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# Severe community-acquired pneumonia due to *Streptococcus pyogenes* in the Newcastle area

Paul A Wilson, Hemalatha Varadhan

## Abstract

### Background

An apparent increase in the incidence of severe community-acquired pneumonia (CAP) caused by *Streptococcus pyogenes* (group A Streptococcus – GAS) was observed during 2017 in the Newcastle area. The study was undertaken to establish whether there was a true increase in severe *S. pyogenes* pneumonia and to explore its epidemiology and clinical features.

### Methods

The study was a retrospective descriptive study of *S. pyogenes* pneumonia set in two tertiary referral hospitals in Newcastle, a large regional city, during the period 2007 to 2018. Subjects were adults identified as having *S. pyogenes* pneumonia by searching a database of severe CAP (defined as requiring intensive care unit [ICU] admission) for the period 2007–2018. Laboratory records were also searched for sterile site isolates of *S. pyogenes* to identify patients not requiring ICU admission.

### Results

There were 13 cases of *S. pyogenes* CAP identified during the study period, of whom 12 (92%) required ICU admission. *S. pyogenes* accounted for 12/728 (1.6%) cases of severe CAP during the study period. The severity of *S. pyogenes* pneumonia was high despite a mean patient age of 48 years and 7/13 (54%) having no significant past medical history. The mortality rate was 2/13 (15%). Viral co-infection was found in 6/12 (50%) of patients tested. Overall 7/12 (58%) of the patients with severe *S. pyogenes* CAP during the study period presented in the winter or spring of 2017.

### Conclusions

*Streptococcus pyogenes* is a rare cause of severe CAP in the Newcastle area, but there was a marked increase in frequency observed during the 2017 influenza season. Further study of the epidemiology of invasive GAS (iGAS) disease in Newcastle is warranted to identify emerging trends in this severe infection.

Keywords: community-acquired pneumonia, *Streptococcus pyogenes*, Newcastle

## Introduction

*Streptococcus pyogenes* commonly causes localised illness such as pharyngitis and skin/soft tissue infections (e.g. impetigo, cellulitis); it sometimes causes asymptomatic colonisation. *S. pyogenes* also causes invasive diseases which include bacteraemia, pneumonia, necrotising fasciitis and streptococcal toxic shock syndrome. During the early 20th century, prior to the introduction of antibiotics, *S. pyogenes* caused about 2–5% of bacterial pneumonia.<sup>1</sup> Large outbreaks of *S. pyogenes* pneumonia were sometimes seen as complications of respiratory virus infections such as influenza and measles.<sup>1</sup> *S. pyogenes* pneumonia has since become a relatively rare disease, with recent publications largely limited to case reports, small case series, reviews of recent literature and larger series of invasive *S. pyogenes* infections of all types (Table 1). The latter include studies from Victoria and Western Sydney as well as tropical Australia (Northern Territory, north Queensland)<sup>2–7</sup> (Table 2).

During the winter and early spring of 2017, it was noticed that there were a number of patients presenting to public hospitals in Newcastle, New South Wales, with severe community-acquired pneumonia due to *Streptococcus pyogenes*. The current study was performed in order to assess whether there was a true increase in the local incidence of *S. pyogenes* pneumonia, and to describe its clinical features in a local population. A secondary aim was to determine the frequency of viral co-infection in these patients.

## Methods

### Setting, data collection

A database was maintained of episodes of severe community-acquired pneumonia, as defined by the requirement for intensive care unit (ICU) admission, at each of two tertiary referral centres in Newcastle (John Hunter Hospital and Calvary Mater Newcastle) during the period 1 January

2007 to 31 December 2018. The data were collected using a combination of prospective and retrospective methods. Information recorded in a spreadsheet included demographic details such as age, sex, comorbidities; clinical characteristics including requirement for inotropic support or mechanical ventilation, presence of acute kidney injury, length of hospital stay; and diagnostic information such as chest x-ray findings, inflammatory markers (C-reactive protein, procalcitonin) and tests for etiology of pneumonia (blood and sputum cultures, urinary *Legionella* and pneumococcal antigens, multiplex respiratory virus nucleic acid amplification tests [NAAT], pleural fluid culture and NAAT). The multiplex respiratory virus NAAT (Ausdiagnostics, Mascot, Australia) was available from 2012 and tested for influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, picornavirus and human metapneumovirus. Prior to 2012, influenza was tested by NAAT and the other viruses by direct fluorescent antibody testing (DFA). The investigation of pneumonia etiology and the choice of diagnostic tests was directed by the treating team. A search was made for further patients with *S. pyogenes* pneumonia who were not admitted to ICU by searching the NSW Health Pathology database for positive blood cultures for *S. pyogenes*, which were cross-checked with admission chest x-ray reports. The study included only adult patients (aged  $\geq 18$  years). *S. pyogenes* was identified using Gram stain followed by serologic antigen testing and MALDI-TOF mass spectrometry (VITEK MS, bioMerieux).

### Definitions

The diagnosis of community-acquired pneumonia was confirmed by the following: a chest x-ray report of a new pulmonary infiltrate documented within 24 hours of hospital admission; a clinical diagnosis of community-acquired pneumonia by the treating team; and clinical and/or laboratory findings consistent with infection. The following criteria were used to define *S. pyogenes* as the cause of community acquired pneumonia: positive blood or pleural fluid culture, or pleural fluid NAAT.

**Table 1: Published case series of *Streptococcus pyogenes* pneumonia**

Ref <sup>a</sup>	Years	Site	Patients	Age <sup>b</sup>	Mortality	Viral coinfection	Previously well
15	1987–2016	all	16	42	38%	25% <sup>c</sup>	63%
16	1981–1997	UK	17	57	47%	6% <sup>d</sup>	35%
17	2006–2015	Spain	40	60	20%	10% <sup>e</sup>	32%
20	2010–2011	UK	10	NS <sup>f</sup>	80%	40% <sup>g</sup>	60%
21	2009	USA	9	37	66%	100% <sup>h</sup>	56%

a Reference.

b Mean age.

c 1 influenza A, 3 influenza B.

d 1 influenza A.

e 3 influenza A, 1 influenza B.

f Not stated.

g 1 influenza A, 3 influenza B.

h 9 influenza A (H1N1).

**Table 2: Invasive GAS infection (iGAS) in Australia: reported case series**

Ref <sup>a</sup>	Time period	Location	iGAS cases	Pneumonia	Incidence per 100,000	Mortality
2	1996–2001	North Queensland	109	10 (9%)	82.5 (Aboriginal and Torres Strait Islander) 10.1 (Non-Indigenous)	7%
3	2002–2004	Victoria	333	36 (10.8%)	2.7	7.8%
4	1998–2009	Northern Territory ("Top End")	295	8 (6.6%)	15.8 (all) 40.6 (Aboriginal and Torres Strait Islander)	13.8%
5	2011–2013	Northern Territory	128	12 (9%)	8.8 (Non-Indigenous) 69.7 (Aboriginal and Torres Strait Islander)	8%
6	2007–2017	Victoria	1,311	NS <sup>b</sup>	2.1	NS <sup>b</sup>
7	2008–2010	Western Sydney, New South Wales	72	2 (2.8%) <sup>c</sup>	NS <sup>b</sup>	8.3%

a Reference.

b Not stated.

c Empyema.

## Results

### Patient characteristics

For the 12-year period from 1 January 2007 to 31 December 2018, a total of 213 adult patients with positive blood cultures for *S. pyogenes* were identified by searching the NSW Health Pathology database. There were 13 identified cases of community-acquired pneumonia due

to *S. pyogenes* in adults, of whom all except one had severe CAP requiring ICU admission. The mean age was 48 years (range 18–77) and median 46 years; seven patients were male and 6 female. There was a striking increase in the number of cases diagnosed in 2017, with 7 of 13 cases (54%) occurring that year, which coincided with a severe influenza season (Tables 3, 4). Two of the patients presenting in 2017 lived less than 10 kilometres apart and presented to

**Table 3: Severe *Streptococcus pyogenes* pneumonia in the Newcastle area**

Year	Number of cases	% of total
2007	1	8.3
2008		
2009		
2010	2	16.7
2011		
2012		
2013		
2014	1	8.3
2015	1	8.3
2016		
2017	7	58.3
2018		

**Table 4: Influenza in NSW and Hunter New England (HNE) LHD<sup>a</sup>**

Year	Influenza total NSW	Flu A	Flu B	HNE LHD cases	HNE LHD incidence per 100,000
2009		1,298 <sup>b</sup>			
2010		546	93		
2011		2,438	1,215		
2012		4,365	1,263		
2013		3,716	2,404		
2014		15,672	2,553		
2015		10,513	18,978	2,643	291
2016	35,409	32,391	3,797	3,264	356.2
2017	102,880	59,468	42,841	11,968	1287.2
2018	17,467	13,625	3,051	1,819	194.1

a NSW = New South Wales; LHD = Local Health District.

b May to December.

hospital one week apart. No contact tracing was conducted, and the homes of the other patients from 2017 were spread across a broad geographical area. Over half of the affected patients (7 of 13, 54%) were previously well without significant past medical history. Coexisting illnesses in the remaining patients included type 2 diabetes mellitus (3 patients, 23%), asthma (2, 15%), chronic obstructive pulmonary disease (COPD,

1), bronchiectasis (1), lung carcinoma treated with radiotherapy (1) and bipolar disorder (1). Seasonal variation was apparent in that most patients presented in winter (8 of 13, 62%) or early spring [i.e. September] (3 of 13, 23%), with the other two admitted during autumn (Table 5).

**Table 5: *S.pyogenes* pneumonia: baseline characteristics<sup>a</sup>**

Case	Age/sex	Date admitted	Comorbidities	CXR <sup>a</sup> consolidation	AKI <sup>b</sup>	Wbc x 10 <sup>9</sup> /L <sup>c</sup>	Viral testing multiplex PCR <sup>d</sup>
1	47/F	31/8/2007	Nil	bilateral	yes	1.9	negative
2	60/M	19/7/2010	type 2 diabetes, lung cancer, radiotherapy	lobar	yes	11.8	negative
3	26/F	25/9/2010	bipolar disorder	multilobar	yes	8.5	negative
4	72/M	11/8/2014	nil	bilateral	yes	5.2	influenza A
5	38/F	20/5/2015	nil	lobar	no	9.7	negative
6	77/M	9/6/2017	type 2 diabetes, bronchiectasis	multilobar	yes	50.6	RSV <sup>e</sup> , picornavirus
7	38/F	8/7/2017	asthma	multilobar, ? empyema	yes	0.7	not done
8	42/M	11/8/2017	nil	lobar, cavitation	yes	4.0	influenza A
9	58/F	18/8/2017	COPD	bilateral	yes	1.4	influenza B
10	46/M	25/8/2017	asthma, type 2 diabetes	lobar	yes	7.2	influenza B
11	18/F	8/9/2017	nil	lobar, ? empyema	no	101.9	negative
12	58/M	22/9/2017	nil	lobar	no	2.3	metapneumovirus
13	44/M	24/3/2018	nil	lobar	no	16.2	negative

a Chest x-ray.

b Acute kidney injury.

c Wbc = white blood count.

d Polymerase chain reaction.

e Respiratory syncytial virus.

## Clinical course

*S. pyogenes* pneumonia was typically severe, with 12 of 13 (92%) patients admitted to ICU and the mortality rate 17% (2 of 12) when the outcome was known (one patient was transferred to a hospital outside the area without follow-up data). The two fatal cases died within 24 hours of presentation. Mechanical ventilation was required for 67% of patients (8 of 12), inotropic support for 67% (8 of 12) and haemodialysis for 33% (4 of 12). Surgery was undertaken in three patients, thoracotomy and decortication of empyema in two and below knee amputation in one. The mean length of stay for survivors was 28.2 days (range 5–116 days).

## Microbiology

The streptococcal etiology for the *S. pyogenes* CAP was defined by positive blood cultures in 85% (11 of 13) of patients. Of the 2 patients with negative blood cultures, one had a positive pleural fluid culture for *S. pyogenes* and the other had Gram positive cocci seen on pleural fluid Gram stain with negative culture but positive 16S rRNA for *S. pyogenes* (Table 6).

## Other laboratory features

A respiratory viral infection was identified in 50% of patients tested (6 of 12). The viruses identified were influenza A (2), influenza B (2), metapneumovirus (1) and respiratory syncytial virus (RSV) / picornavirus co-infection (1). Four of 13 patients (31%) had leucopenia on presentation (white cell count  $0.7\text{--}2.3 \times 10^9/\text{L}$ ; normal range [NR]  $4\text{--}11 \times 10^9/\text{L}$ ); 2 had marked leucocytosis ( $50.6, 101.9 \times 10^9/\text{L}$ ). A majority of patients (9 of 13, 69%) developed acute kidney injury with serum creatinine at least doubled from baseline.

## Radiology

The chest x-ray for most patients showed extensive consolidation which was multilobar in 3 of 13 (23%) and bilateral in 3 of 13 (23%); rapid progression of consolidation was frequent.

## Non-severe *S. pyogenes* CAP

In addition to the 12 patients with severe *S. pyogenes* pneumonia requiring ICU admission, only one other patient was identified over the study period of 2007–2018 who was admitted to hospital with *S. pyogenes* pneumonia of lesser severity (i.e. not requiring ICU admission).

## *S. pyogenes* and severe CAP frequency

There was an increase in the total number of iGAS episodes during 2017, with 49 episodes in that year compared to 29 episodes in 2016 and 12 to 25 cases per year in the other years of the study.

The yearly number of cases of severe CAP (defined by ICU admission) ranged from 42 to 77 during the study period. In 2017 there were 73 episodes, which was the third-highest yearly total recorded during 2007–2018.

*S. pyogenes* accounted for 1.6% (12/728) cases of severe CAP over the course of the study. In 2017, 9.6% (7/73) of the patients with severe CAP had *S. pyogenes* infection; rates for other years studied were between zero and 2% with the exception of 2010 (3.5%, 2/57).

## Discussion

There have been a number of publications describing rates of invasive *S. pyogenes* infection (iGAS) in different geographical areas, including data on the proportion of cases due to pneumonia as well as other types of infection (Table 1). The Australian studies were mostly performed in tropical regions with large Aboriginal and Torres Strait Islander populations. A study of iGAS epidemiology was reported from western Sydney although the patient numbers were relatively small.<sup>7</sup> Pneumonia has accounted for between 6.6%<sup>4</sup> and 10.8%<sup>3</sup> of iGAS infections in published studies from different areas of Australia. The overall mortality from iGAS infection has ranged from 7%<sup>2</sup> to 13.8%<sup>4</sup> in Australian series, with the incidence between 2.1 per 100,000 per year in Victoria<sup>6</sup> and 82.5 per 100,000 per year in

**Table 6: *S. pyogenes* pneumonia: clinical course**

Case	ICU <sup>a</sup>	Ventilation	Inotropes	Positive cultures	Surgery	Mortality
1	yes	unknown	unknown	blood		no
2	yes	yes	yes	blood		no
3	yes	yes	yes	blood	R.BKA <sup>b</sup>	no
4	yes	yes	yes	blood		yes
5	yes	no	no	blood		no
6	yes	yes	yes	pleural fluid 16S rRNA <sup>c</sup>		no
7	yes	yes	yes	blood	thoracotomy, decortication	no
8	yes	yes	yes	blood		no
9	yes	yes	yes	blood		yes
10	yes	yes	yes	blood		no
11	yes	no	no	pleural fluid	VAT, <sup>d</sup> decortication	no
12	yes	no	no	blood		no
13	no	no	no	blood		no

a Intensive care unit.

b BKA = below knee amputation.

c Ribosomal deoxyribonucleic acid.

d Video assisted thoracoscopy.

Aboriginal and Torres Strait Islander people in North Queensland.<sup>2</sup> Large series from western Europe and North America have reported the incidence of iGAS infections to range between 1.5 per 100,000 per year<sup>8</sup> and 6.3 per 100,000 per year,<sup>9</sup> comparable to that reported from Victoria. A consistent finding in larger surveys is that the mortality in GAS pneumonia is about twice that of iGAS infection as a whole.<sup>9</sup>

There have been several case series of *S. pyogenes* pneumonia reported in the literature, as well as a literature review which included 16 cases from the past 3 decades. In the current study, the key features (Table 6) include high mortality and about half of the infections occurring in patients without pre-existing medical problems. A further 4 patients with severe *S. pyogenes* pneumonia have been reported in detail since the above literature review.<sup>10–12</sup> Other recent case series described 6 patients requiring ICU treatment for severe *S. pyogenes* pneumonia over the

period 1999–2016<sup>13</sup> and 3 patients who rapidly died from severe *S. pyogenes* pneumonia with pulmonary haemorrhage.<sup>14</sup>

The current study found a lower mortality rate (15%) than did the literature review for *S. pyogenes* pneumonia (38%)<sup>15</sup> or the two largest case series of GAS pneumonia (20%, 47%).<sup>16,17</sup> Previous studies showed relatively high proportions of otherwise healthy patients (32 to 63%),<sup>15,16</sup> similar to our findings that 6 of 12 (50%) patients with severe *S. pyogenes* pneumonia lacked significant comorbidities. We found that 50% of patients (6/12) had viral coinfection, which was particularly common during the 2017 upsurge in incidence of *S. pyogenes* pneumonia (5 of 7 patients tested) and included human metapneumovirus and RSV as well as influenza; the former two viruses have not been described before in association with *S. pyogenes* pneumo-

nia to our knowledge. The 2017 influenza season reported unprecedented high incidences in New South Wales (Table 3).

We found that *S. pyogenes* was an uncommon cause of severe CAP, accounting for just 1.6% of 728 episodes over the period 2007–2018, but 9.6% of 73 episodes occurring in 2017. *S. pyogenes* pneumonia was usually severe, as shown by the requirement for ICU admission in 12 of 13 patients (92%) admitted to hospital. The rate of preceding influenza infection (4/13; 31%) in this study is noteworthy and warrants further investigation from other locations in Australia. The exact pathogenesis of influenza virus predisposing to *S. pyogenes* pneumonia is not clear but believed to be due to several factors including increased production of fibronectin during influenza infection; increased accessibility of *S. pyogenes* to bind to fibronectin, facilitated by removal of sialic acid residues from the surfaces of host cells; and activation of TGF- $\beta$  by the neuraminidase enzyme. The latter process results in a signalling cascade causing increased fibronectin expression and hence bacterial adherence.<sup>18</sup> The protective effect of influenza vaccine on bacterial superinfection and severe bacterial pneumonia is uncertain. Another study showed that influenza vaccine led to enhanced clearance of microorganisms in the superinfected mice and hence suppressed mortality.<sup>19</sup>

This study is one of the largest case series of adult *S. pyogenes* pneumonia reported in the literature. We employed a search strategy that maximised the identification of cases of *S. pyogenes* pneumonia by using multiple sources of data (ICU database for patient identification, pathology database for blood or pleural fluid cultures) and cross-checking with chest x-ray reports and electronic medical records. The ICU database search terms were intentionally broad (e.g. pneumonia, sepsis, respiratory infection) to avoid missing cases. It is possible that some cases of *S. pyogenes* pneumonia were missed if positive cultures were performed by other pathology services, although the number was expected to be very small. Patients treated in a private hospital may also have been missed.

Potential weaknesses of the study included a subjective definition of severe CAP (though used in numerous past studies), the geographically limited study population, not having detailed local data on overall iGAS incidence and the lack of *emm*-typing of the *S. pyogenes* isolates.

Likely reasons for the increased incidence of *S. pyogenes* pneumonia during 2017 may include the increased circulation and infection rates for influenza (Table 3) and other respiratory viruses, changes in circulating strains of *S. pyogenes* with more virulent strains predominating, and declining community and individual patient antibody titres against the prevalent strains of *S. pyogenes*. Further molecular analysis of the *S. pyogenes* isolates was not possible for reasons of funding, but *emm*-typing may have been helpful to further characterise the local epidemiology of invasive *S. pyogenes* infection. Specifically, the emergence of a new *emm* type or increased circulation of an existing *emm* type with particular tropism for causing pneumonia would have relevance to the community. Results of molecular analysis may also strengthen the case for mandatory public health notification of iGAS episodes, and may contribute toward the potential development of a GAS polyvalent vaccine in the future. To this end, a study which aims to study the local epidemiology of iGAS infection in more detail, with the addition of typing, is underway.

## Conclusion

In the Newcastle area, *Streptococcus pyogenes* was an uncommon cause of severe community-acquired pneumonia during 2007 to 2018, but a dramatic increase in cases occurred during the severe influenza season in 2017. Viral coinfection occurred in half of the patients with severe *S. pyogenes* pneumonia, including RSV and human metapneumovirus as well as influenza A and B. *Streptococcus pyogenes* pneumonia was typically a severe bacteraemic illness with most patients requiring ICU admission and prolonged hospital admission, despite a relatively low age range with many being previously healthy. Further study of the *S. pyogenes* isolates, including *emm*

typing and more data on *S. pyogenes* CAP and overall iGAS incidence in NSW, may help our understanding of the local epidemiology of this severe infection.

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