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ORIGINAL RESEARCH **INTENSIVE CARE**

A retrospective cohort study of the risk factors and outcomes of antibiotic resistance in the intensive care unit

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Abstract

Background: Antibiotic resistance remains a major problem in the intensive care units (ICU). Various risk factors have been documented by various researchers. Similarly some factors have been identified to influence the outcome after the antibiotic resistance has been developed in the patients. This retrospective study aimed to identify and document the risk factors and outcomes in ICU of our hospital.

Methodology: This retrospective, single-centre cohort study, involved 440 patients, treated in the ICU during January 2017 to December 2019. The medical records of the enrolled patients were reviewed to identify the risk factors and outcomes of antibiotic resistance. The data were analysed using the Statistical Package for the Social Sciences (SPSS) software version 26 (SPSS Inc., USA). Statistical tests used included chi-square test, Fisher's exact test, independent t-test, the Mann-Whitney test and simple or multiple logistic regression tests as per requirement.

Results: The prevalence of antibiotic resistance was 22.3%. The odds for antibiotic resistance were increased 2.90 times with medical admission [Odds ratio (OR) 2.897; 95% confidence interval (CI) 1.560, 5.379; $p = 0.01$] and 3.42 times with carbapenem usage (OR 3.418; 95% CI 1.790, 6.526; $p < 0.001$). The odds were 73.2% lower with nitroimidazole usage ($\beta = -1.318$, OR 0.268; 95% CI 0.131, 0.546; $p < 0.001$) and 62.2% lower with macrolide usage ($\beta = -0.973$, OR 0.378; 95% CI 0.150, 0.950; $p = 0.039$). Each day of antibiotic usage increased the odds of antibiotic resistance by 1.07 times (OR 1.072; 95% CI 1.037, 1.111; $p < 0.001$), and each additional antibiotic prescribed increased the odds of antibiotic resistance by 1.72 times (OR 1.717; 95% CI 1.218, 2.423; $p = 0.02$). The antibiotic resistance mortality rate was 68.4%.

Conclusions: Antibiotic resistance increased the mortality rate in the ICU, and the risk factors increased with medical-related admission, carbapenem usage, longer antibiotics duration and more antibiotic usage.

Key words: Antibiotic; Resistance; Intensive care unit; Risk factors; Mortality

Abbreviations: ARO – antibiotic–resistant organisms; MRSA – methicillin-resistant *Staphylococcus aureus; ESBL* – extended-spectrum beta-lactamase; MDR – multidrug-resistant; GNR – Gram-negative rod; MDR GNR – Multi-drug Resistant Gram-Negative Rods; VRE – Vancomycin-resistant enterococcus; CRE – Carbapenem-resistant enterobacteriaceae; BSI – bloodstream infections

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1. Introduction

Infections are a common reason of the admissions to, and of the complications in the intensive care unit (ICU). An infection acquired in the ICU is always challenging, because it can be from multiple sources and usually involves multiple organisms. Antibiotic usage is vital in the ICU, and most of the patients are likely to be started on at least one antibiotic as part of the surgical prophylaxis, empirical therapy or de-escalation therapy. Some patients require multiple antibiotics because of infection from multiple organisms or at multiple sites. The dilemma in decision-making regarding antibiotic therapy is between initiating early empirical therapy with broad-spectrum antibiotics and the risk of emerging antibiotic-resistant organisms (AROs) with extensive usage of broad-spectrum antibiotics.[1,2] AROs remain a big challenge in the management of critically ill patients. A study in one ICU in Indonesia showed that the rate of resistance to ampicillin was 100% for *E. coli, K. pneumoniae, Stenotrophomonas spp., Enterobacter spp. and Serratia spp.*, whereas *Acinetobacter baumannii* showed 83.3% resistance.[3]

AROs can be divided into methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing gram-negatives, vancomycin-resistant enterococci and multidrug-resistant (MDR) Gram-negative rod (GNR) bacteria. Data from an Egyptian medical ICU showed that the prevalence of MRSA, ESBL and MDR gram-negative bacteria in the ICU was 33%, 13%, and 63% respectively.[4] In another report, ESBL producers were reported in 27.6% of cases of ICU-acquired bloodstream infections (BSI), and the factors independently associated with ESBL-producing Enterobacteriaceae (ESBL-PE) as the causative microorganism of ICU acquired BSI were ESBL-PE carriage before ICU acquired BSI.[5] A study in Spain showed that the risk factors for MRSA colonisation/infection in ICU admission were male gender, trauma, critical patient, urgent surgery, admission from other ICUs, hospital wards or long-term facilities, immunosuppression and skin and soft tissue infections.[6] There are limited data on the usage of antibiotics and antibiotic resistance in ICUs in Malaysia. One study reported that the prevalence of carbapenem-resistant *Acinetobacter spp*. infection was 7.3% and that an older age group was the independent risk factor for mortality.[7]

Therefore, this study retrospectively identified the patterns of antibiotic usage and antibiotic resistance, the risk factors and the outcomes of antibiotic resistance in the ICU of a tertiary centre in Malaysia.

2. Methodology

It was a retrospective cohort study of 440 patients that was conducted after obtaining approval from the Human Research Ethics Committee Universiti Sains Malaysia (approval code: 19040232). The requirement of informed consent was waived off by the ethics committee as the study required retrospective data collection from the medical record after written approval from the director of the hospital. The inclusion criteria were patients who were admitted either to the general ICU or the surgical ICU (SICU) of the University Hospital on the East Coast of Malaysia from January 1, 2017 to December 31, 2018, aged 18–65 y and who required antibiotic therapy. The patients who stayed in ICU/SICU for less than 24 h and/or had poor documentation of medical records were excluded from the study. All the selected medical records were reviewed and the demographic data, antibiotic profile and outcomes were recorded. Out of a total of 440 patients included in the study, 98 patients in antibiotic resistance group and 342 patients in non-resistance group.

The sample size was estimated based on 41.7% of the percentage of antibiotic resistance[8] and 13 variables of associated factors for antibiotic resistance. The calculation was based on the method described by Peduzzi et al.,[9] and the calculated sample size was 312. Since the available sample over the two years of our review was 440, we included all the sample up to the total of 440 for the analysis.

The data were analysed using the Statistical Package for the Social Sciences (SPSS) software version 26 (SPSS Inc., USA). The categorical data were compared using the chi-square test or Fisher's exact test. The numerical data were analysed using the independent t-test or the Mann–Whitney test. All the risk factors were initially analysed using the simple logistic regression test, and factors with a $p < 0.25$ were included in the multiple logistic regression test. A $p < 0.05$ was considered statistically significant.

3. Results

The demographic and clinical characteristics of the patients are shown in Table 1.

Table 1: Demographic and clinical characteristics

Demographic	Antibiotic resistance (n=98)	Non-antibiotic resistance (n = 342)
Age * (y)	51 ± 17.5)	48 ± 19.6
Gender **		
Male	59 (60.2)	185 (54.1)
Female	39 (39.8)	157 (45.9)
APACHE II score*	17 ± 7.6)	15 ± 8.1
Indication of admission **		
Medical	63 (64.3)	129 (37.7)
Surgical	35 (35.7)	213 (62.3)
Comorbidities **		
Diabetes mellitus,	27 (27.6)	91 (26.6)
Neoplasm	13 (13.3)	57 (16.7)
Chronic kidney disease	15 (15.3)	25 (7.3)
Prior hospitalization within 6 months	35 (35.7)	72 (21.1)
Past surgical history	16 (18.4)	63 (16.3)
Prior antimicrobial use within 30 days	25 (25.8)	61 (17.8)

** Mean ± SD; ** n (%)*

Table 2: Type of resistance in antibiotic resistance group

	Antibiotic Resistance (n=98)
Prevalence of AROs: (%)	98/440 x 100 = 22.3%

Types of resistance	n (%)
ESBL	28 (21.6)
MDR GNR	64 (49.2)
VRE	6 (4.6)
CRE	16 (12.3)
MRSA	16 (12.3)
Total	130 (100)

All categorical data are expressed in n (%)

The prevalence of antibiotic resistance was 22.3%. MDR GNR organisms were the most detected AROs (49.2%), followed by ESBL organisms (21.6%) (Table 2).

Gram-negative bacteria were the most common (82.2%) AROs. *A. baumannii* was the most frequently detected organism in the antibiotic resistance group (29.2%), followed by *K. pneumoniae* (22.3%). In the non-resistance group too, the gram-negative bacteria were the most common organisms detected (77.8%), and *K. pneumoniae* was the main organism (28.8%) (Table 3).

Table 3: Pathogens isolated in both groups

	Antibiotic resistance (n=98)	Non-antibiotic resistance (n = 342)
Total number of specific organisms isolated: (n)	202	198
GNB: n (%)	**166 (82.2)**	**154 (77.8)**
Pseudomona aeruginosa	26 (12.9)	28 (14.1)
Acinetobacter baumanii	59 (29.2)	13 (6.6)
Klebsiella pneumonia	45 (22.3)	57 (28.8)
Escherichia coli	8 (4.0)	10 (5.1)
Proteus Mirabillis	8 (4.0)	8 (4.0)
Morganellia spp.	4 (2.0)	0 (0)
Others	16 (7.9)	38 (19.2)
GPB: n (%)	**36 (17.8)**	**44 (22.2)**
Enterococcus spp.	14 (6.9)	26 (13.1)
Staphylococcus aureus	22 (10.9)	18 (9.1)

All categorical data are expressed in n (%)

The antibiotic resistance group had significantly more days of antibiotics prescribed than the non-antibiotic resistance group ($p < 0.001$). The number of antibiotics used was also significantly higher in the antibiotic resistance group ($p < 0.001$) than in the non-antibiotic resistance group. The cost of antibiotics was significantly higher in the antibiotic resistance group [Malaysian Ringgit (RM) 1457.02 vs RM 386.82; $p < 0.001$]. The penicillin group was the most used amongst the antibiotic resistance group (30.7%), with piperacillin/ tazobactam the main one prescribed (11.5%). The most prescribed among the specific antibiotics in the antibiotic resistance group was meropenem (16.4%). Cephalosporin was the main antibiotic group prescribed in the non-antibiotic resistance group (39.9%), with cefuroxime the main one (13.8%). Amongst the specific antibiotics in the non-antibiotic resistance group, metronidazole was the most prescribed (19.2%) (Table 4).

The multivariate analysis included all variables with a univariate $p < 0.25$ (Table 5).

Table 4: Demographic of antibiotics usage

Antibiotics		Antibiotic resistance (n=98)	Non-antibiotic resistance (n=342)	*P*
Days on antibiotic [median (IQR)]		20.0 (13.0)	10.0 (9.0)	< 0.001
Number of antibiotics prescribed, (mean ± SD)		3.72 ± 1.61	2.34 ± 1.14	< 0.001
Antibiotic costs (RM) [median (IQR)]		1457.02 (1572.86)	386.82 (809.41)	< 0.001
Specific type of antibiotics, n (%):				
Cephalosporin	Cefuroxime	8 (2.2)	94 (13.8)	
	Ceftriaxone	15 (4.1)	79 (11.6)	
	Ceftazidime	18 (4.9)	46 (6.8)	
	Cefepime	32 (8.8)	42 (6.2)	
	Cefoperazone	17 (4.7)	11 (1.6)	
	Total	**90 (24.7)**	**272 (39.9)**	
Carbapenem	Meropenem	60 (16.4)	76 (11.2)	
	Imipenem	10 (2.7)	18 (2.6)	
	Ertapenem	2 (0.5)	2 (0.3)	
	Total	72 (19.7)	96 (14.1)	
Macrolide	Azithromycin	**16 (4.4)**	**46 (6.8)**	
	Clarithromycin	2 (0.5)	0 (0)	
	Total	**18 (4.9)**	**46 (6.8)**	
Penicillins	Augmentin	14 (3.8)	34 (5.0)	
	C. penicillin	4 (1.1)	8 (1.2)	
	Cloxacillin	26 (7.1)	48 (7.0)	
	Piperacillin/ tazobactam	42 (11.5)	75 (11.0)	
	Ampicillin/ Sulbactam	26 (7.1)	28 (4.1)	
	Total	**112 (30.7)**	**193 (28.3)**	
Fluoroquinolone	Ciprofloxacin	6 (1.6)	12 (1.8)	
	Levofloxacin	0 (0)	2 (0.3)	
	Total	**6 (1.6)**	**14 (2.1)**	
Aminoglycoside	Gentamicin	0 (0)	14 (2.1)	
Glycopeptides	Vancomycin	16 (4.4)	14 (2.1)	
Polymyxin	Polymyxin B	22 (6.0)	4 (0.6)	
Lincosamide	Clindamycin	2 (0.5)	15 (2.2)	
Nitroimidazole	Metronidazole	21 (5.8)	131 (19.2)	
Oxazolidinone	Linezolid	6 (1.6)	0 (0)	

Based on the multivariate analysis (Table 6), the odds for antibiotic resistance were increased 2.9 times with medical admission ($p = 0.01$) and 3.42 times with carbapenem usage ($p < 0.001$). The odds were lower at 73.2% with nitroimidazole usage ($p < 0.001$) and 62.2 % with macrolide usage ($p = 0.039$). Each day of antibiotic usage increased the odds of antibiotic resistance by 1.07 times ($p < 0.001$), and each additional antibiotic prescribed increased the odds of antibiotic resistance by 1.72 times ($p = 0.02$).

The patients' outcomes are shown in Table 7. The antibiotic resistance group recorded a longer ICU length of stay and hospital length of stay than the non-antibiotic resistance group. More patients died after 28 days of ICU admission in the antibiotic resistance group compared to the non-AR group (68.4% vs. 27.2%; $p < 0.001$).

4. Discussion

The rates of ARO infection in the different ICU within the same institution may vary. In our study, the prevalence of antibiotic resistance was 22.3%, and MDR GNR organisms were the most detected

AROs (49.2%). Regarding the specific organisms, *A. baumannii* was the most frequently detected organism in the ARO group (29.2%) in our study. This finding was lower than in the study conducted by Martin-Loeches et al. [10] that showed multidrug-resistant organisms (MDROs) in 35% of the patients with ICU-acquired pneumonia. Similarly, a study by Magira et al. [8] showed 41.75% of MDROs in a single-centre medical ICU in the United States.

Table 5: Simple logistic regression analysis to determine the factors associated with antibiotic resistance

Independent Variables	Crude b	Crude OR (95% CI)	Wald p-value
Age	0.008	1.008 (0.996, 1.020)	0.174
APACHE II score	0.039	1.040 (1.010, 1.070)	0.008
Indication of admission:			
Medical-related	1.089	2.972 (1.862, 4.743)	< 0.001
Comorbidities:			
Chronic kidney disease	0.829	2.292 (1.156, 4.542)	0.018
Prior hospitalization	0.734	2.083 (1.279, 3.394)	0.003
Prior antibiotics use	0.470	1.599 (0.939, 2.725)	0.084
Days in hospital	0.013	1.013 (1.005, 1.020)	0.001
Days in ICU	0.005	1.005 (0.999, 1.010)	0.105
Days on ventilator	0.105	1.110 (1.077, 1.145	< 0.001
Tracheostomy	1.501	4.486 (2.501, 8.047	< 0.001
Dialysis	1.110	3.036 (1.811, 5.090)	< 0.001
Antibiotics:			
Days on antibiotic	0.093	1.098 (1.070, 1.126)	< 0.001
Number of antibiotics	0.813	2.254 (1.815, 2.800)	< 0.001
Penicillin	1.337	3.809 (2.293, 6.326)	< 0.001
Carbapenem	1.778	5.980 (3.661, 9.769)	< 0.001
Aminoglycoside	0.783	2.188 (1.130, 4.236)	0.02
Macrolide	0.370	1.448 (0.796, 2.634)	0.225
Nitroimidazole	-0.823	0.439 (0.259, 0.746)	0.002

Table 6: Multiple logistic regression analysis to determine clinical features associated with antibiotic resistance

Independent Variables	Adjusted b	Adjusted OR (95% CI)	Wald p-value
Indication of admission:			
Surgical-related	0	1	0.01
Medical-related	1.064	2.897 (1.560, 5.379)	
Total antibiotic used	0.541	1.717	0.02
Days on antibiotic	0.070	1.072 (1.037, 1.1108)	< 0.001
Carbapenem usage:			
No	0	1	< 0.001
Yes	1.229	3.418 (1.790, 6.526)	
Nitroimidazole usage:			
No	0	1	< 0.001
Yes	-1.318	0.268 (0.131, 0.546)	
Macrolide usage:			
No	0	1	0.039
Yes	-0.973	0.378 (0.150, 0.950)	

Forward LR method applied. Classification table=77.7% overall percentage correct, Hosmer-Lemeshow test p-value=0.044, Area under ROC curve=87.9%

Another study by Balkhair et al. [11] showed an overall prevalence rate of 10.8% of MDRO cases per 1000 admissions in a tertiary hospital in Oman. In a study conducted in another ICU in Malaysia, the prevalence of MDR *A. baumannii* was 28.43%, which was similar to our finding.[12]

Table 7: The outcomes of both groups

Variables	Antibiotic Resistance (n = 98)	Non-antibiotic Resistance (n = 342)	p-value
Days in hospital, *median* (IQR)[a]	24.0 (27.0)	13.0 (12.0)	< 0.001
Days in ICU, *median* (IQR)[a]	15.0 (19.0)	5.0 (6.0)	< 0.001
Days on ventilator, *median* (IQR)[a]	10.5 (16.0)	3.0 (6.0)	< 0.001
Tracheostomy, *n* (%)	28 (28.7)	28 (8.2)	< 0.001
Dialysis, *n* (%)	33 (33.7)	49 (14.3)	< 0.001
Respiratory dysfunction, *n* (%)	85 (86.7)	163 (47.7)	< 0.001
Liver dysfunction, *n* (%)	6 (6.1)	24 (7.0)	0.757
Kidney dysfunction, *n* (%)	67 (68.4)	103 (30.1)	< 0.001
Cardiac dysfunction, *n* (%)	52 (53.1)	119 (34.8)	0.001
Outcome at 28 days of ICU:			
Death, *n* (%)	67 (68.4)	93 (27.2)	< 0.001
Discharged home, *n* (%)	25 (25.2)	241 (70.5)	
Transferred to another ward, *n* (%)	6 (6.1)	8 (2.3)	

ICU= Intensive care unit; IQR= Interquartile range

In terms of antibiotic demography, our study showed that the antibiotic resistance group had significantly more days of antibiotics prescribed, a greater number of antibiotics prescribed and a higher cost for antibiotic usage than the non-AR group.

The penicillin group was the most used amongst the antibiotic resistance group (30.7%), while meropenem was the main specific antibiotic prescribed (16.4%). Cephalosporin was the main antibiotic group prescribed in the non-antibiotic resistance group (39.9%), with cefuroxime being the main specific one prescribed (13.8%). Amongst the specific antibiotics in the non-antibiotic resistance group, metronidazole was the most prescribed (19.2%). A study by Saxena et al. [13] in the ICU of a tertiary centre in India showed that, overall, the most used antibiotics in their ICU were beta-lactam antibiotics, which were used in 88% of the patients, followed by metronidazole in 80%. Most patients were prescribed two or more antibiotics, while 66% were prescribed 3–5 antibiotics. Their study showed that most of the *Klebsiella* species and *Acinetobacter* species were resistant to the beta-lactam group of antibiotics such as cephalosporins and piperacillin-tazobactam.[13]

On the risk factors for antibiotic resistance, our study showed that the odds of antibiotic resistance were increased 2.9 times with medical-related admission to ICU, 3.42 times with carbapenem usage, 1.07 times with increased days of antibiotic usage and 1.72 times with each additional antibiotic prescribed. The odds were lower at 73.2% with nitroimidazole usage and 62.2% with macrolide usage. El mekes et al.,[14] in their study of antibiotic resistance in a clinical and surgical ICU in Morocco, also identified that the use of quadruple or triple therapy was a significant risk factor for MDR (OR 5.596 and 5.175, respectively). Other factors identified in their study were lack of patient isolation precautions (OR 7.500) and mechanical ventilation (OR 4.926).[14] However, our study did not show significant risk associated with ventilator days. Liu et al.,[15] in their meta-analysis of the risk factors of carbapenem-resistant *K. pneumoniae* (CRKP) infection, identified 16 risk factors associated with CRKP, and exposure to carbapenems was one of the listed risks, as also determined by our study (OR = 4.01). Other significant risk factors in their study were longer length of hospital stay, admission to ICU, prior hospitalisation, longer ICU stay, transplant recipient, steroid use, central venous catheter use, mechanical ventilation, presence of tracheostomy, parenteral nutrition, previous antibiotic use and exposure to aminoglycosides, glycopeptides, quinolones and

anti-pseudomonal penicillins.[15] Some of their significant risk factors were not significant in our study, such as length of hospital stay, admission to ICU, prior hospitalisation, longer ICU stay, mechanical ventilation, presence of tracheostomy and previous antibiotic use. Hu et al.,[16] in their study on CRKP in ICU, identified the number of antibiotic groups and previous exposure to carbapenems as significant risk factors for CRKP, as in our study. Other significant factors in their study were age and prior hospitalisation, which were not significant in our study.16

The outcomes of our study showed that the antibiotic resistance group had longer duration of mechanical ventilation, ICU stay and hospital stay. The percentage of organ dysfunctions was also higher in the antibiotic resistance group. Mortality after 28 days of ICU admission was also higher in the antibiotic resistance group compared to the non-antibiotic resistance group (68.4% vs 27.2%). A study on antibiotic resistance in Morocco showed that the attributable mortality of patients with MDR bacteria in the ICU was about 12%.14 In a prospective observational study among ICU-acquired pneumonia, only the patients with MDROs had a 2.89 times higher ICU mortality than the patients with non-MDROs. The patients with MDRO ICU-acquired pneumonia (ICU-AP) also remained in the ICU for a significantly longer period.10 In a study on a carbapenem-resistant *A. baumannii* population, the mortality rate was 50% among the reviewed patients, which contributed 13.6% of the total ICU mortality.7

5. Conclusions

In conclusion, antibiotic resistance increased the mortality rate in the ICU, and the risk factors increased with medical-related admission, carbapenem usage, and use of antibiotics for longer duration and multiple antibiotic usage.

6. Conflict of interest

Authors declare no conflict of interest

7. Author's contribution

MTM: Concept, design, execution, analysis, interpretation of the data, drafting and final approval of manuscript

WMNWH: Concept, design, execution, analysis, interpretation of the data, drafting, critical revision and final approval of manuscript

AMM, WFWMS, MZM: Concept, design, critical revision and final approval of manuscript

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