THE EFFECT OF MULTIDRUG-RESISTANT ORGANISM INFECTION ON MORTALITY OF BURN PATIENTS AT RSUPN DR. CIPTO MANGUNKUSUMO

CONSÉQUENCE DES INFECTIONS À BMR SUR LA MORTALITÉ DES PATIENTS HOSPITALISÉS DANS L'HÔPITAL NATIONAL DR CIPTO MANGUNKUSUMO

Veronica R.M.,✉ Nelwan E.J., Kumalawati J., Rumende C.M., Chen K., Simadibrata M., Shatri H., Yunir E.

University of Indonesia / RS dr. Cipto Mangunkusumo, Jakarta, Indonesia

SUMMARY. Susceptibility to infection and increased antibiotic resistance place burn patients at risk of infection caused by multidrug-resistant organisms (MDRO). This condition can progress to sepsis, which can increase morbidity and mortality**.** A retrospective cohort study using medical record data of patients treated at RSUPN dr. Cipto Mangunkusumo in the period January 2020 to June 2022 was conducted. Of a total 160 subjects in the study period, 82.5% were aged <60 years, 16.88% had comorbidities, the most common cause of burns was fire (86.25%), the use of medical devices was 90.63%, with a median length of stay of 14 days. The most common Gram-negative MDRO pathogens were *K. pneumoniae* (29.91%), *Enterobacter sp* (22.32%) and *Acinetobacter* (20.54%): 45% of MDRO infected patients died. Bivariate analysis was conducted to find the effect of MDRO infection on burn patient mortality (RR 1,103; 95% CI 1,004-1,211, p=0.046). After adjusting for the role variables, namely: age, comorbidities, TBSA, use of medical devices, length of stay and multivariate analysis, it was found that the variables that had an effect on MDRO infection mortality were length of stay and age. MDRO infection has an effect on the mortality rate of burn patients. Mortality of burn patients due to MDRO infection is greater (45%) compared to non MDRO (21.43%). The most common Gram-negative MDRO pathogen is *K. pneumoniae*.

Keywords: MDRO, mortality, burn

RÉSUMÉ. *Leur sensibilité aux infections et l'augmentation globale de la résistance bactérienne font des brûlés des patients particulièrement à risque d'infections par BMR, pouvant déclencher sepsis/choc septique, qui augmentent morbidité et mortalité. Nous avons revu rétrospectivement les dossiers de 160 patients hospitalisés dans l'hôpital national Dr Cipto Mangunkusumo entre janvier et juin 2022. Parmi eux, 82,5% avaient moins de 60 ans ; 16,88% étaient comorbides ; 86,25% avaient été brûlés par flamme ; 90,63% avaient besoin de matériel invasif. La durée médiane de séjour était de 14 j. Les BGN BMR les plus fréquents étaient* K. pneumoniæ *(29,91%),* Enterobacter *(22,32%) et* Acinetobacter *(20,5%). La mortalité des patients infectés à BMR était de 45% (21,43% pour les non-BMR), avec une association significative BMR-mortalité (OR 1,103 ; IC95 1,004-1,211 ; p= 0,046). En explorant en analyse multivariée les variables classiquement associées à la mortalité (âge, comorbidités, surface brûlée, matériel invasif et durée de séjour), âge et durée de séjour contribuaient à la mortalité par BMR.*

Mots-clés *: BMR, brûlés, mortalité*

✉ Corresponding author: Raja Merlinda Veronica. Email: merlindaveronica27101977@gmail.com
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Introduction

Burn cases are increasing every year, especially in developing countries. This increase is seen in the high rates of morbidity and mortality, which have a significant physical, psychological and economic impact.[1-5] The World Health Organization (WHO) estimates that there are 265,000 deaths from burns every year. In developing countries such as Bangladesh, Columbia, Egypt and Pakistan, 17% of children with burns experience temporary disability while another 18% have permanent disability. The prevalence of burns in Indonesia according to *Riset Kesehatan Dasar* published in 2014 is 0.7%, with the highest incidence in Papua (2%) and Bangka Belitung (1.4%).[2] Deaths from burns in Indonesia reach 195,000 annually. The National Central General Hospital (RSUPN) Cipto Mangunkusumo receives more than 130 burn referral patients from all over Indonesia each year, with the largest number of referrals coming from West Java and East Jakarta. Mortality in adult burn patients at Cipto Mangunkusumo General Hospital in 2009-2010 was 34% and 14.5% at dr. Soetomo in 2007-2011. However, a study in 2017 at Cipto Mangunkusumo General Hospital stated that the mortality rate for burn patients was 24%.[6-8]

Literature review

Multidrug-resistant organism (MDRO) risk factors and culture examination. Some of the risk factors for MDRO are mechanical ventilation, usage of medical device, disease severities (intensive care, comorbidities, septic shock), length of stay in hospital, use of immunosuppressants, exposure to various antibiotics, comorbidities, and invasive surgery.[9]

Risk factors for Carbapenen-resistant *Klebsiella pneumoniae* (CRKP) in patients are history of invasive procedures, diabetes mellitus, solid tumors, tracheostomy, urinary catheter placement, antipseudomonal penicillin therapy, ICU care, exposure to antibiotics for more than 14 days such as glycopeptides, carbapenems, colistin and macrolides. In some cases, CRKP is associated with central venous catheterization, dialysis, hematological malignancies, chronic renal failure, chronic liver disease and bone marrow transplantation.[10-12]

Hospitalized patients with burns are more susceptible to infection due to various factors such as loss of normal barrier, impaired immune system and presence of necrotic tissue, creating an environment suitable for growth and proliferation of pathogens. About 75% of all deaths in burns are related to infection and hospitalization.[9]

Some of the risk factors that affect mortality in burns are age, total body surface area (TBSA), inhalation injury, chronic disease, type of burn, invasive procedures, chronic alcoholism and psychiatric problems. Nele Burselaers et al. reported that the three main risk factors associated with mortality in burns are age, TBSA extent and inhalation injury.

MDRO infection and prognostic patterns in burns. The pattern (HAI) in burn patients follows a predictable timeline (*Fig. 1*). Skin and soft tissue infections occur early during hospitalization, generally in the first week, but pneumonia, urinary tract infections and bacteremia may occur during hospitalization. Mangoni et al. reported that infection occurred with an average onset of >30 days, and the length of stay was associated with the type of bacterial species isolated from burn patients.[13] Falagas et al. reported that there was a relationship between the time since admission and the distribution of Gram negative isolates, from microbiological culture results. In the first 7 days of treatment of *Pseudomonas aeroginosa*, about 8% of all Gram-negative isolates; after 28 days of treatment, this increased to 55%.[8]

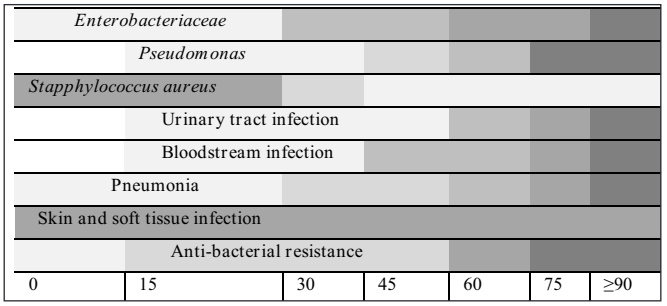

Fig. 1 - Hospital days since burn injury[8]

Research methods

This study is an observational study with a retrospective cohort design using medical record data. This research was conducted at the Burn Unit of RSUPN dr. Cipto Mangunkusumo/Faculty of Medicine, University of Indonesia on patients who were hospitalized from January 2020 to June 2022. The

target population in this study were burn patients treated at the burn unit of RSUPN dr. Cipto Mangunkusumo. The affordable population in question is burn patients treated at the burn unit of RSUPN Dr. Cipto Mangunkusumo ≥48 hours with culture examination results (tissue or blood) and there is growth of pathogens. The research sample is part of the reachable population that meets the research criteria. Data collected were age, gender, history of medical device use, history of comorbidities, TBSA, duration of hospitalization, history of use of empiric and definitive antibiotics, history of sepsis, skin and soft tissue infections, UTI, type of culture, day of last culture collection, results of last culture, MDRO, type of antibiotic resistance, type of pathogen in culture. Data were analyzed using SPSS 22.0. For univariate analysis, data are presented in the form of percentages for categorical data and mean with standard deviation or median with minimum and maximum values for numerical data. The bivariate test was carried out using the chi square test for categorical data and Mann Whitney for numerical data. Multivariate test was performed using logistic regression test.

Table I - Characteristics of burn patients in the burn unit of RSCM

Variable	N = 160 (%)
Gender, n (%)	
Male	100 (62.5)
Female	60 (37.5)
Age (year), mean (SD)	45,6 (15.2)
Age group, n (%)	
≥ 60 years old	28 (17.5)
< 60 years old	132 (82.5)
Comorbid-according to Charlson Index n (%)	
Yes	27 (16.88)
No	133 (83.13)
TBSA, n (%)	
≥ 30%	101 (63.13)
< 30%	59 (36.88)
Medical device, n (%)	
Yes	145 (90.63)
No	15 (9.38)
Ventilator usage, n (%)	87 (54.38)
Cause of burn, n (%)	
Fire	138 (86.25)
Electricity	12 (7.5)
Hot oil/water	10 (6.25)
Length of stay, Median (IQR)	14 (4-59)
Definitive antibiotic	129 (80,63)
MDRO, n (%)	
Yes	146 (91.25)
No	14 (8.75)
Lab parameter	
Leukocyte, Mean (SD)	17179 (9192)
Thrombocyte, Mean (SD)	32228 (14879)
PCT, Median (IRQ)	99 (1-22190)
Mortality, n (%)	
MDRO Mortality	72 (45)
Non MDRO Mortality	3 (21.43)
Source of infection	
Skin and soft tissue	160 (100)
Airway	64 (40)
Urinary tract	9 (5.63)
Sepsis	96 (54.9)

Results

Out of a total of 160 patients, 100 (62.5%) were male and 60 (37.5%) female, with 28 (17.5%) aged ≥60 years and 132 (82) aged <60 years, with a median age of 46 years. There were 27 (16.88%) burn patients who had comorbidities based on the Charlson Index and 133 (83.13%) who did not have comorbidities. There were 101 subjects (63.13%) with TBSA ≥30% and 59 subjects (36.88%) with TBSA <30%. The most common causes of burns were fire with 138 (86.25%) followed by electricity with 12 (7.5%) and hot oil/water with 10 (6.25%). Based on the source of infection, all patients had skin and soft tissue infections (100%), 64 subjects had infection in the respiratory tract (40%), and 9 in the urinary tract (5.63%). Medical devices were used in 145 burn patients (90.63%), not used in 15 (9.38%), and ventilators were used in 87 (54.38%). The median length of stay was 14 days (range 4 to 59) (*Table I*).

Table II shows MDRO pathogens based on the last culture of burn patients treated at the burn unit of RSUPN dr. Cipto Mangunkusumo. It shows that Gram positive MDRO pathogens were *Staphylococcus epidermidis* in 7 (3.13%) and *Staphylococcus aureus* in 1 (0.45%), while non MDRO Gram positive pathogens were *Staphylococcus epidermidis* in 7 (26.92%), *Enterococcus faecalis* (15.38%) in 4, *Staphylococcus saphrophyticus* (7.69%) in 2, and *Staphylococcus aureus* (3.85%) in 1. The most frequently encountered Gram negative MDRO pathogens were *K. pneumoniae* (29.91%), *Enterobacter sp* (22.32%), *Acinetobacter* (20.54%), *P. aeruginosa* (16.52%), *E. coli* (3.13%), *Enterobacter cloacea* (0.89%), *Enterobacter eurugenes* (0.89%), *Proteus vulgaris* (0.89%), *Serratia marcescens* (0.45%), *Burkholderia* (0.45%), *Myroides* (0.45%), and among non MDRO Gram-negative pathogens, the most common are *Enterobacter sp* (23.08%), *K. pneumoniae* (7.69%), *Acinetobacter sp* (7.69%), *Proteus vulgaris* (3.85%) and *Serratia marcescens* (3.85%).

Table II - MDRO pathogen based on last culture

	MDRO n (%)	Non-MDRO n (%)
Gram Positive		
Staphylococcus epidermidis	7 (3.13)	7 (26.92)
Enterococcus faecalis	0 (0)	4 (15.38)
Staphylococcus saphrophyticus	0 (0)	2 (7.69)
Staphylococcus aureus	1 (0.45)	1 (3.85)
Gram Negative		
K. pneumonia	67 (29.91)	2 (7.69)
Enterobacter sp	50 (22.32)	6 (23.08)
Acinetobacter sp	46 (20.54)	2 (7.69)
P. aeruginosa	37 (16.52)	0
E. coli	7 (3.13)	0
Enterobacter cloacea	2 (0.89)	0
Enterobacter eurugenes	2 (3.13)	0
Proteus vulgaris	2 (0.89)	1 (3.85)
Serratia marcescens	1 (0.45)	1 (3.85)
Burkholderia cloacea	1 (0.45)	0
Myroides	1 (0.45)	0

Total MDRO isolates = 224, n (%); Total Non-MDRO isolates = 27, n (%)

Table III shows antibiotic resistance based on pathogens from the last culture. It was found that Methicillin-resistant *Staphylococcus epiddermidis* was in 5 (2.65%), Methicillin-resistant *Staphylococcus aureus* in 1 (0.53%), Extended Spectrum *Beta Lactamase* was in 54 (28.57%), Carbapenem-resistant *Klebsiella pneumoniae* in 47 (24.87%), Carbapenem-resistant *Acinetobacter* in 34 (17.99%), Carbapenem-resistant *Pseudomonas aeruginosa* in 23 (12.17%), Carbapenem-resistant *Enterobacteriaceae* in 23 (12.17%), Carbapenem-resistant *E. coli* in 1 (0, 53%) and Carbapenem-resistant *Myroids* in 1 (0.53%).

Table III - Antibiotic resistance based on pathogen from last culture

Antibiotic resistance	Total (%)
Methicillin-resistant *Staphylococcus epidermidis*	5 (2.65)
Methicillin-resistant *Staphylococcus aureus*	1 (0.53)
Extended Spectrum *Beta Lactamase*	54 (28.57)
Carbapenem-resistant *Klebsiella pneumonia*	47 (24.87)
Carbapenem-resistant *Acinetobacter*	34 (17.99)
Carbapenem-resistant *Pseudomonas aeruginosa*	23 (12.17)
Carbapenem-resistant *Enterobacteriaceae*	23 (12.17)
Carbapenem-resistant *E.coli*	1 (0.53)
Carbapenem-resistant *Myroides*	1 (0.53)

Total isolates 189, n (%)

Based on the results of bivariate analysis, a relative risk of 1.103 (95% CI 1.004-1.211) with a p value of 0.046 makes patients exposed to MDRO infection 10% more at risk of dying during hospitalization compared to non-MDRO patients (*Table IV*).

Table IV - Analysis of MDRO infection mortality in burn patients at the Burn Unit of RSUPN Dr. Cipto Mangunkusumo.

MDRO	Mortality n (%)		RR (IK 95%)	p value
	Yes	No		
Yes	72 (45.00)	74 (46.25)	1.103 (1,004-1,211)	0,046
No	3 (21.43)	11 (78.57)		

RR: Relative Risk; *significance p <0,05

Table V shows the relationship between confounding variables, namely age, co-morbidities, TBSA, use of medical devices, and length of stay on mortality of burn patients in the burn unit of RSUPN dr. Cipto Mangunkusumo. In the age category, there were 28 research subjects aged ≥60 years, of which 17 subjects (60.71%) died during the hospitalization period. The Mann-Whitney test shows a significant relationship with p-value = 0.106. A significant relationship was found between comorbidities and burn patient mortality. Of the 27 study subjects with comorbidities, 17 of them (62.96%) died during the hospitalization period. The chi-square test shows a significant relationship with p-value = 0.066. The percentage of TBSA shows a significant relationship with the mortality of burn patients. Of a total 101 subjects with TBSA ≥30%, 67 of them (66.34%) died during the treatment period. The Mann-Whitney test shows a significant relationship with a p-value <0.000. Of the 145 subjects who used medical devices during their hospitalization, 74 subjects (51.03%) died during their hospitalization, with the results of the chi-square test showing a significant relationship with a p-value of 0.01. Length of stay also showed a significant relationship with a p-value <0.000. The Chi square test and the Mann Whitney test proved that there was a relationship between mortality in burn patients in the burn unit of RSUPN dr. Cipto Mangunkusumo with confounding variables such as age ≥60 years, comorbidities, TBSA ≥30%, use of medical devices, and length of stay.

Table V - Relationship of confounding variables to research subject mortality

Variable	Mortality n (%)		p-value
	Yes	No	
Age group, n (%)			
≥ 60 years old	17 (60.71)	11 (39.29)	0,106
18 - <60 years old	58 (43.94)	74 (56.06)	
Comorbid, n (%)			
Yes	17 (62.96)	10 (37.04)	0,066
No	58 (43.61)	75 (56.39)	
TBSA, n (%)			
≥ 30%	67 (66.34)	34 (33.66)	<0,000
10 - < 30%	8 (13.56)	51 (86.44)	
Medical device use, n (%)			
Yes	74 (51.03)	71 (48.97)	0,01
No	1 (6.67)	14 (93.33)	
Length of stay (days), median (IRQ)	10 (4-41)	21 (6-59)	<0.000

Variables that had p <0.25 in the bivariate analysis were included in the multivariate analysis. Variables included in the multivariate analysis were TBSA, length of stay, use of medical devices, comorbidities, and age. In multivariate analysis with logistic regression, a fully adjusted odds ratio was obtained between the MDRO infection category and worsening after adding the confounding variables, gradually starting from the smallest p value in the bivariate, namely TBSA, length of stay, use of medical devices, comorbidities and age changes in adjusted odds ratio for events. The worsening outcome at each additional confounding variable can be seen in *Table VI*. Thus crude OR 3.568 (0.956-13.317) was obtained, p value 0.046, and adjusted OR 3.692 (0.815-16.716), p value 0.090; length of stay and age were confounding variables.

Length of stay and age are confounding variables because of the change in coef B >10%

Crude OR 3,568 (0.956-13.317), *p value* 0,046

Adjusted OR 3,692 (0,815-16,716), *p value* 0,090

Discussion

Subject characteristics

This research is a retrospective cohort study conducted at the wound unit of RSUPN dr. Cipto Mangunkusumo in patients who were hospitalized from January 2020 to June 2022. Based on gender, there were more male subjects (62.5%) than women (36.57%). The mean age of the subjects in this study was 46 years, and 132 subjects (82.5%) were aged <60 years while 17.5% were aged ≥60 years. The age distribution in this study was not much different from the study at the Bali General Hospital conducted by Samsarga et al.,[1] which reported ages <60 years with a mean age of 36 years and more were male (74.3%). Research in Kumasi Ghana by Richcane et al. also reported more subjects aged <60 years (40.7%) compared to age ≥60 years (1.2%) and more males (59.3%).[14] Similarly, Chen et al. in Taiwan reported that most were <60 years old and male (59.5%).[15] A study conducted by Ellithy et al. reported that age >60 years was a predictor of death in burn patients and that middle-aged women had a higher risk of death, twice as much as men.[16] A similar age grouping was also carried out by Santos et al., where the research subjects were divided into those aged 65 and over and under 65 years.[17]

Co-morbidities were defined as the presence of distinct and co-existing diseases during the clinical course. The use of the Charlson Index as a classification of comorbidities is commonly used to assess risk factors and predictors of prognosis.[18] In this study, a Charlson index >2 was found in 27 subjects

Table VI - Multivariate analysis of variables influencing MDRO infection mortality in burn patients

Variable	OR MDRO-Mortality (IK 95%)	p value	Coefficient B	Changes in Coef. B
Crude OR :				
MDRO	3,568 (0.956-13.317)	0,046	1.272	
Adjusted OR :				
+ TBSA	3,515 (0,824-14,980)	0,089	1,256	1.26%
+ Length of stay	6,713 (1,230-36,628)	0,028	1,840	46.49%
+ Medical device use	3,546 (0,796-15,791)	0,097	1,266	0.79%
+ Comorbid	3,692 (0,815-16,716)	0,090	1,306	3.15%
+ Age >60 years old	3,228 (0,711-14,658)	0,129	1,172	10.2%

(16.88%). Salehi et al.[19] reported the prevalence of comorbidities in burn patients (18.5%) and comorbidities with old age increased to 57%; diabetes and heart failure were the most frequent comorbidities. Knowlin et al. evaluated the Charlson Index in burn patients with TBSA >50% for mortality and found comorbidity to have a significant effect on comorbidity. Knowlin et al.[20] reported that in burn patients who suffer from diabetes there is a decrease in sensory and motor function, which causes a delay in withdrawing the extremity when exposed to a heat source. With the presence of microangiopathy and changes in neutrophils, there will be interference with phagocytosis and this will cause failure in wound healing.

In this study, there were 101 subjects (63.13%) with TBSA ≥30%. Similar results were also obtained in Chen et al.'s[21] study showing that burn patients with TBSA ≥30% (67.6%) also reported an increase in the type of isolate with an increase in TBSA. Yeong et al.'s[22] study reported that the probability of death in burns with TBSA <30% was 1.7% without bacteremia but would increase to 5.7% if there was bacteremia, and TBSA ≥30% increased the risk of mortality 16 times, with the possibility of death (40.8%) if bacteremia is found. ALfadli et al.[3] also reported that TBSA ≥35% had a risk of hospitalization >14 days and had a greater risk of nosocomial infections, and the most common pathogen was Acinetobacter.

The biggest cause of burns in this study was fire with 138 (86.25%) followed by electricity (7.5%) and hot oil/water (6.25%). The same thing was also found by research conducted by Hamzaoi et al.,[23] which reported that the most common cause was fire (52.38%) followed by hot water (28.57%) and electricity (7.93%). According to Alfadly et al.[3] in their research, fire is the most common cause of burns (62.69%), followed by hot water (27.86%). National Burn Respiratory 2017 reported the most common type of cause in burn patients was fire (76% of reported cases). Patients with fire burns experience damage to the skin, loss of physical barriers, and impaired immune function that allows pathogens to enter the body. A total of 145 (90.63%) subjects in this study used medical devices and more than 50% used ventilators. Similar results were also reported by Ellithy et al.:[16] more than 60% of burn patients treated in the intensive care unit (ICU) used a ventilator. Ressne et al.[24] in Iraq reported using a ventilator as much (92%) in bacteremia patients, compared to nonbacteremia (23%) while Chen et al. reported 62.2% burn patients using a ventilator.[25] The use of medical devices is thought to be a source of infection. It is commonly found in patients, such as the use of peripheral and central venous catheters, urinary catheters, nasogastric tubes and mechanical ventilators, because the use of medical devices can cause trauma to the skin or mucosa and with the entry of bacteria into the blood.

In this study, the first most common source of infection was from the skin and soft tissue (100%), followed by the respiratory tract (40%), and the urinary tract (5.63%), and in this study 96 (54.9%) experienced sepsis. Lin et al.[26] also had reported bacteremia (31%) and MDRO (18.2%) infection with pathogens, more common in third-degree TBSA and caused by inhalation injury. The same study also reported patients with bacteremia undergoing longer hospitalization ($p < 0.001$), prolonged use of mechanical ventilation ($p < 0.001$) and sepsis ($p < 0.001$). Samsarga et al.[1] reported that there was a relationship between MDRO infection and duration of antibiotic administration, sepsis, pneumonia and death. The same investigator also found MDRO infection associated with sepsis with OR 36.53 (95% Cl 2.05-652.45) and an increased risk of death with OR 57.09 (95% Cl 1.41-2318.87) and TBSA. Chen et al.[27] also reported that the most common sources of hospital-associated infection (HAI) found in burn patients were bacteremia (bloodstream infection), urinary tract infection (UTI), pneumonia, tracheobronchitis, skin and soft tissue infections, and surgical site infection (SSI). This is related to the length of stay, the number of surgical procedures performed, and several surgical procedures that can increase the risk of death and the high cost of treatment.

The length of stay of patients in the burn unit in this study was 4 to 59 days and administration of empiric antibiotics was 160 (100%). Chan et al.[26] reported the average length of stay of burn patients was 18 days. Samsarga et al.[1] reported that the median duration of antibiotics with MDRO infection

was 7 days and the duration of antibiotics was not associated with length of stay and AKI. Almost similar results were also reported by Langeveld et al. It was found that MDRO infection was not associated with length of stay and administration of antibiotics. This shows the type of bacteria, and the duration of antibiotic administration is influenced by the patient's clinical response and surgical interventions such as tangential excision and skin grafting.

Microorganism pattern based on last culture

In this study, various types of MDRO and non-MDRO bacteria were found as the cause of infection in burn patients. The majority of pathogens obtained from culture results are Gram negative bacteria. From the results of the last culture examination of tissue or blood, it was found that the most common pathogens causing the first MDRO infection were *K. pneumoniae* (29.91%), the second *Enterobacter* (22.32%), the third *Acinetobacter* (20.54%), the fourth *P. aeruginosa* (16.52%) and the fifth *E. coli* (3.13%), while the most common non-MDRO pathogenic infections found were *Enterobacter* (23.08%), *K. pneumoniae* (7.69%) and *Acinetobacter* (7.69%). Gram-positive pathogens as a cause of MDRO infection in tissue or blood cultures were *Staphylococcus epidermidis* (3.13%), *Staphylococcus aureus* (0.45%); and non-MDRO Gram-positive pathogens were *Staphylococcus epidermidis* (26.92%). Chen et al.[23] reported that the most common Gram negative bacteria found in burn patients were *P. aeruginosa*, *Acinetobacter baumannii*, *Klebsiella spp*, *Stenotrophomonas spp*, *E. coli* and *Enterobacter cloaceae*. The same researcher also reported that as many (30%) were caused by MDRO infection and the most frequently encountered were *Acinetobacter baumannii* resistant to carbapenem (14.6%), *Klebsiella* resistant to carbapenem (2.4%). The most common pathogens encountered during treatment days 8 to 28 were *A. baumannii*, *Chyseobacterium spp*, *S. maltophilia*, but the most common pathogen found in tissues was *P. aeruginosa*, which was usually found on days of hospitalization <14 days and the MDRO infection by a Gram-positive pathogen was MRSA (11.3%). Burn patients in the ICU have more predisposing factors for infection, namely wider and deeper TBSA, longer wound healing, impaired immune function, multiple organ dysfunction, and longer hospitalization. The ICU environment can increase the risk of pathogen transmission such as with equipment use, bacterial colonization on equipment surfaces, medical waste and invasive procedures such as central vein use, catheters, tracheotomy, bronchoscopy, mechanical ventilation. The increased risk of MDR in injured patients can occur due to prolonged use of antibiotics, repeated invasive procedures, and long hospitalizations.

Sajitha et al.[28] in Ghana reported that the most common pathogens found in tissue culture were *Pseudomonas sp* (30.2%) and *Acinetobacter sp*. (20.9%). *Proteus mirabilis* and *Staphylococcus aureus* are rare pathogens, each found in 2.3%. Frana et al.[29] reported bacteremia caused by Gram negative bacteria (46%), Gram positive (40%) and fungi (14%). The most commonly encountered microorganisms were *Enterococcus*, *Candida*, *Pseudomonas*, *Enterobacter*, *S. aureus*, *Staphylococcus coagulase* negative and *Klebsiella*. Blanco et al.[30] reported that the most common pathogens were *P. aeruginosa*, *A. baumannii*, *E. coli*, *Klebsiella pneumoniae* and *S. aureus*. The occurrence of MDRO infection which causes bacteremia is an important problem caused by damage to the skin as a barrier to entry of pathogens, especially in patients without early excision, debridement, grafting, and TBSA >40%. This situation can be reduced by isolation, aggressive infection control, appropriate antimicrobial therapy, debridement, monitoring and placement of diagnostic equipment in each patient's room to prevent cross-contamination between patients. Procedures that have the potential to cause cross-contamination in burn patients, such as hydrotherapy, are carefully managed and implemented with the goal of minimizing risks. Additionally, early excision and grafting techniques are employed to ensure prompt and effective treatment. Chen et al.[23] reported that the pathogens that cause HAI in burn patients are caused by water-borne bacteria such as *Ralstonia spp*, *A. baumannii*, *Chryseobacterium spp*, and *P. aeruginosa*, therefore these pathogens can be considered with day of treatment <14 days.[31,32]

In this study Methicillin-resistant *Staphylococcus epiddermidis* was found more frequently (2.65%)

when compared to Methicillin-resistant *Staphylococcus aureus* (0.53%) and in this study antibiotic resistance was more common in Gram negative pathogens. The resistance was Extended Spectrum *Beta Lactamase* (28.57%), Carbapenem-resistant *Klebsiella pneumonia* (24.87%), Carbapenem-resistant *Acinetobacter* (17.99%). Moreau et al.[31] reported that Gram-negative MDR pathogens were higher than Gram-positive MDR pathogens in the burn ICU and there was a significant increase in Carbapenem-resistant *K. pneumoniae* (CRKP) and Carbapenem-resistant *A. baumannii* from 2011 (60%) to 2019 (81.8%). Tan et al.[32] also reported that the most common MDR pathogens were *A. baumannii* (73.6%), *P. aeruginosa* (27.5%) and *K. pneumoniae* (25.3%). Antibiotic resistance mechanisms include production of inactive enzymes (β-lactamase converting enzymes and aminoglycosides), modification of target sites, decreased drug penetration, overexpression of efflux pumps and genetic resistance namely gyr A and parC, and the molecular mechanisms of antibiotic resistance differ in different bacteria. Gong et al.[11] reported that the five most common genes in MDR *A. baumannii* were OXA-23, AmpC, IS-AmpC, PER, VIM and SIM while in carbapenem-resistant *P. aeruginosa* it occurred due to inactivation of the porin oprD gene mutant and overexpression of the gene ampC β-lactamase. Carbapenem-resistant *K. pneumonia* occurs because more than 90% overproduce β-lactamase (blaCTX-M-10, blaSHV, blaTEM, blaCTX-M-14), b-lactamase blaACT, and carbapenemase blaKPC. The mec A and mec C genes, which are produced by penicillin-binding proteins, play a role in the resistance of *S. aureus* to β-lactam antibiotics.[24,33]

Analysis of MDRO infection mortality in burn patients at the burn unit of RSUPN dr. Cipto Mangunkusumo

In this study, the mortality of burn patients with MDRO infection reached 45% (p=0.046), with a relative risk = 1.103 (95% CI 1.004-1.211), making patients exposed to MDRO 10% more at risk of dying during hospitalization compared with patients without exposure to MDRO. The results of the chi-square test also showed a strong relationship between MDRO mortality and infection in burn patients. Langeveld et al. reported mortality of burn patients with MDRO infection (10.6%) to be higher than mortality of patients without MDRO infection (6.3%). A study conducted by Theodorou et al. also found similar results, where *P. aeruginosa* was the focus MDRO in this study. Research conducted at tertiary hospitals in Indonesia by Samsarga et al.[11] found a significant relationship between mortality and MDRO infection in burn patients (OR = 9.75; 95% KI = 2.00 - 47.50) and the same researchers also demonstrated that burn patients with MDRO were at significantly higher risk of dying during hospitalization. Similar results were found in the study by Tanuwijaya et al.[2] which compared bacteremia due to MDRO with burn patients, where higher mortality was found (RR = 18.6; 95% CI = 11.1-31.1; p-value <0. 01).

In this study, after adjusting for confounding variables, namely: TBSA (p <0.000), length of stay (p <0.000), use of medical devices (p <0.01), comorbidity (p <0.066), age (p = 0.106), in multivariate analysis it was found that length of stay and age were confounding variables, while variables that were not confounding variables for mortality in burn patients with MDRO infection were TBSA, medical devices and comorbidities. In this study OR (95% CI) after being adjusted with TBSA was 3.515 (0.824-14.980), plus medical devices became 3.546 (0.796-15.791), and comorbidities 3.692 (0.815-16.716).

After multivariate analysis, age was a confounding variable that also influenced the mortality of MDRO infection in burn patients: OR (95% CI) = 3.228 (0.711-14.658) and a change in Coef B of 10.2%. Old age is a risk factor for increased mortality in burn patients. This is consistent with the study by Galeiras et al.,[34] which reported that age and mortality are linearly proportional if the population of children under 18 years is not included. Research conducted by Moreau et al.[31] created AGESCORE, a score that has been validated in predicting mortality after experiencing thermal injury based on age. In this scoring, the risk of mortality in burn patients increases with age. This condition is caused by old age, when there is a decrease in the function of the respiratory and cardiovascular systems, so that the mortality of elderly patients when they experience

injuries also increases due to failure of compensation from the cardio-respiratory function.[30] Apart from that, old age is associated with physiological decline of the skin, so that the immune function in elderly patients tends to be lower than in adult patients.[32,35]

The median length of stay in this study was 14 days (4-59) and after multivariate analysis it was found that length of stay was a confounding variable that also affected MDRO infection mortality in burn patients with OR (95% CI = 6.713 (1.23-36.628) and changes in Coef. B 46.49%. A study conducted by Van et al.[35] in The Netherlands reported that the length of stay of burn patients in the burn unit was an average of 13 days (SD 16) and the patients treated came from referral health facilities. From an administrative perspective, long length of stay is associated with morbidity due to injury, cost and quality of care. Chukamei et al.[36] reported that length of stay was influenced by antibiotic use, previous medical history, type of insurance, degree of burn, organ affected and lower socioeconomic status, which was associated with poorer health status, more susceptibility to injury and increased risk of hospitalization.

Strengths and limitations of research

The strengths of this study are that it is a study that examines the effect of MDRO infection on mortality in burn patients and uses a cohort design where the cohort design can explain the relationship between subjects and risk factors and effects. The independent and dependent variable data included in the analysis are complete and can be analyzed. This study also considered several confounding variables so that the relationship between MDRO infection and acquired mortality was independent.

The weakness of this study is that it is retrospective with data taken from medical records. Researchers cannot control the circumstances, quality, and standardization of measurement of variables in past studies, especially variables that are prone to recall bias.

Conclusion

There is an effect of MDRO infection on the mortality of burn patients. The proportion of MDRO infection mortality in burn patients at RSUPN dr. Cipto Mangunkusumo is greater (45%) than the proportion of burn patient mortality without MDRO infection (21.43%). Gram-positive MDRO pathogens in burn patients at RSUPN dr. Cipto Mangunkusumo include *S. aureus* and *S. epidermidis*, while the most common Gram-negative MDRO pathogens include *K. pneumoniae*, *Enterobacter sp*., *Acinobacter*, *P. aeruginosa* and *E. coli*.

Suggestions

Wound patient mortality is influenced by MDRO infection, length of stay and age so that optimal management of this condition is needed. Treatment of infection must be carried out with a holistic approach, especially in the management of infection, identification of pathogens, antimicrobial therapy and prevention of the spread of nosocomial infections.

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