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Empiric Antibiotic Prescribing For Community Acquired Pneumonia and Patient Characteristics Associated with Broad Spectrum Antibiotic Use

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ABSTRACT

Objectives: To assess adherence to the Australian Therapeutic Guideline (ATG) for the empirical management of community acquired pneumonia(CAP) during the first 24 hours of admission and to investigate patient characteristics associated with the prescription of broad spectrum antibiotics in mild to moderately severe pneumonia.

Methods: A retrospective cross-sectional study of patients admitted with CAP over a 12 month period under the General Medical Unit was undertaken. CAP was defined by acute onset of respiratory symptoms with a new chest X-RAY infiltrate for which the treating team made a diagnosis of CAP. Pneumonia severity was assessed using the CORB score. Relevant data were collected by review of medical records.

Results: 395 patients with CAP were identified, of which 285 were included. Mean age 66 ± 16 years; Males 53% and 12% from residential care. 167 (59%), 75 (26%), and 43 (15%) patients were in the mild, moderate and severe CAP groups, respectively. 93% patients received antibiotic cover for both typical and atypical pathogens, although 35% in the mild to moderate group received parenteral macrolide. 178 (62%) received Ceftriaxone; 92 (55%), 53 (71%) and 33 (77%) with mild, moderate and severe CAP, respectively. Compliance with ATG was seen in 16%, 27% and 72% cases of mild, moderate and severe CAP, with an overall compliance of 26%. Advanced age and dependent in personal activities of daily living (PADL) had a significant univariate association with ceftriaxone prescription. However, in the multivariate analysis only advanced age was found to have a significant association (OR1.78, CI1.23-2.01). The length of stay was similar between those who received ceftriaxone (4.3 ± 2.4 days) and benzylpenicillin (4.1 ± 2.0 days)

Conclusion: Adherence to the ATG guideline is poor, especially in the mild to moderately severe disease. Older patients are more likely to receive ceftriaxone. Studies are required to identify the barriers to adherence to CAP guidelines and factors that influence the prescription of broad spectrum antibiotics.

INTRODUCTION

Community Acquired Pneumonia (CAP) is one of the most common reasons for hospitalisation and a significant cause of morbidity and mortality [1]. Guidelines have been developed in an attempt to optimise the management of CAP, and adherence

to them has been shown to result in improved clinical outcomes [2-5]. While broad-spectrum empiric antibiotic treatment may be appropriate for patients who are more seriously ill, inappropriate uses of broad spectrum antibiotics may lead to the emergence of drug resistant organisms and potentially increase the health-care cost [6-8]. Previous studies have shown that compliance with CAP antibiotic guidelines has been poor in Australian hospitals and third generation cephalosporins have been widely and inappropriately used for mild and moderately severe pneumonia [7,9]. In light of these findings, during the last decade, interventions such as antibiotic stewardship programs have been introduced in most Australian hospitals to optimise antibiotic prescribing. In addition, CAP guidelines have been made available online for easy access to prescribers. However, the efficacy of these interventions has not been adequately evaluated. Furthermore, there is limited information on patient characteristics that may be associated with broad spectrum antibiotic prescription and the effects of non-compliance with guidelines on patient outcomes. Therefore, the present study was designed to assess the adherence to the Australian Therapeutic Guideline **(Table 1)** for managing CAP and to describe antibiotic prescribing patterns for the empirical management of CAP during the first 24 hours [10]. In addition, the study also investigated patient characteristics that may be associated with the prescription of broad spectrum antibiotics (i.e. ceftriaxone) versus narrow spectrum antibiotics (i.e. benzylpenicillin) for mild to moderately severe pneumonia and whether this antibiotic prescription pattern had any effect on patient outcomes.

Table 1. Australian therapeutic guideline for community acquired pneumonia [10].

Severity of Pneumonia	Antibiotic recommended
Mild	Amoxicillin 1 g 8 hourly orally for 5 to 7 days or Doxycycline 100 mg 12 hourly orally, for 5 to 7 days. Combination therapy is recommended if symptoms are not improved in 48 hours. Clarithromycin 500 mg 12 hourly orally for pregnant women
Moderate	Benzylpenicillin 1.2 g 6 hourly IV and Doxycycline 100 mg 12 hourly orally. • *If patient cannot tolerate penicillin:* Ceftriaxone 1 g daily IV, instead of benzylpenicillin. • *In case of hypersensitive allergy:* Moxifloxacin 400 mg daily Orally, for 7 days
Severe	Ceftriaxone 1 g daily IV or Cefotaxime 1 g 8 hourly IV + Azithromycin 500 mg IV daily. • *In case of hypersensitivities*: Moxifloxacin 400 mg IV, daily

METHODS / MATERIAL

Design: A retrospective cross-sectional study of patients admitted with community acquired pneumonia.

Setting: General Medicine Unit in a teaching hospital, Melbourne, Australia.

Participants and measurements

Patients aged ≥ 18 years who were admitted with the diagnosis of CAP from 1st October 2013 until 30th September 2014 were studied. Potential cases of CAP were identified from the hospital health information database using the ICD-10 codes J09 to J18 for the diagnosis of Pneumonia. CAP was defined by acute onset of respiratory symptoms with a new chest X-ray infiltrate and for which the treating team made a diagnosis of CAP. The following patients were excluded: patients diagnosed as having hospital acquired or aspiration pneumonia; patients with chronic lung disease such as interstitial lung disease, bronchiectasis or advanced chronic obstructive pulmonary disease on home oxygen therapy or with known bacterial colonisation; patients receiving immunosuppressive treatments (defined as receiving a daily average prednisolone dose ≥ 7.5 mg or other immunosuppressive medications); and patients who were considered for palliative treatment within 48 hours of admission. The pneumonia severity was assessed using the CORB (Confusion, Oxygen Saturation, Respiratory Rate, and Blood Pressure) score. The CORB assessment parameters include the following: confusion; oxygen Saturation less than 90% on room air; respiratory rate > 30 per minute; and systolic blood pressure less than 90 mmHg. A point was given for each parameter to compute the total score. A CORB score of 0, 1, ≥ 2 indicates mild, moderate and severe CAP, respectively. We used CORB score as it is an Australian derived and validated tool that is used to predict the requirement for intensive respiratory or vasopressor support in CAP and in-hospital mortality [9]. It is also used in the Australian therapeutic guideline to classify the severity of CAP for the purpose of guiding antibiotic prescription [10]. The study was approved by the local ethics committee.

Data collection

The relevant demographic, clinical, laboratory and outcome data were extracted by review of medical records by medical staff using a structured data collection sheet. The following information was collected: age, gender, usual residence (home vs. residential care), usual comorbidities, usual medications, history of allergy (particularly penicillin allergy), information on personal activities of daily living (PADLs- transferring, walking, toileting, bathing, dressing and feeding), antibiotics prescribed within 24 hours of admission, the parameters required for computing the CORB score, relevant laboratory data, admission to High-Dependency Unit (HDU) or Intensive Care Unit (ICU) and admission outcomes such as length of stay(LOS) and death. The burden of total co-morbidities was assessed by calculating the Charlson Comorbidity Index (CCI) Score.

Primary outcome measures: 1) Prescription of antibiotics as per the Australian Therapeutic Guideline for mild, moderate and severe CAP, as determined by the CORB score. Compliance with the guideline for the treatment of typical and atypical pathogens was estimated separately, as well as combined together. History of penicillin allergy was considered when estimating

the compliance for the cover of typical pathogens. For example, prescription of ceftriaxone for a patient with moderately severe pneumonia in the context of penicillin allergy was deemed compliant with ATG. However, prescription of ceftriaxone for mild pneumonia in the context of penicillin allergy was deemed 'non-compliant' as parenteral administration of antibiotic is not indicated for mild pneumonia as per ATG **(Table 1)** [10].

Secondary outcome measures: Patient characteristics associated with the prescription of ceftriaxone versus benzylpenicillin for mild to moderately severe pneumonia and the adverse outcomes of hospitalisation between these two groups. As variations in the prescription of antibiotics for covering atypical pathogen could be a confounder, we considered only patients who received ceftriaxone or benzylpenicillin and an oral atypical cover (either oral macrolide or doxycycline) as recommended by the ATG for this subgroup analysis. We did not include patients who did not receive any atypical cover or who received atypical cover parenterally (i.e. parenteral macrolide) [10]. Patients who received ceftriaxone due to penicillin allergy were also not included for the same reason. Adverse outcomes of hospitalisation such as requiring admission to HDU/ICU, LOS and in hospital death were compared between these two groups.

Statistical analysis

Descriptive information on sample characteristics was presented as absolute number of cases and percentage of total group data or with mean ± standard deviation (SD). A univariate group comparison of patients who received benzylpenicillin versus those who received ceftriaxone in the mild and moderately severe pneumonia categories was undertaken for all demographic and clinical characteristics, as well as for major outcome variables using Student's T-test for continuous and chi squared test for non-parametric data. Two tailed $P<0.05$ was taken to indicate statistical significance. A separate multivariate stepwise logistic regression was employed to determine the variables that had a significant independent association with the prescription of ceftriaxone. The independent variables used in the logistic regression analysis included age, gender, pre-admission living arrangement (home Vs, residential care), comorbidities such as cardiovascular, respiratory, diabetes and chronic kidney disease, as well as Charlson Comorbidity Index score. Adjusted odds ratios with 95% confidence intervals, and p values were determined for the significant independent variables.

RESULTS

395 patients were identified from the health information database with the diagnosis of CAP during the study period. Of these, 110 patients were excluded **(Figure 1).** The remaining 285 patient were included in the analysis **(Figure 1).** The mean age was 66 ± 16 years, 151 (53%) were males and 134 (47%) were females. 251 (88%) were from home and 34 (12%) patients were from residential care facilities.

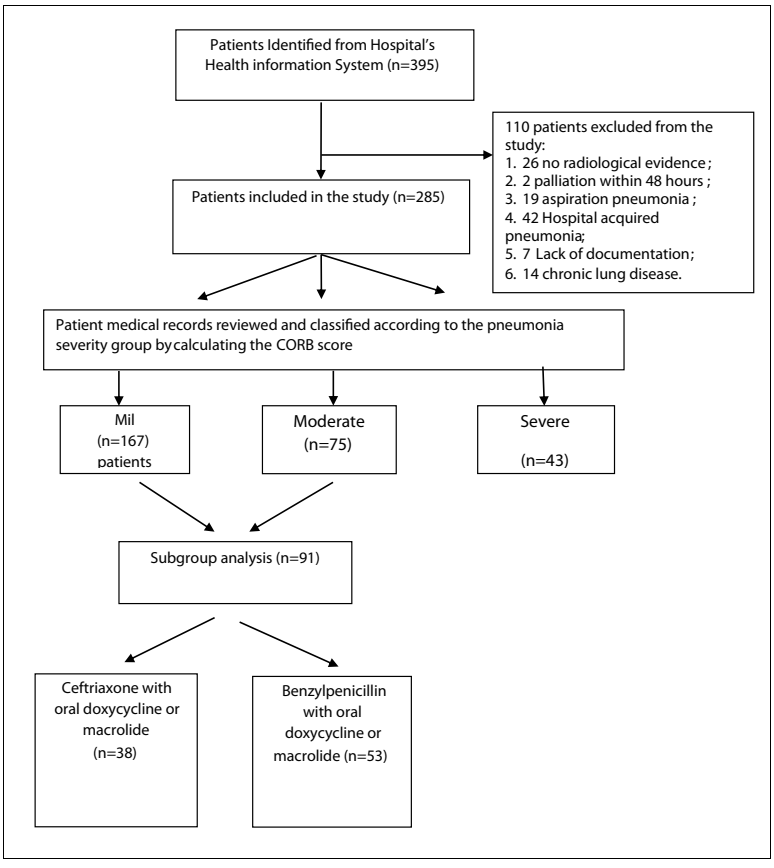

Figure 1. Flow diagram showing the design of this study.

Of the 285 patients, 167 (59%), 75 (26%) and 43(15%) patients were in the mild, moderate and severe CAP groups, respectively. 265 (93%) patients received empirical antibiotic cover for both typical and atypical pathogens. However, 59 (35%) and 34 (45%) patients in the mild and moderately severe pneumonia groups received atypical cover parenterally. 9 (3%), 7 (2.4%), 3 (1%) patients in the mild, moderate and severe pneumonia groups did not receive atypical cover.

The pattern of antibiotic prescription by pneumonia severity is shown in Figures 2A and 2B. Ceftriaxone with intravenous macrolide was used in 104 (36%) patients; 50 (48%), 30 (29%) and 24 (23%) in the mild, moderate and severe CAP groups, respectively. Ceftriaxone with either oral macrolide or doxycycline was used in 71 (25%) patients. Benzylpenicillin with oral doxycycline or macrolide was used in 61 (21%) patients. Benzylpenicillin and intravenous macrolide was used in 10 (4%) patients. Tazocin was used alone in 4 (1.4%) patients (2 mild, 1 moderate and 1 severe CAP), and in combination with intravenous azithromycin in 8 (3%) patients (2 in mild, 1 in moderate and 5 in severe CAP). Ceftriaxone was the most widely used antibiotic, including in the mild and moderately severe groups **(Figure 2A).** In total Ceftriaxone was used in 178 (62%) patients; 92 (55%), 53 (71%) and 33 (77%) patients in the mild, moderate and severe CAP groups, respectively. Parenteral macrolide was used in 122 (43%) patients; 59 (35%), 34 (45%) and 30 (68%) in the mild, moderate, and severe groups respectively **(Figure 2B).**

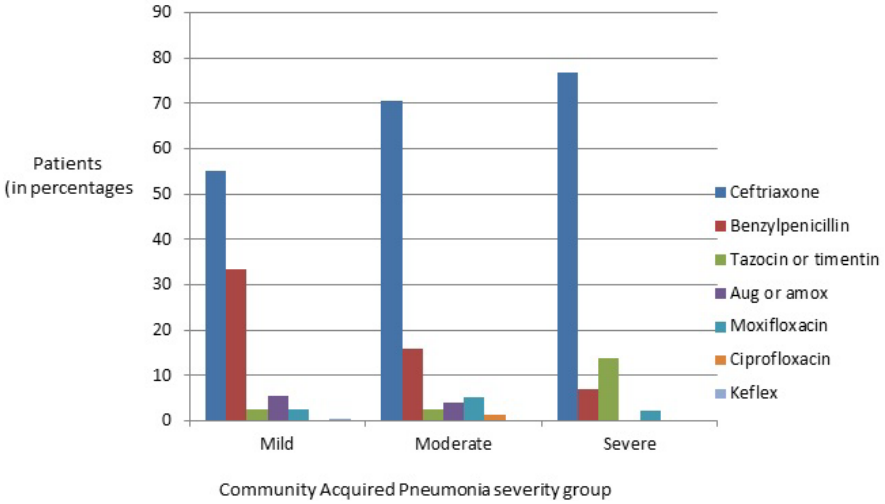

Figure 2A. Antibiotic prescription pattern by severity of pneumonia (for typical pathogens).

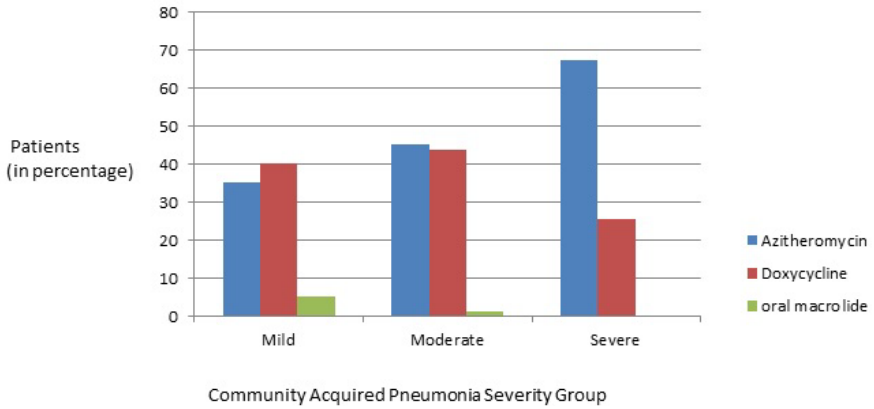

Figure 2B. Antibiotic prescription pattern by severity of pneumonia (for atypical pathogens).

When compliance with ATG recommendations for typical pneumonia pathogen cover was assessed, 25 (14%), 23 (32%) and 30 (93%) in the mild, moderate and severe CAP groups, respectively, received antibiotics as per the guideline **(Figure 3)**, and this translated into an overall compliance of 31%. This was after making adjustments for patients with penicillin allergy. The compliance for atypical pneumonia pathogen cover in the mild, moderate and severe CAP groups were 158 (59%), 68 (45%), 40 (67%), respectively, and this gave an overall compliance of 57%. When antibiotic prescription for covering typical and atypical pathogens were considered together, the overall compliance was 26%; 27 (16%), 20 (27%) and (31) 72% patients in the mild, moderate and severe CAP groups, respectively, received antibiotics in concordance with the ATG recommendations.

The univariate group comparison of patients who received benzylpenicillin versus those who received ceftriaxone in the mild and moderately severe CAP are shown in **Table 2.** The groups were well matched for gender, residential facility and comorbidities, but differed significantly in age and PADL status. Patients who received ceftriaxone were significantly older and more likely to be dependent in at least one PADL. However, in the multivariate stepwise logistic regression analysis the only variable that had a significant independent association with ceftriaxone prescription was advanced age (OR 1.78 (CI 1.23-2.01), P = 0.016). The length of stay was not significantly different between the two groups. There were no deaths or admissions to HDU/ICU in either group.

Table 2. Group comparison of patients who received ceftriaxone versus benzylpenicillin.

	Ceftriaxone	Benzylpenicillin	P value
Total patients	38	53	
Age	70 (SD16)	61 (SD19)	0.031
Gender (Male)	17 (44%)	30 (57%)	0.264
Patient from Residential care facility	8 (21%)	5 (9%)	0.118
PADL status (Dependent in at least one ADL)	13 (34%)	8 (15%)	0.032
Heart failure	13 (34%)	11 (21%)	0.150
Cerebrovascular disease	7 (18%)	3 (6%)	0.055
Respiratory	9 (24%)	7 (13%)	0.195
Diabetes	5 (13%	7 (13%)	0.994
Chronic Renal Disease	7 (18%)	8 (15%)	0.673
Charlson Comorbidity Index (Mean)	2.08 ± 2.1	1.62 ± 2.3	0.340
Admission to HDU/ICU, Death 30 day mortality	0	0	
Length of Stay (days)	4.3 (2.4 SD)	4.1 (2.0)	0.698

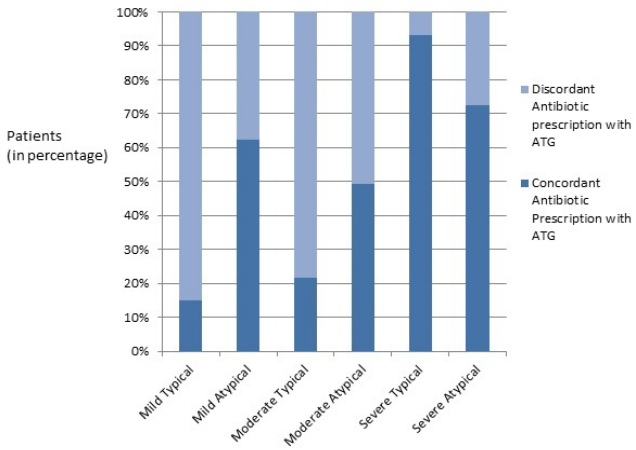

Figure 3. Antibiotic prescription as per Australian therapeutic guideline recommendation.

DISCUSSION

The study confirms that adherence to the Australian Therapeutic Guideline for the management of CAP was poor, especially in patients with mild to moderately severe pneumonia. The discordance with CAP guideline was largely due to the high level use of ceftriaxone in mild and moderately severe pneumonia. In addition, intravenous use of azithromycin in these groups also contributed to this discordance. The findings further suggest that age may influence the choice of antibiotic prescription for CAP and prescribers may chose ceftriaxone over benzylpenicillin for older patients. The findings also suggest that the prescription of ceftriaxone for mild to moderate disease was not associated with any superior patient outcome when compared to the prescription of benzylpenicillin.

Although adherence to CAP antibiotic guideline has been variably reported, consistent with findings of the present study, most previous Australian studies have reported poor compliance [7,8,11]. Furthermore, the consistent finding in most Australian studies was the widespread use of ceftriaxone for the treatment of mild and moderately severe pneumonia [7,8,11]. For example, M. Almatar et al. [7], in a recent retrospective study in a large tertiary hospital, reported an overall compliance of 16.1% with pneumonia antibiotic guidelines. The compliance in the mild, moderate and severe groups was 3.1%, 20.7% and 25.4%, respectively. In agreement with our study, the study further demonstrated wide spread use of ceftriaxone (56%) in mild to moderately severe pneumonia. Trad and Basich in a recent retrospective study demonstrated similar findings in a regional Australian hospital. The overall compliance in this study was 23%, and 73% of patients received Ceftriaxone [11]. Contrasting these findings Charles et al. [12], in a multi-centre prospective study, reported a greater compliance rate with Australian Therapeutic Guidelines. However, it should be noted that the primary objective of this study was to determine the antibiotic sensitivity patterns for CAP pathogens, and the study was not designed to assess compliance with treatment guidelines.

It was observed in our study that 93% of patients received antibiotic cover for both typical and atypical pathogens, and this may suggest an improvement in compliance for covering atypical pathogens in accordance with ATG recommendations when compared with previous Australian studies. For example, Buising et al. in their study in 2008 [13] showed that only 62% of patients received antibiotic cover for atypical pathogen. A greater compliance for covering atypical pathogens has also been reported in other recent Australian studies; Almatar and Triad reported that over 90% of their patients received atypical cover, although the route of administration of macrolide was not reported by them. These observations may suggest that there has been a greater awareness among prescribers for covering atypical pathogens recently. However, it is difficult to conclude whether this was due

to the improved adherence to ATG recommendations as most patients in our study (35% of mild and 45% of moderately severe pneumonia) received macrolide parenterally, and this was not consistent with ATG recommendations.

As compared with Australian studies, most American studies have shown a better overall compliance with CAP guidelines. For example, Mortensen et al. [4] and Frei et al. [5] reported a compliance rate of 77% and 57%, respectively. However, it should be noted that most American studies have used the American Thoracic Society (ATS) guideline, which has significant differences when compared to the Australian Therapeutic Guideline. For example, the ATS guideline recommends the use of third generation cephalosporins for non-ICU inpatient care and it incorporates the use of quinolones as first line treatment [14]. Whereas the Australian guideline restricts the use of Cephalosporins to patients with severe pneumonia and recommends quinolones only for patients with penicillin allergy [10]. Furthermore, there are also differences in the approach to the assessment of pneumonia severity between these two guidelines. Therefore, any meaningful comparison of these studies is difficult.

Studies have also investigated the barriers to compliance with antibiotic guidelines. They have recognised various patient and prescriber related factors, as well as work place related issues contributing to the poor compliance with guidelines. Some of the recognised prescriber and work place related factors include lack of awareness, confusion due to the availability of multiple guidelines, lack of time to calculate pneumonia severity scores and lack of easy access to guidelines [7,15-17]. Among the patient related factors, comorbidities and impaired functional status have been associated with poor adherence to guidelines [18]. Our study suggests that advanced age is associated with an increased prescription of ceftriaxone. Dependent status in PADLs was also found to have a significant univariate association with ceftriaxone prescription, although this was not found to have a significant independent association with the use of ceftriaxone. We also did not find any significant association between comorbidities and antibiotic prescription. This may be due to the limited statistical power because of the small size, particularly, that of the ceftriaxone group. Physician's clinical judgement is often cited as a reason for not following antibiotic guidelines [7,17]. Although this was not specifically assessed in this study, it is unlikely that the extremely high rates of the prescription of ceftriaxone for mild (55%) and moderately (76%) severe disease can be explained on the basis clinical judgement alone.

Various initiatives, particularly antimicrobial stewardship program, have been introduced in Australian Hospitals to optimise antibiotic prescribing [19]. Antimicrobial stewardship program and online availability of ATG have been introduced in our hospital about 8 years ago. The antimicrobial stewardship program includes the requirement of obtaining electronic approval for the prescription of broad spectrum antibiotics and a bi-weekly review of antibiotic use by the infectious diseases team. We in our study did not specifically assess the efficacy of these interventions, although the overall results of the study appear to suggest that there is a need for further efforts to improve antibiotic prescribing for CAP.

The results of the study should be interpreted within the context of some potential strengths and weaknesses. The study did not investigate the reasons for poor compliance with antibiotic guideline or evaluate the efficacy of current interventions, namely the antimicrobial stewardship program and the online availability of the Australian guidelines for CAP that are in place in our hospital to optimise antibiotic prescription. Furthermore, being a retrospective study where information was collected by review of medical history, the study suffers from the usual limitations of a retrospective design, including selection, information and classification biases. Despite these limitations, the study provides useful information on contemporary antibiotic prescription pattern for CAP in Australia. Although the results may not be generalisable, given it is a single centre study, it should be noted that other recent Australian studies have confirmed similar findings. Perhaps as evidenced in some studies, a multi-faceted educational program in conjunction with other initiatives may improve adherence to CAP guideline. Consequent to this study, we have currently designed a qualitative study to explore the barriers to the adherence to CAP antibiotic guideline.

CONCLUSION

Compliance with the Australian Therapeutic Guideline for the management of CAP is poor, especially in the mild and moderately severe pneumonia groups. Advanced age appears to be a risk factor for the over prescription of ceftriaxone. Further studies are required to identify the barriers to adherence to CAP guidelines and to identify factors that are associated with broad spectrum antibiotic use.

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