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Mortality incidence among critically ill burn patients infected with multidrug-resistant organisms: A retrospective cohort study

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Abstract

Introduction: Many risk factors have been reported to increase mortality among burn patients. Previously, a higher mortality incidence was reported in acute burn patients infected with multidrug-resistant organisms (MDROs) when compared to patients infected with non-MDROs. However, considering this as an independent risk factor for mortality in acute burn patients is not yet confirmed.

Methods: We conducted an observational retrospective study in Qatar. We included adult patients admitted to the surgical intensive care unit (ICU) between January 2015 and December 2017 with burn injuries involving either at least 15% of the total body surface area (TBSA) or less than 15% with facial involvement. All patients developed infection with a positive culture of either MDRO or non-MDRO. The primary outcome was in-hospital mortality. Other outcomes included days of mechanical ventilation, ICU, length of stay in hospital, and requirement of vasoactive agents.

Results: Fifty-eight patients were included in the final analysis: 33 patients in the MDRO group and 25 patients in the non-MDRO group. Six patients (18.2%) died in the MDRO group versus four patients (16%) in the non-MDRO group ($P = 1$). No significant difference was observed between the two groups with regard to the ICU length of stay. However, there was a trend towards increased median length of stay in hospital in the MDRO group: 62 days versus 45 days in the non-MDRO group ($P = 0.057$). No significant differences were observed in the other outcomes.

Conclusion: In severely burned patients, infection with MDRO was not associated with increased mortality. There was a trend towards increased hospitalisation in MDRO-infected patients. Further studies with a larger sample size are needed to confirm these results.

Keywords
Burns, multidrug resistance, infection, mortality, intensive care unit

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Lay Summary

Many factors affect mortality in burn patients admitted to the intensive care unit, such as age, total body surface area involved in the injury, and others. In this retrospective study, we evaluated whether wound infection with a bacterial organism resistant to multiple classes of antibiotics (multidrug-resistant) is considered an independent risk factor for mortality in critically ill burn patients. We included 58 patients requiring intensive care admission with burn injuries involving 15% or more of the total body surface area or less than 15% but with facial involvement. A total of 33 patients were infected with multidrug-resistant organisms (MDROs) and 25 patients with non-MDROs. Six patients (18.2%) from the MDRO group died versus four (16%) in the non-MDRO group. The MDRO group required a longer stay in hospital and an average of one more day on a mechanical ventilator. We concluded that wound infection with MDROs might not increase mortality when compared to wound infection with non-MDROs, although other studies with a larger number of patients involved need to be conducted to validate these results.

Introduction

Burns are considered one of the leading causes of accidental injuries and death worldwide.[1,2] Although most burn patients seeking medical advice do not require hospitalisation, severe burn injuries can lead to significant morbidity and mortality.[3,4]

The chances of survival after a severe burn injury significantly increased in the second half of the past century[5] due to several therapeutic developments, such as early excision and grafting,[6,7] advances in critical care nutrition[8] and the evolution of specialised burn centers.[5] Several risk factors may contribute to increasing mortality among adult burn patients, including total body surface area (TBSA) affected, old age, inhalation injury[7,9–11] and infection.[12] Burn patients are more prone to developing invasive infections secondary to the breakdown of the natural skin barrier, which may be serious enough to progress to sepsis or septic shock.[13]

In the last two decades, multidrug-resistant organisms (MDROs) have been a considerable burden for critically ill patients, secondary to the limited therapeutic options, especially for Gram-negative pathogens. MDROs are a group of organisms found to be resistant to more than one antibiotic class.[14] Common nosocomial MDROs are methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus, Pseudomonas, Acinetobacter* and extended-spectrum beta-lactam *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae*. Despite being associated with a big commitment, increasing mortality with MDROs compared to non-MDROs in critically ill patients remains controversial.[15]

In critically ill burn patients, the available data are limited. In a recent retrospective study, mortality was not higher in burn patients infected with MDRO when compared to patients infected with non-MDROs.[16] However, to the best of our knowledge, no data are available from the Middle Eastern population. The aim of the present retrospective study was to evaluate whether infection with MDROs is associated with a higher mortality incidence among critically ill burn patients in Qatar.

Methods

Patients

This was a retrospective cohort observational study conducted in the surgical intensive care unit (SICU) at Al-Wakra Hospital in Qatar. Data were collected retrospectively from electronic medical records for eligible patients admitted from January 2015 until December 2017. The inclusion criteria were: all adult patients (age > 18 years) admitted to the SICU with burn injuries had either at least 15% of TBSA or less than 15% of TBSA with facial involvement and developed infection with either MDROs or non-MDROs. We defined infection as a positive culture plus the initiation of an antimicrobial agent. MDROs are defined in Table 1. The exclusion criteria were: electrical burn injury; < 15% of TBSA without facial involvement; or burn patients with trauma requiring specialised trauma care. This study was approved by the ethical committee, Medical Research Center, Hamad Medical Corporation (No. MRC-01-18-376).

Outcomes

The primary outcome was in-hospital mortality. Other outcomes included days of mechanical ventilation, admission to the ICU, length of stay in hospital and requirement of vasoactive agents.

Table 1. Definitions of MDROs.

Organism	MDRO definition*
Staphylococcus aureus	Methicillin-resistant *S. aureus*
Acinetobacter spp.	Any *Acinetobacter spp.* that has tested as either intermediate or resistant to at least one drug in at least three of the following six categories: 1. Extended-spectrum cephalosporins (cefepime, ceftazidime, cefotaxime, ceftriaxone) 2. Fluoroquinolones (ciprofloxacin, levofloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem) 5. Piperacillin group (piperacillin, piperacillin/tazobactam) 6. Ampicillin/sulbactam
Escherichia coli	Any *E. coli* that has tested as either intermediate or resistant to at least one drug in at least three of the following five categories: 1. Extended-spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone) 2. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem, ertapenem) 5. Piperacillin group (piperacillin, piperacillin/tazobactam)
Enterobacter spp.	Any *Enterobacter spp.* that has tested either intermediate or resistant to at least one drug in at least three of the following five categories: 1. Extended-spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone) 2. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem, ertapenem) 5. Piperacillin group (piperacillin, piperacillin/tazobactam)
Klebsiella spp.	Any *Klebsiella spp.* that has tested either intermediate or resistant to at least one drug in at least three of the following five categories: 1. Extended-spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone) 2. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem, ertapenem) 5. Piperacillin group (piperacillin, piperacillin/tazobactam)
Pseudomonas aeruginosa	Any *P. aeruginosa* that has tested either intermediate or resistant to at least one drug in at least three of the following five categories: 1. Extended-spectrum cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone) 2. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) 3. Aminoglycosides (amikacin, gentamicin, tobramycin) 4. Carbapenems (imipenem, meropenem, doripenem, ertapenem) 5. Piperacillin Group (piperacillin, piperacillin/tazobactam)
Enterococcus faecium	Vancomycin-resistant *E. faecium*
Enterococcus faecalis	Vancomycin-resistant *E. faecalis*

*MDRO definitions are according to the local microbiology documents that are derived from the National Healthcare Safety Network, Centres of Disease Control and Prevention antimicrobial resistance phenotype definitions, 2015.
MDRO, multidrug-resistant organism.

Statistical analysis

Baseline characteristics and outcome data were described as the mean with standard deviation for continuous variables, the median with interquartile range for ordinal variables and frequencies with percentages for categorical variables. We compared normally distributed continuous variables using an independent t-test and compared ordinal and non-normally distributed continuous variables using

the Mann–Whitney test. For categorical variables, the chi-square test or Fisher's exact test were used according to the expected frequencies of observations.

We compared patients who an MDRO infection to those without an MDRO infection with adjustment for potential confounding variables that were selected based on the previous literature. These variables included sex, age, TBSA, inhalational injury, and sequential organ failure assessment (SOFA) score on admission. Although co-morbidities were associated with higher mortality in previous studies of burn patients, we could not adjust for them due to the infrequent number of these co-morbidities in the studied cohort. We used exact logistic regression for the comparison of mortality. First, associations of potential confounders with mortality were analysed using univariable exact logistic regression. Then, variables with $P < 0.2$ were used to adjust the association of MDRO infection with mortality. All P values were two-sided, and results of statistical tests with $P < 0.05$ were considered significant. The analysis was conducted using STATA MP version 16 for Windows.

Results

Baseline characteristics

A total of 95 patients were screened; 58 patients met the inclusion criteria, with 33 patients in the MDRO group and 25 in the non-MDRO group. Three patients had a history of hypertension before admission versus one patient in the non-MDRO group, and two patients had a history of diabetes mellitus in the MDRO group versus one patient in the non-MDRO group. Both SOFA scores and burn percentages were higher in the MDRO group. More patients in the MDRO group had skin infection as a source of infection than the non-MDRO group (90.9% vs. 76%, respectively). There was a median of two surgical debridement procedures per patient in the MDRO group versus one surgical debridement procedure per patient in the non-MDRO group. The most common culprit in both groups was *P. aeruginosa*, and the percentage of MDR pseudomonas strains was higher than the non-MDRO: 72.7% and 52%, respectively. Additionally, all the *Acinetobacter baumannii* were MDR strains (Table 2).

Outcomes

Six patients (18.2%) died in the MDRO infection group, while four patients (16%) died in the non-MDRO infections (crude odds ratio = 1.16; 95% confidence interval [CI] = 0.24–6.36; $P = 1$) as shown in Table 3. Univariable analysis showed that age, TBSA, inhalational injury and SOFA score on admission were associated with mortality at the level of significance of $P < 0.2$ (Table 4). When the association of MDRO infection with the incidence of mortality was adjusted for these four variables, the adjusted odds ratio of mortality was 0.71 (95% CI = 0.01–78.25; $P = 1$). The other clinical data of the study cohort are presented in Table 5.

Discussion

The present study evaluated the association between infection with MDR pathogens among burn patients and mortality. We found that infection with MDR pathogens is not associated with a higher incidence of mortality. Although there was a trend towards increased mortality and length of ICU stay, these results were not statistically significant.

Several risk factors are associated with increased mortality in burn patients. In a cohort of 4927 patients with burn injury admitted to Parkland Memorial Hospital burn unit, TBSA affected, presence of inhalation injury, and age above 60 years were considered independent mortality predictors. Moreover, in the same cohort, the risk of death increased two times more in middle-aged women than in men.[3] Co-morbidities such as diabetes mellitus, renal insufficiency and chronic obstructive pulmonary disease were associated with increased mortality in burn patients, especially if they had more than one co-morbidity.[4,17]

Studies have shown that burn injury is associated with a higher incidence of MDR infections.[18,19] However, the association between infections with resistant bacteria and the risk of mortality is not robust. There is conflicting evidence on whether infections caused by MDR pathogens are associated with a higher risk of mortality and morbidity.[20–24] Several studies failed to demonstrate that infections with MDR pathogens are independently associated with an increased risk of mortality.[18,25,26] However, these studies showed conflicting results about secondary clinical outcomes, such as length of hospital stay.

Theodorou et al.[26] evaluated the clinical outcomes of bacteraemia caused by MDR *P. aeruginosa* among 87 burn injury patients and found that neither mortality nor ICU length of stay was affected. This study focused only on *P. aeruginosa* and did not include other MDR pathogens.

Table 2. Baseline characteristics.

	MDROs (n = 33)	Non-MDROs (n = 25)	Overall (n = 58)
Age (years)	35.3 ± 15.28	31 ± 13.6	33.46 ± 14.7
Male sex	27 (81.8)	22 (88)	49 (84.5)
Diabetes mellitus	2 (6.1)	1 (4)	3 (5.2)
Hypertension	3 (9.1)	1 (4)	4 (6.9)
Cancer	0 (0)	1 (4)	1 (1.7)
Coronary artery disease	1 (3)	0 (0)	1 (1.7)
Respiratory disorder	1 (3)	1 (4)	2 (3.4)
PaO2/FiO2 ratio	414.47 ± 263	448 ± 257	429 ± 285.5
Platelet count (10^3/uL)	312 ± 155.9	328 ± 119.2	319.6 ± 140.3
Glasgow Coma Scale (median (IQR))	15 (0)	15 (0)	15 (0)
Bilirubin (umol/L)	21.8 ± 12.45	22.2 ± 23.89	21.98 ± 18
Creatinine (umol/L)	87.39 ± 38.4	88.12 ± 42.8	87.7 ± 39.8
Total SOFA score on admission (median (IQR))	3 (4.5)	2 (4)	3 (4.3)
Mechanism of burn			
Flame	31 (57.4)	23 (42.6)	54 (93.1)
Scald	1 (3)	2 (8)	3 (5.2)
Chemical	1 (3)	0 (0)	1 (1.7)
Burn percent (%)	52.91	43.44	48.8 ± 24.57
Inhalation injury	15 (45.5)	11 (44)	26 (44.8)
Numbers of operations/debridements (median (IQR))	2 (2)	1 (0.5)	1 (1)
Mechanical ventilation	21 (63.6)	15 (60)	36 (62.1)
Source of infection			
Burn wounds	30 (90.9)	19 (76)	49 (84.5)
Lung	0 (0)	5 (20)	5 (8.6)
Urine	3 (9.1)	1 (4)	4 (6.9)
Organisms			
Pseudomonas aeruginosa	24 (72.7)	13 (52)	37 (63.8)
Acinetobacter spp.	5 (15.2)	0 (0)	5 (8.6)
Stenotrophomonas maltophilia	1 (3)	1 (4)	2 (3.4)
Klebsiella, non-ESBL	0 (0)	3 (12)	3 (5.2)
Klebsiella, ESBL	1 (3)	0 (0)	1 (1.7)
Escherichia coli, non-ESBL	1 (3)	1 (4)	2 (3.4)
Escherichia coli, ESBL	1 (3)	0 (0)	1 (1.7)
MSSA	1 (3)	5 (20)	6 (10.3)
MRSA	5 (15.2)	0 (0)	5 (8.6)
Others	1 (3)	4 (16)	5 (8.6)

Values are given as n (%) or mean ± SD unless otherwise specified.

ESBL, extended-spectrum beta-lactamases; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SOFA, sequential organ failure assessment score.

Table 3. Primary outcome.

	MDROs (n = 33)	Non-MDROs (n = 25)	OR (95% CI)	*P* value
Mortality	6 (18.2)	4 (16)	1.16 (0.24–6.36)	1
Mortality, adjusted*			0.71 (0.01–78.25)	1

Values are given as n (%).
*Adjusted for age, total body surface area, inhalation injury and sequential organ failure assessment score on admission.
CI, confidence interval; MDRO, multidrug-resistant organism; OR, odds ratio.

Table 4. Univariable exact logistic regression analysis of predictors of mortality among the study cohort.

Outcome: mortality	OR	95% CI	*P* value
Female sex	0.56	0.11–5.2	1
Age (years)	1.03	0.99–1.08	0.129
TBSA (%)	1.05	1.02–1.08	0.002
Inhalation injury	3.48	0.69–23.47	0.159
SOFA score at admission	1.29	1.05–1.63	0.013
MDRO	1.16	0.24–6.36	1

CI, confidence interval; MDRO, multidrug-resistant organism; OR, odds ratio ; SOFA, sequential organ failure assessment; TBSA, total body surface area.

Table 5. Other clinical outcomes.

	MDROs (n = 33)	Non-MDROs (n = 25)	*P* value	Overall (n = 58)
Total SOFA score on infection	8 (7.5)	6 (7.5)	0.257	6 (8)
Days of mechanical ventilation*	4 (8)	3 (6.5)	0.521	3 (7)
ICU admission days*	12 (25)	14 (17)	0.934	12 (22)
Hospital days*	62 (48)	45 (28)	0.057	54 (50)
Vasopressor agents required (n (%))	18 (54.5)	15 (45.5)	0.272	28 (8.3)

Values are given as median (IQR) unless otherwise specified.
*Analysis done among survivals only.
ICU, intensive care unit; IQR, interquartile range; MDRO, multidrug-resistant organism; SOFA, sequential organ failure assessment.

Another study that involved burn injuries from the United States military found that bacteraemia caused by MDR pathogens was associated with higher mortality for combat operations in the univariate analysis. However, the results were no longer significant after including potential confounders in the multivariate analysis.[18] The latter two studies included bacteraemia as the sole source of infection, which limits the extrapolation of their findings to other types of infection.

Van Lngeveled et al.[16] assessed the impact of antibiotic resistance on length of stay and survival among 126 patients admitted to the burn unit and found no mortality difference between those who had MDR pathogens and those who did not. However, infections with MDR pathogens were associated with more surgical procedures, longer mechanical ventilation duration, more antibiotic exposure and longer hospital stay.

Recently, a study from sub-Saharan Africa found that colonisation with MDR *Enterobacteriaceae* is associated with an increased risk of mortality after burn injury.[27] This finding needs to be interpreted with caution, as the study groups were selected based on exploratory analysis, not as a priori. Additionally, the results were based on the presence of colonisation, not the incidence of infections.

The present study provides additional evidence that other types of infections caused by MDR pathogens, in addition to bacteraemia, may not be associated with an increased risk of mortality. In the present study, patients with MDRO infections had a more prolonged hospital stay, required more wound debridements and required longer mechanical ventilator support than the non-MDRO group. However, none of these outcomes had statistical significance. This discrepancy in the morbidity outcomes from the study by Van Lngeveled et al.[16] could be explained by the smaller sample size in our study. Theoretically, the lack of association with mortality can be explained by the fact that MDR pathogens are still treatable with some antibiotics unless the isolate is pan-resistant to all antimicrobial classes.

One of the limitations of this study is the retrospective design, which may have introduced some bias. Another limitation is the small number of observed events, as only 10 of the 58 patients in the sample were deceased, which limited the statistical power of the analysis. We tried to improve the analysis model using an exact regression model, which allowed adjusting for age, TBSA, inhalation injury and admission SOFA score. These factors were found by the univariable exact logistic regression to be an independent risk factor for mortality, as described in the methods section. It remains unclear whether the lack of association between MDR infections and mortality is true or due to the limited sample size of the study. Hence, larger studies are required to answer this question.

Conclusion

Severely burned patients with MDRO infections did not have a higher mortality risk than other infected burn patients. MDRO-infected burn patients may require longer hospitalisation and longer duration of mechanical ventilation. However, further studies and a larger sample size are needed to validate these findings.

Declaration of Conflicting Interests

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