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Paediatric empyema in New Zealand: a tale of two cities

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ABSTRACT

AIMS: We aimed to identify the causative organisms and sensitivities in community-acquired paediatric empyema at Starship Children's Hospital and Christchurch Hospital and to determine if current antibiotic recommendations are appropriate.

METHODS: Retrospective analysis was undertaken of all cases with clinical, radiological, and microbiological evidence of empyema at Starship Children's Hospital and Christchurch Hospital between June 2009 and March 2013 (3.8 years), and January 2009 and May 2014 (5.4 years) respectively.

RESULTS: Ninety-eight children were managed with empyema at Starship Children's Hospital and 30 children at Christchurch Hospital. *Staphylococcus aureus* was the most common pathogen identified at both sites followed by *Streptococcus pneumoniae*. A significant proportion had no pathogen identified. Amongst *S.aureus* isolates, 1/5th were methicillin-resistant, contributing 8% of all culture positive empyema cases. Māori and Pacific groups were over-represented. Cases occurred more often in boys and those <5 years. Blood cultures and *S.pneumoniae* pleural antigen were important in diagnosis.

CONCLUSIONS: Our audit confirms the important role of *S.aureus* in paediatric empyema in New Zealand and a high rate of this disease, particularly in the North Island. Antimicrobial susceptibilities of the pathogens of empyema demonstrate current initial antibiotic recommendations at both centres would cover more than 80% of pathogens, although MRSA is a significant contributor.

Introduction

Empyema thoracis (empyema) is an accumulation of infected fluid in the pleural space¹ complicating less than 1% of childhood pneumonia.^{2,3} There is a reported incidence of 0.7–3.3 per 100,00 worldwide,¹ however studies suggest the incidence of paediatric empyema in Western nations has increased since the mid-1990s.⁴ Although mortality is low in developed countries, childhood empyema can lead to significant morbidity and place strain on health resources.² The most common causative pathogens described are *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA).^{2,3} In indigenous populations, and in New Zealand, very high rates of invasive staphylococcal infections have been reported.^{5–8} Significant geographic variation has been seen with *S.aureus* infection,

with a 'North–South' gradient observed.⁹ This may be due to differing population groups, but other geographic factors such as healthcare, vaccination access, and climatic difference may be important.

Starship Children's Hospital (SCH) is Auckland's tertiary paediatric hospital, receiving patients for medical and surgical management of paediatric empyema from within the Auckland District Health Board catchment area, as well as referrals for surgical management from Counties-Manukau, Waitemata and Northland. Additional tertiary and quaternary referrals are received from outside these DHBs.

Christchurch Hospital (CCH) is the South Island's largest tertiary hospital, receiving patients for management of paediatric empyema from within the Canterbury District Health Board catchment area, as well as referrals to paediatrics surgery for surgical management from across the South Island.

Since 2011 Starship Children's Hospital clinical guidelines have recommended use of either amoxicillin/clavulanic acid or cefuroxime as first-line empiric antibiotic for empyema treatment.¹⁰ Christchurch Hospital's paediatric empiric antimicrobial guidelines currently recommend cefotaxime plus flucloxacillin as first-line therapy.

The Thoracic Society of Australia and New Zealand (TSANZ) recommend that initial empirical choice of antibiotics must cover *S. pneumoniae* and *S. aureus*, either through benzylpenicillin with the addition of flucloxacillin or through amoxycillin/clavulanic acid or a cephalosporin, such as cefotaxime or ceftriaxone, with the addition of flucloxacillin.^{1,2}

The primary aim of this study is to identify the causative organisms and susceptibilities in community-acquired empyema managed at Starship Children's Hospital and Christchurch Hospital, to determine if current antibiotic recommendations are appropriate.

Secondary aims included investigation of seasonal trends, demographic factors, and presentation of paediatric empyema at each centre, and to examine the diagnostic yield of blood cultures and *S. pneumoniae* antigen testing.

Methods

Retrospective analysis was undertaken of all cases with clinical, radiological, and microbiological evidence of empyema at Starship Children's Hospital and Christchurch Hospital between June 2009 and March 2013 (3.8 years), and January 2009 and May 2014 (5.4 years) respectively. Starship Children's Hospital typically accepts children up to age of 16 and Christchurch Hospital accepts referrals for children aged less than 18 years.

Data from children resident in the greater Auckland and Northland DHBs were analysed together, as well as combined data from children from across the South Island in order to examine differences between north and south.

Case finding was via hospital discharge coding data with search terms including key clinical diagnoses and associated surgical procedures. Data were obtained from electronic hospital records and clinical notes review.

Inclusion criteria

All empyema cases admitted to Starship Children's Hospital or under Christchurch Hospital's Department of Paediatric Surgery between the specified time periods and satisfying at least one of the following criteria:

1. Patients with microorganism cultured from the pleural space and/or lung tissue
2. The presence of pus in the pleural space as demonstrated on microscopy of pleural fluid or gross findings on operative procedure
3. Fibrinopurulent material seen in the pleural space on ultrasound and/or CT

Exclusion criteria

Empyema cases secondary to surgical complications, iatrogenic causes, or malignancy were excluded.

Uncomplicated parapneumonic effusion, lung abscess (unless complicated by a bronchopleural fistula and empyema), or empyema only at a source other than the pleural cavity eg, pericardial were not included.

Organisms isolated from non-sterile sites, such as sputum or bronchoalveolar lavage, were not included. Typical blood culture contaminants (such as *S. epidermidis*) were excluded.

Ethics approval was sought from Health and Disability Ethics Committees but was deemed unnecessary (ref 14/STH/124).

Results

Ninety-eight children were treated for community-acquired empyema at Starship Children's Hospital between June 2009 and March 2013, an average of 26 cases per year for children aged 0-18 years (rate 5.8/100,000).¹¹ Thirty children were treated for community-acquired empyema at Christchurch Hospital between January 2009 and May 2014, an average of six cases per year (rate 2.2/100,000). Paediatric empyema occurred 1.2-2.8 times more commonly in the Auckland and Northland region, compared with the South Island (p-value 0.0023).

Empyema occurred more commonly in children aged <5 years (71% total; 73% SCH; 63% CCH) with more than half of cases aged

Figure 1. Age at presentation with community-acquired empyema at Starship Children's Hospital (June 2009 to March 2013) and Christchurch Hospital (January 2009 to May 2014)

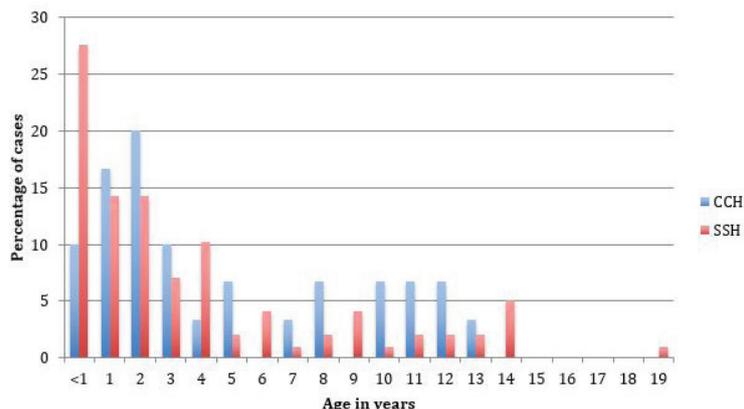
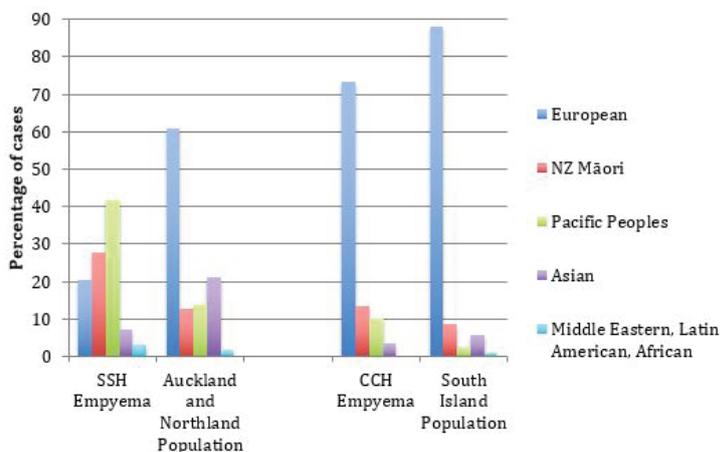


Figure 2. Ethnic distribution of cases of community-acquired empyema at Starship Children's Hospital (June 2009 to March 2013) and Christchurch Hospital (January 2009 to May 2014) compared with population distribution data (New Zealand Census 2013)



< 2 years (54% total; 56% SCH; 47% CCH) (Figure 1). Cases occurred more commonly in boys compared with girls in both centres (63% male).

In Auckland and Northland, 42% of empyema cases were children of Pacific ethnicity. Census data from 2013 shows Pacific groups comprise 12% of Auckland/Northland population.¹¹ Children of Māori ethnicity compromised 28% of empyema cases (Auckland Northland region census data shows 13% Māori), European 20% (61% census data), Asian 7% (21% census data), and Other 3% (2% census data) (Figure 2).

In the South Island, 73% of empyema cases occurred in children identifying as Europeans (compared with census data showing European to be 88% of South Island population), followed by Māori 13% (9% census data), Pacific 10% (2% census data) and Asian 3% (6% census data) (Figure 2).

Seasonal trends

The number of cases of empyema fluctuated over the course of the year with both centres experiencing peaks in winter and spring months (38% and 28% respectively) and less cases presenting in the summer months (Figure 3).

Mode of infection

Community-acquired pneumonia was the most common mode of infection (95% total; 93% SCH; 100% CCH), followed by disseminated sepsis (primary source other than lung) (5% total; 7% SCH; 0% CCH).

Microbiology

A total of 109 organisms were isolated from sterile sites (85 SCH; 24 CCH) (Figure 4, Table 1). Serology confirmed an additional 4 cases (3 of *Mycoplasma pneumoniae*, 1 of *Chlamydomphila pneumoniae*).

Staphylococcus aureus was the most common organism isolated (42% total; 46%

Figure 3. Seasonal trends in community-acquired empyema at Starship Children's Hospital and Christchurch Hospital between January 2009 and May 2014

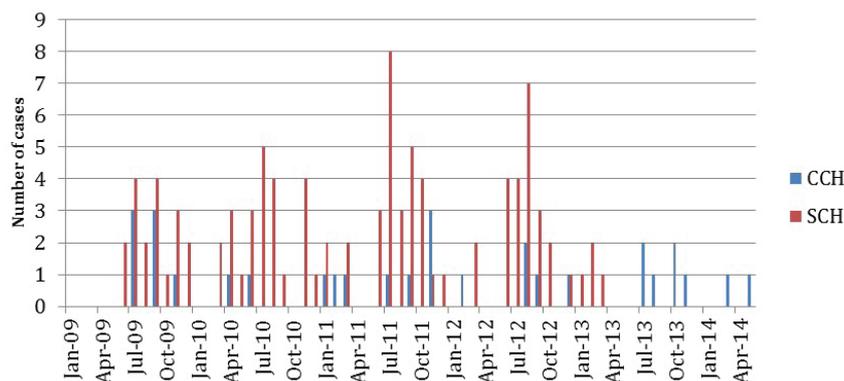
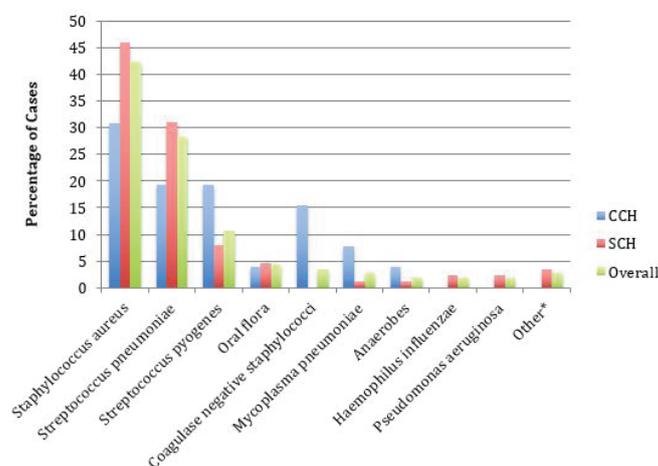


Figure 4. Organisms isolated from sterile sites and by serology presenting with empyema at Starship Children's Hospital (June 2009 to March 2014) and Christchurch Hospital (January 2009 to May 2014)



* Other included *Achromobacter* (1), *Chlamydomyces pneumoniae* (1), and *Mycobacterium avium intracellulare complex* (1)

SCH; 30% CCH), followed by *Streptococcus pneumoniae* (28% total; 31% SCH; 19% CCH), and *Streptococcus pyogenes* (11% total; 8% SCH; 19% CCH).

Of the 48 *Staphylococcus aureus* isolated, 38 (79%) were methicillin-sensitive (80% SCH; 75% CCH) and 10 (21%) were methicillin-resistant (20% SCH; 25% CCH).

Overall, MRSA comprised 9% of all organisms detected (9% SCH; 8% CCH) and was present in 8% of all cases.

Five of 7 cases of disseminated sepsis were due to *S.aureus*.

Of the 128 community-acquired cases, 32 (25%) had no pathogen identified with culture, antigen detection, or nucleic acid detection from sterile sites (23% SCH; 30% CCH).

There was no significant difference between centres in the rates of causative empyema pathogens.

Diagnosis

Blood culture was performed in 96% of cases (97% SCH, 93% CCH). At least one blood culture was positive in 27% (29% SCH; 21% CCH) of cases and amongst new positive cultures, 83% (86% SCH; 67% CCH) were considered clinically relevant.

S. pneumoniae pleural antigen testing was performed in 26% (33/126) of patients who had pleural samples (30% SCH; 13% CCH). The antigen was positive in 4 of 4 culture-proven pneumococcal cases and confirmed an additional 9 cases where all other sterile site cultures were negative. An additional case was confirmed from CSF antigen, where pleural fluid was not sampled.

Discussion

We present the first national data on the microbiology of paediatric empyema.

Table 1.

Organisms identified in paediatric empyema cases from Starship Children's Hospital (June 2009 to March 2013) and Christchurch Hospital (January 2009 to May 2014); Empiric coverage from recommended treatment guidelines

Organism	Number of Isolates (SCH) N=87	Number of Isolates (CCH) N=26	SCH Empyema Guidelines EITHER OR		CCH Empyema Guidelines Cefotaxime AND Flucloxacillin	TSANZ Empyema Guidelines Penicillin AND Flucloxacillin
			Amoxycillin/clavulanate	Cefuroxime		
Methicillin sensitive <i>Staphylococcus aureus</i>	32	6	S	S	S	S
Methicillin resistant <i>Staphylococcus aureus</i>	8	2	R	R	R	R
<i>Streptococcus pneumoniae</i>	27	5	S	S	S	S
<i>Streptococcus pyogenes</i>	7	5	S	S	S	S
Oral flora	4	1	S	V/S	V/S	V/S
Coagulase negative staphylococci	0	4	V	V	V	V
<i>Mycoplasma pneumoniae</i> and <i>Chlamydia pneumoniae</i>	2	2	R	R	R	R
Anaerobes	1	1	S	R	R	R
<i>Haemophilus influenzae</i>	2	0	S	S	S	S
<i>Pseudomonas aeruginosa</i>	2	0	R	R	R	R
Other	2	0	R	R	R	R
Proportion Susceptible to Guideline Recommendations			81 – 84%	74 – 82%	74 – 82%	74 – 82%

Other: includes *Achromobacter* and *Mycobacterium avium intracellulare complex*
S = Susceptible, V = Variable, R = Resistant

Only one prior publication has examined paediatric empyema in New Zealand reviewing surgical management at a single centre prior to 2008.¹⁰ International trends show that paediatric empyema is increasing and a recent review of South Auckland paediatric empyema data also shows a clear and dramatic increase in rates over the last 15 years.^{12,13} Our reported rates of 2.2 to 5.8 per 100,000 for children up to 18 years are high compared to other developed countries. National discharge data from the United States reported incidence of paediatric empyema in children aged up to 18 years had risen from 3.8 to 5.5/100,000 and in UK for children aged <15 years, empyema incidence is reported as 3.7/100,000. Australia has reported a lower rate of only 1/100,000 for children aged <18yrs.¹⁴⁻¹⁸

Our review shows *Staphylococcus aureus* (*S.aureus*) was the most common organism

implicated in community-acquired paediatric empyema, which contrasts with other developed countries, where *Streptococcus pneumoniae* (*S.pneumoniae*) is most common.¹⁷⁻¹⁹ An Australian study using blood and pleural fluid samples to identify empyema pathogens with both culture and PCR identified *S.pneumoniae* as the most common empyema organism accounting for 52% of cases whilst *S.aureus* was detected in only 10%.¹⁹ However, New Zealand rates of invasive *S.aureus* sepsis, which includes sepsis with a respiratory focus, has been described as amongst the highest in the world.⁹ We found *S.aureus* as the major causative pathogen of paediatric empyema in both the North and South islands, with no statistically significant difference. The proportion of *S.aureus* isolates that were methicillin-resistant (MRSA) was 20%, which represents 8.8% of all organisms detected (9.2% SCH; 7.7% CCH). The one

prior study of paediatric empyema in New Zealand, between 2003-2008 at SCH, showed similar high rates of *S.aureus* (24/46 positive cultures, 52%; our data 48/113, 42%).⁷ However, MRSA isolates comprised only 2/46 (4%) isolates in this prior audit. Our data show MRSA may be an increasingly important proportion of New Zealand paediatric empyema. In contrast, national data showed between 2001 and 2011 MRSA did not appear to increase, remaining as a proportion of 12% of *S. aureus* infections in the face of clear increases overall in invasive MSSA infections.^{9,20}

Current empiric antimicrobial protocols at both hospitals are aligned with Thoracic Society of Australia and New Zealand guidance, and provide good coverage against the range of pathogens we have identified causing empyema. With MRSA causing less than 10% of paediatric empyema at present neither site specifically recommends initial antibiotics to cover MRSA. Clinicians need to be aware of MRSA infection and potential risk factors (eg previous infection with MRSA in child or family member) and consider MRSA infection if there is a lack of response to empiric antimicrobial therapy, disseminated infection at presentation, or when blood cultures are flagging Gram-positive cocci.

Children of Māori or Pacific ethnicity were over-represented in cases of empyema. Children of Māori ethnicity, despite representing less than 13% of the Auckland/Northland population and less than 9% of South island population, made up 28% of cases at SSH, and 13% in CCH.¹¹ Children identifying as Pacific constitute over 13% of Auckland and 2% of the Canterbury population, yet this group was 42% of cases at SCH, and 10% in CCH. Although ethnicity data collected by health records can be misclassified,²¹ our data support prior evidence that show high rates of admission for respiratory disease in children in New Zealand compared with other developed countries, including Australia.²² There is substantial ethnic inequality in rates of respiratory infectious disease admissions, and this is most apparent in the youngest age groups.^{23,24} Differences in risk factors for infectious diseases, such as over-crowding, poor housing, and passive smoke exposure, are

likely to play a key role, but also aspects such as poor access to primary health care for these groups.^{25,26}

In empyema it appears that blood cultures played an important role in diagnostics and were positive in 27% of patients. This is in contrast to uncomplicated pneumonia, where blood culture yield is typically poor.²⁷

Use of rapid antigen methods on pleural fluid are increasingly recognised for diagnosis in pleural empyema. Our audit shows that both major paediatric centres are using 'Binax NOW' *Streptococcus pneumoniae* antigen test (Binax, Portland, USA) as a diagnostic tool. International literature supports this, with results from 'Binax' comparable in sensitivity (>80%) and specificity to pneumococcal PCR.²⁸⁻³¹ Detecting pneumococcal antigen in pleural fluid by rapid test is easy, quick, and enables early rationalisation to appropriate narrow-spectrum antibiotics, particularly in the context of prior antibiotics where culture negativity of pleural fluid is more likely. A significant proportion of our empyema cases remain without a pathogen identified. Methods such as molecular techniques and pneumococcal antigen tests on pleural fluid can enable the pathogens of empyema and their true burden to be elucidated. *S.pneumoniae* is the pathogen most often identified in culture-negative pleural specimens when molecular diagnostic tools are applied,³¹ which is important in understanding the impact of conjugate pneumococcal vaccines (PCV), particularly newer generation PCV13 which covers 'empyema' serotypes (serotypes 1,3 and 19A).^{17,19,32}

Several childhood vaccines have the potential to prevent respiratory infections that can lead to empyema. These include *Haemophilus influenzae* type b (Hib) and the new PCV13, both funded for New Zealand children with high coverage rates across the country. There were only two cases of *Haemophilus influenzae* seen in our audit, both nontypable. Seasonal influenza vaccine has been funded in Canterbury for all aged less than 18 years since 2011, however the uptake of this vaccine has remained below 30% in this population. Elsewhere in NZ influenza vaccine is only funded for children aged less than 5 years who have a history of significant respiratory illness. The majority of cases

of empyema are seen in children aged <5 years and the increases in empyema admissions observed elsewhere are most marked in this age group.¹⁵ Targeting vaccination strategies such as access to influenza vaccination for all children under 5 years are important strategies to address this vulnerable age group.

As an audit our data has several limitations including the retrospective nature of the data and reliance on hospital records. Our data collection spans 2009 when pandemic H1N1 influenza caused significant respiratory illness burden across New Zealand.^{33,34} However, we provide an important snapshot into the nature of empyema across two centres in New Zealand and raise important questions. For both the North and South island, *S.aureus* is the dominant pathogen in paediatric empyema, accounting for over one third of culture-positive cases. Current empiric antibiotic guidelines cover this important pathogen, however MRSA coverage may be

needed for some—particularly those most unwell or with disseminated sepsis, more indicative of *S.aureus* disease. Recently introduced PCV13 is expected to have better coverage of empyema caused by *S.pneumoniae*, although emergent invasive serotypes are still possible and improved diagnostic testing of empyema can help to clarify the ongoing role of *S.pneumoniae*. A Paediatric Surveillance Unit study is currently looking at all hospitalisations for paediatric empyema in New Zealand and will prospectively collect information on current management and incidence to compare with data such as ours.³⁵ Questions remain as to whether empyema is increasing across the country or only in certain population groups, and the impact of recent changes to pneumococcal vaccination. For New Zealand, where dominant pathogens are different from other developed countries, important issues around the best surgical management, as well as long-term outcome from childhood empyema, are also raised.

Competing interests: Nil

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