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Etiology of Community-Acquired Pneumonia in Western Australian Metropolitan Hospitals: Missed Opportunities for Pneumococcal Vaccination

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Abstract

Background and Objectives: Community-Acquired Pneumonia (CAP) is a leading cause of hospitalization and death worldwide. Knowledge of local pathogens guides antimicrobial treatment, however the etiology of CAP in Western Australia has not been well studied. We hypothesized that *Streptococcus pneumonia, Chlamydia pneumonia, Mycoplasma pneumonia* and respiratory viruses would be common pathogens detected in patients hospitalized with CAP. We further hypothesized that the pneumococcal vaccination would impact upon rates of *Streptococcus pneumonia* detection.

Methods: A retrospective analysis of two hospital medical record databases identified all patients 18 years or older admitted with CAP in 2015. Patients with recent hospitalization, significant immune suppression, chronic respiratory disease or active cancer were excluded. All investigations ordered during admission were reviewed.

Results: 184 patients met the necessary criteria with radiographic evidence and clinical features of CAP. Mean age was 66 years (range, 20-96), 19 patients required admission to intensive care and 3 patients died. There were 75 pathogens detected in 55 patients (30%). The most common pathogens detected were influenza virus (7%), *Streptococcus pneumonia* (7%) and *Haemophilus influenza* (7%). Only one of seven 'high-risk' patients with isolated *Streptococcus pneumonia* was appropriately vaccinated.

Conclusions: Causative agents were not detected in the majority of patients. Bacteria were most frequently detected, however influenza virus was the most common single pathogen detected. There were missed opportunities in administering pneumococcal vaccinations in the community. We believe a prospective study ensuring consistent and updated diagnostic protocols is overdue.

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Introduction

Community-acquired pneumonia (CAP) is the leading cause of hospitalization and death worldwide [1-3]. Despite advances in medical care and antimicrobial therapy, the mortality rate for admitted patients remains at 2-5% [4]. Lack of local knowledge of pathogens causing CAP requires selection of empirical antimicrobial treatment, which has a substantial impact on patient prognosis [5-6]. In the pre-antibiotic era, *Streptococcus pneumonia* was responsible for 95% of cases of pneumonia [7]. Improved etiological investigations, the introduction of the Pneumococcal Polysaccharide Vaccine (PPV) in adults, [8] the nearly universal administration of the pneumococcal conjugate vaccine in children, [9] and decreased smoking rates have all been recognized as contributing factors in the decline of *S. pneumonia* pneumonia [10]. The apparently lower proportion of *S. pneumonia* has led to speculation that viruses are responsible for an increased proportion of CAP in adults. It is difficult to determine if this is true or reflects recent advances in viral diagnosis, the difficulty of establishing the etiology of pneumonia or the prevalence of dual infections [11]. A recent prospective, multicenter, population-based, active surveillance study in the United States demonstrated that respiratory viruses were more frequently detected than bacteria in patients presenting with CAP[4]This study identified the likely causative pathogen in 38% of cases; of these, one or more viruses were identified in 23% of cases, bacteria in 11% and fungal/mycobacteria in 1%. The most commonly identified pathogens were human rhinovirus (9% of patients), influenza virus (6%) and *S. pneumonia* (5%). The Australian CAP Study (ACAPS), one of Australia's most rigorous studies on CAP, identified the likely causative pathogen in 46% of patients

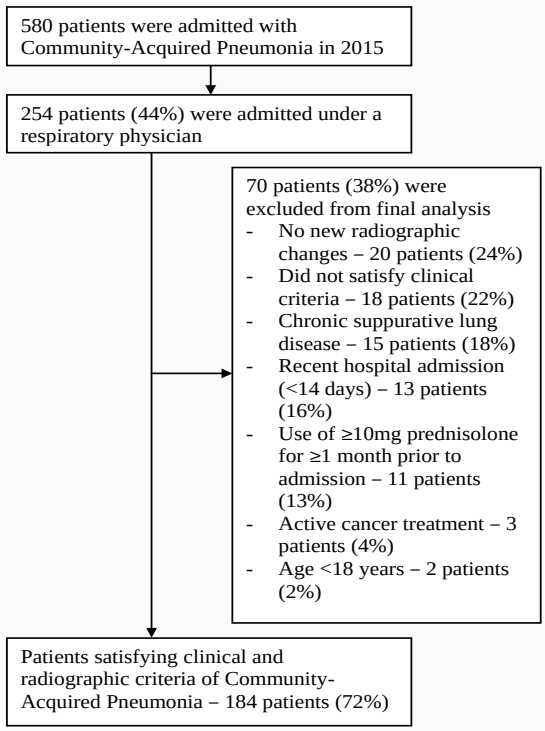

Figure 1: Eligibility and Enrolment of Patients with CAP.

[12] of these pathogens, one or more bacteria were detected in 38% of cases and respiratory viruses were detected in 15%. *S. pneumonia* (14% of patients) and *Mycoplasma pneumonia* (9%) were most frequently detected [12]. This study is based on data greater than 10 years old and prior to the greater availability of viral PCR. Despite advances in diagnostic technology, many patients with suspected CAP receive empiric antimicrobial therapy without identification of the likely causative pathogen [13]. Early initiation of therapy increases the likelihood of an optimal outcome in hospitalized patients [14]. However carries the risk of over-prescribing with consequent super infection by resistant pathogens or selection of antibiotic resistance [15]. The PPV was added to the Australian Pharmaceutical Benefits Scheme in 2005 for adults older than 65 years and with conditions that increase the risk of invasive pneumococcal disease (IPD) (Table 1) [16]. Following the introduction of the PPV, the incidence of IPD in adults older than 65 has reduced by 29% from 2002-2004 to 2006-2007 [16]. As pneumonia is the most common manifestation of IPD in adults [16]. This suggests that the PPV has had a substantial impact on the frequency of *S. pneumonia* pneumonia. The rate of the PPV vaccination in patients whom present with *S. pneumonia* pneumonia is however not well known. The aim of this study is to determine the etiology of CAP in two private hospitals in metropolitan Perth, Western Australia. It is hypothesized that in patients with clinical and radiographic evidence of CAP, *S. pneumonia , Chlamydia pneumonia, M. Pneumonia* and respiratory viruses would be commonly detected. We further hypothesized that in patients with *S. pneumonia* infection, the rates of pneumococcal vaccination would be low and may represented a missed opportunity for preventative measures.

Materials and Methods

Study design and setting

This study was completed in two stages. Stage one involved a pilot study of 20 patients admitted to hospital with CAP. This allowed identification of data available for retrospective extraction from patient medical records. Stage two involved completing the study using readily available data identified in stage one. Patients were retrospectively identified from two private metropolitan Perth hospitals (507 and 555 beds respectively). All patients admitted to either hospital from January 1st 2015 to December 31st 2015 with 'Pneumonia' were identified from hospital medical records. A waiver of patient consent was obtained and human research ethics approval was obtained at both hospitals and the supervising university.

Inclusion criteria

Inclusion criteria for the study were as follows; age >18 years; chest radiograph or computed tomography scan within 48 hours prior to or following admission demonstrating features of pneumonia; at least 2 symptoms consistent with pneumonia (new or increased cough, new or increased sputum expectoration, tachypnea, hypoxemia, hemoptysis, temperature >38.0˚C or <36.1˚C, pleuritic chest pain, altered mental state, examination findings [crackles or bronchial breath sounds on auscultation; dullness on percussion]) and admission under a respiratory physician. Patients were excluded if they had been discharged from any hospital within the previous 14 days, had significant immune suppression (HIV infection, use of greater than or equal to 10mg prednisolone daily in the previous month), active cancer treatment, prior organ transplantation, chronic superlative lung disease (bronchiectasis, cystic fibrosis) or suspected aspiration pneumonia.

Data collection

Data was collected from hospital medical records using a standardized tool, including patient demographics, co-morbidities, clinical features, radiologic findings, antibiotics use prior to admission, severity score (CURB-65) and outcomes (length of stay, admission to the Intensive Care Unit (ICU) and mortality). The result of all microbiological studies completed during admission were reviewed, including blood culture, sputum culture/polymerase chain reaction (PCR) assay, respiratory serology, *M. pneumonia* antibodies, nasopharyngeal swab PCR assay, pleural fluid PCR assay, bronchoalveolar-lavage specimen culture, oropharyngeal swab PCR assay and urine antigen detection (*Legionella pneumophilia* and *S. pneumonia)*.

Outcome measures

The primary outcome measure was pathogen etiology. Secondary outcomes measures included length of stay, admission to ICU, in-hospital mortality and disease severity. Severity was calculated using the CURB-65 score and used to classify patients into groups; Group 1, scores of 0-1; Group 2, score of 2; and Group 3, scores of 3-5 [17]. Furthermore, we determined investigations that we felt were important in the assessment of CAP and examined the frequency in which these investigations had been performed. We also contacted the general practitioner of patients with detected *S. pneumonia* or influenza virus to investigate whether the appropriate vaccinations were up to date.

Statistical analysis

Statistical analysis was completed using SPSS software. Descriptive statistics were calculated for proportions and frequency data. Logistic regression was used to determine the relationship between severity of presenting disease, detected pathogens and outcome measures.

Table 1: Conditions associated with increased risk of Invasive Pneumococcal Disease (IPD)[16].

Category A – Highest risk of IPD	Category B – Increased risk of IPD
Functional or anatomical asplenia*	Chronic cardiac disease§
Immunocompromising conditions‡	Chronic lung disease¶
Proven or presumptive cerebrospinal leak	Diabetes mellitus
Cochlear implants	Down syndrome
Intracranial shunts	Alcoholism
	Chronic liver disease
	Preterm birth at <28 weeks gestation
	Tobacco smoking
*	Sickle cell disease or other haemoglobinopathies, congenital or acquired asplenia, splenic dysfunction
‡	Congenital or acquired immune deficiency (including symptomatic IgG subclass or isolated IgA deficiency), immunosuppressive therapy or radiation therapy where there is sufficient immune reconstitution for vaccine response to be expected, haematological and other malignancies, solid organ transplant, haematopoietic stem cell transplants, HIV infection, chronic renal failure and relapsing or persistent nephrotic syndrome
§	Particularly cyanotic heart disease or cardiac failure in children, excluding hypertension only (adults)
¶	Chronic lung disease in preterm infants, cystic fibrosis, severe asthma in adults (requiring frequent hospital visits and use of multiple medications)

Results

Study population

There were 254 patients admitted with CAP under a respiratory physician between two hospitals, 70 patients were excluded (Figure 1). Patients were most frequently excluded due to lack of new radiologic changes or not satisfying clinical criteria. Following exclusion, 184 patients were eligible for analysis.

Patient demographics

Demographics details of included patients are described in (Table 2). There were nine patients from a retirement village or nursing home included in this study.

Co-morbidities

Frequency of patient co-morbidities is outlined in (Table 2). There were 106 patients (57.61%) with at least one co-morbidity. The most common co-morbidities were chronic respiratory disease (38.59%) and chronic heart disease (23.37%).

Detected pathogens

Pathogens were detected in 55 patients (29.89%) and more than 1 pathogen was detected in 16 patients (8.70%). Bacteria were detected in 39 patients (21.20%), viruses in 26 patients (14.13%) and fungi in 2 patients (1.09%). The most common pathogens detected were influenza virus (7.07%), *S. pneumonia* (6.52%) and *Haemophilus influenza* (6.52%). Frequency of detected pathogens is described in (Table 3).

Multiple pathogens

In patients with greater than 1 pathogen detected, two pathogens were detected in 13 patients (7.07%), three pathogens in 2 patients (1.09%) and four pathogens in 1 patient (0.54%). The Kruskal-Wallis test demonstrated no statistical difference in the number of pathogens identified between patients presenting with mild, moderate and severe CAP (p = 0.53). Respiratory viruses were detected alone in 14 patients (7.61%) and with a co-bacterial pathogen in 11 patients (5.98%).

Severity and ICU admission

Severity of presentation was the only significant predictor of ICU admission, OR 0.71 (95% CI 1.36-3.59), p = 0.001 (Wald Criterion). Patients admitted to the ICU were marginally more likely to have a pathogen detected (9 of 19 patients) compared to those not admitted to the ICU (46 of 165 patients) (p = 0.079). Severity according to pathogens is outlined in Table 4. Patients admitted to ICU were older (mean age 77.93 years compared to 66.63 years, p = 0.134) and displayed an increased number of co-morbidities (1.21 compared to 0.82, p = 0.23).

Investigations

Investigations ordered during admission are outlined in (Table 5). Sputum culture/PCR assay and nasopharyngeal swab PCR assay provided the greatest diagnostic yield; detecting a pathogen in 26 patients (28.57%) and 7 patients (23.33%) respectively. Blood cultures were most commonly ordered (98 patients), however were only positive for 9 patients (9.18%).

Vaccination

There were 105 patients older than 65 years of age and 29 patients below 65 at increased risk of pneumococcal infection and influenza virus [16-20]. Pneumococcal infection – Of the 12 patients with isolated *S. pneumonia*, five were over the age of 65 and two others were considered at increased risk of pneumococcal disease due to chronic lung disease. Only one patient, whom was greater than 65 years of age and had isolated *S. pneumonia*, received the pneumococcal vaccination within five years prior to admission. *Influenza virus* - Of the 13 patients with isolated influenza virus, three were over 65 and three others were considered at increased risk, including two with chronic respiratory disease and one with chronic liver disease. All patients above 65 years received the annual influenza vaccination prior to admission, however only one patient below 65 years at increased risk received the annual influenza vaccination prior to admission.

Discussion

This is the first study examining the etiology of CAP in two major private hospitals in Perth, Western Australia. As hypothesized, *S. pneumonia* was not as frequently detected as previous studies [12,18-19,21]. Respiratory viruses were commonly detected. Infection with *C. pneumonia* and *M. pneumonia* was rare in this cohort. Influenza virus was the most common pathogen detected in this study.

Table 2: Patient Characteristics.

Characteristics	No. of patients (%)
Male Sex	93 (50.5%)
Age at admission	
18-49 years	34 (18.5%)
50-64 years	48 (26.1%)
65-79 years	58 (31.5%)
>80 years	44 (23.9%)
Mean age	66.23 years
Patient comorbidities*	
Chronic lung disease	71 (38.6%)
Chronic heart disease	43 (23.4%)
Diabetes mellitus	20 (10.9%)
Neurological disorder	16 (8.7%)
Chronic kidney disease	15 (8.1%)
Chronic liver disease	1 (0.5%)
Splenectomy	1 (0.5%)
Retirement village/ nursing home resident	9 (4.9%)
Aboriginal and Torres Strait Islanders	0 (0%)
Admission source	
Emergency department	148 (80.4%)
Referred from community	36 (19.6%)
Antibiotics prior to admission	61 (33.1%)
Severity (CURB-65)	
Group 1 (0-1)	120 (65.2%)
Group 2 (2)	48 (26.1%)
Group 3 (3-5)	16 (8.7%)
Admission to ICU	19 (10.3%)
Mean length of stay	5.84 days
Death during hospitalization	3 (1.6%)
*	Any underlying medical condition including chronic lung disease (asthma, chronic obstructive pulmonary disease, obstructive lung disease or pulmonary fibrosis), chronic heart disease (coronary artery disease, congestive cardiac failure, but not hypertension), neurological disorder (epilepsy, cerebral palsy, dementia or history of stroke), chronic kidney disease (with or without dialysis) and chronic liver disease (hepatitis, cirrhosis or hepatic failure).

Table 3: Pathogen detection in patients admitted with CAP.

Organism	No. (%)
Influenza virus	13 (7.1%)
Streptococcus pneumoniae	12 (6.5%)
Haemophilus influenzae	12 (6.5%)
Respiratory syncytial virus	5 (2.7%)
Parainfluenza virus	5 (2.7%)
*Chlamydophilia species**	4 (2.2%)
Coagulase negative staphylococcus	4 (2.2%)
Legionella species‡	3 (1.6%)
Staphylococcus aureus	3 (1.6%)
Mycoplasma pneumoniae	1 (0.5%)
Other§	13 (7.1%)
* ‡ §*	*Chlamydophilia* species consisted of *Chlamydophilia pneumoniae* (3 episodes) and *Chlamydophilia psittaci* (1 episode). *Legionella* species consisted of *Legionella longbeachea* (2 episodes) and *Legionella pneumophilia* (1 episode). Other organisms were *Moraxella catarrhalis* (2 episodes), *Strenotrophomonas maltophilia* (2 episodes), *Aspergillus fumigatus complex* (2 episodes), Adenovirus (2 episodes) *Pseudomonas aeruginosa* (1 episode), *Streptococcus pyogenes* (1 episode), *Corynebacterium* species (1 episode), Entero virus/Rhinovirus (1 episode) and Human metapneumovirus (1 episode).

Despite reviewing all investigations during hospitalization, pathogen detection was lower than recent studies [4,12,19, 22-29] This is likely a result of the retrospective nature of the study, an inability to obtain lower respiratory tract specimens in all patients, antibiotic use prior to admission and incomplete sampling. Complete sampling in patients not administered antibiotics prior to admission can increase pathogen detection to ~90% [27]. Is it likely that a prospective study utilizing new technologies, such as real-time quantitative PCR testing of sputum samples for *S. pneumonia* , *H. influenzae* and *Moraxella catarrhalis* [27] would increase pathogen detection, and in our view such a study is overdue. The most common bacterial pathogens detected were *S. pneumonia* and *H. influenza*. Despite regular detection of *S. pneumonia* , this study reinforces that it is not as frequently detected in CAP as once thought [4,12,27-29]. While *S. pneumonia* was most commonly detected via sputum culture/PCR assay and blood cultures, the scant use of urinary antigen detection in conjunction with the low sensitivity of blood cultures [30] suggests a proportion of patients were undetected. Of the 12 patients with isolated *S. pneumonia*, seven were eligible for the pneumococcal vaccination, however only one patient received the vaccination. This represents a missed opportunity to reduce the severity of pneumococcal infection, or avoid significant infection altogether, in the at risk population. Atypical pathogens, *M. pneumonia, L. pneumophilia* and *C. pneumonia*, were detected less frequently than expected. A significant proportion of patients with these pathogens presented with moderate or severe CAP, a phenomenon previously discussed by Lui et al. [31]. This supports the importance of investigating for so called atypical pathogens, particularly as they do not respond to beta-lactam therapy alone and other treatment, such as a macrolide, doxycycline or quinolone, is indicated [31] Respiratory viruses were detected in 14% of patients and as a whole, were detected more frequently than any single bacterial pathogen. The frequency of viral detection was consistent with the 15% reported by Charles et al [12] and John stone, [28] however less than the 23-32% in other studies [4,29,32]. In such patients, it is difficult to distinguish whether the detected virus was the sole pathogen, acting as a predisposing factor or presenting as a co-pathogen [11]. In this study, nearly half of all patients with detected viral pathogens had a co-pathogen, the majority of which were bacterial. While it has been suggested that viral-bacterial co-infection is associated with severe disease [11]. This study did not identify any difference in severity between those with a viral pathogen alone compared to viral-bacterial co-infection. Influenza virus was the most commonly identified pathogen in this

Table 4: Severity on admission Severity (CURB-65 Score).

Etiologic Agent	No. of episodes	Group 1 (0, 1) - Mild	Group 2 (2) - Moderate	Group 3 (3, 4, 5) - Severe
Influenza virus	13	11 (84.6%)	2 (15.4%)	0 (0%)
Streptococcus pneumoniae	12	10 (83.3%)	1 (8.3%)	1 (8.3%)
Haemophilus influenza	12	5 (41.3%)	6 (50.0%)	1 (8.3%)
Respiratory syncytial virus	5	1 (20.0%)	3 (60.0%)	1 (20.0%)
Parainfluenza virus	5	3 (60.0%)	2 (40.0%)	0 (0%)
Chlamydophilia species	4	2 (50.0%)	1 (25.0%)	1 (25.0%)
Coagulase negative staphylococcus	3	2 (66.7%)	1 (33.3%)	0 (0%)
Legionella species	3	2 (66.7%)	1 (33.3%)	0 (0%)
Staphylococcus aureus	3	1 (33.3%)	1 (33.3%)	1 (33.3%)
Mycoplasma pneumoniae	1	1 (100%)	0 (0%)	0 (0%)
No pathogen detected	129	88 (68.2%)	31 (24.0%)	10 (7.7%)

Table 5: Investigations ordered during admission.

No. of investigations	(% of patients)
Blood culture	98 (53.2%)
Sputum culture/PCR assay	91 (49.4%)
Respiratory serology	87 (47.3%)
Mycoplasma pneumonia antibody	50 (27.2%)
Nasopharyngeal swab PCR assay	30 (16.3%)
Pleural fluid PCR assay	6 (3.2%)
Bronchoalveolar-lavage specimen culture	5 (2.7%)
Oropharyngeal swab PCR assay	5 (2.7%)
Urine antigen detection (*L. pneumophilia* or *S. pneumoniae*)	5 (2.7%)

study and was consistent with previous studies [4,12]. Nearly half of the patients with influenza virus had a bacterial co-pathogen, of which half were *S. pneumonia*. As bacterial co-infection with influenza virus is a known cause of severe pneumonia and mortality [11] influenza virus testing and use of empiric antiviral therapy in addition to antibiotic therapy is appropriate [4]. Especially during the influenza season. In this study, 77% of patients with influenza virus were less than 65 years of age, which contrasts with previous studies [4]. This may reflect greater use of the influenza vaccination in patients 65 years or older and adds weight to the recommendation that the routine influenza vaccination should be administered to all persons aged ≥6 months who do not have contraindications [33] The number of patients who died during admission was consistent with previous studies [4]. These patients were older (87.61 years compared to 65.87 years), not as likely to receive antibiotics prior to admission and had an increased number of co-morbidities, including two patients on home oxygen for idiopathic pulmonary fibrosis. Two of the three patients who died were admitted to ICU and a pathogen was isolated in only one patient (*S. aureus*). This is a retrospective study and many patients did not receive all investigations. Many patients did not receive all investigations that would likely form part of the protocol in a prospective study. This study was completed in a private hospital and may not be generalizable to all Western Australian hospitals. Despite this, results are consistent with previous CAP studies from private and public hospitals in Australia, one of the hospitals is directly serviceable by an emergency department and the other is part of the large Metropolitan Health Service network in Western Australia with direct access to a large emergency department. There were no patients of Aboriginal and Torres Strait Islander heritage and this study does not shed light on likely pathogens in the group. This study adds to the understanding of the microbiological cause, subsequent management and prognosis of CAP in Western Australia. Influenza virus was the most common pathogen detected, however bacterial pathogens were more commonly detected than viral pathogens. *S. pneumonia* remains an important cause of CAP but appears to be less prevalent than historical studies. Of the patients with isolated *S. pneumonia* and influenza virus, many were not vaccinated reflecting missed opportunities for preventative measures in the community.

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