A retrospective case series of 44 patients with community-acquired \textit{Staphylococcus aureus} pneumonia

Darren Bowles, Kyle Perrin

\textbf{Abstract}

\textbf{Aim} \textit{Staphylococcus aureus} (\textit{S. aureus}) community-acquired pneumonia (CAP) is a potentially devastating and life-threatening infection. Early detection and appropriate treatment is important to prevent morbidity and death. The aim of this case series was to investigate the patient demographics, clinical features, antibiotic treatment and complications of cases of community-acquired \textit{S. aureus} pneumonia occurring in the Wellington region.

\textbf{Method} The case records of patients with radiographically confirmed community-acquired pneumonia and laboratory evidence to support \textit{S. aureus} as the causative organism admitted to Wellington Regional Hospital over a 5-year period (2007-2012) were retrospectively reviewed.

\textbf{Results} A total of 48 presentations in 44 patients met the inclusion criteria. The majority of patients (63.6\%) had underlying comorbidities. Although the mean CURB65 score was only one and fever was uncommon, 30\% of patients were admitted to ICU and 16\% died in hospital. Significant infective complications occurred in 48\% with new lung cavitation in 20\%.

\textbf{Conclusion} This series of patients with staphylococcal pneumonia confirms the significant morbidity and mortality of the infection. A low CURB65 score and lack of objective fever should not detract from the possibility of \textit{S. aureus}. The presence of bacteraemia in patients with \textit{S. aureus} pneumonia needs to be regarded as a potentially deleterious finding that may necessitate a change in treatment.

\textit{Staphylococcus aureus} (\textit{S. aureus}) remains a significant cause of community-acquired infection as indicated by steadily increasing hospital admission rates since the early 1990s.\textsuperscript{1} While skin and soft tissue infections account for the majority of staphylococcal infections in New Zealand (NZ),\textsuperscript{2} \textit{S. aureus} is also a recognised cause of both community- and hospital-acquired pneumonia.\textsuperscript{3}

\textit{S. aureus} is a relatively uncommon cause of community-acquired pneumonia (CAP), accounting for 0.2\%–4\% of all cases in the UK\textsuperscript{4,5}, between 1\% to 10\% in the US,\textsuperscript{6} and 2\%–3\% in NZ.\textsuperscript{7,8} The proportion of community-acquired pneumonia infections attributable to \textit{S. aureus} has remained fairly constant over the last half-century.\textsuperscript{9} \textit{S. aureus} has been found to be responsible for 23\% of all cases of severe community-acquired pneumonia admitted to an intensive care unit in NZ.\textsuperscript{10}

Early diagnosis of \textit{S. aureus} CAP is important to effectively treat this potentially fulminant infection.\textsuperscript{11,12} This serious condition has in recent times been further brought to prominence following episodes of pandemic influenza and the emergence
of Panton-Valentine leukocidin toxin (PVL)-producing strains, including community-associated methicillin-resistant *S. aureus* (CA-MRSA) in the Oceania region.\(^2,13\)

The aim of this case series was to investigate the patient demographics, clinical features, antibiotic treatment and complications of cases of *S. aureus* CAP in the Wellington region of NZ.

**Method**

All patients diagnosed with CAP with concomitant isolation of *S. aureus* from sputa, pleural fluid and/or blood admitted to Wellington Regional Hospital (WRH) over a 5-year period (2007-2012) were retrospectively reviewed. Approval to use patient record data was sought from the Decision Support Unit (DSU) at WRH. The authors decided that Ethics Committee approval was not required for the case series review. Patient data was de-identified and treated with the utmost confidentiality.

Case records were identified using the ICD-10 code for ‘pneumonia due to staphylococcus’ (J15.2). Additional cases were identified from the sputum culture results database of the WRH microbiology laboratory. Inclusion criteria included focal consolidation on chest radiograph (CXR) consistent with a new diagnosis of CAP and microbiological confirmation of *S. aureus*.

We excluded cases with no evidence to support *S. aureus* as the underlying infective cause of CAP, hospital-acquired *S. aureus* pneumonia and cases where evidence supported a primary vascular site of inoculation with *S. aureus*.

Sources of information included patient case files, digital radiology, microbiological data and patient electronic records. Data were collected on patient demographics, clinical history and observations, laboratory blood results, radiological investigations, antibiotic treatment and infective complications.

Information was collected using a data template and transferred to a Microsoft Excel software database prior to analysis.

**Results**

Forty-four subjects meeting the inclusion criteria were identified over a 5-year period (2007–2012). Four patients re-presented with *S. aureus* pneumonia between 5 days and 4 months following their initial presentation, hence there were 48 presentations in total available for analysis.

The median age was 57 years; 36% were aged 56–75 years; 20% were aged over 75 years and 16% (n=7) were aged 16–25 years. The majority (56.6%) were current or ex-smokers.

Ethnicity was stated as NZ European in 28 and Māori in 8 patients; 54% (n=37) of patients were resident in areas designated either deciles 9 or 10. (Deciles 9 and 10 signify socially deprived residential areas according to the New Zealand Deprivation Index.\(^{14}\))

A total of 63.6% (n=28) of the patients had underlying comorbidities as shown in Table 1.
Table 1. Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>(1)</td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Chronic hepatitis C viral infection</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Long-term corticosteroid therapy</td>
<td>13.6 (6)</td>
</tr>
<tr>
<td>Long-term immunosuppressive drug therapy</td>
<td>11 (5)</td>
</tr>
</tbody>
</table>

Of the eight patients with chronic renal impairment, two were receiving regular haemodialysis at the time of admission and five patients had an estimated glomerular filtration rate (eGFR) between 19–33 ml/min/1.73m².

Overall 39.6% (n=19/48) of presentations occurred in the 3 months Sept–Nov. For all 48 presentations the median time from symptom onset to hospital admission was 4 days.

Sweats, rigors and chills were reported by three, seven and six patients respectively. One patient described a preceding flu-like illness. Five patients, whose ages ranged from 57 to 88 years, were acutely confused at presentation.

The mean and median CURB65 scores for all 48 presentations were 1; 14 patients had a score of 1 and 13 patients had a score between 2–5. The frequency of CURB65 scores of 2 and above is provided in Table 2.

Data was available to assess Systemic Inflammatory Response Syndrome (SIRS) criteria for 45 presentations of which 84% (n=38) satisfied the American College of Chest Physicians (ACCP) definition of SIRS.¹⁵

Table 2. Distribution of CURB65 scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Number of presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Baseline clinical features are shown in Table 3.
Table 3. Baseline clinical features

<table>
<thead>
<tr>
<th>Observations</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness</td>
<td>64.5 (31/48)</td>
</tr>
<tr>
<td>Cough</td>
<td>68.8 (33/48)</td>
</tr>
<tr>
<td>Fever (≥37.5)</td>
<td>43 (19/44)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>43 (21/48)</td>
</tr>
<tr>
<td>Chills</td>
<td>6.8 (3/44)</td>
</tr>
<tr>
<td>Rigors and chills</td>
<td>6.8 (3/44)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>18 (8/44)</td>
</tr>
<tr>
<td>Oxygen saturation (median, %)</td>
<td>93</td>
</tr>
<tr>
<td>SBP/DBP (median, mmHg)</td>
<td>125/70</td>
</tr>
<tr>
<td>Respiratory rate (median, breaths per min)</td>
<td>24</td>
</tr>
<tr>
<td>Confusion</td>
<td>11 (5/44)</td>
</tr>
</tbody>
</table>

39.6% (n=19/48) of admission chest radiographs showed evidence of multifocal consolidation. Radiological evidence of new lung cavitation was seen in 20% (n=9), secondary pneumothorax in 6.8% (n=3) and pleural effusion in 27% (n=12).

Median results for the baseline blood samples showed: Hb 122 g/L; White cell count 10.64×10⁹/L; Neutrophil count 9.17×10⁹/L; Platelet count 199×10⁹/L; Alb=30 g/L and CRP=142 mg/L.

S. aureus was cultured from 90.7% (n=39/43) of sputum samples collected. Of these 87% (n=34) were reported as moderate or heavy growth of S. aureus. In total 33 sets of blood cultures were collected from 31 patients. Blood cultures were positive for S. aureus in 36% (n=12). Of these, three patients did not produce sputum, four patients had moderate or heavy growth of S. aureus in sputa, three patients had light growth of S. aureus in sputa and two patients’ sputa were negative for S. aureus.

Pleural aspirates were performed in six patients with radiographic evidence of a pleural effusion, of these 50% (3/6) were culture positive for S. aureus.

S. aureus was flucloxacillin-sensitive in 86% (n=24/28) of isolates. Erythromycin resistant S. aureus was found in 12.5% (n=2/16) of sputum isolates. MRSA was identified on sputum culture in four patients and blood culture in one additional patient. Four of the five patients tested for influenza were positive for concurrent infection.

Intravenous cefuroxime or ceftriaxone were used as initial therapy in 79% (n=38) of presentations. Addition of a macrolide in combination with a cephalosporin occurred in 65% (n=31) of presentations.

Of those who were coadministered a macrolide, 67% received oral roxithromycin, 16% received intravenous erythromycin and 7% received intravenous clarithromycin. Intravenous flucloxacillin was used in 9% (n=4) and anti-MRSA agents (glycopeptides, clindamycin and cotrimoxazole) were used in 9% (n=4) of patients, including three treated with intravenous vancomycin.

Revision of intravenous antibiotic therapy occurred in 62.5% of presentations (n=30); in 60% (n=18/30) this included a change to intravenous flucloxacillin. The median time from admission to the first revision of antibiotic therapy was 3 days for 89.5%
(n=43) of presentations, which generally correlated with confirmation of culture results.

An anti-MRSA agent was introduced at subsequent revisions of therapy in a further 27% (n=12). The median time from admission to revision of antibiotic therapy to flucloxacillin and/or an anti-MRSA agent was 4 days for 36 presentations.

In total, intravenous flucloxacillin was used in 64% (n=28), intravenous clindamycin in 16% (n=7) and intravenous vancomycin in 18% (n=8).

Duration of inpatient antibiotic therapy ranged from 3 to 49 days with a median of 10 days for all 48 presentations. Length of hospital stay ranged from 3 to 50 days, with a median of 11 days for 45 presentations.

In total 48% (n=21) of patients developed significant infective complications as shown in Table 4.

Table 4. *S. aureus* CAP complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lung cavitation</td>
<td>20 (9/44)</td>
</tr>
<tr>
<td>Pleural effusion (incl. empyema)</td>
<td>27 (12/44)</td>
</tr>
<tr>
<td>Empyema</td>
<td>7 (3/44)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>7 (3/44)</td>
</tr>
<tr>
<td>ARDS</td>
<td>16 (7/44)</td>
</tr>
<tr>
<td>Pleural aspirate positive</td>
<td>50 (3/6)</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>36 (12/33)</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>7 (3/44)</td>
</tr>
</tbody>
</table>

Seventy-five percent (n=9/12) of cases with positive blood cultures developed significant infective complications compared to 38% (n=8/21) with negative blood cultures.

A total of 13 (30%) patients were admitted to ICU, all required mechanical ventilation, and 11 additionally required inotrope therapy. Of the 13 ICU patients, nine had multifocal consolidation on their admission CXR, 8 had blood cultures positive for *S. aureus* and 4 died in hospital.

Overall in-hospital mortality was 16% (n=7/44). A further three patients with significant comorbidities died within 6 months of discharge from hospital.

**Discussion**

This is the first retrospective case series of consecutive patients with CAP due to *S. aureus* in NZ. It confirms that this infection is more prevalent in patients with comorbidities who have social deprivation and demonstrates that the infection is associated with significant morbidity and mortality.

Despite initially low CURB65 scores and a lack of fever at presentation, patients in this case series had a high rate of ICU admission and death.

There was high use of intravenous cephalosporins, particularly cefuroxime, and oral roxithromycin, in accordance with the WRH antibiotic guidelines for CAP. Antibiotic
treatment was changed in the majority of patients after an appropriate period correlating to confirmation of culture results.

Patients who required ICU admission tended to have multifocal consolidation on their admission CXR and bacteraemia on blood culture.

Limitations of this case series include the retrospective nature of the data and the small number of patients found to meet the inclusion criteria. The presence of S. aureus in sputum in isolation is not necessarily indicative of underlying pulmonary infection. However the official microbiological sputum analysis report, and patient’s past sputa data, were reviewed to distinguish between colonisation and infection.

The findings were similar to a UK case series by Woodhead et al who found a comparable number of cases complicated by new cavitation and pneumothorax, and that the presence of bacteraemia was associated with adverse outcomes.

At baseline assessment, S. aureus pneumonia is clinically indistinguishable from that caused by other pathogens. However, useful indicators include radiological evidence of multifocal consolidation, cavitation, pneumatoceles or secondary pneumothorax.

The treatment of undifferentiated community-acquired pneumonia should follow the local antibiotic guidelines, and be guided by severity assessment at baseline. Upon microbiological confirmation of S. aureus a change of treatment to antibiotic therapy with high anti-staphylococcal activity should be considered. Intravenous flucloxacillin is appropriate for the initial treatment of the majority of methicillin-susceptible S. aureus (MSSA) strains. Longer intravenous antibiotic courses for up to two weeks duration have been recommended to treat patients with uncomplicated staphylococcal bacteraemia.

Virulent PVL-positive S. aureus strains, including both MSSA and CA-MRSA, resistant to standard anti-staphylococcal antibiotic treatment are a recognised cause of severe CAP associated with high mortality. In recent years there has been a reported increase in the prevalence of PVL-positive CA-MRSA strains in Australia. In NZ, 18% of Auckland MSSA clinical isolates causing pneumonia have been found to be PVL-positive.

Several cases of fatal necrotising pneumonia due to PVL-positive MSSA and CA-MRSA have been described in Australia. At least one case of necrotising pneumonia due to PVL-positive MSSA has been described in NZ.

11% of S. aureus isolates in this case series were methicillin-resistant. No S. aureus isolates in this series were tested for PVL toxin. It is possible that PVL-positive S. aureus went undetected among the most severely affected patients in this case series.

CA-MRSA strains are universally resistant to all currently available beta-lactams. Recommended antibiotic therapy for CAP caused by PVL-positive S. aureus, both MSSA and CA-MRSA strains, includes intravenous clindamycin and linezolid, and rifampicin. Clindamycin and linezolid achieve good lung penetration and have the ability to reduce toxin formation via bacterial protein synthesis inhibition, while rifampicin kills intracellular staphylococci. A caveat to the use of clindamycin for
long treatment courses is the exclusion, subsequent to starting treatment, of inducible resistance using a D-test.\textsuperscript{35}

Treatment failure has been associated with the use of vancomycin as first-line antibiotic therapy for necrotising staphylococcal pneumonia\textsuperscript{36}. Vancomycin poorly penetrates lung tissue, failing to attain levels at or above the MIC for MRSA\textsuperscript{37}. Other concerns with vancomycin include its lack of bacterial toxin inhibition and increasing reports of resistance.\textsuperscript{38,39} For these reasons vancomycin is generally not recommended for the treatment of MRSA pneumonia. Another agent that should be avoided for the treatment of staphylococcal pneumonia is the lipoglycopeptide daptomycin which is inactivated by pulmonary surfactant.\textsuperscript{40}

Testing for PVL toxin may be indicated in patients presenting with confirmed severe \textit{S. aureus} CAP, particularly with necrotising features and haemoptysis. A longer course of intravenous antibiotic therapy of up to 2 weeks duration should be considered for patients with uncomplicated \textit{S. aureus} bacteraemia or culture positive pleural fluid.

For severe MSSA and MRSA CAP it is recommended that the managing medical/intensive care team seek the advice of the local infectious disease/clinical microbiology team at the earliest opportunity.

In conclusion, \textit{S. aureus} as a causative organism should be suspected in patients presenting with severe community-acquired pneumonia, particularly with radiological evidence of multifocal consolidation and findings suggestive of underlying tissue necrosis such as cavitary changes.

This case series suggests that low CURB65 scores and absence of fever at presentation should not detract from the possibility of \textit{S. aureus} as the underlying cause. Adequate doses of intravenous anti-staphylococcal antibiotics must be started as soon as microbiological confirmation is available, and there should be a high index of suspicion for subsequent complications should patients fail to respond appropriately to treatment.

\textbf{Competing interests:} None.

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