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Hypoalbuminemia and Central Venous Catheter as Risk Factors for Multidrug-resistant Healthcare-associated Pneumonia in an Intensive Care Setting

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Authors' contributions

This work was done in collaboration among all the authors. Authors ILGW and FI designed the study, performed the analysis of the study and wrote the first draft of the manuscript. Authors ILGW, FI, NB and TJS supervised the study and analysed the data. All the authors managed the literature search writing of the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The rapid emergence of antibiotic-resistant bacteria is a threat to global health particularly in the area of healthcare-associate pneumonia (HCAP) where there is high rate of mortality. In general, guidelines should serve as a framework that needs to be complemented by local antibiogram data due to multiple factors influencing the development of multidrug-resistant (MDR) HCAP. Failure to administer prompt and appropriate empirical therapy would often result in a high mortality rate. Based on these concerns, the aim of the study was to evaluate the appropriate empirical use of antibiotic and risk factors of MDR HCAP based on local pathogen resistant pattern. This was a

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retrospective analysis on HCAP in critical care of a tertiary-care hospital with data from January 2016 to December 2018. Patients diagnosed with HCAP: hospital-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP), with positive bacterial cultures were included into the study. Of the 269 patients and isolates included, 160 (59.5%) had MDR strains. The top causative pathogens isolated were *Acinetobacter baumannii* (n=104, 38.7%), *Pseudomonas aeruginosa* (n=66, 24.5%), *Klebsiella spp* (n==55, 20.4%), and *Staphylococcus aureus* (n=16, 5.9%). The incidence of inappropriate empirical antibiotic was significantly higher in patients with MDR HCAP (n=135, 84.4%) compared to those with non-MDR HCAP (n=34, 31.2%) ($p < 0.001$). Mortality was significantly higher in patients receiving inappropriate empirical therapy (n = 118, 72.4%) compared to those receiving appropriate empirical antibiotic (n = 36, 54.5%) (P = 0.009). The independent risk factors for MDR HCAP identified in this study were hypoalbuminemia (odds ratio [OR] 3.43, 95% confidence interval [CI] 1.08 – 10.87, p = 0.036) and indwelling central venous catheter (OR 5.65, 95% CI 1.13 – 28.18, p = 0.035). This work serves as a basis for a center-specific guideline to improve antibiotic use among HCAP patients in intensive care setting.

Keywords: Antibiogram; hospital-acquired pneumonia; multidrug-resistant; risk factors; ventilator-associated pneumonia.

1. INTRODUCTION

The rapid emergence of antibiotic-resistant bacteria is a threat to global health, which significantly reduces the efficacy of antibiotics at an alarming rate. Pneumonia is of particular interest due to widespread antibiotic resistance even among common causative pathogens. Healthcare-associated pneumonia (HCAP) consisting of both hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), has one of the highest mortality rates [1]. It is often a severe infection that is associated with an increase in mortality, morbidity and cost of treatment [1]. Management of HCAP especially those caused by multidrug-resistant (MDR) pathogens are challenging and the need to understand its risks are imminent to ensure optimal treatment.

The incidence of MDR HCAP and efficacy of certain antibiotics differs from one place to another [2]. This is particularly distinct when comparing between Asian and Western countries. The common non-fermenters found in Asian countries are highly resistant to antimicrobial agents. *Acinetobacter spp* from this region were reported to exhibit high MDR and extensively drug-resistant rate of 82% and 51.1% respectively [3]. Data from Europe shows a diverse prevalence of MDR *Acinetobacter spp* from less than 1% to more than 50% in certain countries [4]. Whereas United States reported prevalence for MDR *Acinetobacter baumannii* of 38.1% [5]. Countries in Asia have reported prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) HCAP ranging from 5% to 18% [6].

The rising rate of MDR HCAP is a cause for concern as it is often associated with inappropriate initial antibiotic therapy. In patients with late-onset HCAP, those receiving inadequate initial antibiotic therapy has a significantly higher mortality rate (42.9% versus 23.8%) compared to those who received adequate initial antibiotic therapy [7]. Furthermore, it also increases the risk for prolong duration of mechanical ventilation, intensive care unit (ICU) stay, higher hospitalization cost, higher rates of infection recurrence and greater mortality [8]. As such, there is a need to ensure appropriate antibiotics are administered for optimum outcome.

A deeper insight of risk factors of MDR pathogens is also imminent to ensure optimum care is delivered. Although multiple risk factors for MDR pathogens have been identified, studies still show varying results [2,9]. Currently, only one meta-analysis on risk factors of MDR is available which was conducted by the Infectious Diseases Society of America (IDSA) / American Thoracic Society (ATS) guideline [9]. They found that prior antibiotic use within 90 days were the most significant risk factors for MDR HAP, VAP, and certain pathogens [9]. Septic shock, acute respiratory distress syndrome, five or more days of hospitalisation, and acute renal displacement therapy were also identified as risk factors for MDR VAP [9]. However, the guideline further mentioned that there are other potential risk

factors that were not listed in the final result due to lack of conclusive evidence [9].

In most cases, guidelines merely serve as a framework that needs to be complemented by local antibiogram data [2,9]. Moreover, treatment recommendations from guidelines such as IDSA/ATS, British Thoracic Society or European Respiratory Society are made based upon microbiological pattern and resistance of respective regions and therefore would not be the best fitting practice guideline in other regions [2,3,9]. Through development of a local antibiogram, empirical antibiotic therapy more specific to individual healthcare settings can be given while reducing excessive use of broad-spectrum antibiotic and its accompanying collateral damage [10]. Guideline-directed therapy based on local resistance pattern have been shown to result in improved appropriate initial treatment with reduction of 14-days mortality without an increase in antibiotic [10]. Based on these concerns, the aim of the present study was to evaluate the appropriateness of empirical antibiotic for treatment of HCAP and identify risk factors for development of MDR HCAP.

2. METHODOLOGY

2.1 Study Design

This was a retrospective observational single-centered study conducted in an ICU of a tertiary hospital in Malaysia. All adult patients from January 2016 to December 2018 in the ICU with a diagnosis of new onset HCAP: both HAP and VAP with positive bacterial cultures were included in the study. Those with incomplete data were excluded. The selection of the cases was based on positive bacteriological culture results. In practice, microbiologic specimens were always obtained before starting new empirical antibiotics and only attained via bronchoalveolar lavage and tracheal aspirate. All cases with positive cultures were then screened for HAP or VAP. HAP was defined as pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission and VAP was defined as pneumonia occurring more than 48 hours after endotracheal intubation [9]. For the diagnosis of pneumonia, a patient must have a new and persistent radiographic infiltrate plus at least two of the following signs of infection: new onset of fever above 38^{o}C, purulent sputum, leukocytosis, and decline in oxygenation. Seligman et al. [11] Patients with incomplete data, or pneumonia caused by Mycobacterium tuberculosis were excluded. All patients' data was collected using hospital electronic medical records.

2.2 Data Collection

The data collected included age, gender, date of hospital and ICU admission, date of mechanical ventilation and extubation, source of culture, pathogens isolated, strain of resistant, initial empirical antibiotic, pathogen susceptibility, comorbidities/clinical conditions (traumatic brain injury, post-surgery, chronic lung disease, chronic renal disease, chronic liver disease, chronic dialysis during the preceding 30 days, diabetes, immunosuppression, extrapulmonary infection, sepsis, shock, hypoalbuminemia (< 30 g/dL), positive MRSA history within the previous 90 days), invasive procedure (tracheostomy, dialysis, central vein catheterization, urinary tract catheterization, mechanical ventilation, nasogastric tube feeding), and drug use (use of gastric acid suppressive agents, use of antibiotic within the previous 30 days, corticosteroid therapy [1,2,8,9] Immunosuppression included any immunosuppressive diseases, such as congenital or acquired immunodeficiency, hematologic diseases, neutropenia (1,000/mm3), treatment with immunosuppressive drugs within the previous 30 days, or corticosteroids in daily doses of at least 10 mg/day of a prednisone equivalent for more than 2 weeks [12]. Corticosteroid therapy referred to those in immunosuppressive doses (prednisone ≥ 1 mg/kg per day or equivalent [12].

2.3 Study Outcomes

The following pathogens were considered MDR: MRSA; extended-spectrum β-lactamase-producing gram-negative *Enterobacteriaceae spp*, such as *Klebsiella spp, E. coli,* and *Proteus spp*; sulfonamide-resistant *Stenotrophomonas spp* [11]. Other organisms were considered MDR if they were found to be resistant to at least three of the following antibiotic classes: antipseudomonal cephalosporins or penicillin, macrolides, carbapenems, fluoroquinolones, and aminoglycosides [13].

Empirical antibiotic therapy was considered to be appropriate when the patient received at least one in vitro active/sensitive antimicrobial agent within 24 hours after blood cultures were obtained and before susceptibility results were available. The dosage and route of administration were ensured to be in accordance

with the current medical standards. It was considered inappropriate when an antibiotic tested report resistant, intermediate or non-susceptible as an outcome [14]. Susceptibility of empirical antibiotics that were not done were considered as 'not tested'. Positive isolates without administration of empirical antibiotic were considered as 'not given' [14].

Mortality rates were determined using in-hospital all-cause mortality for hospital stay of current infection. At the end of admission, patients were documented as death or discharged. Patients that were transferred out from hospital during current admission for any reasons were considered as 'transferred out from hospital'. Patients or family members that requested and were discharged against physician advise were documented as 'at own risk discharged from hospital'.

2.4 Sample Size

The sample size to determine if there were any statistical difference in appropriateness of empirical antibiotic therapy between the non-MDR and MDR group was calculated using the formula from Fleiss (1981) [15], where the variables are dichotomous. The significance level and power were set at 0.05 and 0.8 respectively. Using previous study to estimate the possible frequency of MDR pneumonia, the calculated sample size was 65 cases per group [14]. Based on the rule of needing ten outcomes for each independent variable, the required sample size to determine association between 22 risk factors and MDR pathogens was 220 samples [16].

2.5 Statistical Analysis

Statistical analysis was performed using IBM® Statistical Package for Social Sciences for Windows version 24 (IBM Corp., Armonk, N.Y., USA). Demographic, clinical, microbiological characteristics, and antibiotic use were presented using descriptive statistics. Data which were normally distributed was represented using mean ± standard deviation and compared using independent T-test. Descriptive data was expressed in numbers and percentage, and compared using Chi-square. Variables were examined using univariate analysis to determine association with MDR pathogens. From univariate analysis, variables with $P \leq 0.25$ as well as variables which were found to be significant risk factors in previous studies were entered into the multivariate model. All tests performed were two-tailed and a P-value less than 0.05 was considered as statistically significant.

3. RESULTS

3.1 Demographic Data and Clinical Characteristics

A total of 269 HCAP patients were included in the study. The baseline characteristics of patients with non-MDR and MDR are described in Table 1. The predominance of MDR was significantly higher in patients with VAP (n=145, 90.6%) compared to those with HAP (n=15, 9.4%) (P = 0.012). There was a higher incidence of MDR with the presence of indwelling central venous catheter (MDR 97.5% versus non-MDR 90.8%, P = 0.024) and use of antibiotic within the previous 30 days (MDR 99.4% versus non-MDR 93.6%, P = 0.026) compared to the non-MDR group.

There were a total of 269 pathogens with 109 isolates for non-MDR and 160 isolates for MDR (Table 2). In the non-MDR group, the most commonly isolated pathogen was *P. aeruginosa* (n=60, 55%), followed by *Klebsiella spp* (n=16, 11.9%) and *Stenotrophomonas maltophilia* (n=13, 11.9%). Whereas in the MDR group, *Acinetobacter baumannii* (n=99, 61.9%) was the most common isolated pathogen followed by *K. pneumoniae* (n=35, 21.9%) and *S. aureus* (n=11, 6.9%). If the isolated pathogens were not segregated according to MDR status, the top causative pathogens would be *A. baumannii* (n=1041, 38.7%), followed by *P. aeruginosa* (n=66, 24.5%), *K. pneumoniae* (n=37, 3.8%).

The pattern of resistance of the top causative pathogens can be seen in Table 2. Majority of the *A. baumannii* pathogen were MDR with complete susceptibility to Colistin and about half of the isolates were susceptible to Tigecycline (n=51, 52%). Following international standardized definition for MDR, most of the *P. aeruginosa* were considered non-MDR (60/66). Nearly all non-MDR *P. aeruginosa* showed more than 90% susceptibility to tested antibiotics and all the MDR *P. aeruginosa* were susceptible to Colistin (n=6, 100%). A large fraction of *Klebsiella spp* (39/55) were classified as MDR as most of them were ESBL producers. However, all *Klebsiella spp* isolated showed full susceptibility to Carbapenem (n=55, 100%). About 68% (n=11) of the *S. aureus* isolated were MRSA. All the *S. aureus* isolated were susceptible to

Trimethoprim/sulfamethoxazole, Gentamicin, Vancomycin, and Linezolid (n=16, 100%).

3.2 Appropriate Use of Empirical Therapy

Of the total 269 cases, 237 received empirical antibiotic therapy. Appropriate use of antibiotics was then analysed based on susceptibility of empirical antibiotics when compared to culture and sensitivity results. Five out of the 237 cases that received empirical management received dual antibiotic therapy with the rest of the cases receiving monotherapy. When comparing the appropriate use of empirical antibiotic between the non-MDR and MDR group based on antibiotic susceptibility, there was a significantly higher inappropriate antibiotic therapy in the MDR group (n=135, 84.4%) compared to the non-MDR group (n=34, 31.2%) ($P < 0.001$) (Table 3).

Further analyses on the outcomes of appropriate antibiotic treatment were evaluated. Four outcomes were reported for patients treated for HCAP in the critical care (Table 3). There was no difference in either discharged or death between non-MDR and MDR group, with an in-hospital mortality rate of 67.5% (n=108) (MDR) versus 59.6% (n=65) (non-MDR). However, if the in-hospital mortality rate was compared between patients receiving inappropriate and appropriate empirical antibiotic therapy, the former had a significantly higher mortality rate (n = 118, 72.4%) compared to those receiving appropriate empirical antibiotic (n = 36, 54.5%) ($P = 0.009$).

3.3 Risk Factors for MDR HCAP

A univariate and multivariate logistic regression analysis was performed to identify the risk factors for MDR HCAP (Table 4). Potential risk factors from the univariate analysis with a P-value ≤ 0.25 and variables which were found to be significant risk factors in previous studies (on mechanical ventilation prior to diagnosis of HCAP and on gastric acid suppresant drugs) were then included in the multivariate analysis. The backward conditional multivariate logistic regression model was statistically significant ($\chi^2 = 21.299$, df = 794, $P = 0.001$), and demonstrated that hypoalbuminemia and presence of indwelling central venous catheter were significant risk factors for MDR HCAP. Patients with hypoalbuminemia were 5.65 times more likely to get MDR HCAP ($P = 0.036$) and patients with presence of indwelling central venous catheter were 5.42 times more likely to also have similar outcome ($P = 0.035$). In this logistic regression analysis, multicollinearity of the variables was checked and not found. Hosmer-Lemeshow test ($\chi^2 = 0.072$, df = 1, $P = 0.789$) suggests the model was a good fit. The model was able to explain 10.3% of the variance in MDR risk factors for HCAP and correctly classify the outcome for 64.3% of the cases.

4. DISCUSSION

HCAP must be managed appropriately with prompt and accurate empirical antibiotic following association with high rate of mortality [1]. In order to achieve this, it would be prudent to establish local antibiogram and microbiological pattern. The prevalence of MDR HCAP in our critical care setting was found to be at a much higher rate as compared to two larger scale studies [17,18], which was due to MDR from VAP rather than HAP (Table 1). Patients with VAP are commonly expected to have a higher prevalence of MDR HCAP due to differences in core pathogens compared to HAP [19], such as *A. baumannii*, and ESBL-producing *Klebsiella spp*. Furthermore, mechanical ventilation itself increases the occurrence of MDR HCAP as VAP patients are mostly in much more severe conditions with longer ICU stay [18]. In general, the distribution of causative pathogens in our setting did not differ much from previous studies with a higher prevalence for *A. baumannii*, *P. aeruginosa* but lower *S. aureus* [3,6] (Table 2). In comparison to the US, *S. aureus* ranked first as causative pathogens, accounting for 24.4% of VAP cases, while the prevalence of MRSA was 13.3% for VAP [20]. Previous study has shown that while *S. aureus* was isolated in a smaller proportion in ICUs from Asia, the percentage of MRSA in VAP cases caused by *S. aureus* was extremely high at 77.5% [21], comparatively similar to the current findings.

The overall appropriate empirical treatment rate for HCAP in our study was less than desirable and much lower compared to that previously reported [22] (Table 3). This could be attributed to the high incidence of MDR HCAP in our center. As a large fraction of the pathogens consist of MDR *A. baumannii*, other than Colistin, almost all other agents would fail as empirical therapy. Our study demonstrated that the overall appropriateness of Meropenem, Piperacillin/ Tazobactam, Cefepime, and Colistin if given as empirical therapy against top causative Gram-

negative pathogens would be 50.2%, 36.4%, 38.2% and 99.6% respectively. As such, the need for rapid and reliable diagnostics for determining pathogens represents a major unmet need in managing critically ill patients. To suggest a much broader empirical therapy within the ICU setting would be precarious and should be given careful consideration as this could lead to resistance towards the very few antibiotics that are effective.

Various factors have been identified as risk for MDR HCAP [2,9,11,12,19]. In the present single-centered study, hypoalbuminemia and presence of indwelling central venous catheter before diagnosis of HAP and VAP were the only independent risk factors for HCAP caused by MDR pathogens. This can be considered as a novel finding as these risk factors have not been reported in previous similar studies for HCAP [2, 9,11,12,19]. That being said, hypoalbuminemia

Table 1. Baseline characteristics of the study population (n = 269)

Variables	Non-MDR n = 109	MDR n = 160	P value
Age, years, mean ± SD	50.89 ± 17.1	54.39 ± 15.1	0.074
Gender, n (%)			
Male	69 (63.3)	106 (66.3)	0.619
Female	40 (36.7)	54 (33.7)	
Pneumonia Onset			
Early	24 (22.0)	36 (22.5)	0.926
Late	85 (78.0)	124 (77.5)	
Pneumonia Category			
HAP	22 (20.2)	15 (9.4)	0.012
VAP	87 (79.8)	145 (90.6)	
Comorbidities & Clinical Condition			
Traumatic brain injury	13 (11.9)	9 (5.63)	0.070
Chronic lung disease	12 (11.0)	25 (15.6)	0.283
Chronic renal disease	18 (16.5)	30 (18.8)	0.638
Chronic liver disease	8 (7.34)	12 (7.50)	0.961
Chronic dialysis within previous 30 days	6 (5.50)	14 (8.75)	0.323
Diabetes	46 (42.2)	63 (39.4)	0.643
*Immunosuppression	7 (6.42)	16 (10)	0.307
Extrapulmonary infection	57 (52.3)	97 (60.6)	0.176
Sepsis	49 (45.0)	83 (51.9)	0.265
Shock	32 (59.4)	60 37.5)	0.168
Hypoalbuminemia (< 30 g/dL)	100 (91.7)	154 (96.3)	0.073
Positive MRSA within previous 90 days	1 (0.92)	2 (1.25)	0.800
Invasive Procedures			
Tracheostomy	19 (17.4)	23 (14.4)	0.498
Dialysis	34 (31.2)	66 (41.3)	0.095
Central venous catheter	99 (90.8)	156 (97.5)	0.024
Urinary catheter	106 (97.2)	155 (96.9)	0.860
Mechanical ventilation	108 (99.1)	157 (98.1)	0.524
Nasogastric tube feeding	109 (100)	156 (97.5)	0.999
Post-surgery	55 (50.5)	67 (41.9)	0.102
Drug Use			
Gastric acid suppressive agents	107 (98.2)	159 (99.4)	0.376
Antibiotic within the previous 30 days	102 (93.6)	159 (99.4)	0.026
#Corticosteroid therapy	21 (19.3)	44 (27.5)	0.123

**Immunosuppression included any immunosuppressive diseases, such as congenital or acquired immunodeficiency, hematologic diseases, neutropenia (1,000/mm^3) and treatment with immunosuppressive drugs within the previous 30 days, or corticosteroids in daily doses of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.*

#Corticosteroid therapy refers to those in immunosuppressive doses (prednisone ≥ 1 mg/kg per day or equivalent)

has been identified as a risk factor for MDR Gram-negative bacilli infection among pulmonary tuberculosis patients [23]. This was due to underlying chronic hepatic insufficiency with accompanying hypoalbuminemia indicating impaired immunity which increases susceptibility to MDR infections [23]. In our case, hypoalbuminemia could be an indication of the severity of critically ill patients and its accompanying factors such as prolonged ICU stay or longer mechanical ventilation which predisposes patient to infections. Hypoalbuminemia as a risk factor could also be caused by previous acute reaction to recent history of infection or colonization by MDR infection which is a risk factor for infection by MDR pathogens [24].

While presence of indwelling central venous catheter has not been reported as a risk factor for MDR HCAP, it is however frequently reported as a risk factor for other MDR infection, particularly bacteremia [24,25]. Consequently, we are still unable to explain the possible reason for association between presences of indwelling central venous catheter with development of MDR HCAP. If using rationale of pathogen translocation, pneumonia is usually the source of infection causing bloodstream infection and not the other way around [26]. Since these findings were not found in previous studies, we suggest that the result be interpreted with prudence as there is a possibility these factors are caused by variables not investigated in the current study. Although certain guidelines have reported association between risk factors and individual MDR infections, subgroup analysis of risk factors and top causative pathogens in our study did not find such association [9,12].

Our study design had a few limitations. Firstly, we used a retrospective design in an attempt to minimize bias, we ensured that all patients had microbiological evidence of infection and each patient had met criteria for pneumonia together with evidence of an infiltrate. However, there could be cases of HCAP but were not detected due to negative culture as a consequence of previous antibiotic therapy. Secondly, the data came from a single-center critical care unit and thus may not be generalized to other wards or institution. Still, by doing a single-center study as opposed to multi-center we were able to determine characteristic that may be specific to our center only. Consequently a more targeted empirical antibiotic guide can be developed for precise treatment instead of a general recommendation that might be inadequate for certain centers.

Table 2. Top causative pathogens and antibiotic susceptibility (n = 241)

Pathogens	***In-vitro* antibiotic susceptibility (%)**	
	Non-MDR	**MDR**
Acinetobacter baumannii	**n = 5**	**n = 99**
Penicillin		
Ampicillin/Sulbactam	5 (100)	0 (0)
Piperacillin/Tazobactam	3 (60.0)	0 (0)
Cephalosporins		
Cefoperazone/Sulbactam	5 (100)	0 (0)
Ceftazidime	5 (100)	0 (0)
Carbapenems		
Meropenem	3 (60.0)	0 (0)
Imipenem	3 (60.0)	0 (0)
Doripenem	3 (60.0)	0 (0)
Aminoglycosides		
Amikacin	5 (100)	6 (6.1)
Gentamicin	5 (100)	4 (4.1)
Others		
Ciprofloxacin	5 (100)	1 (1.0)
Tigecycline	5 (100)	51 (52)
Colistin	5 (100)	99 (100)

Pathogens	*In-vitro* antibiotic susceptibility (%)	
	Non-MDR	**MDR**
Pseudomonas aeruginosa	**n = 60**	**n = 6**
Penicillin		
Piperacillin/Tazobactam	55 (91.7)	0 (0)
Cephalosporins		
Ceftazidime	55 (91.7)	1 (16.7)
Cefepime	59 (98.3)	3 (50.0)
Carbapenems		
Meropenem	55 (91.7)	0 (0)
Imipenem	53 (88.3)	0 (0)
Doripenem	56 (93.3)	2 (33.3)
Aminoglycosides		
Amikacin	60 (100)	4 (66.7)
Gentamicin	60 (100)	4 (66.7)
Others		
Ciprofloxacin	58 (96.7)	5 (83.3)
Colistin	59 (98.3)	6 (100)
***Klebsiella* spp**	**n = 16**	**n = 39**
Penicillin		
Ampicillin	0 (0)	0 (0)
Amoxycillin/Clavulanate	16 (100)	7 (17.9)
Piperacillin/Tazobactam	16 (100)	8 (20.5)
Cephalosporins		
Cefoxitin	15 (93.8)	28 (71.8)
Cefuroxime	16 (100)	0 (0)
Cefoperazone	16 (100)	2 (5.1)
Cefotaxime	16 (100)	2 (5.1)
Ceftazidime	16 (100)	4 (10.3)
Cefepime	16 (100)	3 (7.7)
Carbapenems		
Meropenem	16 (100)	39 (100)
Imipenem	16 (100)	39 (100)
Ertapenem	16 (100)	39 (100)
Doripenem	16 (100)	39 (100)
Aminoglycosides		
Amikacin	16 (100)	31 (79.5)
Gentamicin	16 (100)	22 (56.4)
Others		
Ciprofloxacin	16 (100)	8 (20.5)
Trimethoprim/sulfamethoxazole	15 (93.8)	11 (28.2)
Staphylococcus aureus	**n = 5**	**n = 11**
Penicillin		
Penicillin	2 (40)	0 (0)
Cloxacillin	5 (100)	0 (0)
Aminoglycosides		
Gentamicin	5 (100)	11 (100)
Others		
Clindamycin	5 (100)	8 (72.7)
Erythromycin	4 (80.0)	2 (18.2)
Linezolid	5 (100)	11 (100)
Rifampicin	5 (100)	10 (90.9)
Trimethoprim/sulfamethoxazole	5 (100)	11 (100)
Vancomycin	5 (100)	11 (100)

**Consists of K.oxytoca, K. ozaenae, K. pneumoniae, Klebsiella spp*

Table 3. Empirical antibiotic susceptibility and outcome between non-MDR and MDR pathogens (n = 269)

	Non-MDR (%)	MDR (%)	P value
Empirical Susceptibility			
Inappropriate	34 (31.2)	135 (84.4)	
Appropriate	52 (47.7)	16 (10.0)	< 0.001
Not tested	16 (14.7)	6 (3.8)	
Not given	7 (6.4)	3 (1.9)	
Outcome			
Discharged from hospital	42 (38.5)	46 (28.7)	0.115
In-hospital death	65 (59.6)	108 (67.5)	
Transferred out from hospital	2 (1.8)	4 (2.5)	
At own risk discharged from hospital	0 (0)	2 (1.3)	

Table 4. Factors causing MDR HCAP among the study population (n = 269)

Variables	Beta	OR	Lower 95% CI	Upper 95% CI	P-value
	Univariate Logistic Regression				
Traumatic brain injury	-0.821	0.440	0.181	1.069	0.070
Post-surgery	-0.409	0.665	0.407	1.085	0.102
Chronic lung disease	0.403	1.497	0.717	3.125	0.283
Chronic renal disease	0.154	1.167	0.613	2.219	0.638
Chronic liver disease	0.023	1.024	0.404	2.594	0.961
Chronic dialysis within 30 days	0.498	1.646	0.612	4.426	0.323
Diabetes	-0.117	0.890	0.542	1.459	0.643
Immunosuppresion	0.482	1.619	0.643	4.078	0.307
Extrapulmonary infection	0.340	1.405	0.859	2.297	0.176
Sepsis	0.278	1.320	0.810	2.151	0.265
Shock	0.367	1.444	0.857	2.433	0.168
Hypoalbuminemia	0.953	2.593	0.913	7.358	0.073
Positive MRSA previous 90 days	0.313	1.367	0.122	15.265	0.800
Tracheostomy	-0.229	0.795	0.410	1.544	0.498
Dialysis	0.437	1.549	0.927	2.587	0.095
Central venous catheter	1.371	3.939	1.203	12.905	0.024
Urinary catheter	-0.131	0.877	0.205	3.750	0.860
Mechanical ventilation	-0.724	0.485	0.050	4.720	0.533
Nasogastric tube feeding	-20.844	0	0	0	0.999
Gastric acid suppressive agent	1.089	2.972	0.266	33.187	0.375
Antibiotic previous 30 days	2.390	10.912	1.323	90.002	0.026
Corticosteroid therapy	0.463	1.589	0.882	2.865	0.123
	[a]Multivariate Logistic Regression				
Post-surgery	-0.463	0.629	0.376	1.053	0.078
Hypoalbuminemia	1.232	3.428	1.081	10.872	0.036
Central venous catheter	1.731	5.649	1.132	28.180	0.035
Mechanical ventilation	-3.226	0.040	0.001	1.342	0.072
Antibiotic previous 30 days	2.130	8.412	0.834	84.826	0.071

**Immunosuppression included any immunosuppressive diseases, such as congenital or acquired immunodeficiency, hematologic diseases, neutropenia (1,000/mm^3), treatment with immunosuppressive drugs within the previous 30 days, or corticosteroids in daily doses of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.*

[#]Corticosteroid therapy refers to those in immunosuppressive doses (prednisone ≥ 1 mg/kg per day or equivalent)

5. CONCLUSION

Given the increasing trend of MDR pathogens that is affected by multiple factors, it is not possible for guidelines alone to offer recommendations that provide optimal coverage for individual healthcare settings. There is a necessity for continuous monitoring of

respective antibiogram and antibiotic prescribing pattern to supplement guideline recommendations to ensure optimal management that is tailored to local setting is given. In the current work, MDR risk factors such as hypoalbuminemia and indwelling central venous catheter were identified. These risk factors can help to guide antibiotic therapy when microbiological evidence is not available or inconclusive. Current findings serve as a basis to develop a center-specific guideline to improve antibiotic use among HCAP in intensive care setting.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

This study was approved by the Universiti Kebangsaan Malaysia Research Ethics Committee (UKM PPI/111/8/JEP-2019-074) and Ministry of Health Medical Research & Ethics Committee (NMRR-18-3495-45177).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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