Letter to the Editor

Empiric Meropenem-based versus Ceftazidime-based Therapy for Severe Community-Acquired Pneumonia in a Retrospective Cohort Study

Dear Editor,

Optimal antibiotic regimen is unknown for severe community-acquired pneumonia (SCAP) which has mortality rates of up to 67% locally.[1] Recommended empiric regimens from the West cannot be extrapolated to our region where melioidosis is endemic[2] and *Streptococcus pneumoniae* penicillin resistance is common.[3] Unfortunately, studies that compare optimal antibiotic regimens for SCAP in Southeast Asia are lacking.

Considering local epidemiology, our hospital's guidelines recommended ceftazidime as empiric therapy for SCAP due to its activity against *Burkholderia pseudomallei*. To complement its poorer activity against *S. pneumoniae,*[4] levofloxacin or moxifloxacin was added for pneumococcal and atypical coverage. However, physicians could deviate from the guidelines and use meropenem with a macrolide instead. Anecdotally, we observed higher mortality rates in patients on empiric ceftazidime-based regimen. Hence, this retrospective study was conducted with a primary objective of comparing 30-day all-cause mortality between the 2 regimens.

Materials and Methods

We conducted a single-centre, retrospective cohort study in Singapore General Hospital from January 2011 to April 2015. This study was approved by Singhealth Centralised Institutional Review Board (IRB No. 2010/114/E) and consent to participate in it was waived in view of the retrospective nature of the study. Patients were screened using pharmacy antibiotic consumption records. They were included if they were adults (≥21 years old) and initiated with ceftazidime or meropenem for SCAP within 48 hours of hospitalisation. Community-acquired pneumonia (CAP) was determined based on radiological findings and/or presence of clinical signs and symptoms within 48 hours of hospitalisation.[5-7] SCAP was defined as requiring admission to the intensive care unit (ICU) and mechanical ventilation within 48 hours of hospitalisation.[5] The exclusion criteria were: 1) hospital or long-term care facility admission for at least 2 days within the last 90 days or exposure to healthcare risk factors (haemodialysis, receipt of intravenous drug therapy or wound care) within the last 30 days; 2) interstitial lung disease or bronchiectasis; 3) recent organ transplant within the last 6 months; 4) active malignancy with neutropaenia; and 5) changes in antibiotics within 48 hours of initiation or receipt of antibiotics other than ceftazidime, meropenem, macrolides, fluoroquinolones and doxycycline during the first 48 hours.

Relevant demographic, clinical, laboratory and microbiology data were collected using electronic medical records. Primary cause of death was determined from primary physicians' documentation in the medical records.

The primary outcome was all-cause mortality within 30 days of CAP onset. Secondary outcomes included CAP-attributable mortality, clinical response at end of antibiotic therapy, duration of ICU and hospital stay and 30-day readmission from date of discharge. Clinical recovery and clinical improvement were defined as resolution and partial resolution of presenting signs and symptoms of pneumonia, respectively. Clinical failure was defined as persistence or worsening of these signs and/or symptoms during treatment.

Statistical analyses were performed using IBM® SPSS® Statistics version 23 (IBM Corporation, Armonk, NY). Pearson chi-square or Fisher's Exact tests were used for nominal data. Independent samples T-test was used for normal continuous data while Mann-Whitney U test was used for non-normal data. Univariate analysis was performed using Kaplan-Meier survival analysis with log-rank test. Multivariate Cox regression analysis was used to adjust for potential confounders. All statistical tests were performed at 95% two-sided confidence level.

Results

A total of 100 patients were included (59 ceftazidime, 41 meropenem). A flowchart on the patient screening process is shown in Figure 1. Patient demographics and microbiology results are summarised in Tables 1 and 2. More patients in the meropenem group (n = 29, 71%) were admitted in the last 2 years of the study period (2014 to 2015) compared to the ceftazidime group (n = 17, 29%), thereby reflecting the change in prescribing trends in our institution.

Few patients had positive bacterial cultures and most were sensitive to narrower spectrum antibiotics, including ceftazidime and fluoroquinolones, with only 1 case of extended spectrum beta-lactamase producing *K. pneumonia* in the meropenem group. The meropenem group had significantly more positive respiratory cultures (n = 13,

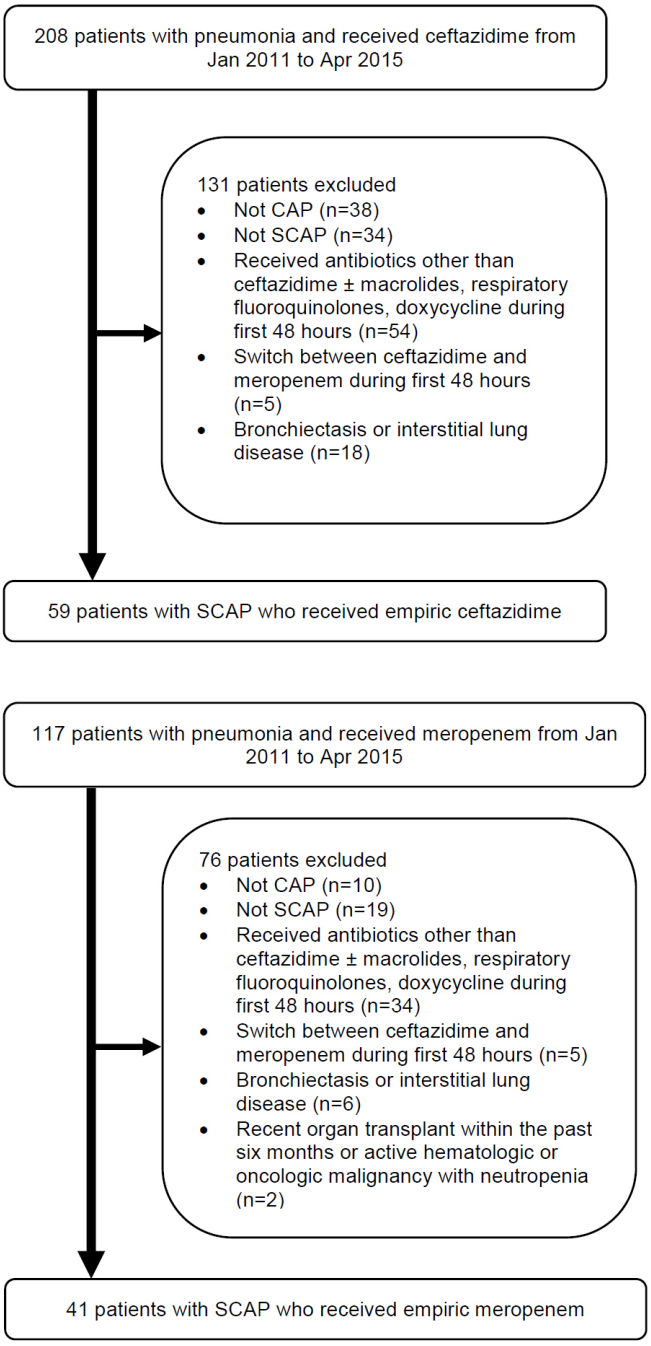

Fig. 1. Flowchart of patient selection process. CAP: Community-acquired pneumonia; SCAP: Severe community-acquired pneumonia.

32%) compared to the ceftazidime group (n = 4, 7%; P = 0.001). It also had more cases of documented bacteraemia (n = 14, 34% vs n = 8, 14%, respectively; P = 0.015).

All doses were appropriately titrated based on renal function. Median doses were 4 g/day in the ceftazidime group and 3 g/day in meropenem subjects. More patients presented with acute renal failure in the ceftazidime group

Table 1. Patient Baseline Characteristics

Baseline Characteristics	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
Median age (IQR)	64 (56 – 75)	62 (54 – 74)	0.375
Male (%)	33 (56%)	30 (73%)	0.079
Race (%)			0.964
Chinese	37 (63)	26 (63)	
Indian	5 (9)	3 (7)	
Malay	14 (24)	9 (22)	
Others	3 (5)	3 (7)	
Charlson Comorbidity Index (IQR)	5 (3 – 6)	5 (3 – 7)	0.367
Comorbidities (%)			
Diabetes mellitus	26 (44)	16 (39)	0.615
Ischaemic heart disease	17 (29)	8 (18)	0.291
Heart failure	6 (10)	4 (10)	1.000
Chronic kidney disease	8 (14)	7 (17)	0.628
Liver cirrhosis	0	2 (5)	0.166
Malignancy	5 (9)	9 (22)	0.056
Pulmonary disease*	7 (12)	4 (10)	1.000
Obesity†	6 (10)	2 (5)	0.466
Immuno-compromised state‡	2 (3)	3 (7)	0.398
APACHE II score (IQR)	20 (17 – 28)	22 (18 – 28)	0.582
CURB-65 score (IQR)	2 (1 – 4)	3 (2 – 4)	0.277
Pneumonia Severity Index (IQR)	4 (4 – 4)	4 (4 – 4)	0.658
Positive respiratory culture (%)	4 (7)	13 (32)	0.001
Endotracheal tube aspirate	4 (100)	13 (100)	
Broncho-alveolar lavage	0	1 (8)	
Documented bacteraemia (%)	8 (14)	14 (34)	0.015
Viral PCR test performed (%)§	32 (54)	24 (59)	
Positive respiratory virus infection	13 (41)	7 (29)	0.376

IQR: Interquartile range; NA: Not applicable; PCR: Polymerase chain reaction

*Pulmonary diseases include asthma and chronic obstructive pulmonary disease.

†Obesity is defined as body mass index of at least 30 kg/m^2.

‡Immunocompromised state is defined as presence of acquired immune deficiency syndrome or receipt of any immunosuppressive agent (such as methotrexate and tacrolimus) or prednisolone ≥20 mg/day for at least 2 weeks (or equivalent). The ceftazidime group had 1 patient with acquired immune deficiency syndrome and 1 patient with rheumatoid arthritis on methotrexate while the meropenem group had 2 patients on chronic systemic steroid therapy.

§The respiratory virus multiplex polymerase chain reaction test kit was used to detect the following: respiratory syncytial virus, influenza A and B, parainfluenza 1 to 3, metapneumovirus, rhinovirus, human coronavirus OC43 and 229E and adenovirus. Among those with positive respiratory virus infection, influenza was the most common in the meropenem group (n = 4). Rhinovirus was the most common in the ceftazidime group (n = 5) followed by influenza (n = 4).

‖Mortality cases were excluded.

Table 1. Patient Baseline Characteristics (Cont'd)

Baseline Characteristics	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
Average daily dose (IQR)	4 g (3 – 6 g)	3 g (2 – 3 g)	NA
Concurrent antibiotic used (%)			<0.001
None	1 (2)	0	
Moxifloxacin	49 (83)	7 (17)	
Levofloxacin	3 (5)	2 (5)	
Azithromycin	4 (7)	30 (73)	
Doxycycline	2 (3)	2 (5)	
Duration of therapy (IQR)‖	3 (2 – 4)	3 (2 – 4)	0.954

IQR: Interquartile range; NA: Not applicable; PCR: Polymerase chain reaction
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‖Mortality cases were excluded.

Table 2. Bacterial Cultures Isolated from Patients' Respiratory or Blood Specimens

Culture Site and Bacteria Isolated	Ceftazidime (n = 59)	Meropenem (n = 41)
Respiratory tract (%)	4 (7)	13 (32)
Streptococcus pneumoniae	2 (3)	
Beta-haemolytic *Streptococcus*	1 (2)	2 (5)
Haemophilus influenzae	1 (2)	1 (2)
Moraxella catarrhalis		1 (2)
Klebsiella pneumoniae		5 (12)
Pseudomonas aeruginosa		2 (5)
Methicillin-sensitive *Staphylococcus aureus*		1 (2)
Mycobacterium tuberculosis	2 (3)	2 (5)
Mycobacterium avium complex		1 (2)
Blood (%)	8 (14)	14 (34)
Klebsiella pneumoniae		6 (15)
Klebsiella species	3 (5)	1 (2)
Streptococcus pneumoniae	2 (3)	3 (7)
Streptococcus intermedius	1 (2)	
Beta-haemolytic *Streptococcus*		2 (5)
Haemophilus influenzae		1 (2)
Burkholderia pseudomallei	1 (2)	
Rhodococcus species	1 (2)	
Pseudomonas aeruginosa		1 (2)
Concordant blood and respiratory cultures (%)		
Klebsiella pneumoniae		5 (12)
Streptococcus pneumoniae	2 (3)	
Beta-haemolytic *Streptococcus*		2 (5)
Haemophilus influenzae		1 (2)
Pseudomonas aeruginosa		1 (2)
Discordant blood and respiratory cultures (%)		
S. pneumoniae (blood), *P. aeruginosa* and *M. avium complex* (sputum)	2 (3)*	1 (2)

*Only 2 patients in ceftazidime group have blood cultures that were unlikely to be respiratory pathogens (*Rhodococcus* species and *Streptococcus intermedius*). Respiratory cultures for both patients were negative.
Note: In the ceftazidime group, there were 2 cases of concurrent pulmonary tuberculosis and 1 case of acquired immune deficiency syndrome with concurrent *Pneumocystis jiroveci* pneumonia and *Rhodococcus sp.* bacteraemia. In the meropenem group, there were 3 patients with concurrent pulmonary mycobacterium infection.

(n = 40, 68%) compared to the meropenem group (n = 24, 59%; *P* = 0.435). Hence, more patients in the ceftazidime group did not receive the recommended dose of 6 g/day. After excluding mortality cases, median duration of empiric ceftazidime or meropenem therapy was 3 days in both groups before modifications were made to antibiotic therapy.

Median time to all-cause mortality was significantly shorter in the ceftazidime group (7 days from CAP onset) than in meropenem group (>30 days, *P* = 0.002) as shown in Figure 2. It also had significantly greater 30-day all-cause mortality (n = 37, 63% vs n = 12, 29%, respectively; *P* = 0.001). After adjusting for the confounder (immunocompromised state) in the multivariate Cox regression analysis, patients on ceftazidime were thrice more likely to die earlier than those on meropenem (HR = 2.9; 95% CI, 1.5%-5.7%; Table 3).

CAP-attributable mortality was not significantly different between both groups (Table 3, Fig. 3). After adjusting for the confounder (documented bacteraemia with the same pathogen isolated from respiratory site), patients on ceftazidime were thrice more likely to die earlier from CAP compared to patients on meropenem (HR = 2.9; 95% CI, 1.2%-7.0%; Table 3). We also noted that more patients on the ceftazidime-based regimen (n = 11) died from cardiovascular cause compared to meropenem patients (n = 0), 7 of whom died within 72 hours.

Significantly more patients on meropenem had clinical recovery (n = 24, 59%) compared to ceftazidime patients (n = 17, 29%; *P* = 0.003). A total of 28 (68%) patients had antibiotic de-escalation after a median of 3 days

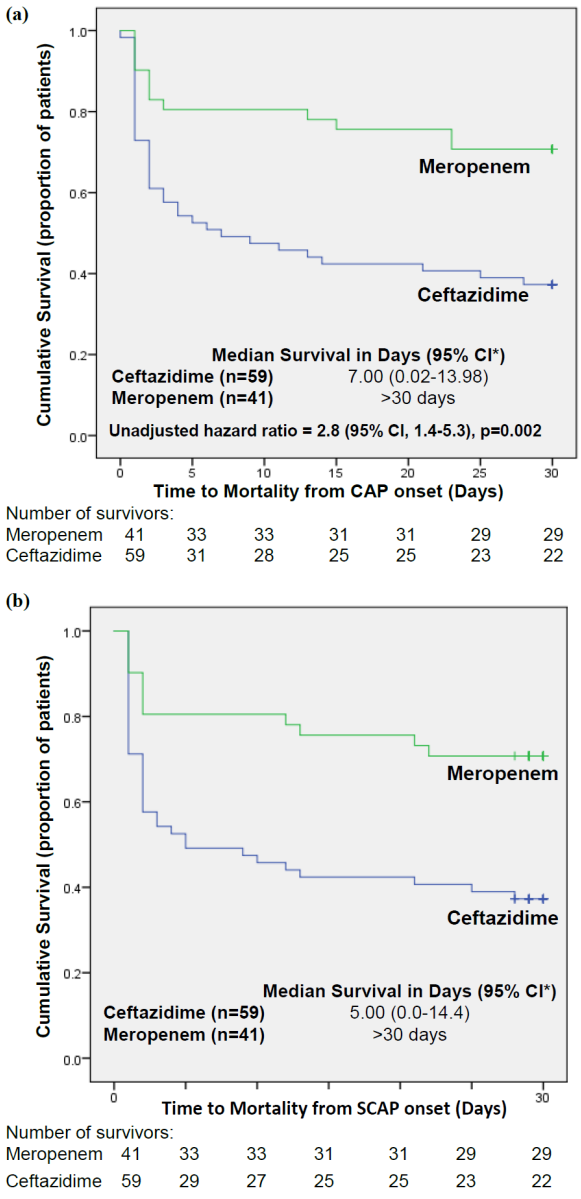

Fig. 2. Kaplan-Meier survival curve with all-cause mortality as outcome measure. A: Median time to all-cause mortality from onset of CAP was significantly shorter in the ceftazidime group (7 days) versus the meropenem group (median was not reached). B: Median time to all-cause mortality from onset of SCAP was significantly shorter in the ceftazidime group (5 days) versus the meropenem group (median >30 days as more than 50% of patients were still alive beyond 30 days). CAP: Community-acquired pneumonia; CI: Confidence interval; SCAP: Severe community-acquired pneumonia.

(interquartile range, 1-4 days). They were de-escalated to ceftriaxone (n = 8, 20%), ceftazidime with fluoroquinolones (n = 6, 15%), fluoroquinolone monotherapy (n = 5, 12%), co-amoxiclav (n = 3, 7%) and piperacillin-tazobactam (n = 3, 7%). In contrast, 13 (22%) patients in the ceftazidime group had antibiotic escalation to a carbapenem after a median of 2 days (interquartile range, 1-4 days). There was no significant difference between both groups in length of ICU and hospital stays and 30-day readmission.

Table 3. Clinical Outcomes and Results of Multivariate Analysis

Clinical Outcomes	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
30-day all-cause mortality (%)*	37 (63)	12 (29)	0.001
30-day CAP-attributable mortality	20 (34)	9 (22)	0.195
Clinical response (%)			0.007
Failure	35 (59)	12 (29)	0.003
Improvement	7 (12)	5 (12)	1.000
Recovery	17 (29)	24 (59)	0.003
Change in empiric antibiotic therapy (%)			<0.001
None	27 (46)	13 (32)	0.158
Escalation	13 (22)	0	0.001
De-escalation	19 (32)	28 (68)	<0.001
Length of hospital stay in days (IQR)†	8 (6 – 22)	14 (7 –31)	0.435
Duration of ICU stay in days (IQR)†	3 (2 – 7)	4 (2 – 8)	0.356
30-day readmission (%)†	3 (14)	4 (14)	1.000
Multivariate Analysis	**Hazards Ratio**	**95% Confidence Interval**	***P* Value**
All-cause mortality as outcome measure (demographic factors)			
Ceftazidime use	2.931	1.514 – 5.673	0.001
Immunocompromised state	3.139	1.106 – 8.914	0.032
CAP-attributable mortality as outcome measure (demographic factors)			
Ceftazidime use	2.935	1.229 – 7.010	0.015
Documented bacteraemia (same pathogen isolated from respiratory site)	3.139	1.324 – 7.442	0.009

CAP: Community-acquired pneumonia; ICU: Intensive care unit; IQR: Interquartile range

*In the ceftazidime group, other documented causes of death included cardiovascular causes (n = 11), pulmonary tuberculosis (n = 1), severe H1N1 infection (n = 1), acquired immune deficiency syndrome (n = 1), toxin ingestion (n = 1), pancreatitis (n = 1) and liver failure (n = 1). In the meropenem group, other causes of death included injury from fall (n = 1), stroke (n = 1) and invasive pulmonary aspergillosis in a non-immunocompromised host (n = 1).

†Mortality cases were excluded.

Note: Other potential confounders that were found not to be significant included age, gender, race, Charlson Comorbidity Index, APACHE II score, CURB-65 score, Pneumonia Severity Index, positive respiratory culture, documented viral respiratory tract infection, diabetes mellitus, congestive heart failure, chronic kidney disease, liver cirrhosis, malignancy, pulmonary disease, obesity, immunocompromised state, concurrent fluoroquinolone use and concurrent macrolide use.

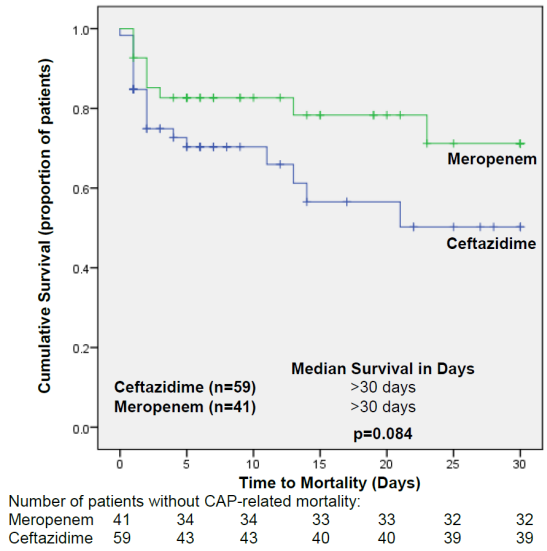

Fig. 3. Kaplan-Meier survival curve with CAP-attributable mortality as outcome measure. There was no statistically significant difference in median time to CAP-attributable mortality in both ceftazidime and meropenem groups. However, the ceftazidime group showed earlier CAP-attributable mortality. CAP: Community-acquired pneumonia.

Discussion

This is the first study that compared outcomes between 2 beta-lactam regimens in adult patients with SCAP in a region where melioidosis may be common. Our study suggests that ceftazidime-based regimen was significantly associated with early all-cause and CAP-attributable mortality (after adjustment for confounders) and greater clinical failure compared to meropenem-based regimen. This difference could be due to a few reasons. First, the inoculum effect is more commonly observed in cephalosporins compared to carbapenems.[8] The inoculum effect is a phenomenon in which higher minimum inhibitory concentrations are observed when the initial bacterial burden is high. This effect may be more significant in severe pneumonia where high bacterial burden is expected. Second, the immunomodulatory effects from macrolides could have contributed to better outcomes in meropenem-based regimens.[9] However, in our multivariate analysis, concurrent macrolide use was ruled out as confounder. Further studies are required to confirm the clinical significance of these contributing factors.

We also observed more early cardiovascular-related deaths in the ceftazidime group. CAP has been associated with cardiovascular complications, which contributes up to 60% increased risk in short-term mortality.[10] The systemic inflammatory response to pneumonia and hypoxemia could have led to endothelial dysfunction, myocardial injury, arrhythmias and heart failure.[11] Hence, lower efficacy of the ceftazidime-based regimen could potentially have resulted in greater incidence of cardiovascular complications and earlier mortality. Other plausible reasons for this observation could be cardiotoxicity risk from concurrent fluoroquinolone use and a greater number of patients with underlying ischaemic heart disease in the ceftazidime group. However, similar to fluoroquinolones, macrolides are known to have QTc-prolonging effects that carry the risks of cardiac arrhythmias and sudden cardiac deaths.[12-15] Unfortunately, there are no head-to-head comparison studies that can confirm which of the 2 classes of antibiotics carry greater cardiotoxicity risk. In our analysis, neither agents increased the risk of overall mortality and were ruled out as confounders. A complex interplay of various factors (underlying cardiac comorbidities and risk factors, severity of sepsis, concurrent use of macrolides or fluoroquinolones) could have contributed to this observation. Hence, further studies are required to confirm these findings.

One result of our study is that it may encourage more empiric carbapenem use, thereby leading to concerns over carbapenem abuse. However, we need to emphasise that in our study, patients on meropenem-based regimens were promptly de-escalated after a median of 3 days. To avoid carbapenem overuse, antimicrobial stewardship is necessary to ensure prompt antibiotic de-escalation as soon as patients have achieved adequate clinical response after 3 days.

A major limitation of this study is its retrospective design. It was a challenge to retrospectively determine the cause of death, especially when multiple factors were involved. As such, we had to rely on primary physicians' documentation of the cause of death. Second, our study had only 1 confirmed case of melioidosis which is against the trend observed in earlier studies. Nevertheless, empiric melioidosis cover is still important given that melioidosis can be endemic, especially during the monsoon season in our region.[1,2,15] Third, there may still be confounders that are unaccounted for. For example, the identification of causative pathogens in pneumonia is a challenging task due to its low yield of positive cultures. The reported rate of positive blood cultures in patients with CAP in Australia and Singapore was only around 7% to 8%.[16,17] It is therefore a difficult task to establish whether the difference in pathogens could be a contributing factor. We were also unable to evaluate whether certain cardiovascular comorbidities (such as pre-existing arrhythmias) could have contributed to more cardiovascular-related deaths, especially with concurrent macrolide or quinolone use. Finally, as more patients in the meropenem group were admitted in the last 2 years of the study period, we were not able to rule out the contribution of improvements in ICU care to better patient outcomes in these patients. A randomised, controlled trial will help to address the limitations of this study.

Conclusion

Empiric meropenem-based regimen appeared to be associated with lower mortality than ceftazidime-based regimen in SCAP. More studies are needed to establish optimal antibiotic regimen for SCAP in regions where empiric melioidosis cover may be required.

Acknowledgement

The authors would like to thank the infectious disease department in Singapore General Hospital for feedback on the manuscript.

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