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MICROBIOLOGY

Low utilisation of diagnostic microbiology for community acquired pneumonia in regional Victoria

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Summary

Aims: Diagnostic microbiology for community acquired pneumonia (CAP) provides useful information for patient management, infection control and epidemiological surveillance. Newer techniques enhance that information and the time interval for obtaining results. An audit of diagnostic microbiology utilisation, microbiological aetiology, and influence of results on prescribing practices in CAP in a regional Australian hospital setting was performed.

Methods: Clinical, microbiological and outcome data were collected by medical record review of patients discharged from Ballarat Hospital with a diagnosis of CAP over a 12 month period.

Results: Of 184 identified CAP episodes, 47 (25.5%) had no diagnostic microbiology performed. Respiratory virus polymerase chain reaction (PCR) was rarely performed (2.7% of all episodes). Acute serology was frequently requested, however paired acute and convalescent serology was infrequently performed (5/75 testing episodes; 6.7%). CAP severity was not correlated with microbiological investigation intensity. The most common pathogens identified were *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* (5.4% and 2.2%, respectively). Diagnostic testing appeared to rarely influence antimicrobial prescribing.

Conclusions: In this setting, diagnostic microbiological tests such as respiratory virus PCR and urinary antigen tests are under-utilised. In contrast, sputum and serological investigations are commonly requested, however rarely influence practice. Interventions to facilitate efficient usage of diagnostic microbiology are required.

Key words: Community acquired pneumonia, investigation, microbiology.

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INTRODUCTION

Community acquired pneumonia (CAP) is a common presentation to emergency departments and a frequent reason for hospital admission. Of admitted patients, 30 day mortality in Australian hospitals is 5.7%, but varies with severity.^{1,2} Local and international groups have published guidelines for the management of CAP, including the use of antibiotics and microbiological investigations.^{3–5} The underlying microbial cause of CAP in various populations has been well described, however more limited data are available for CAP in Australian

rural settings.¹ Ballarat Hospital is the largest hospital in the Grampians region of Victoria, and services an estimated 224 000 people spread over 48 000 square kilometers. It provides 221 acute inpatient beds and services the regional centre of Ballarat (population 96 000). This 12 month retrospective audit of CAP admissions to Ballarat Hospital was conducted to assess frequency of investigation, microbial aetiology and corresponding clinical outcomes.

MATERIALS AND METHODS

Setting and patient selection

Patient records from all patients admitted to Ballarat Hospital with a discharge diagnosis of CAP between 1 October 2007 and 30 September 2008 were retrieved and reviewed. Patients meeting all the following criteria were included: discharge diagnosis of CAP, clinical syndrome compatible with CAP, consolidation on chest radiography (as reported by a radiologist), and age ≥ 18 years. Patients with suspected aspiration pneumonia, hospital acquired pneumonia, significant immunosuppression (active treatment for malignancy, prior organ transplantation, HIV, use of >10 mg of prednisolone per day in the previous month, or equivalent immunosuppressive agent), or transfer from another healthcare facility were excluded. Parameters allowing calculation of the pneumonia severity index (PSI), discharge data, length of stay and antibiotic treatment regimens were collected.⁶ Where available, results of blood cultures, sputum microscopy and culture, urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* (PUAT and LUAT, respectively), nose and/or throat swabs for respiratory viruses and acute and convalescent serology for respiratory pathogens were recorded from the hospital pathology system. Ethics approval was not required for this retrospective audit.

Microbiological investigations

Microbiological investigations were performed as per treating clinician discretion, with reference to recommendations in national guidelines.⁷ Conventional techniques were used for aerobic and anaerobic blood cultures, sputum microscopy and culture. A significant result on sputum microscopy and culture was only recorded if all of the following criteria were met: sample was collected within 24 h of admission, there was a predominance of neutrophils on microscopy, and if both microscopy and culture were concordant. Nose and/or throat swabs for respiratory viruses (influenza A and B, parainfluenza 1–3, picornavirus, respiratory syncytial virus and adenovirus) were processed for multiplex polymerase chain reaction (PCR) as previously described.⁸ Serology for *Mycoplasma pneumoniae* was by particle agglutination (Serodia; Fujirebio, Japan), *L. pneumophila* by immunofluorescence (*L. pneumophila* serogroup 1–6 IgG; QML Pathology), influenza A and B by complement fixation (Victorian Infectious Diseases Reference Laboratory; VIDRL), *Coxiella burnetii* phase I and II by complement fixation (VIDRL) and *Chlamydia* group serology by ELISA (SeroELISA; Savyon Diagnostics, Israel) with speciation by immunofluorescence if required. PUAT (BinaxNOW pneumococcal urinary antigen

detection kit) and LUAT (BinaxNOW *Legionella* urinary antigen EIA kit) were performed on un-concentrated urine specimens as per the manufacturer's instructions (Alere, USA).

Outcome measures

The proportion of patients having microbiological investigation and the yield (proportions of tests performed returning a positive result) of various tests were expressed as percentages. Association between PSI and the number of tests performed and likely yield of causative pathogen was assessed using Mann–Whitney U test.

Where a pathogen was identified, this was interpreted as the probable causative pathogen if any of the following criteria were met: culture of an organism known to cause CAP from blood cultures; any positive urinary antigen; compatible sputum culture and microscopy in a good quality sputum specimen (defined above); an initial antibody titre ≥ 160 for *M. pneumoniae* or ≥ 4 -fold rise between acute and convalescent phase (*M. pneumoniae*, *L. pneumophila*, *Chlamydia* species or influenza A/B); elevation of *C. burnetii* phase 2 antibodies (IgG or IgM); or detectable respiratory virus by PCR in nose or throat swabs.

Microbiological investigations were determined to have influenced antibiotic prescribing where antibiotic spectrum changed to target the identified pathogen.

Statistical analysis

Data collection and analysis was performed using Microsoft Excel (Microsoft, USA) and Stata version 9 (StataCorp, USA).

RESULTS

Over the 12 month period, 422 episodes of CAP were identified in 396 patients. Patient records were reviewed in 391 patients, with 184 episodes of CAP meeting the inclusion criteria. The main reasons for exclusion were absence of radiological changes, suspected aspiration or hospital acquired pneumonia, immunosuppression or malignancy. In all included patients, complete clinical data allowing determination of PSI, length of stay and in-hospital mortality was available. The cohort had a median age of 72 years with a 7.1% in-hospital mortality rate (12.5% for PSI class 4–5 CAP), 14.1% intensive care unit (ICU)/high dependency unit (HDU) admission rate and 5 day median length of stay. PSI distribution across classes 1–5 was 11.4%, 16.3%, 15.8%, 34.8% and 21.7%, respectively.

Microbiological investigations and CAP aetiology

No microbiological investigation was performed in 47 of 184 (25.5%) patient episodes, with a median of one investigation performed per episode [interquartile range (IQR) 0, 3]. Investigation intensity was the same in mild to moderate (PSI 1–3) and moderate to severe (PSI 4–5) CAP [median number of investigations per CAP episode 1.5 (IQR 0, 3) and 1 (IQR 1, 2) respectively; Mann-Whitney test, $z = 0.66$, $p = 0.51$]. Blood cultures were taken in nearly 60% of episodes, and were the most common microbiological investigation, whereas assessment for respiratory viruses was rarely undertaken (2.7% of episodes; Fig. 1). Further, use of respiratory virus PCR, PUAT and LUAT was particularly low in PSI 4–5 CAP (2.9%, 15.4% and 20.2%, respectively).

Of all 184 episodes, at least one probable causative pathogen was identified in 24 episodes (13.0%). The most common pathogens identified were *S. pneumoniae* and *M. pneumoniae* (Table 1). One patient had *S. pneumoniae* detected by both sputum analysis and PUAT, and another patient had simultaneous detection of *Haemophilus influenzae* and *Moraxella catarrhalis* in sputum.

Yield of tests

Overall, 24 of 137 (17.5%) episodes where at least one microbiological investigation was performed had a probable

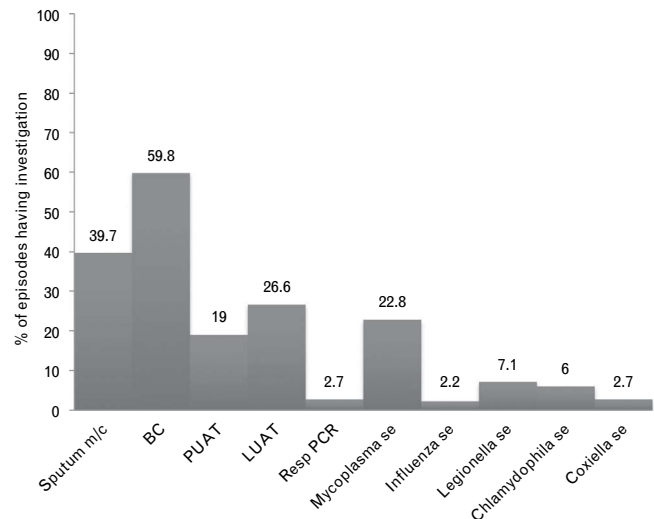


Fig. 1 Proportion of episodes having specific microbiological investigations to determine CAP aetiology. m/c, microscopy and culture; PUAT, pneumococcal urinary antigen test; LUAT, Legionella urinary antigen test; Resp PCR, respiratory virus polymerase chain reaction; se, serology.

causative pathogen identified. Yields (and 95% confidence intervals) for the more commonly performed tests were as follows: blood cultures 3.6% (95% CI 1.1–9.3%), LUAT 0% (95% CI 0–8.7%), sputum m/c 13.7% (95% CI 7.4–23.6%), PUAT 5.7% (95% CI 0.6–19.6%) and *Mycoplasma* serology 9.5% (95% CI 3.2–22.6%). Respiratory virus PCR appeared to have the highest yield of all microbiological investigations (20%; 95% CI 2–64%), however low utilisation compromises interpretation. Low test utilisation limited significance of yield calculations for other investigations.

The yield of the microbiological investigations according to PSI was not associated with PSI severity (PSI 1–3 yield 6.8% per test compared to PSI 4–5 yield 8.4%; Mann–Whitney test, $z = -0.19$, $p = 0.85$). The number of episodes in which a probable causative pathogen was identified was insufficient to make a comparison between pathogen and mortality or length of stay.

Influence of investigation results on antimicrobial prescribing

In 24 episodes a probable causative pathogen was identified. In 23 of these episodes, results were available within a clinically useful timeframe (prior to discharge, death or completion of prescribed antibiotic course), however in one patient results were only available post-mortem (blood culture growing methicillin resistant *Staphylococcus aureus*). In six of these 23 episodes (26.1%) where a probable causative pathogen was identified, the result appeared to influence antibiotic prescribing, while in the remaining cases, broad-spectrum or combination antimicrobials were continued.

DISCUSSION

In the largest study of microbial aetiology of CAP in Australia, a likely pathogen was identified in 45.6% of 885 episodes.¹ Studies of microbial aetiology in CAP in various settings have identified a pathogen in 7–80% of patients.^{3,4,9–13} Much of this diagnostic variation is accounted for by intensity of investigation and study setting.^{14,15} Thus the 13.0% pathogen identification rate of our study is not unexpected given invasive

Table 1 Causative pathogens in CAP and microbiological identification techniques

Pathogen	Total episodes, <i>n</i> (%)	Microbiological method
<i>Streptococcus pneumoniae</i> *	10 (5.4)	8 × sputum m/c, 2 × UAT, 1 × BC
<i>Mycoplasma pneumoniae</i>	4 (2.2)	4 × serology
<i>Haemophilus influenzae</i>	3 (1.6)	3 × sputum m/c
<i>Moraxella catarrhalis</i>	2 (1.1)	2 × sputum m/c
MSSA	2 (1.1)	1 × BC, 1 × sputum m/c
MRSA	1 (0.5)	1 × BC
Parainfluenza	1 (0.5)	1 × resp PCR
<i>Escherichia coli</i>	1 (0.5)	1 × BC
<i>Chlamydomphila</i> sp.	1 (0.5)	1 × serology
<i>Legionella</i> sp.	0 (0.0)	NA
Episodes with pathogen†	24 (13.0)	

* One patient had *S. pneumoniae* detected by both sputum culture and urinary antigen.

† One patient had both *H. influenzae* and *M. catarrhalis* isolated from sputum.

BC, blood cultures; m/c, microscopy and culture; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *S. aureus*; NA, not applicable; resp PCR, respiratory virus polymerase chain reaction; UAT, pneumococcal or legionella urinary antigen test.

diagnostic methods were not employed and that the study was a retrospective audit of clinical practice.

Streptococcus pneumoniae (5.4%) was the most commonly identified pathogen, and reflects the findings of similar studies where *S. pneumoniae* has been less frequently identified as a pathogen in CAP compared with historical studies.¹² *Mycoplasma pneumoniae* was the next most frequent pathogen (2.2%), although it is well known that *M. pneumoniae* rates vary significantly with epidemics occurring approximately every 4 years.⁴ Three episodes of *S. aureus* CAP (1.6%) and one episode of *Escherichia coli* CAP (0.5%) were identified, and although previously reported, these pathogens are unusual causes of CAP and may reflect inaccuracies in case ascertainment.¹ Overall, relative rates of various pathogens were similar to those in other temperate Australian and international studies.^{1,3,4,13,16}

Diagnostic microbiological investigation in CAP is controversial.^{3,17} Blood and sputum cultures (where available) are recommended when certain clinical criteria are met (e.g., patients in the ICU, moderate to severe CAP, cavitating lesions, failure of outpatient therapy or presence of a pleural effusion).^{3,4} Serological studies for *M. pneumoniae*, *Chlamydomphila* species, *Legionella* species, and influenza are more useful for epidemiological data, whereas investigations such as respiratory virus PCR and urinary antigen tests provide more timely results which may directly impact patient care.^{18,19} In this study where 56.5% had at least moderate to severe CAP (PSI class 4–5), the median number of microbiological investigations performed per patient episode was low at one per episode.

In moderate to severe CAP (104 episodes), 64.4% had blood cultures collected and 39.4% had sputum collected, which is comparable to prior studies.¹⁵ Lack of fever or prior antibiotic administration may explain the low blood culture collection rate, however such data were not collected. Blood cultures have limited sensitivity in CAP, but excellent specificity once contaminants are excluded.³ Their greater utility is in the ability to provide prognostic information, facilitate monitoring of antimicrobial susceptibility profiles of invasive pathogens, allow detection of unexpected bacteraemia (e.g., infective endocarditis) or important pathogens (e.g., *S. aureus*, *Pseudomonas aeruginosa*) and provide a clue for identifying patients with underlying predisposing conditions (e.g., pneumococcal bacteraemia and HIV or hyposplenism). In this study, blood

culture yield was low at 3.6%, however positive cultures appeared to provide prognostic information (2/4 bacteraemic patients did not survive to discharge) and dictated a change in antimicrobial prescribing (1 patient with methicillin resistant *S. aureus* and 1 patient with methicillin sensitive *S. aureus* requiring targeted therapy).³ Thus blood culture collection is recommended for all hospitalised patients with moderate to severe CAP, irrespective of patient temperature.

Sputum microscopy and culture when available (up to 40% of patients are unable to produce an appropriate sputum sample) has both limited sensitivity and specificity.³ In this study, sputum was collected in 39.7% of CAP episodes, with a positive yield of 13.7%. This is lower than previously reported (19.7%) and possibly related to stricter sputum analysis criteria.¹ Sputum identified a likely pathogen in 10 episodes, and appeared to influence antimicrobial prescribing in only two episodes (2.7% of episodes where a sputum was collected). Sputum analysis is non-invasive, relatively cheap, potentially influences patient management and allows epidemiological surveillance of CAP pathogens and associated antimicrobial susceptibility. However limitations include inherent poor specificity, and the difficulty in detecting pathogens such as *M. pneumoniae*, *Legionella* species and *Chlamydomphila* species. Given the low rate of influence of sputum diagnostics, it could be argued that sputum collection be avoided in mild to moderate CAP unless there is clinical suspicion of resistant or unusual pathogens (e.g., *S. aureus*, *P. aeruginosa*, *Mycobacteria* species, *Nocardia* species, *Acinetobacter baumannii*, *Burkholderia pseudomallei*), or failure to respond to therapy.

Only 2.7% of patients underwent testing for respiratory viruses (2.9% for moderate to severe CAP) and this accounts for the low rate of respiratory virus identification (0.5%). Respiratory viruses are becoming increasingly recognised as causes of CAP, and identification allows therapeutic intervention, accurate implementation of infection control practices, while also informing vaccination and public health policy and providing valuable supportive evidence for vaccination to patients and staff.^{20,21} Possible explanations for low testing rates include perceived lack of a therapeutic intervention, moderate influenza activity during the study period and because of a perceived delay in receipt of results due to specimen referral to an external laboratory.²² Given the recent pandemic of H1N1 influenza A, an increase in diagnostic testing for influenza pneumonia may be expected. Additionally, it has

only been relatively recently that multiplex respiratory virus nucleic acid amplification tests of flocculated swabs of the nasopharynx have become readily available.²³

The absolute yield of respiratory virus PCR was limited in this study due to low utilisation. Published studies have demonstrated a yield of 12–13% for respiratory virus PCR in CAP, which is relatively high for CAP investigations.^{21,24} Thus, this test should be recommended for all inpatients with moderate to severe CAP, or those with clinical or epidemiological features suggestive of a viral aetiology, particularly during seasonal peaks. An important caveat is that although molecular techniques for respiratory viruses have been reported to increase microbiological diagnostic sensitivity in CAP, the significance of detecting pathogens such as coronaviruses and rhinoviruses remains uncertain.²⁰ Additionally, testing in smaller centres may be associated with significant costs and time delays due to specimen referral.

Of those with moderate to severe CAP, 20.2% had LUAT and 15.4% had PUAT performed. Urine is more commonly available for testing than sputum, and with a rapid turn around time and greater sensitivity and specificity than sputum, urinary antigen studies should be the preferred investigation option for those with moderate to severe CAP. Disadvantages include lack of antimicrobial susceptibility information, cost and the limited serotypes detected by LUAT (only *L. pneumophila* serotype 1 is reliably detected, which accounts for 80–95% of community acquired legionella).^{3,25} Additionally, the yield of PUAT and LUAT was low at 5.7% and 0%, respectively. Nevertheless, a positive result allows antibiotic rationalisation, may limit further diagnostic testing and facilitates early detection of *Legionella* outbreaks.⁴

In this study, paired acute and convalescent serological evaluation was rarely performed (in only 5/75 instances where acute serology was performed was convalescent serology performed). Aside from *M. pneumoniae* IgM testing, isolated evaluation of acute serological samples is rarely helpful and can be misleading. A more rational approach would be to store acute samples and await a convalescent sample before testing both in parallel. Yield of serological testing was highest for *M. pneumoniae*, however the specificity of a single antibody titre ≥ 160 (the definition used in this study, as recommended by the manufacturer), has been criticised.²⁶

Serological tests remain vital for pathogens where identification via other means is limited (e.g., *M. pneumoniae*, *Chlamydia* species and *C. burnetti*), however molecular techniques have improved diagnostic accuracy and timing.^{12,21} Local availability and cost restrict the widespread implementation of these techniques.¹² Given limitations of serological studies, little influence on antimicrobial prescribing would be expected, and is supported by this study where antimicrobial prescribing appeared to be influenced by only one of 75 serological tests performed.

To summarise the above controversies, Table 2 provides recommendations for diagnostic microbiology in CAP. These recommendations have been adapted from local and international guidelines, and incorporate findings from our study.^{3,4,12,17,19,27} To facilitate implementation, and ensure sustained utilisation, we propose development of local clinical pathways. Clinical pathways improve adherence to treatment guidelines, although assessment of impact on investigation utilisation (other than as part of 'bundles of care') is limited.^{28,29}

Table 2 Recommended microbiological investigations for CAP according to severity

Investigation	Outpatient	Inpatient (non-severe)*	Inpatient (severe)†
Influenza PCR	O	R†	R†
Respiratory virus PCR	NR	O†	R†
Blood cultures	NR	R	R
Legionella UAT	NR	O	R
Pneumococcal UAT‡	NR	O	R
Sputum m/c §	NR	O	R
Serological studies	NR	O	O
Other investigations¶	NR	O	O

*Severe CAP = all patients admitted to either HDU or ICU. Non-severe CAP = all other admitted patients.

†Respiratory virus PCR usually includes influenza A/B. Respiratory virus molecular studies are particularly encouraged during seasonal outbreaks.

‡Not for use in children.

§Collect prior to antibiotic administration.

||Includes *Mycoplasma* sp., *Chlamydia* sp., *Legionella* sp., influenza, Q fever and other rarer causes of CAP. Epidemiological risk factors may prompt serological evaluation. Blood for serology should at the very least be stored for all those with severe CAP, and a convalescent sample collected on an as needed basis.

¶Includes bronchoscopy and bronchoalveolar lavage, investigations for *Mycobacterium tuberculosis*, and molecular techniques for *Mycoplasma* sp., *Legionella* sp., *Chlamydia* sp., *Pneumocystis jiroveci* and fungal pathogens.

NR, generally not recommended; O, optional; PCR, polymerase chain reaction; R, generally recommended; UAT, urinary antigen test; m/c, microscopy and culture.

Our study had a number of important limitations. As a single centre retrospective audit, the findings need to be cautiously applied to other population groups. Local guidelines and practices may have influenced utility of diagnostic investigations and antimicrobial prescribing which also limits generalisation. Low overall numbers and limited diagnostic utility, especially with respiratory virus PCR, may compromise the findings. The PSI is known to have a number of limitations, and thus by using the PSI in this study, correlates of severity are inherently restricted. Sputum was not routinely cultured for *Legionella* sp., serology for non-pneumophila *Legionella* species was not performed (which have been shown to be important contributors to CAP in Australia) and evaluation for uncommon CAP pathogens was not assessed (e.g., *Mycobacterium tuberculosis*, fungal pathogens, *Nocardia* species, *Bordetella pertussis*).³⁰ Strict criteria applied to sputum analysis may have underestimated diagnostic utility and hence the influence on antibiotic management. No cost-benefit analysis of investigations was performed.

This study demonstrates that the microbiology of CAP in a regional setting mirrors that of CAP in other temperate settings.¹ This study also demonstrates that in routine clinical practice, microbiological investigations, particularly respiratory virus PCR and urinary antigens, are under-utilised, especially in admitted patients with moderate to severe CAP. While diagnostic yield for blood cultures is low, positive results strongly influence management and provide important prognostic information. Other investigations such as serological testing and sputum studies appear to have limited impact on patient management, and due to their poor specificity, could be reserved for specific clinical situations. Increasing clinician awareness of modern microbiological techniques in the assessment of patients with CAP, and incorporation into CAP clinical pathways, may lead to improved and efficient utilisation of these resources.^{28,29}

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