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ORIGINAL ARTICLE

Prescribing Practice of Third Generation Cephalosporins in Medical Wards at Hospital Queen Elizabeth II (HQEII)

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ABSTRACT

Cephalosporins are amongst the most used antibiotics in hospital settings worldwide. The antibiotic report collated by the Pharmacy Department from Hospital Queen Elizabeth II (HQEII) in 2018 reflected high usage of third-generation cephalosporins in medical wards, and indeed HQE II was one of the top users nationwide. This study aimed to evaluate the prescribing pattern of third-generation cephalosporins in medical wards as per National Antimicrobial Guidelines (NAG) 2019. A prospective, observational study was conducted in medical wards from June 2019 till January 2020. Patients who were started with third-generation cephalosporins (ceftazidime, ceftriaxone, cefotaxime, cefoperazone/sulbactam) were recruited, where 137 patients were enrolled with 60.6% were males. The mean age of patients was 53±16.8 years old. Antibiotics were initiated as per NAG recommendation. Cultures were taken before antibiotic initiation. Respiratory-related infections (*n* = 54, 39.4%) were the main indication and, antibiotics were continued as definite therapy in 38 patients (27.7%). The median duration of antibiotic treatment was 5 days (interquartile range = 3). Ceftazidime (*n* = 85, 62%) was most prescribed followed by ceftriaxone (*n* = 48, 35%) and cefotaxime (*n* = 4, 2.9%) respectively. It was worth noting that ceftazidime was primarily used as empirical therapy for melioidosis (n = 64, 75.3%), particularly in patients with diabetes mellitus (*n* = 40, 62.5%), chronic kidney disease (*n* = 27, 42.2%), and/or occupational exposure (*n* = 4, 6.3%). The mean ceftazidime duration for empirical melioidosis was 3.2±1.6 days. Overall, third-generation cephalosporins were appropriately prescribed in medical wards as per NAG 2019. Further exploration of ceftazidime usage in empirical melioidosis is warranted.

INTRODUCTION

Infectious disease contributes significantly to the widespread morbidity and mortality worldwide (Christensen et al., 2009). Antimicrobials are given to treat these infections and are frequently prescribed in hospitals and healthcare facilities (Van & Gyssens, 2001). Before initiation of antimicrobials, a thorough clinical assessment of the patient will be required to ascertain the patient's underlying disease process and to predict potential pathogens involved if it is an infection. This initial assessment should be supplemented with relevant laboratory investigations to establish a definitive microbiological diagnosis and to determine the susceptibility of the organism to various antibiotics (Dellit et al., 2007). Selecting the most suitable antibiotic is vital because inappropriate use of antibiotics can contribute to the growing numbers of bacteria becoming resistant to antibiotics (Shankar et al., 2005; Yulia et al., 2018) thus making it more difficult to treat.

Among the most commonly used antibiotic in hospital settings worldwide are cephalosporins (Shankar et al., 2005), which range from the first generation to the fifth generation. Notably, the antibiotic spectrums for cephalosporins broaden with each generation, with the newer generation covering more gram-negatives. Third-generation cephalosporins are broad-spectrum antibiotics used in various clinical situations. These are marked by its 'stability to the common beta-lactamases of gram-negative bacilli and are highly active against *Enterobacteriaceae, Neisseria* and *Haemophilus influenzae* (McGowan & Tenover, 1997). Studies have linked the use of broad-spectrum antibiotics such as third-generation cephalosporins to the emergence of antibiotic resistance (Pinto et al., 2004).

According to the antibiotic report collated by the Department of Pharmacy from Hospital Queen Elizabeth II, cephalosporin usage in this hospital is currently among the top in the state of Sabah. The third-generation cephalosporins available in this hospital are ceftriaxone, cefotaxime, ceftazidime and cefoperazone-sulbactam. They are found to have the highest usage from medical wards. Thus, the focus of this study was to determine its prescribing practice in medical wards at Hospital Queen Elizabeth II in terms of indication of third-generation cephalosporins and the dosing regimen appropriateness (drug, dose, frequency, and duration) by the NAG, 2019. Data collected from this study can provide valuable feedback to physicians in terms of current prescribing practice and its appropriateness in the treatment plan. An improved understanding of cephalosporin utilization at this facility can allow for better antimicrobial management and reduce the risk of antibiotic resistance.

MATERIALS AND METHODS

This study was conducted in the medical wards of HQEII for a period of seven months, from June 2019 to January 2020, with ethical permission by the Medical Research and Ethics Committee of Kementerian Kesihatan Malaysia (NMRR-19-560-46541) and involved 137 admitted patients. The study was described as a prospective observational study. The inclusion criteria were adult patients aged 18 and above, patients admitted to medical wards at HQEII (Medical extension ward, male medical ward, and medical high dependency unit), and patients who have started on third-generation cephalosporins (ceftriaxone, ceftazidime, cefotaxime, and cefoperazone/sulbactam) by the medical discipline. The following parameters: age, gender, relevant medical history, the reason for hospitalization, diagnosis, type, and regimen of third-generation cephalosporins used, and relevant laboratory parameters were recorded for all patients. All the collected data were analyzed

by descriptive statistical analysis using Statistical Package for Social Sciences (SPSS) version 27.

RESULTS

A total of 137 patients from medical wards were recruited, 83 (60.6%) patients were male and 54 (39.4%) patients were female. To compare, the number of male patients was notably higher than female patients. The mean age of the patients was 53 $\pm$ 16.8 years old. Out of 137 patients, 23 (16.8%) patients had no underlying medical illness and most of the patients (*n* = 114, 83.2%) presented with comorbidities such as hypertension (*n* = 74, 54%), diabetes mellitus (*n* = 66, 48.2%), chronic kidney disease (*n* = 52, 38%), and/or risk factors to start on third-generation cephalosporins (Figure 1).

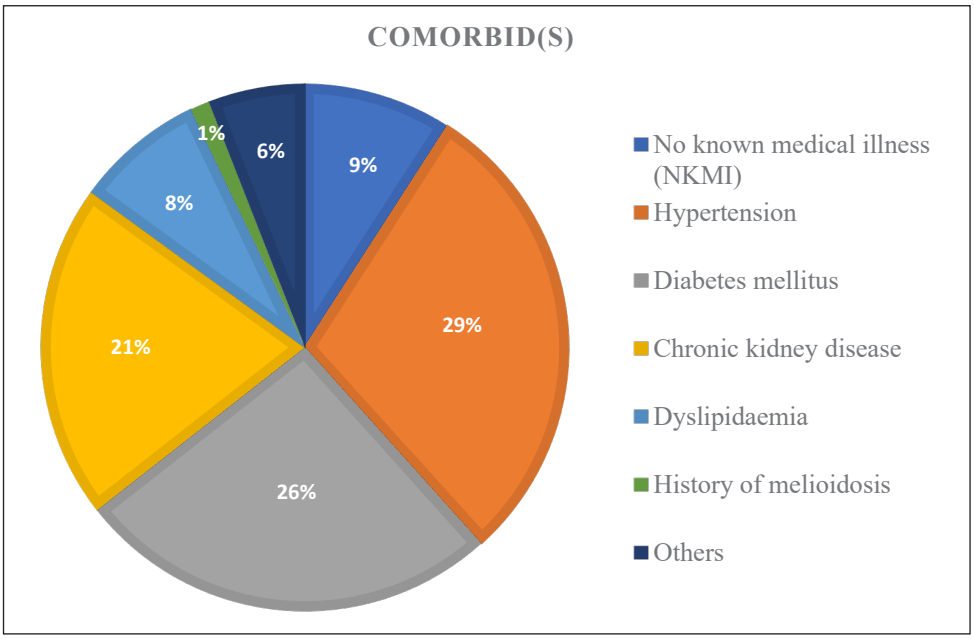

Figure 1 Demographic data of study population (*n* = 137)

All patients (*n* = 137, 100%) had their blood culture taken before antibiotics initiation which was in line with the NAG 2019 where microbiological investigations (culture or serology) should be taken before antimicrobial commencement. The results from the culture and sensitivity tests serve as a guide for the physician to choose specific antibiotic therapy to improve patients' outcomes in combating the microorganisms. From the available third-generation cephalosporins, ceftazidime had the highest usage (*n* = 85, 62%) followed by ceftriaxone (*n* = 48, 35%) and cefotaxime (*n* = 4, 2.9%) (Figure 2).

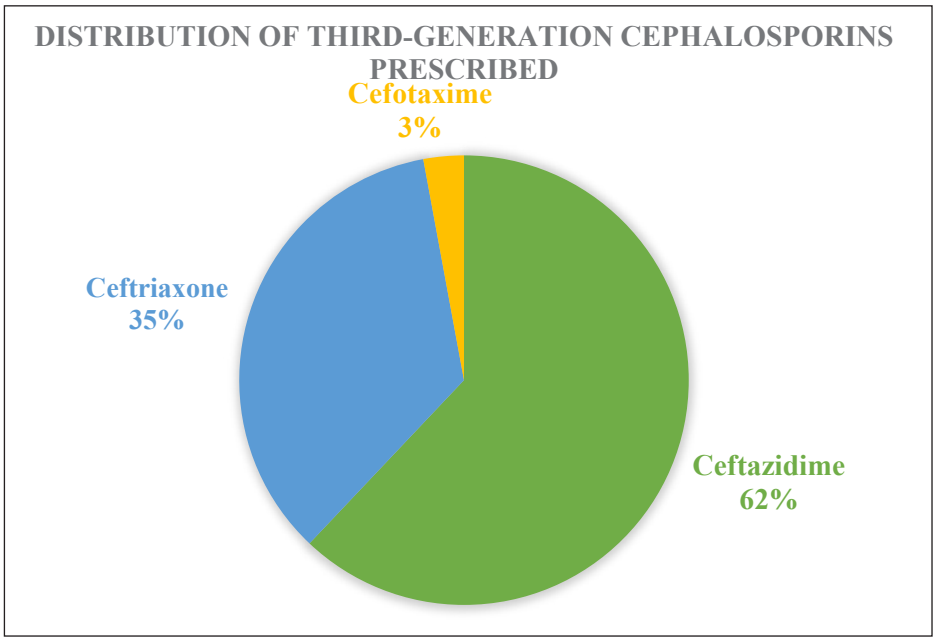

Figure 2 Distribution of third-generation cephalosporin prescribed (*n* = 137)

Third-generation cephalosporin antibiotics were either used empirically or following specific evidence of infection with a median duration of antibiotics for three days in total (IQR = 3) and a mean of three days as empirical cover for melioidosis (SD = 1.565). A higher percentage was reported for patients who were treated empirically (*n* = 99, 72.3%) compared to patients with definitive therapy (*n* = 38, 27.7%).

From the analyzed data, it was found that respiratory infection was diagnosed the most by the system that third-generation cephalosporins were prescribed for which involving 54 (39.4%) patients out of 137 patients and other indications were described in Figure 3. However, in most cases, third-generation cephalosporins were mainly prescribed for an empirical cover of melioidosis (*n* = 64, 46.7%), with ceftazidime being prescribed the most for this indication (Table 1).

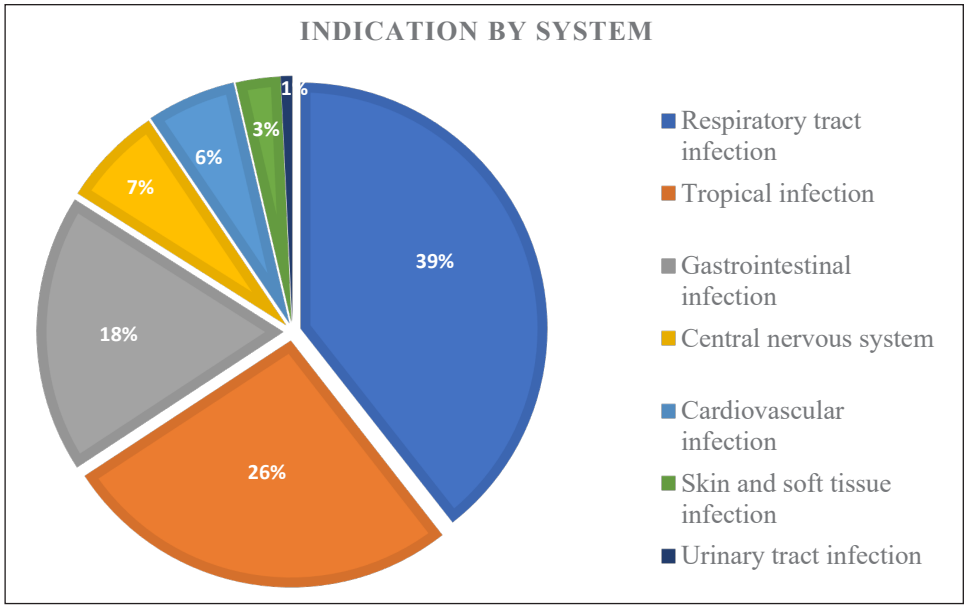

Figure 3 System-based indications of third-generation cephalosporin (*n* = 137)

Out of the 85 patients that were prescribed ceftazidime, 64 (75.3%) patients were empirically treated for melioidosis and only 13 patients (15.3%) were treated as confirmed cases of melioidosis (Table 1). For ceftriaxone, it was mostly prescribed for community-acquired pneumonia (*n* = 14, 29.2%), followed by infective acute gastroenteritis (*n* = 10, 20.8%) and meningitis (*n* = 9, 18.8%) while cefotaxime was used for empirical cover for spontaneous bacterial peritonitis in liver cirrhosis patients as directed in the NAG 2019.

Table 1 Specific indications where third-generation cephalosporins were prescribed (n=137)

Indications for each third-generation cephalosporins	*n* (%)
Ceftazidime (*n* = 85)	
Empirical melioidosis	64 (75.3%)
Confirm melioidosis	13 (15.3%)
Catheter-related bloodstream infection (CRBSI)	7 (8.2%)
Urosepsis	1 (1.2%)
Ceftriaxone (*n* = 48)	
Community-acquired pneumonia (CAP)	14 (29.2%)
Infective acute gastroenteritis (AGE)	10 (20.8%)
Meningitis	9 (18.8%)
Cholecystitis	4 (8.3%)
Sepsis	4 (8.3%)
Leptospirosis	3 (6.3%)
Others	4 (8.3%)
Cefotaxime (*n* = 4)	
Empirical cover spontaneous bacterial peritonitis (SBP)	4 (100%)

DISCUSSION

Antimicrobials are commonly prescribed in healthcare facilities to treat infections and must be handled with care to ensure the safety and effectiveness of treatment of underlying infections. However, the widespread use of broad-spectrum antimicrobials such as third-generation cephalosporins has led to the emergence of antibiotic resistance (Gashe et al., 2018) and World Health Organization (WHO) reveals that high levels of *Escherichia coli* and *Klebsiella pneumoniae* resistance to third-generation cephalosporins in Southeast Asia region. For example, 37.7% of extended-spectrum beta-lactamase (ESBL) producing *E. coli* were resistant to third-generation cephalosporins in Cambodia (Ruppé et al., 2009), 45.5% in Vietnam (Nguyen et al., 2016) and 46.3% in Malaysia (Ho et al., 2012). The present study was conducted to determine the prescribing pattern of third-generation cephalosporins because of high usage in medical wards of HQEII.

Gender analysis revealed that the number of males (*n* = 83, 60.6%) patients prescribed with third-generation cephalosporins was higher compared to females. This was in agreement with both studies conducted in a teaching hospital (Reddy et al., 2015) and the general medicine and surgical inpatient department of a tertiary care hospital in India (Naveen et al., 2018), which reported a higher number of male patients compared to female patients. Besides, this study also shown that a total of 114 (83.2%) patients presented with comorbidities, and only 23 (16.8%) patients presented with no known medical illness. This is similar to a study conducted by Naveen et al. in 2018 where 62.7% of the patients presented with underlying comorbidity.

Among the third generation cephalosporins available in HQEII, it was found that ceftazidime (n=85, 62%) was widely prescribed in medical departments which mainly used for the coverage of melioidosis followed by ceftriaxone (35%) and cefotaxime (7.5%). On the other hand, a similar study that looked at the prescribing practice of third-generation cephalosporins in Spain found that ceftriaxone instead had the highest usage (66%) followed by cefotaxime (26.5%) and ceftazidime (7.5%) having the lowest usage (Pinto et al., 2004). Another study conducted by Lemire et al. (1996) also shown that ceftriaxone

had the highest usage followed by cefotaxime and ceftazidime. In contrast, Kaliamoorthy et al. (2012) found that cefotaxime was the most frequently prescribed among parenteral third-generation cephalosporins. This discrepancy could be due to the differences in the local demographic where the study was conducted. Melioidosis is endemic to Malaysia with Sabah contributed approximately 6% of melioidosis mortality cases from 2011 till 2013 in Malaysia. Additionally, Kota Kinabalu reporting the highest number of melioidosis cases statewide (Nathan et al., 2018), further highlighting the gravity of this infection to the local region.

The use of third-generation cephalosporins by medical discipline was mainly to cover respiratory tract infections ($n = 54$, 39.4%). However, a specific indication that the antibiotics were prescribed was for empirical melioidosis ($n = 64$, 46.7%) and confirmed melioidosis ($n = 13$, 9.5%) with a correct dose of IV Ceftazidime 2g every 6 hourly based on initial intensive therapy of Royal Darwin Guideline (Currie, 2014). For renal failure patients, dose adjustments were made based on the Sanford Antimicrobial Guidelines 2018. Based on the Guideline for Clinical and Public Health Management of Melioidosis in Sabah, patients that present with symptoms of community-acquired pneumonia (CAP) with underlying risk factors of melioidosis such as diabetes mellitus, chronic kidney disease, and/or social history such as working as a farmer will be started with melioidosis treatment where ceftazidime is the first-line of treatment given the high risk of melioidosis (Currie, 2015). This is in line with NAG 2019 whereby if patients present with pneumonia and are suspected of melioidosis, the appropriate treatment for melioidosis should be started.

As pneumonia is the most common clinical presentation of melioidosis where it may be the primary presenting factors or it may develop secondary to initial disease at a distant focus (Meumann et al., 2012), admitted patients with signs and symptoms of CAP and/or risk of melioidosis are likely to be started on third-generation cephalosporins. Reported data affirmed pneumonia cases in Singapore and Thailand were due to melioidosis which accounted for 33.1% (Sim et al., 2018) and 20% (Currie, 2003) respectively. Besides, several studies have reported that patients who presented with pneumonia were also diagnosed with melioidosis (Currie, 2003; Kingsley et al., 2016).

Not only that, diabetes mellitus is one of the most common risk factors for melioidosis in Malaysia which accounts for about 38-75% of cases (Kingsley et al., 2016; Nathan et al., 2018). Patients with chronic lung disease and/or chronic renal failure and/or liver disease and/or other conditions that cause immune suppression also have a higher risk to be infected with melioidosis (Kingsley et al., 2016; Nathan et al., 2018; Puthucheary, 2009). Moreover, some occupational groups are at higher risk of contracting the disease for example workers in agricultural and construction sectors, military personnel, eco-tourists, and persons involved in rescue operations due to the possibility of contacting contaminated soil or water, and these are the main economic activities in Kota Kinabalu, Sabah (Nathan et al., 2018).

In terms of treatment specificity, it was found that 99 (72.3%) patients were treated empirically and 38 patients (27.7%) continued as a definitive treatment after the release of culture and sensitivity results. This is in contrast to a study conducted by Reddy et al. (2015) where they found that 81% of their study population received disease-specific therapy while only 19% of the patients were treated empirically. This may be explained by local practice of melioidosis management where patients admitted to medical wards with signs and symptoms of melioidosis such as pneumonia in addition to specific comorbidities will be started with ceftazidime as empirical cover for melioidosis.

Delays in diagnosis and initiating appropriate antibiotic therapy for melioidosis due to difficulties in clinical recognition and laboratory diagnosis often lead to poor outcomes and might lead to mortality that can exceed 40% in some regions in addition to extensive osteomyelitis which needs aggressive and often repeated surgical debridement of necrotic bone (Wiersinga et al., 2018). Furthermore, Zueter et al. (2016) reported that incomplete treatment, or missed or delayed diagnosis contributed to the occurrence of recurrent infection. They investigated that four patients of their case series developed a recurrent infection and all of them succumbed to death during the last infection episode (Zueter et al., 2016). A study conducted in Pahang by How et al. (2005), reported that patients were at 40% and 25% higher risk of relapse for those who did not receive specific therapy and those who received specific therapy for less than two weeks, respectively.

Hence, this can explain the higher percentage for empirical melioidosis (*n* = 64, 75.3%) compared to confirmed cases of melioidosis (*n* = 13, 15.3%) out of 85 patients that were prescribed with ceftazidime. Indirectly, this may clarify the high usage of third-generation cephalosporins specifically ceftazidime in medical wards of HQEII, which is especially worrisome because high usage of third-generation cephalosporins may lead to bacterial resistance. Concerning this matter, a better method of diagnosing patients could be implied such as specifying criteria for patients that have ceftazidime as empirical melioidosis. A study conducted in northeast Thailand revealed that patients infected with melioidosis had significantly higher glycated haemoglobin (HbA_1c) levels compared to the other-septicemia group and non-infectious group (Suputtamongkol et al., 1999). Secondly, there should be a need to review the choice of antibiotics based on the severity of the presentations. In cases of high-grade fever, the empirical treatment comprised of imipenem, ceftazidime, meropenem, or piperacillin/tazobactam, while in severe fewer cases, in particular with suspected skin abscess origin, cloxacillin, cefotaxime, cefuroxime, metronidazole, azithromycin, fluconazole or ceftriaxone can be used (Zueter et al., 2016). However, a study that compared mortality rate between treatments using amoxicillin/clavulanic acid and ceftriaxone or cefotaxime in community-acquired septicemia found that 53.9% of mortality were associated with amoxicillin/clavulanic acid and 71% were associated with cefotaxime or ceftriaxone, suggesting that empirical regimens for treatment of presumed community-acquired septicemia that contain cefotaxime or ceftriaxone are not appropriate for melioidosis (Chaowagul et al., 1999). Ceftazidime remains the mainstay of treatment as it has the lowest mortality rate compared to other antibiotics (Chaowagul et al.,1999; Suputtamongkol et al.,1994; White et al.,1989). Lastly, the time frame in initiating the empirical therapy using ceftazidime should be reviewed as the duration for the result of the culture and sensitivity would take longer, around 3 to 5 days depending on the severity of the cases since the test is being outsourced due to non-availability of the equipment at HQEII. In endemic areas where laboratory diagnostic facilities are unavailable or delayed, empirical antibiotic regimens for rapidly progressing pneumonia and/or sepsis need to cover for empirical melioidosis (Kingsley et al., 2016).

Ceftriaxone was mainly used for respiratory tract infections, principally pneumonia (*n* = 14, 29.2%) out of 48 patients corroborated in the study done in Ethiopia (Ayele et al., 2018) with a correct dose of IV ceftriaxone 2 gm every 24 hours. Based on the NAG 2019, the use of ceftriaxone in pneumonia patients is indicated for moderate and severe community-acquired pneumonia and early onset of hospital-acquired pneumonia. However, ceftriaxone is the second choice of antibiotics in treating pneumonia while amoxicillin/clavulanic acid is the preferred

choice of agent in treating pneumonia with a dose of IV amoxicillin/clavulanic acid 1.2 g every 8 hours for five to seven days. Thus, any patient which is started with ceftriaxone for pneumonia will be changed to IV amoxicillin/clavulanic acid within 3 days after being reviewed by the antimicrobial stewardship team of HQEII. This indirectly will reduce the usage of the third generation of cephalosporins in the medical wards of HQEII.

Ceftriaxone also was prescribed for infective acute gastroenteritis (AGE) wherein in severe cases that need hospitalization, ceftriaxone may be considered as effective against gram-negative bacteria (Kim et al., 2019). From our findings, 20.8% of patients receiving ceftriaxone was indicated for AGE with symptoms of chronic diarrhoea compared to another study where only 9.5% (Reddy et al., 2015) and 1.6% of patients receiving ceftriaxone for gastrointestinal disease (Durham et al., 2017) and only 1.3% in patients who presented with diarrhoea (Sonda et al., 2019). The other indications were meningitis with a correct dose of IV Ceftriaxone 2 g every 24 hours which is recommended as an empirical treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporins is not to be expected (van de Beek et al., 2016), cholecystitis, sepsis as it proved by as safe and effective when used as a single drug in the therapy of septicaemia and other serious infections involving bacteraemia (Foster, 1991) and leptospirosis as an efficient, convenient to be administered once daily compared over other third-generation cephalosporins and safe regimen as it needs no dosage adjustment for renal failure (Raptis et al., 2006). Furthermore, ceftriaxone can give the additional advantage of being an excellent empirical therapy for other infections which mimic the clinical presentation of leptospirosis (Naing et al., 2017).

Out of 137 patients, only 4 patients (3%) were started with cefotaxime. A study conducted in Trinidad found that 26.5% of patients were started with cefotaxime (Pinto Pereira et al., 2004) and only 1% of patients was started with cefotaxime in India (Chandrasekhar et al., 2020). Up until today, no other studies that research the use of third-generation cephalosporins state the specific use of cefotaxime and other antibiotics under third-generation cephalosporins. In our study, cefotaxime was prescribed only in liver cirrhosis patients as empirical cover for spontaneous bacterial peritonitis (SBP) which is in line with the NAG 2019. Spontaneous bacterial peritonitis is an infection of ascitic fluid and it is a common severe complication in patients with liver cirrhosis (Lata et al., 2009). IV cefotaxime 2gm every 8 hours for 5 days is the antibiotic of choice for SBP as it achieves excellent ascetic fluid levels and covers for most common causative microorganisms such as *E. coli*, *K. pneumonia* and *Streptococcus pneumonia* (Koulaouzidis et al., 2007). It has shown high efficacy for SBP, ranging from 77% to 98% of cases (Felisart et al., 1985; Navasa et al., 1996; Rimola et al., 1995; Runyon et al., 1991)

Based on the data collected, the median total duration of antibiotics prescribed was five days. This is in line with the observation done by two studies with the average duration of antibiotic prescribed was five days (Reddy et al., 2015; Shankar et al., 2003). The duration of antibiotics prescribed for empirical melioidosis was three days which is in line with the in-house Antimicrobial Stewardship policy of HQEII where the team will review the use of broad-spectrum antibiotics that are used empirically at 72 hours after antibiotics initiation or once a week at least. However, our finding is contrary to another study by Mettler et al. (2007) that reviewed the empiric use of antibiotics. They found that the empiric therapy lasted a mean of 7.5 days after admission due to few reasons stated by the authors. To prevent the emergence of antimicrobial resistance, an antibiotic with the narrowest possible spectrum should be selected for the continuation of therapy once

culture and susceptibility data are available and the antibiotics should be off if the culture result is negative (Leekha et al., 2011).

CONCLUSION

From this study, it can be concluded that third-generation cephalosporins based on indication, dose, frequency, and duration in medical wards of HQEII were appropriately prescribed as per NAG 2019. Ceftazidime had the highest usage among third-generation cephalosporins which was mostly indicated for empirical melioidosis because of a high case of melioidosis in Sabah. However, further exploration in prescribing ceftazidime for empirical melioidosis is warranted as 75.3% of ceftazidime was used for empirical melioidosis compared to only 15.3% for treating melioidosis cases. A better method of diagnosing patients could be implied before initiating ceftazidime in suspected melioidosis cases. Reviewing the choice of antibiotics based on the severity of presentations and the time frame in initiating the empirical therapy while waiting for culture and sensitivity results are necessary. Lastly, collaboration is needed among healthcare workers to reduce antibiotic resistance.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

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