratified according to disease severity. Rapid urine antigen testing looks promising as an early way of detecting some pathogens including \(S\) pneumoniae and \(L\) pneumophila. More experience is needed before recommending these tests as a reliable way of directing more accurately the initial antibiotic choice for CAP.

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 Palfreyman and the team of technical and medical staff at Nottingham Public Health Laboratory for their dedication to the study, Anne Isakkola in Finland who coordinated the microbiology specimens, and physicians at Nottingham City Hospital for allowing us to study their patients.
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