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Article

Association of Multidrug Resistance Bacteria and Clinical Outcomes of Adult Patients with Sepsis in the Intensive Care Unit

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Abstract: Background: Multi-drug resistance organisms (MDRO) often cause increased morbidity, mortality, and length of stays (LOS). However, there is uncertainty whether the infection of MDRO increase the morbidity, mortality, and ICU-LOS. Objective: This study performed to determine the prevalence of MDRO in ICU, site of infection and the association of MDRO or site of infection with mortality. Secondary outcome was determined by ascertaining the association of MDRO or site of infection with (ICU-LOS). Methods: A retrospective cohort study was performed with adult sepsis patients in ICU. Univariate and multivariate (MVA) logistic regression with cox regression modeling were performed to compute the association of MDRO on ICU-mortality. MVA modelling was performed for ICU-LOS predictors. Results: Out of 228 patients, the isolated MDRO was 97 (42.5%) of which 78% were gram-negative bacteria. The mortality rate among those with MDRO was 85 (37.3%). The hospital acquired infection (HAI) was significantly predictor for ICU-LOS in univariate linear regression (R^2 = 0.034, P=0.005). In MVA linear regression, both *Enterococcus faecalis* infection and *Acinetobacter baumannii* (AC) -MDRO were predictors for ICU-LOS with (R^2 = 0.478, P<0.05). In the univariate cox regression, only the infection with AC- MDRO was a risk factor for ICU-mortality with [HR =1.802 (95% CI: 1.2 – 2.706; P = 0.005)]. Conclusions: Identifying risk factors for MDRO addresses the appropriate administration of empirical antibiotics and effectively control of source of infection which would reduce mortality and ICU-LOS. The usage of broad- spectrum antibiotics should be limited for those having substantial risk factors to acquire MDRO.

Keywords: multidrug resistance organism; sepsis; adequate empirical antibiotics; source of infection; APACHE II; ICU length stay; predictors; risk factors; mortality

1. Introduction

Clinical studies have consistently agreed that there is an increased risk of mortality in patients with MDRO infection relative to those having non-MDRO infection. This could be related to inappropriate use of antibiotics in the empirical stage [1]. Patients in ICU are

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at increased risk of acquiring MDRO as MDRO seem to be more prevalent in ICU than other wards and therefore, patients are at increased risk of infection and prolonged hospital stay. This is particularly observed in patients who are immunocompromised , having organ transplantation, history of antibiotics exposure and with central venous catheters[2,3]. In addition, the rapid growth of MDRO had avoided the delivery of appropriate empirical antibiotics which is the key factor of outcomes in severe patients. The increasing rate of antibiotics resistant was related directly with increased mortality, morbidity and the cost of healthcare associated infection especially in ICU[4]. Besides that, MDRO infection is known to be the main cause of inadequate empirical antibiotic therapy in ICU [5]. In USA, the annual incidence of antibiotics resistant bacteria in critically ill patients was associated with more than 700,000 (HAI). While in Europe, higher incidence of *Carbapenemase-producing enterobacteriaceae* (CPE) is reported, specifically *Carbapenem-hydrolysing oxacillinase-48* (OXA-48) and *New Delhi Metallo-betalactamase* (NDM)-*producing enterobacteriaceae* associated infection [5,6]. *Acinetobacter baumannii* (AC), *Pseudomonas*, *Enterobacteriaceae* MDRO are considered as the most detrimental factors in ICU; mostly combined with HAI or nosocomial infection [7,8,10,11].

Based on the Extended Prevalence of Infection in Intensive Care (EPIC) II study which reported that ICU infection incidence was 51%, wherein the major source of infection was respiratory source 64% and the main isolated organism was *Staphylococcus aureus* 20.5%, whereas gram- negative organism was 62.2% e.g. (*Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Pseudomonas* spp. and *Acinetobacter* spp.). This is therefore pertinent in the context of global antibiotic resistance scenario with extensively affected regions being South-East Asia and Middle East where antibiotics can be easily procured over the counter and even without prescription. [5, 6, 10, 12, 13, 14].

Due to the alarming increasing trend of gram-negative bacteria especially MDRO *Enterobacteriaceae* with ESBL, the selection of antibiotics to target the ESBL-producing gram negative bacteria should be based not only on the total use of antibiotics in hospital but also on inappropriate use of fluoroquinolones and second or third-generation cephalosporins [15,13,14,4].

In one of the meta-analysis, patients with MDRO -*Carbapenem-resistant enterobacteriaceae* (CRE) especially *Carbapenem-resistant klebsiella pneumoniae* (CRKP) were reported to have a higher mortality than patients with carbapenem-sensitive bacteria [18]. Several studies have investigated the substantial association of MDRO and mortality or ICU-LOS. However, the current research-with different setting, the clinical course of critically ill patients may be influenced by few other factors post infection with (MDRO) and thus with different-consequences. The clinical and microbiological characteristics of ICU sepsis patients are not well known and might be different from general population. Besides, the higher incidence of hospitalization and antibiotic exposure, prevalence of MDRO over ICU sepsis patients is high[19]. Therefore, determining the causative microorganisms and their antibiotic susceptibility in this unit is important to both guide empirical treatment and to reduce mortality and morbidity. The current research analysed the relationship of MDRO bacteria and their predictors and risk factors or clinical outcomes, i.e., mortality and (ICU-LOS) The current study primary was performed to determine the association of MDRO and site of infection amongst critically ill patients with their predicators or risk factors on ICU mortality. Secondary outcome was to determine the association of MDRO or site of infection on ICU-LOS. The current data is of significance in the context of Malaysian health care setting as to augment the mindfulness of impact of sepsis across the country and therefore strengthen the requirement of continuous research work probably into prophylactic and therapeutic areas for sepsis and as well as to pave the way for resource allocation.

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2. Materials and Methods

Study design and settings

This cohort study was performed in the ICU department of a tertiary hospital (0.526 square kilometres) in Selangor, Malaysia, with an observational retrospective design. The hospital is a major tertiary hospital located in Selangor state (130 acres) (on the west coast of Peninsular Malaysia). It consists of 620 beds and offers secondary and tertiary services for health care [20]. Before the commencement of the study, prior approval from the local ethics committee Research Ethics Committee (REC) and Research Management Institute (RMI)- UiTM Shah Alam was obtained. Information on patients was obtained from the ICU and pharmacy departments. Data was collected from the hospital's computerised system/medical records of patients diagnosed with sepsis based on ICD-10 or three criteria for systemic inflammatory response syndrome (SIRS) classification and admitted between 2015 and 2016. The SIRS criteria; core temperature >38°C or <36°C (>100.4°F or <96.8°F), elevated heart rate (>90 beats/min) (tachycardia), respiratory rate >20 breaths/min or PaCO2 <32 mm Hg or mechanical ventilation for acute respiratory process (tachypnoea) and WBC count >12,000/mm^3 (12 × 109 cells/L) or <4,000/mm^3 (4 × 109 cells/L) or >10% immature neutrophils [20].

The researcher confirmed the screening for the signs of sepsis and MDRO isolation or site of infection was counterchecked by the ICU clinician followed by doublechecking of the data from the computer systems through patient files records of the relevant department [12-14]. To determine whether the infection was HAI or CAI infection, the definition of Louis et al. (1995) was followed [21]. The results were screened for all the microbiological samples collected after the patients admitted to ICU and before patient received empirical antibiotics to decide if the isolated microorganism was infected or colonized. A positive culture isolated from normally sterile sites, including blood, was considered infected. The positive culture from sputum samples was considered infected if it had 3 SIRS criteria. The isolates from non-sterile sites such as urine or wound were considered infected if accompanied with documented infection at site of isolation. All the other positive cultures that did not meet these criteria were considered colonized and therefore, not included as active infection isolates. MDRO was identified as microorganisms not sensitive to at least one antimicrobial agent in at least three different antimicrobial categories [22]. Patients included in this study stayed in the ICU for at least three days or more and were tracked for empirical antibiotic therapy, MDRO, site of infection, source of infection, vital signs, and clinical information with organ function parameters for up to seven days [13,14].

Definition of Variables, Inclusion, and Exclusion Criteria:

Patients with a reported infection were identified by means of an electronic microbiology database analysis, medical records followed by clinicians verified results.

The variables included demographic data, comorbidity, history of antibiotic use prior to admission to the ICU, history of surgery, time of surgery, mechanical ventilation (duration), site of infection (hospital or community-acquired infection), source of infection (e.g. respiratory, surgical, or urinary tract infection (UTI). It is to be noted that the adequacy of empirical antibiotics evaluated based on the isolated microorganisms has to be sensitive to at least one of combined empirical antibiotic and (time, dose and frequency of administration) were in line with local/international guidelines.

Also, the daily record of the normal functioning and profiling function of the organs (e.g. kidney, liver, cardiac, and others, which were determined daily for each patient according to the physician clinical record sheets), laboratory findings (e.g. renal function profile, liver function profile, cardiac enzymes and blood profiles) and ("Acute Physiology and Chronic Health Evaluation II")APACHE II severity index assessment sheets. APACHE II was calculated on first day of admission using online clinical calculator and included the worse vital sign records. For the isolated microorganisms, the different

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sources of culture (blood, sputum, wound, tissue, urine) with sensitivity or resistant patterns for each source were studied. The same culture source may be repeated to obtain the isolation, or different isolation patterns.

As follows, the inclusion criteria were:

I. Patients above 18 years of age and non-pregnant females who have been admitted to the ICU for at least 3 days to obtain antibiotic culture sensitivity results [26].
II. ICU patients who were diagnosed with sepsis or-exhibited three signs of SIRS.
III. Patients administered with antibiotics in the ICU.
IV. Only first admission can be included

Criteria for patient exclusion

The conditions for exclusion were as follows:

I. More than 2 weeks of ICU hospitalisation (only the first 7 days were included in the data set for patients who had stayed for more than 7 days but less than 14 days).
II. Incomplete data or documents that are missing; and
III. Patients with febrile neutropenia, cystic fibrosis, burns and HIV (absolute neutrophil count<1000 cells/mm^3).

Statistical analysis

SPSS® version 23.0 for Windows® was used for data analysis, descriptive analysis (percentage and frequency), categorical (mean ± SD for normal distributed variables) and (median and range for non-normal distributed variables) continuous data variables. The level of significance was set at $P<0.05$. The t-test or Mann-Whitney u test is used to compare the ongoing data of the two classes. The ANOVA or Kruskal-Wallis test compared the data, such as demographic data, baseline clinical characteristics, comorbidities, history of antibiotics, source, or site of infection, MDRO, calculated with either ICU-LOS or APACHE II score, of the ≥3 groups. Using χ^2 or Fisher's exact test, the discrete data were compared using demographic data, baseline clinical characteristics, comorbidities, antibiotic history, source, or site of infection, mortality related MDRO.

Univariate and multivariate logistic/Cox regressions were used to analyse the risk factors for mortality by using backward and forward methods based on goodness-of-fit principles. Using the Hosmer-Lemeshow test, the model was assessed. To establish the predictors for ICU-LOS, simple linear regression and multiple linear regression were applied. Based on the principles of best fit, backward, stepwise, and forward methods were chosen during the selection of the variable. To compare the probability of survival in ICU for patients with MDRO infection and those with non- MDRO infection, the Kaplan-Meier analysis and log-rank test were conducted.

Practice variations inevitably and appropriately are expected when clinicians consider the needs of individual patients, the resources available, and the limitations unique to an institution or type of practice. By using post-hoc stratification restriction, the contributing factors were controlled effectively or reduced. Moreover, by using forward and backward statistical modelling for the best fit, multivariate analysis was conducted to analyse the possible effects of one variable while simultaneously optimising for the effects of several other factors.

Ethical Approval and Consent to Participate

Ethical approval was obtained from the Research Ethics Committee (REC), Research Management Institute (RMI)- UiTM Shah Alam (No.600 -RMI (5/1/6) and Medical Research and Ethics Committee (MREC) and Ministry of health (MOH) via National Medical Research Register (NMRR) No. (NMRR-14-1400-22268). The confidentiality of the patients' data was ensured and no intervention on the patient management. Only the researcher had access to online patient's records/data anonymously based on inclusion and exclusion criteria, no patients involved during this study and unnecessary informed con-

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sent was obtained from patients according to UiTM Shah Alam Research Ethics Committee (REC) approval. All methods were carried out in accordance with relevant guidelines and regulations/declaration of Helsinki.

3. Results

A total of 365 patients diagnosed with sepsis or demonstrated signs of sepsis were admitted to the adult ICU ward during study period. Only 228 patients out of 365 met the inclusion criteria.

Demographic and clinical characteristics association with mortality was shown in (Table 1) while demographic and clinical characteristics association with MDRO infection was shown in (Table 2). A total of 119 (52.2 %) males and 74 (32.5 %) females were included and there were significant association between the patient races and mortality (P=0.03) while MDRO was not significant variable for ICU mortality as shown in (Table 1). There was no significant difference between MDRO and non-MDRO groups in terms of demographic data (age, gender, race), comorbidities, type of surgery, MV, history of antibiotics used and mortality rate as in (Table 2). Among the patients 191(83.8%) had septic shock and 83 (36.4%) had MDRO. A significant difference was observed between MDRO infection and community acquired infection (CAI) 118 (51.8%) P (<0.01) (Table 2). The mortality rate in those with CAI was 42.5% while in those with HAI was 42.1% respectively as shown in (Table 1). From (228) the total patients, there were 130 cases (57%) of positive isolated microorganisms. While the total prevalence of MDRO was 97 (42.5%) of which gram-negative bacteria (78%) and the rest were gram-positive (22%). The mortality rate among those with MDRO was 85 (87.6%) (Table 1&3). The distribution of common MDRO was as follows; *Acinetobacter/MDRO.AC* 35 (15.4%), *Klebsiella pneumonia/Klebsiella spp. /ESBL- klebsiella,* 32 (14.0%), *P. aeruginosa* 17 (7.5%), *Enterococcus faecalis* 14 (6.1%), *Staphylococcus aureus-MRSA* 13 (5.7%), and *Enterobacteriaceae/Citrobacter koseri (diverse)- ESBL* 13(5.7%) respectively (Figure 1). As shown in (Table 3) the most prevalent MDRO was *Acinetobacter spp. (AC)* (15.35%) and the major source of isolated MDRO was from the blood (37.14%). The MDRO- AC was resistant to all antibiotic (26 sample) imipenem (1 sample), polymyxin-netilmicin (2 samples), sulperazone- unasyn, piperacillin/tazobactam, amikacin, ciprofloxacin, and ceftazidime (1 sample). Also, the isolated samples are shown in.in Figure (2) which illustrated the isolated blood microorganisms of which the most isolated MRDO was AC-MDRO. In univariate analysis, there were significant associations between MDRO with history of surgery before ICU admission, surgery as source of infection, skin-soft tissue infection, inadequate empirical AB, ICU-LOS, and history hospital stay before ICU (P<0.05) as in (Table 2).

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Table 1. The Association of Demographic and Baseline Clinical Characteristics of Entire Sample with Mortality.

Parameters/ outcomes	Non-Survivor (n=193) No (%)	Survivor (n=35) No (%)	P value
Age			
< 48	52 (22.8)	5 (2.2)	0.405 a*
48 – 58	44 (19.3)	11 (4.8)	
59 – 66	47 (20.6)	9 (3.9)	
67+	50 (21.9)	10 (4.4)	
Total	193 (84.6)	35 (15.4)	
Gender			
Male	119 (52.2	18 (7.9)	0.266 b*
Female	74 (32.5	17(7.5)	
Total	193 (84.6)	35 (15.4)	
Race			
Malay	122 (53.5)	19 (8.3)	0.030# a*
Chinese	20 (8.8)	10 (4.4)	
Indians	39 (17.1)	5 (2.2)	
Others	12 (5.3)	1 (0.4)	
Total	193 (84.6)	35 (15.4)	
Surgery			
Yes	127 (55.7)	25 (11)	0.565 b*
No	66(28.9)	10 (4.4)	
Total	193 (84.6)	35 (15.4)	
Surgery			
Yes	127 (55.7)	25 (11)	0.565 b*
No	66(28.9)	10 (4.4)	
Total	193 (84.6)	35 (15.4)	
Hx. Time of surgery			*

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Current -1 week	107 (69.5)	21 (13.6)	0.606 a*
>1 week- 6 month	13 (8.4)	2 (1.3)	
>6 month	8 (5.2)	3 (1.9)	
Total	128 (83.1)	26 (16.9)	
Type of surgery			
Skin soft T.S /DFU/	27 (17.3)	5 (3.2)	0.690 a*
Orthopaedics/Polytrauma	15 (9.6)	3 (1.9)	
Neurosurgery	45(28.8)	7 (4.5)	
Abd surgery/liver & Biliary sepsis/	37 (23.7)	8 (5.1)	
Others(cardiac-Urological-tracheostomy)	6 (3.8)	3 (1.9)	
Total	130 (83.3)	26 (16.7)	
Classification of Infection Site			
Community acquired infection	97 (42.5)	21 (9.2)	0.359 a*
Healthcare associated infection	96 (42.1)	14 (6.1)	
Mental state			
Alert	21 (9.2)	7 (3.1)	0.295 a*
Confused	171 (75.0)	28 (12.3)	
Coma	1(0.4)	0	
Total	193(84.6)	35(15.4)	
GCS -Day1			
(Severe GCS)	169 (74.1)	28 (12.3)	0.256 a*
(Moderate GCS)	8 (3.5)	1 (0.4)	
(Mild GCS)	16 (7.0)	6 (2.6)	
Total	193 (84.6)	35 (15.4)	
MDRO	Yes 85 (37.3) No 108 (47.4)	12 (5.3) 23(10.1)	0.354 a*

a*- chi square, b*- fisher exact, # significant value(P<0.05)

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Table 2. Univariate Association of Baseline clinical characteristics and MDRO.

Characteristics	Total N 228 (%)	MDROs N 97(%)	Non-MDROs N 131(%)	P value*
Age				0.797
< 48	57 (25)	23 (10.1)	34 (14.9)	* a
48 – 58	55 (24.1)	23 (10.1)	32 (14.0)	
59 – 66	56 (24.6)	27 (11.8)	29 (12.7)	
67+	60 (26.3)	24 (10.5)	36 (15.8)	
Male Gender	137 (60.1)	59 (25.9)	78 (34.2)	0.892 * b
Race				0.531
Malay	141 (61.8)	61 (26.8)	80 (35.1)	* a
Chinese	30 (13.2)	14 (6.1)	16 (7.0)	
Indians	44 (19.3)	15 (6.6)	29 (12.7)	
Others	13 (5.7)	7 (3.1)	6 (2.6)	
Hx. Of Surgery during ICU admission	152 (66.7)	74 (32.5)	78 (34.2)	**0.01# *a**
Type of Surgery				0.075
Skin & soft tissue infection	17 (7.5)	9 (3.9)	8 (3.5)	* b
Orthopaedics	6 (2.6)	3 (1.3)	3 (1.3)	
Neurosurgery	52 (22.8)	19 (8.3)	33 (14.5)	
Abdominal	36 (15.8)	25 (11)	11 (4.8)	
Cardio	3 (1.3)	1 (0.4)	2 (0.9)	
DFU-Amputation-gangrene	15 (6.6)	8 (3.5)	7 (3.1)	
Biliary sepsis	2 (0.9)	1(0.4)	1 (0.4)	
Polytrauma-trauma	12 (5.3)	5 (2.2)	7 (3.1)	
Urological, genital	4 (1.8)	2 (0.9)	2 (0.9)	
UGIB[1]	3 (1.3)	1 (0.4)	2 (0.9)	
Tracheostomy- others	2 (0.9)	0 (0)	2 (0.9)	
Comorbidities	111 (48.7)	45 (19.7)	66 (28.9)	0.593
DM				* a
HTN	152 (66.7)	61 (26.8)	91 (39.9)	0.322 * a
Asthma	16 (7.0)	5 (2.2)	11 (4.8)	0.436 * b
COPD	8 (3.5)	5 (2.2)	3 (1.3)	0.290 * b
CAD	48 (21.1)	18 (7.9)	30 (13.2)	0.512 * a
CHF	34 (14.9)	10(4.4)	24 (10.5)	0.132 * b
CRF	36 (15.8)	15 (6.6)	21 (9.2)	1.000 * b
Co-Malignancy	8 (3.5)	5 (2.2)	5 (1.3)	0.290 * b
Liver disease	21 (9.2)	11 (4.8)	10 (4.4)	0.362 * b
GCS[2]	197 (86.4)	80 (36.4)	114 (50)	0.950
Severe				* a
Moderate	9 (3.9)	4 (1.8)	5 (2.2)	
Mild	22 (9.6)	10 (4.4)	12 (5.3)	
Mental Status	28(12.3)	13 (5.7)	15 (6.6)	0.454
Alert				* a
Confused	199 (87.3)	83 (36.4)	116(50.9)	
Coma	1(0.4)	1 (0.4)	0 (0)	

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Hx of AB used during last two weeks before ICU admission	174 (76.3)	75 (32.9)	99 (43.4)	0.875 * a
Received MV	226 (99.1)	97 (42.5)	129 (56.6)	0.509 *a
Diagnosis	34 (14.9)	11 (4.8)	23 (10.1)	0.062 * b
Sepsis				
Severe Sepsis	3 (1.3)	3 (1.3)	0 (0)	
Septic shock	191 (83.8)	83 (36.4)	108 (47.4)	
Site transferred to ICU	78 (34.2)	27 (11.8)	51 (22.4)	0.372 * a
ED[3]				
MW[4]	81 (35.5)	37 (16.2)	44 (19.3)	
SW[5]	65 (28.5)	31 (13.6)	34 (14.9)	
Others	4 (1.8)	2 (0.9)	2 (0.9)	
Classification of Infection Site	118 (51.8)	40 (17.5)	78 (34.2)	**0.007#** * **a**
Community acquired infection				
Healthcare associated infection	110 (48.2)	57 (25.0)	53 (23.2)	
Source of Infection	131 (57.5)	53 (23.2)	78 (34.2)	0.499 * a
RTI				
UTI	29 (12.7	15 (6.6)	14 (6.1)	0.318 * b
ABD	60 (26.3)	30 (13.2)	30 (13.2)	0.223 * a
Skin soft T.S inf. (SSTIs)	50 (21.9)	28 (12.3)	22 (9.6)	**0.035#** * **a**
Surgery	124 (54.4)	62 (27.2)	62 (27.2)	**0.016#** * **a**
Unknown	14 (6.1)	7(3.1)	7 (3.1)	0.587 * b
Adequate empirical AB	64 (28.1)	14 (6.1)	50 (21.9)	**<0.001#** ***a**
ICU death	193 (84.6)	85 (37.3)	108 (47.4)	0.354 * a
ICU-LOS (day)	56 (24.6)	16 (7.0)	40 (17.5)	**0.004#** ***a**
< 5.0				
5.0 - 6.0	48 (21.1)	18 (7.9)	30 (13.2)	
7.0 - 11.4	67 (29.4)	28 (12.3)	39 (17.1)	
11.5+	57 (25.0)	35 (15.4)	22 (9.6)	
Hosp-LOS before ICU (day)	99 (43.4)	36 (15.8)	63 (27.6)	**0.010#** * **a**
Zero				
1-2	72 (31.6)	27 (11.8)	45 (19.7)	
+3	57 (25.0)	34 (14.9)	23 (10.1)	
MV[6] Duration (day)	39 (17.3)	16 (7.1)	23 (10.2)	0.221 * b
1-3				
4-6	71 (31.4)	24 (10.6)	47 (20.8)	
7	88 (38.9)	44 (19.5)	44 (19.5)	
>7	28 (12.4)	13 (5.8)	15 (6.6)	

[1]Upper gastrointestinal bleeding, [2]Glasgow coma scale, [3]Emergency department, 4Medical ward,5Surgical ward, 6Mechanical ventilation *Chi-square or Fisher exact test, # significant value(P<0.05)

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Table 3. The sensitivity patterns of MDRO-organisms and their main sources of isolated culture sample.

MDRO -organisms	Total isolation from 228 patients (%)	Source of isolated culture sample (N, %)	Sensitivity to antibiotics	Resistant to antibiotic
MRSA*a	13 (5.7%)	Blood=4(30.76) Nasal =2(15.38) Sputum=7 (53.84)	GEN =1 IPM=1 LEZ=2 MUP=3 OXA=1 VAN=5	ALL*=2 OXA=9
Pseudomonas aeruginosa	17 (7.45%)	Blood=4(23.52) Knee aspiration=1(5.88) Sputum=10(58.82) CSF=2(11.76)	AMK=1 AMK- TAZ -CIP-CFP-CAZ=1 AMK-CIP-CXM-GENT-SXT=1 CEP=5 IPM=4 SPZ-TAZ-AMK-CIP-GEN-CAZ=3	AMK-TAZ-CIP- CEP-CAZ =1 AMC= 5 AMK-CIP-CXM-GENT=1 GENT=1
Klebsiella pneumoniae/ESBL *Klebsiella pneumoniae*	32(14%)	Blood=18(56.25) wound=3(9.37) Sputum=9(28.12) Tissue-CSF=1(3.12) Urine=1(3.12)	AMK-TAZ-CIP-FEB-CAZ=1 AMK-CIP-CXM-GEN=1 CRE-CIP=1 CAZ-TAZ-IPM=2 IPM=8 IPM-MEM-ETP-AMK=5 PB1=2 SPZ= 2 SPZ-AMC-CXM-GEN=5	ALL*=2 AMK-CIP-CXM-GEN-SXT=1 AMP=2 AMC=3 CFP-CIP=1 CXM-NET-AMC-AMP=1 IPM=1 SPZ-TAZ-AMK-CIP-GEN-CAZ=5 SPZ-AMC-CXM-GEN=1
Enterococcus faecalis	14 (6.1%)	Blood=4(28.57) wound=3(21.42) Tissue-CSF=3(21.42) Urine=4(28.57)	AMK-CIP-CXM-GEN-SXT=1 AMP-GEN-VAN-TGC=6 AMP= 3 CXM-NFN-AMC-AMP=1 VAN=3	AMP-GEN-VAN-TGC=1 AMP=1 CIP=1 GEN=3 SPZ-TAZ-AMK-CIP-GEN-CAZ=1 VAN=1
MDRO-AC.*b	35(15.35%)	Blood=13(37.14) wound=2(5.71) Tissue-CSF=4(11.42) Urine=2(5.71) Sputum=14(40)	AMK=1 IPM-MEM-ETP-AMK=1 PB1=15 SPZ=1 SPZ-TAZ-AMK=1 TGC=9	ALL*=26 IPM=1 PB1-NET=2 SPZ-TAZ-AMK-CIP-GEN-CAZ=1
*Enterobacteriaceae - ESBL*c- *Escherichia coli*	13(5.7%)	Blood= 7(53.84) wound=3(23.07) Tissue-CSF=1(7.69) Urine=1(7.69) Sputum=1(7.69)	AMK=1 AMK-TAZ-CIP-CFP-CAZ=1 CP-CIP=1 XCM-NET-AMC-AMP=1 IPM=2 IPM-MEM-ETP-AMK=3 PB1=1 SPZ=1 SPZ-AMC-CXM-GEN=3	ALL*=2 AMP=3 CXM=1 CXMSPZ-CIP-SXT=2 GEN-SXT=1 SPZ-AMC-CXM-GEN=1

a: MRSA: *Methicillin-resistant staphylococcus aureus* , b: *Acinetobacter baumannii* -multi resistant organisms, c: Extended-spectrum beta-lactamases

*ALL= Pandrug resistant bacteria to all antibiotics, AMP= ampicillin, AMC= amoxicillin/clavulanate, AMK= amikacin, CIP= ciprofloxacin, CEP= cefepime, CAZ= ceftazidime, CXM= cefuroxime, CTX= cefotaxime, CP= carbapenem, ETP=ertapenem, GEN= gentamicin, IPM= imipenem, LEZ =linezolid, MUP=mupirocin, MEM=meropenem, NFN=nitrofurantoin, NET =netilmicin, OXA= oxacillin,

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SPZ= sulperazone-unasyn, TAZ= piperacillin/tazobactam, TGC= tigecycline, SXT= trimethoprim-sulphamethoxazole, PB1= polymyxin, VAN= vancomycin

Besides, in the univariate analysis, all bacterial isolates were not significantly related with survival. However, there was only significant association between the isolation of MDRO-AC. bacteria and ICU-LOS($p<0.001$) as in (Table 4). In addition, in simple linear regression, the model of MDRO-AC was significantly associated as predictor for ICU-LOS with $R^2 = 0.046$ and B coefficient = 5.330 (95% CI: 2.155 – 8.505; *P* = 0.001). The patient who acquired the MDRO-AC was more likely to stay in ICU with 5.3 days than the patients who did not have the same bacterial infection as in (Table 5). Meanwhile, in simple linear regression, the *Enterococcus faecalis* infection was a predictor for ICU-LOS with R^2= 0.034 and B coefficient = 6.846. The patients who acquired infection with *Enterococcus faecalis* were more likely to have increment in ICU-LOS by 6.8 days as in (Table 5). Furthermore, in multivariable linear regression both *Enterococcus faecalis* and MDRO-AC were significantly predictors (R^2=0.478) for increasing the ICU-LOS, B-coefficient= 4.062 (95% CI: .412-7.713; *P*=.029) and B-coefficient=2.554 (95% CI: .064- 5.044, *P*=.044) respectively as shown in (Table 5). On the other hand, in univariate cox regression only the infection with MDRO-AC was a risk factor for ICU mortality (HR=1.802; 95% CI: 1.2-2.706; *P*=.005). This could explain the risk of death which might be increased by 80 % in case of infection with MDRO-AC. Besides, the CAI as site of infection was ICU mortality risk factor (HR=1.389, 95 % CI 1.041-1.854, P=0.026). In addition, in multivariate cox regression, the only infection with MDRO-AC has increased the risk of death by 89.8% with (HR=0 .102; 95% CI: .013-.780; *P*=.028) as in (Table 6).

Table 4. Association of isolated MDRO organisms with their outcomes (mortality -APACHE II score-ICU-LOS).

Parameters-EST/Outcomes	ICU-Death	P value	APATCHE II (Severity index)	P value	ICU-LOS-DAY	P value
Staphylococcus aureus (MRSA)	Yes 12=5.3% no 181=79.4% total 193=84.6%	0.697 b*	31.00(IQR=23.00-35.00)	0.360 f*	7.00(IQR=5.00-11.75)	0.196 f*
Pseudomonas aeruginosa	Yes 16=7.0% No 177=77.6% Total 93=84.6%	0.482 b*	31.00(IQR=23.00-35.00)	0.804 f*	7.00(IQR=5.00-11.75)	0.520 f*
Klebsiella pneumonia /Klebsiella Spps/ESBL *Klebsiella*	Yes 26=11.4% No 167=73.2% Total 193=84.6%	0.597 b*	31.00(IQR=23.00-35.00)	0.367 f*	7.00(IQR=5.00-11.75)	0.050 f*
Acinetobacter/MDRO.AC	Yes 29=12.7% No 164=71.9% Total 193=84.6%	0.799 b*	31.00(IQR=23.00-35.00)	0.884 f*	7.00(IQR=5.00-11.75)	**<0.001** f*
Enterobacteriaceae/*Citrobacter koseri* (diversus) ESBL	Yes=11=4.8% No=182=79.8% Total= 193=84.6%	1.000 b*	31.00(IQR=23.00-35.00)	0.359 f*	7.00(IQR=5.00-11.75)	0.884 f

a*- chi square, b*- fisher exact test, c*-t-test, d*- ANOVA, e*- Kruskal Wallis test, f*- Mann Whitney u test, g*-SD= standard deviation, h*-(IQR) the interquartile range, i*-OR= odd ratio (logistic test), j*-Linear regression (R^2), k*=not significant

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Table 5. The univariate and multivariate linear regression of MRDO organisms as predictors for increasing ICULOS.

Variable	B-coefficient	Simple linear regression R^2 (95% CI)	P-value	Multivariable linear regression R^2 (95% CI)	B - coefficient	P-value
AC- MDRO bacteria*	5.330	0.046 (2.155-8.505)	**0.001**	0.478 (.064- 5.044)	2.554	**0.044**
Enterococcus faecalis	6.846	0.034 (2.049-11.644)	**0.005**	0.478 (.412- 7.713)	4.062	**0.029**
HAI Infection	3.310	0.034 (-5.61- -1.006)	**0.005**	-----	---	---

* Acinetobacter baumannii -multi drug resistant organisms

Table 6. The univariate and multivariate cox regression risk factor for ICU mortality.

Variable	B-coefficient	Univariate cox regression HR (95% CI)	P-value	Multivariate cox regression HR (95% CI)	B - coefficient	P-value
AC- MDRO* bacteria	0.589	1.802 (1.2-2.7)	**0.005**	0.102 (.013-.780)	-2.278	**0.028**
Enterococcus faecalis	0.385	1.47 (0.831-2.6)	0.186	--------	-----	---
CAI Infection	0.329	1.389 (1.041-1.854)	**0.026**	--------	-------	---

* Acinetobacter baumannii -multi resistant organisms

4. Discussion

The current research has identified the clinical characteristics of infection associated with MDRO in ICU as well as the predictors with risk factors for mortality and ICU-LOS. Majority of patients were male, elderly and diagnosed with septic shock. The most prevalent MDRO was gram negative bacteria namely MDRO-AC and *Klebsiella pneumoniae/ESBL Klebsiella pneumoniae,* which isolated from blood cultures. The source of MDRO infection was surgery, abdominal infection and skin and soft tissue (SSTI) infections like diabetic foot ulcer (DFU). In addition, this study found the inadequate empirical antibiotics was associated with MDRO infection. It appears that patients who received inadequate empirical antibiotic were more likely to develop MDRO infection. Besides, the history of hospital stay before ICU admission have increased the vulnerability of patients to acquire MDRO infection. Furthermore, MDRO infection was more observed among those with longer ICU stay than those who have shorter period. This explains that the length of hospital or ICU stay demonstrated increased risk of MDRO infection. The current finding is consistent with the study done in China which evaluated the risk factors for mortality in ICU patients with *Acinetobacter. baumannii* VAP. [23].

The current research also reported that AC- MDRO infection was a risk factor for ICU mortality. Similarly, other related retrospective studies were conducted to analyse the risk factors for mortality in ICU sepsis patients with *Acinetobacter baumannii* -VAP. It has been shown that gram-negative bacteria were the most common pathogens (46.0%) and were associated with increased ICU mortality [22, 30]. Furthermore, the coherent findings of Chernen, *et.al* (2013) study reported that there was an increase in gram -negative infection from 38.26% to 48.1%. The share of *klebsiella pneumoniae* isolates and *Acinetobacter spp*. were amplified from 8.1 to 18.9% [24]. Likewise, Li et al, (2017) conducted a surveillance study of nosocomial infection in intensive care units of 177 hospitals. The isolation rate of gram-negative bacteria MDRO were *Carbapenem-resistant Acinetobacter baumannii* 80.53%,

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Carbapenem-resistant Pseudomonas aeruginosa 39.94%, *Carbapenem-resistant Klebsiella pneumoniae* 24.86%, and *Carbapenem-resistant Escherichia coli* 9.23% [25]. The current study by MVA has found that both *enterococcus faecalis* and AC- MRDO infection were a significant independent predictor for ICU-LOS (P=0.005). The similar findings of other study conducted to measure the clinical outcomes of *Enterococcus faecalis* reported that prevalence was 57.6% in ICU and the mortality was significantly associated with polymicrobial bacteria and ICU-LOS [26]. Meanwhile, other prospective, observational, multicentre study informed that the isolated *Enterococcus spp*. in ICU was 10.2% and the predominant species was *Enterococcus faecalis* (82.4%) [27].

Moreover, the recent study stated the infection of *Enterococcus faecalis* was a risk factor for ICU mortality. A similar study compared the clinical outcome differences between *Vancomycin-resistant enterococcus* caused by *Enterococcus faecalis or Enterococcus faecium.* The *Enterococcus faecium* was more resistant to antibiotics (ampicillin and teicoplanin) and showed higher mortality [27]. Meanwhile, existing study found that there was no significant association between multi- drug resistance microorganisms (MDRO) and predictors for survival. Similarly, a retrospective observational cohort study was conducted by Lye *et al.,* (2012) with MDRO gram negative bacteria in severe sepsis and septic shock patients at two large Singaporean hospitals. The study informed through multivariable analysis that MDRO was not associated with mortality rather related to longer 6.1 days hospital LOS in survivor [28]. Furthermore, the consistent findings by a prospective, observational study conducted in sepsis ICU to measure the antibiotics bacterial resistance, had shown that the patients with MDRO were significantly received inadequate empirical antibiotics more frequently and long ICU-LOS than patients with sepsis due to non MDRO with higher mortality (P<0.05) [29]. Also, the current findings are in accordance with a prospective study which reported that patients with MDRO infection would have higher chance to receive inadequate empirical antibiotics [30]. Also, the findings of other retrospective studies are consistent with the current study which were conducted to measure the clinical outcomes of nosocomial gram -negative bacteria in ICU. The results showed that exposure to carbapenem would increase the hazard risk (HR=4.087) of acquiring the infection of *Carbapenem resistant AC*. MDRO [31][32].

5. Conclusions

The outcomes of the current research indicated that recognizing the risk factors for MDRO infection could lead to more effective use of empirical antibiotics thereby minimizing the source of infection, lowering mortality and ICU-LOS. The high prevalence of MDRO organisms has a role in the patients' mortality. The infection of MDRO is also related to poor clinical outcomes and longer ICU-LOS. Furthermore, inadequate empirical antibiotic therapy was a major contributor to MDRO infection. The predominant microorganisms were gram-negative bacteria with MDRO organisms e.g., AC- MDRO. The overuse of broad-spectrum antibiotics should be limited to those with significant risk factors for acquiring MDRO organisms. This addresses the significance of antimicrobial stewardship programs. Antibiotics guidelines are expected to be in concordance with infection control strategy, thereby the emergence and transmission of MDRO infection is minimized. The local and regional guidelines must be in line with the local epidemiological and microbiological data. Future recommendations must envisage the analysis of available regulations and guidelines for improving the management of MDRO infection in critically ill sepsis patients.

6. Limitations

The small sample size in our study may reduce the possibility to show a difference in mortality between the two groups. A larger sampling size may be needed to show the difference. Due to the retrospective design of this study, the data may be incomplete or missed during the retrieval of information. This study was based on one ICU in single tertiary hospital for a limited period and therefore, may not be fully representative to

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other hospitals. The criteria of sepsis definition was not in agreement with the latest definition by (Sepsis-3)[33].

Author Contributions: K.A.A., N.A.A and Y. H. have involved in conceptualization, investigation, resources, analyzed the data and writing original draft preparation. K.A.A., S.J. and M.S. prepared tables, figures and revised the manuscript. All authors read and approved the final manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Please contact author for data requests.

Conflicts of Interest: The authors declare no conflict of interest."

References

[1] S. Busani *et al.*, "Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria : Risk Factors and Impact of Sepsis Treatments," *J. Intensive Care Med.*, pp. 1–7, 2017, doi: 10.1177/0885066616688165.

[2] T. H. McConville, S. B. Sullivan, A. Gomez-Simmonds, S. Whittier, and A. C. Uhlemann, "Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study," *PLoS One*, vol. 12, no. 10, pp. 1–14, 2017, doi: 10.1371/journal.pone.0186195.

[3] M. L. Ling *et al.*, "Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore.," *Antimicrob. Resist. Infect. Control*, vol. 4, p. 26, 2015, doi: 10.1186/s13756-015-0066-3.

[4] V. Q. Dat *et al.*, "Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: Aetiology, drug resistance, and treatment outcome," *BMC Infect. Dis.*, vol. 17, no. 1, pp. 1–11, 2017, doi: 10.1186/s12879-017-2582-7.

[5] M. S. Niederman, "Use of broad-spectrum antimicrobials for the treatment of pneumonia in seriously ill patients: maximizing clinical outcomes and minimizing selection of resistant organisms.," *Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am.*, vol. 42 Suppl 2, pp. S72-81, Jan. 2006, doi: 10.1086/499405.

[6] M. H. Kollef *et al.*, "The intensive care medicine research agenda on multidrug-resistant bacteria, antibiotics, and stewardship.," *Intensive Care Med.*, 2017, doi: 10.1007/s00134-017-4682-7.

[7] G. Zilahi, A. Artigas, and I. Martin-loeches, "What's new in multidrug-resistant pathogens in the ICU? Background," *Ann. Intensive Care*, vol. 6, 2016, doi: 10.1186/s13613-016-0199-4.

[8] J. Denis *et al.*, "Multidrug-resistant Pseudomonas aeruginosa and mortality in mechanically ventilated ICU patients," *Am. J. Infect. Control*, vol. 000, pp. 4–9, 2019.

[9] A. E. Sileem, A. Mohamed, and M. S. Meleha, "Egyptian Journal of Chest Diseases and Tuberculosis Acinetobacter baumannii in ICU patients : A prospective study highlighting their incidence , antibiotic sensitivity pattern and impact on ICU stay and mortality," *Egypt. J. Chest Dis. Tuberc.*, no. 0422–7638, pp. 1–6, 2017.

[10] P. Agaba, J. Tumukunde, J. V. B. Tindimwebwa, and A. Kwizera, "Nosocomial bacterial infections and their antimicrobial susceptibility patterns among patients in Ugandan intensive care units : a cross sectional study," pp. 1–12, 2017, doi: 10.1186/s13104-017-2695-5.

[11] B. Tümmler, "Emerging therapies against infections with Pseudomonas aeruginosa [version 1 ; peer review : 2 approved]," vol. 8, pp. 1–15, 2019.

[12] R. D. Savage *et al.*, "Pathogens and antimicrobial susceptibility profiles in critically ill patients with bloodstream infections: a descriptive study," *C. Open*, vol. 4, no. 4, pp. E569–E577, 2016, doi: 10.9778/cmajo.20160074.

[13] L. R. Peterson, "Bad bugs, no drugs: no ESCAPE revisited.," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, vol. 49, no. 6. United States, pp. 992–993, Sep. 2009, doi: 10.1086/605539.

[14] D. M. Livermore, R. Hope, G. Brick, M. Lillie, and R. Reynolds, "Non-susceptibility trends among Enterobacteriaceae from bacteraemias in the UK and Ireland, 2001–06," *J. Antimicrob. Chemother.*, vol. 62, no. suppl_2, pp. ii41–ii54, Nov. 2008, [Online]. Available: http://dx.doi.org/10.1093/jac/dkn351.

[15] E. B. Nimmich *et al.*, "Development of institutional guidelines for management of gram-negative bloodstream infections: Incorporating local evidence," *Hosp. Pharm.*, vol. 52, no. 10, 2017, doi: 10.1177/0018578717720506.

[16] J. D. Knudsen, S. E. Andersen, and for the B. I. Group, "A Multidisciplinary Intervention to Reduce Infections of ESBL- and AmpC-Producing, Gram-Negative Bacteria at a University Hospital," *PLoS One*, vol. 9, no. 1, p. e86457, Jan. 2014, [Online]. Available: http://dx.doi.org/10.1371%2Fjournal.pone.0086457.

[17] P. Musicha *et al.*, "Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998 – 2016): a surveillance study," *Lancet Infect. Dis.*, vol. 3099, no. 17, 2017, doi: 10.1016/S1473-3099(17)30394-8.

[18] P. P. Kohler, C. Volling, K. Green, E. M. Uleryk, P. S. Shah, and A. McGeer, "Carbapenem Resistance, Initial Antibiotic Therapy, and Mortality in Klebsiella pneumoniae Bacteremia: A Systematic Review and Meta-Analysis," *Infect. Control Hosp. Epidemiol.*, pp. 1–10, 2017, doi: 10.1017/ice.2017.197.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 21 September 2022 doi:10.20944/preprints202209.0326.v1

[19] C. M. Denkinger, A. D. Grant, M. Denkinger, S. Gautam, and E. M. C. D'Agata, "Increased multi-drug resistance among the elderly on admission to the hospital--a 12-year surveillance study.," *Arch. Gerontol. Geriatr.*, vol. 56, no. 1, pp. 227–230, 2013, doi: 10.1016/j.archger.2012.05.006.

[20] R. P. Dellinger, M. M. Levy, A. Rhodes, D. Annane, H. Gerlach, and S. M. Opal, "Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012," *Intensive Care Med.*, vol. 39, 2013, doi: 10.1007/s00134-012-2769-8.

[21] J. L. Vincent *et al.*, "The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee.," *JAMA*, vol. 274, no. 8, pp. 639–644, Aug. 1995.

[22] A.-P. Magiorakos *et al.*, "Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance.," *Clin. Microbiol. Infect.*, vol. 18, no. 3, pp. 268–281, Mar. 2012, doi: 10.1111/j.1469-0691.2011.03570.x.

[23] M. Ju *et al.*, "Risk factors for mortality in ICU patients with Acinetobacter baumannii ventilator-associated pneumonia: impact of bacterial cytotoxicity.," *J. Thorac. Dis.*, vol. 10, no. 5, pp. 2608–2617, May 2018, doi: 10.21037/jtd.2018.04.86.

[24] T. V Chernen'kaia, L. A. Borisova, I. V Aleksandrova, S. I. Rei, O. V Nikitina, and D. A. Kosolapov, "[Pattern dynamics of bacteriemia and sepsis pathogens in ICU patients of emergency service].," *Antibiot. i khimioterapiia = Antibiot. chemoterapy [sic]*, vol. 58, no. 5–6, pp. 11–16, 2013.

[25] Y. Li, X. Cao, H. Ge, Y. Jiang, H. Zhou, and W. Zheng, "A study on the targeted surveillance of nosocomial infection in intensive care units of 177 hospitals in Jiangsu Province of China," *J. Hosp. Infect.*, 2017, doi: https://doi.org/10.1016/j.jhin.2017.10.009.

[26] M. Ceci, G. Delpech, M. Sparo, V. Mezzina, S. Sanchez Bruni, and B. Baldaccini, "Clinical and microbiological features of bacteremia caused by Enterococcus faecalis.," *J. Infect. Dev. Ctries.*, vol. 9, no. 11, pp. 1195–1203, Nov. 2015.

[27] F. Alvarez Lerma, M. Palomar, J. Insausti, P. Olaechea, M. A. Alcala, and A. Blanco, "[Enterococcal infections in critically ill patients admitted to ICU].," *Med. Clin. (Barc).*, vol. 121, no. 8, pp. 281–286, Sep. 2003.

[28] D. C. Lye *et al.*, "The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study.," *Clin. Microbiol. Infect.*, vol. 18, no. 5, pp. 502–508, May 2012, doi: 10.1111/j.1469-0691.2011.03606.x.

[29] O. Bataar *et al.*, "Rate and pattern of antibiotic resistance in microbiological cultures of sepsis patients in a low-middle-income country's ICU.," *Middle East J. Anaesthesiol.*, vol. 22, no. 3, pp. 293–300, Oct. 2013.

[30] B. Jovanovic *et al.*, "Trauma and Antimicrobial Resistance Are Independent Predictors of Inadequate Empirical Antimicrobial Treatment of Ventilator-Associated Pneumonia in Critically Ill Patients," *Surg. Infect. (Larchmt).*, vol. 22, no. X, pp. 1–8, 2021, doi: 10.1089/sur.2020.306.

[31] W. I. Sligl, T. Dragan, and S. W. Smith, "Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes.," *Int. J. Infect. Dis.*, vol. 37, pp. 129–134, Aug. 2015, doi: 10.1016/j.ijid.2015.06.024.

[32] L. S. Munoz-Price *et al.*, "Evaluating the Impact of Antibiotic Exposures as Time-Dependent Variables on the Acquisition of Carbapenem-Resistant Acinetobacter baumannii.," *Crit. Care Med.*, vol. 44, no. 10, pp. e949-56, Oct. 2016, doi: 10.1097/CCM.0000000000001848.

[33] M. Singer *et al.*, "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).," *Jama*, vol. 315, no. 8, pp. 801–10, 2016, doi: 10.1001/jama.2016.0287.