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## Multiple-Drug Resistance in Burn Patients: A Retrospective Study on the Impact of Antibiotic Resistance on Survival and Length of Stay

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### Abstract

Despite improvements in early treatment, survival following burn injury remains challenged by sepsis and multiple organ dysfunction syndrome (MODS). Additionally, susceptibility to infections and growing antibiotic resistance places burn patients at increased risk for infections with multiple-drug resistant organisms (MDROs). We therefore aimed to evaluate the impact of MDRO infections on survival and hospital length of stay, as well as examine the role of these organisms in the development of complications, such as acute kidney injury, sepsis, and MODS. To study this, we included all burn patients with infections, admitted between January 1, 2012, and December 31, 2013. Patients were divided into two groups: patients with infections caused by MDROs and patients with infections caused by susceptible organisms. Data were collected on all available cultures, as well as demographic, injury, and treatment-related variables from the medical record. The number of operative procedures (median: 2 vs 1,  $P < .0001$ ), ventilator days (21 vs 0 days,  $P < .0001$ ), total antibiotic days (21 vs 7 days,  $P < .0001$ ), and length of hospitalization (39 vs 14 days,  $P < .0001$ ) were significantly different in the MDRO group vs the nonresistant group. While MDRO infection was not associated with patient mortality, univariable logistic regression analyses demonstrated  $>20\%$  TBSA (odds ratio [OR] = 4.30, 95% confidence interval [CI]: 1.14–16.29,  $P = .03$ ), acute kidney injury (OR = 10.93, 95% CI: 2.74–43.57,  $P = .001$ ), sepsis (OR = 19.20, 95% CI: 3.79–97.27,  $P < .001$ ), and MODS (OR = 85.49, 95% CI: 12.97–563.28,  $P < .0001$ ) significantly increased the odds of patient mortality. These findings suggest that infections with MDROs are associated with a greater number of surgical procedures, longer duration of mechanical ventilation, more antibiotic days, and longer hospitalization.

The mortality following burn injury has gradually declined over the past few decades.<sup>1–3</sup> This is largely due to improved treatments, such as early excision and grafting of the burn wound,<sup>4</sup> continuous feeding of a high-carbohydrate, high-protein diet to treat significant nutritional deficiencies,<sup>5,6</sup> and advancements in critical care. Despite improvements in early treatment, long-term survival remains challenged, mainly due to sepsis<sup>7</sup> and multiple organ dysfunction syndrome (MODS).<sup>8,9</sup> Accordingly, sepsis and MODS are currently the leading causes of death in both pediatric<sup>8</sup> and adult burn patients.<sup>9</sup>

Acute kidney injury (AKI) characterized by a sudden decrease in kidney function, whether it occurs early or late in a hospitalization, is commonly associated with MODS or serves as a precursor to MODS.<sup>10</sup> Patients with AKI often progress to a need for renal replacement therapy (RRT), are at risk of developing chronic kidney disease, and suffer from an increased mortality.<sup>11</sup> Frequently, AKI occurs as a result of antibiotics used for treatment of infectious complications. The combination of vancomycin<sup>12</sup> and piperacillin/tazobactam<sup>13</sup> is an example of this. Similarly, recovery from AKI may be impaired by certain antibiotics. An example of this is elderly patients or patients with hypertension treated with aminoglycosides, who have been shown to be less likely to recover from AKI.<sup>14</sup>

Sepsis, AKI, and MODS are often preceded by infectious complications. In burn patients, prevention and treatment of infection is especially difficult because of an impaired immune response. The combination of an impaired immune response characterized by decreased T-cell function following injury,<sup>15</sup> a disruption of the protective skin barrier from burn injury<sup>16</sup> allowing pathogens to spread easily throughout the rest of the body, and long hospitalizations with multiple surgical procedures and the use of catheters and other invasive devices places burn patients at an increased risk of infectious complications.<sup>9</sup>

One of the biggest challenges in treating bacterial infections is their resistance to antibiotic treatment. Several studies have been performed in multiple countries to identify the most frequently occurring multiple-drug resistant organisms (MDROs) in specific burn units. *Pseudomonas aeruginosa*,<sup>17–19</sup> *Staphylococcus aureus*,<sup>17,19</sup> and *Acinetobacter baumannii*<sup>13,20</sup> are among the most frequently cultured sources of infection in burn patients. These pathogens are often resistant to many of the antimicrobial treatments we use today, and there are very few new antimicrobial agents being developed. Information on the clinical impact of infections caused by these MDROs in burn patients is scarce, and as the incidence of MDROs grows, the clinical impact will likely grow as well.

With this in mind, we sought to evaluate the impact of MDROs in burn patients on survival and length of stay in the hospital, as well as examine the role of MDROs in the development of complications such as AKI, sepsis, and MODS.

## METHODS

### Study Design and Data Collection

After approval from the institutional review board, we conducted a single-center retrospective review of both pediatric and adult burn patients who were admitted to the burn

intensive care unit (BICU) or the burn ward between January 1, 2012, and December 31, 2013.

Patients were included if they had clinical findings consistent with a burn wound infection, such as erythema, swelling, warmth, and increased pain (including burn wound cellulitis, graft infection, and infection of surgical wounds). Patients were also included if they developed symptoms of hospital-related infections, such as pneumonia, urinary tract infections (UTIs), or catheter infections (including central venous catheters) during their stay. Pneumonia, UTIs, and catheter infections were defined according to the Centers for Disease Control guidelines.<sup>21</sup> Patients with infections that were present before the burn incident (such as upper respiratory infections) were excluded from this study if they did not develop any other infections during their admission. We included patients in the MDRO group once they had at least one positive culture for an MDRO, and all cultures (before and after the positive culture for MDROs) were included in the MDRO group analysis.

We collected the following data from the electronic medical record: age, sex, mechanism of burn, percentage of TBSA burned, inhalation injury, length of stay, length of mechanical ventilation, and length of antibiotic treatment. Furthermore, we gathered the sensitivity analysis of all available cultures to determine the degree of drug resistance of all cultured bacteria. And finally, we collected data on the incidence of sepsis, AKI, and MODS.

### Definition of Clinical Parameters

TBSA was calculated by use of a Burnman computer program (Sage diagram, LLC, Portland, OR) that calculates burn size according to the Lund Browder method. Bronchoscopy was performed in patients with suspected inhalation injury to confirm the diagnosis. The degree of inhalation injury was scored according to the abbreviated injury score.<sup>22</sup> Length of stay was defined as the time between admission and discharge from the hospital or death. Length of mechanical ventilation was defined as the time between intubation or need for mechanical ventilation to the time where patients were spontaneously breathing without need for mechanical support. Sepsis, severe sepsis, and septic shock were defined according to the Surviving Sepsis Campaign Guidelines set by the Society of Critical Care Medicine.<sup>23</sup> We reviewed incidences of acute kidney injury via Acute Kidney Injury Network criteria.<sup>24</sup> And finally, MODS was graded according to the Denver scoring system.<sup>25</sup>

We included the following bacteria in our analysis: methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE), extended-spectrum (beta)-lactamase-producing *Enterobacteriaceae* (ESBL), and *Klebsiella pneumoniae* carbapenemase (KPC). All other bacteria (such as *P. aeruginosa* and *A. baumannii*) were considered MDROs if they showed resistance to at least three of the tested antibiotics in the sensitivity analysis. Patients who had at least one positive culture with an MDRO were considered MDRO patients. All other patients were included in the non-MDRO group.

## Microbiology

When patients were clinically suspected of having pneumonia (such as through change in secretions and increased oxygen requirement), a quantitative bronchoscopic alveolar lavage was performed. Urine cultures were performed when patients were suspected of having a UTI. Both aerobic and anaerobic cultures were performed in case of suspected skin infections. All cultures were performed according to a standard protocol. Cultures were incubated for 3 days at approximately 37°C. After identification of bacterial strains, the antibiotic susceptibility of all cultured pathogens was determined.

## Statistical Analysis

The statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC). Pearson  $\chi^2$  and Fisher's exact tests were used to assess differences on all categorical variables by the MDRO group. Independent samples *t*-tests and Wilcoxon-Mann-Whitney tests were employed to compare the distribution of continuous variables. Comparisons on patient age were expressed as means and standard deviations; medians and interquartile ranges were reported for all other continuous variables because of their nonnormal distributions. For categorical variables, results included the number and percentage of patients within each level. For all tests, an alpha <0.05 was considered statistically significant.

Univariable logistic regression models were then used to assess the effect of select risk factors on patient mortality. Because of the low number of observed events (10 deceased patients), a multivariable model was not generated for this analysis.<sup>26</sup> Rather, an additional univariable logistic regression model was considered in a sensitivity analysis for patients with a TBSA of 5 to 40%. This subanalysis included only patients (*n* = 64) with a moderate to high likelihood of MDRO risk, thereby controlling for important differences on select comorbidities.

## RESULTS

### Clinical Characteristics

Over the 2-year period, 1355 patients were admitted and a total of 126 patients were found to have at least one positive culture requiring treatment and were thus included in this study. Table 1 summarizes the characteristics for the MDRO (*n* = 47) vs non-MDRO (*n* = 79) groups. Age was similar between groups, with a mean of 49.2 years in MDRO patients versus 45.5 years in non-MDRO patients. MDRO patients had larger burns with a median %TBSA of 15% vs 5.1% (*P* = .001), and required significantly more operative procedures than patients in the non-MDRO group (2 vs 1, *P* < .0001). MDRO infections were associated with longer hospitalization (39 vs 14 days, *P* < .0001), longer need for mechanical ventilation (21 vs 0 days, *P* < .0001), and longer duration of antibiotic treatment (21 vs 7 days, *P* < .0001). Gender was evenly distributed among the MDRO and the non-MDRO groups (*P* = .84). Flame burns were more common in patients with MDROs than in those with non-MDROs (76.1% vs 47.4%, *P* = .004), although the incidence of inhalation injury was the same for both groups (*P* = .92). The incidence of sepsis was significantly higher in the MDRO group than in the non-MDRO group (38.3% vs 12.7%, *P* = .001). Similarly, AKI occurred more frequently in the MDRO group than in the non-MDRO group (27.7% vs

8.9%,  $P = .01$ ), and MDRO patients required RRT more frequently (12.8% vs 0%,  $P = .002$ ). Incidence of MODS (10.6% vs 3.8%,  $P = .15$ ) and mortality (10.6% vs 6.3%,  $P = .50$ ) were not statistically different, though a possible trend was noted.

### Localization and Sources of Infections

The different types of infection for MDRO and non-MDRO patients are highlighted in Table 2, while Table 3 shows which bacteria were cultured most often in both groups for Gram-negative and Gram-positive bacteria, respectively. Often, patients had more than one positive culture for a specific pathogen during their stay in the BICU, which is why the number of cultures is higher than the number of patients. Table 4 summarizes the incidence and location of the most commonly found MDROs. This table shows that the majority of cultured bacteria were Gram-negative (67.8%) and MDRO infections were most frequently located in the urinary tract (37.3%) or the lungs (47.5%).

### Mortality

Univariable logistic regression analysis results, as shown in Table 5, demonstrate that >20% TBSA, sepsis, AKI, need for RRT, and MODS were associated with an increase in the odds of patient mortality. By contrast, MDRO infection was not independently associated with mortality (odds ratio [OR] = 1.76, 95% confidence interval [CI]: 0.48–6.44,  $P = .39$ ). In the subset of patients ( $n = 64$ ) with a moderate to high likelihood of MDRO risk (TBSA 5–40%), the effect of MDROs on patient mortality was even less pronounced (OR = 1.32, 95% CI: 0.25–7.10,  $P = .75$ ).

## DISCUSSION

Although survival following burn injury has improved greatly because of improvements in treatment,<sup>4–6</sup> fighting infections remain a challenge. Several studies have sought to identify the most common multiple-drug resistant pathogens,<sup>17–20</sup> but the impact of MDROs on survival and other outcome parameters remains unclear. In our study, we aimed to shed some light on this issue by examining 126 burn patients with infections who were admitted to our burn unit. By means of univariable analyses, we assessed for differences in several important clinical variables of patients with and without MDRO infections.

Importantly we found, MDRO infections resulted in longer hospitalization (median: 39 vs 14 days,  $P < .0001$ ), longer need for mechanical ventilation (21 vs 0 days,  $P < .0001$ ), and longer duration of antibiotic treatment (21 vs 7 days,  $P < .0001$ ). Patients with MDRO infections had larger burns (median: 15% vs 5.1 %TBSA,  $P = .001$ ) and were more commonly flame burns (76.1% vs 47.4%,  $P = .004$ ).

Theodorou et al<sup>17</sup> conducted a similar study to our own. Their main goal was to investigate the role of resistance of *P. aeruginosa* on survival and length of stay. In their study, the presence of resistant *P. aeruginosa* strains was not significantly correlated with prolonged hospitalization, although they did see a similar trend. During our study period, we were able to include more patients, which could explain why we did see a significant difference. However, this discrepancy may also be explained by the difference in geographical setting

(US vs Germany) and by the fact that we looked at other multiple-drug resistant pathogens as well.

A similar trend was seen by Özgür et al<sup>27</sup> in patients admitted to an adult Intensive Care Unit (ICU) in Turkey. They examined the impact of the presence of pneumonias caused by MDR *A. baumannii* strains on ICU length of stay and duration of mechanical ventilation. They found that ventilator-associated pneumonias caused by resistant *P. aeruginosa* strains resulted in a prolonged ICU and hospital stay.

It is a logical assumption to think that patients with infections caused by MDROs are at greater risk to develop sepsis or MODS because they are more difficult to treat. Accordingly, we found a significantly higher incidence of sepsis in the MDRO group than in the non-MDRO group (38.3% vs 12.7%,  $P = .001$ ). This confirms our hypothesis that burn patients with MDRO infections are more likely to progress into a state of sepsis or organ failure. Additionally, the presence of septic episodes was associated with a significant increase in the odds of patient mortality in the univariable analysis, with OR = 19.20 (95% CI: 3.79–97.27,  $P < .001$ ). MODS and AKI were also associated with increased mortality in the univariable analysis, with OR = 85.49 (95% CI: 12.97–563.28,  $P < .0001$ ) and OR = 10.93 (95% CI: 2.74–43.57,  $P = .001$ ), respectively.

In addition to these differences in sepsis and organ failure, our study uncovered significant differences in antibiotic duration between the two treatment groups. While these totals accounted for treatment of multiple infections per patient rather than a single course of antibiotics, this finding calls attention to the highly discussed topic of optimal duration of antibiotic therapy. While insufficient length of treatment could result in recurrent infection, prolonged duration of treatment is associated with adverse drug events, higher costs, and increased prevalence of drug-resistant bacteria.<sup>28</sup> Highlighting this point, Daneman et al's<sup>29</sup> retrospective cohort study of bacteremic ICU patients to determine pathogen and patient-related factors associated with prolonged duration of antimicrobial therapy found that most patient or pathogen characteristics were not associated with treatment duration and that survival bias precluded a valid assessment of the association between duration and survival. In our study, duration of antibiotic treatment was based on clinical response to treatment, and also influenced by operative interventions such as excision and grafting, which may have served to lengthen duration of antibiotic therapy.

Although several studies<sup>30–32</sup> show that patients with resistant MDROs such as *P. aeruginosa* have an increased mortality rate, data on the impact of MDROs on mortality in burn patients is very limited. In our study, mortality rates did not differ in the two groups. To our knowledge, no other studies have been performed that evaluate the impact of MDRO infections on mortality in burn patients. Also, because many of the known risk factors for mortality and risk factors for MDRO infections are the same, such as burn size, AKI, and sepsis, it is difficult to assess the impact of MDRO infections on mortality and it is possible that the number of patients in this study is too small to demonstrate whether MDRO infections are independently associated with mortality.

## Strengths and Limitations

One of the strengths of this study is that it includes multiple MDROs, rather than limiting analysis to one or a select few MDROs. In contrast, many similar studies have only looked at the role of one particular pathogen, such as *P. aeruginosa* or *A. baumannii*. Since patients often endure infections with multiple pathogens at a time or repeated infections, it is only reasonable to consider more than one pathogen in a study. We have also presented an overview of the most common sources of infections in burn patients, which will hopefully raise awareness on the risks of infection in burn patients amongst clinicians. The study is limited by the fact that it is retrospective and that there was no distinction made between patients admitted to the BICU or to the burn floor. This was mainly because patients often alternate between these locations, making it difficult to establish when and where patients were infected. An additional limitation to this analysis is the small number of observed events, as only 10 of the 126 patients in the sample were deceased, which limited the statistical approach to univariable analyses.

## CONCLUSION

Patients with infections caused by MDROs require longer hospitalization, longer need for mechanical ventilation, longer duration of antibiotic treatment, and a greater number of surgical procedures. MDRO patients are more prone to develop sepsis and AKI. Additional studies and greater sample size are needed to validate these findings and further investigate the potential impact of MDROs on mortality.

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**Table 1**

## Baseline and clinical variables

Baseline Clinical Variables	Non-MDRO Patients (n = 79)	MDRO Patients (n = 47)	P
Age (years) (mean, SD)	45.5 (25.7)	49.2 (20.6)	.41
%TBSA (median, IQR)	5.1 (1.7–16.31)	15 (5.95–30.71)	.001
Burn operations (median, IQR)	1 (0–1)	2 (1–6)	<.0001
Length of hospital stay (median, IQR)	14 (9–23)	39 (19–74)	<.0001
Days on mechanical ventilation (median, IQR)	0 (0–7)	21 (0–59)	<.0001
Days on antibiotic treatment (median, IQR)	7 (4–11)	21 (10–48)	<.0001
Patient sex			.84
Male	49 (62.0%)	30 (63.8%)	
Female	30 (38.0%)	17 (36.2%)	
Type of burn (n = 124)			.004
Flame	37 (47.4%)	35 (76.1%)	
Scald	27 (34.6%)	4 (8.7%)	
Chemical	6 (7.7%)	2 (4.4%)	
Other	8 (10.3%)	5 (10.9%)	
Inhalation injury	65 (82.3%)	39 (83.0%)	.92
Patients with AKI	7 (8.9%)	13 (27.7%)	.01
Need for RRT	0 (0%)	6 (12.8%)	.002
Patients with septic episode	10 (12.7%)	18 (38.3%)	.001
Patients with MODS	3 (3.8%)	5 (10.6%)	.15
Mortality	5 (6.3%)	5 (10.6%)	.50

*AKI*, acute kidney injury; *IQR*, interquartile range; *MDRO*, multiple-drug resistant organism; *MODS*, multiple organ dysfunction syndrome; *RRT*, renal replacement therapy.

Independent samples *t*-test and Wilcoxon-Mann-Whitney tests were used to compare all continuous variables. Pearson  $\chi^2$  and Fisher's exact tests were used to compare all categorical variables.

**Table 2**

## Incidence and sites of infection

	Non-MDRO Patients (%) (n = 79)	MDRO Patients (%) (n = 47)
UTI	16 (20.2)	23 (48.9)
Lung	26 (32.9)	32 (68.1)
Blood	11 (13.9)	16 (34.0)
Skin	37 (46.6)	31 (66.0)
Catheter	0 (0)	8 (17)

*MDRO*, multiple-drug resistant organism; *UTI*, urinary tract infection. There were 110 infections in 47 MDRO patients and 100 infections in 79 non-MDRO patients for an average of 1.3 infections per non-MDRO patient and 2.3 infections per MDRO patient.

**Table 3**

Incidence of most frequently cultured Gram-positive and Gram-negative bacteria

	Non-MDRO Patients (%) (n = 79)	MDRO Patients (%) (n = 47)
Gram-positive bacteria		
<i>Staphylococcus aureus</i>	18 (22.8)	26 (55.3)
<i>Staphylococcus</i> species, coagulase negative	5 (6.3)	9 (19.1)
<i>Enterococcus</i> species	4 (5.1)	15 (31.9)
<i>Streptococcus</i> species	10 (12.7)	7 (14.9)
Gram-negative bacteria		
<i>Pseudomonas aeruginosa</i>	8 (10.1)	17 (36.1)
<i>Klebsiella pneumoniae</i>	0 (0.0)	7 (14.9)
<i>Enterobacter</i> species	1 (1.3)	9 (19.1)
<i>Acinetobacter baumannii</i>	0 (0.0)	3 (6.4)
<i>Proteus mirabilis</i>	3 (3.8)	4 (8.5)
<i>Escherichia coli</i>	9 (11.4)	14 (29.7)
<i>Morganella morganii</i>	0 (0.0)	3 (6.4)

Results are given as number of patients with a positive culture and the total percentage of these patients in the total patient population.

Table 4

## Most frequently cultured MDROs and their location

	Urine (%) (n = 22)	Lung (%) (n = 28)	Blood (%) (n = 12)	Skin (%) (n = 23)	Catheter (%) (n = 2)
Gram-positive bacteria, n (%)					
<i>Staphylococcus</i> species (including MRSA)	1 (4.6)	10 (35.7)	5 (41.7)	7 (30.4)	0 (0)
Streptococcus species	1 (4.6)	1 (3.6)	1 (8.3)	0 (0)	0 (0)
Vancomycin-resistant <i>Enterococcus</i>	1 (4.6)	0 (0)	1 (8.3)	0 (0)	0 (0)
Total gram-positive	3 (13.6)	11 (39.3)	7 (58.3)	7 (30.4)	0 (0)
Gram-negative bacteria, n (%)					
<i>Escherichia coli</i>	7 (31.8)	4 (14.2)	0 (0)	2 (8.7)	0 (0)
<i>Pseudomonas aeruginosa</i>	3 (13.6)	2 (7.1)	2 (16.7)	2 (8.7)	1 (50)
<i>Morganella morganii</i>	2 (9.2)	1 (3.6)	0 (0)	2 (8.7)	0 (0)
<i>Klebsiella pneumoniae</i>	1 (4.6)	2 (7.1)	1 (8.3)	1 (4.3)	1 (50)
<i>Acinetobacter baumannii</i>	2 (9.2)	4 (14.2)	1 (8.3)	5 (21.7)	0 (0)
<i>Enterobacter</i> species	1 (4.6)	3 (10.7)	1 (8.3)	3 (12.0)	0 (0)
Other	3 (13.6)	1 (3.6)	0 (0)	1 (4.3)	0 (0)
Total Gram-negative	19 (86.4)	17 (60.7)	5 (41.7)	16 (69.6)	2 (100)

MDRO, multiple-drug resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*.

**Table 5**

Univariable logistic regression results for patient mortality

<b>Risk Factor</b>	<b>OR (95% CI)</b>	<b>P</b>
Age	1.01 (0.99–1.04)	.32
Inhalation injury	0.83 (0.16–4.22)	.83
MDRO infection	1.76 (0.48–6.44)	.39
>20% TBSA	4.30 (1.14–16.29)	.03
AKI	10.93 (2.74–43.57)	.001
Need for RRT	7.00 (1.11–44.20)	.04
Septic episode	19.20 (3.79–97.27)	<.001
MODS	85.49 (12.97–563.28)	<.0001

95% CI, 95% confidence interval; AKI, acute kidney injury; MDRO, multiple-drug resistant organism; MODS, multiple organ dysfunction syndrome; OR, odds ratio; RRT, renal replacement therapy.

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