Short Research Article

The prevalence of multi-drug resistant organisms and their outcomes in an ICU in Mauritius: an observational study

Abstract

Aims: To assess the prevalence of multi-drug resistant organisms (MDRO) in an ICU of Mauritius and determine the relationship between antibiotic resistance and mortality as well as length of stay and duration of antibiotic use.

Study design: Retrospective case control study.

Place and duration of study: This study examined the data of patients who were admitted from 2015 to 2016 at an ICU in Port Louis, Mauritius.

Methodology: 128 patients on whom cultures were ordered were included. Adjustment was performed using multivariate Cox regression and negative binomial regression.

Results: Out of 214 organisms that were isolated, 68% were an MDRO; 78% of *Enterobacteriaceae* were ESBL, 86% of *Acinetobacter* spp., 30% of *Enterobacteriaceae* and 80% of *Pseudomonas* spp. were carbapenem resistant while 53% of *Staphylococcus aureus* were MRSA. After adjustment, MDRO were linked to a non-statistically significant 13% increase in mortality (*P* = .056), a rise in hospital length of stay from 19 days to 29 days (*P* = .0013) and an escalation in duration of antibiotic use from 11 days to 24 days (*P* = 1.3E-10).

Conclusion: Infections with MDRO are common in Mauritius and strategies should be put into place to reduce their prevalence.

Keywords: *Multidrug resistant; Prevalence; Intensive care units; Mauritius; Anti-bacterial agents*

Introduction

The World Health Organization (WHO) recognizes the threats posed by multi-drug resistant organisms (MDRO) and in 2015, the World Health Assembly endorsed a global action plan to respond to antimicrobial resistance. Priority pathogens listed by the WHO that require the urgent development of new antibiotics include carbapenem resistant *Acinetobacter baumannii* (CRAB), carbapenem resistant *Pseudomonas aeruginosa* (CRP), carbapenem resistant *Enterobacteriaceae* (CRE), extended-spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL) and methicillin resistant *Staphylococcus aureus* (MRSA). This research seeks to characterize the prevalence and mortality rate of patients infected with these MDRO within the Intensive Care Unit (ICU) in an island in the Indian Ocean. To our knowledge, this is the first study in Mauritius that looks at MDRO in the ICU setting and the data should help policymakers take national decisions that will reduce the damage caused by MDRO.

Materials and Methods

This retrospective study looked at all patients aged ≥ 18 years who were admitted to the ICU at a 600-bed hospital in Mauritius from July 2015 till December 2016 and on whom cultures were ordered; the inclusion criteria also required that only organisms on which susceptibilities were done should be incorporated in the study. 128 patients were included (see Figure 1). 60 patients who harbored MDRO were the cases while 68 patients with drug-susceptible organisms or negative cultures were controls. MDRO was defined as any bacterium that demonstrated acquired resistance to at least 3 antibiotic classes.

Blood cultures were performed using the BACTEC automated blood culture system; bacteria were identified using gram stain and the Analytical Profile Index (API) system. Susceptibility testing was carried out using the Kirby Bauer method; the minimum inhibitory concentration (MIC) was determined via the E-Test and the national laboratory used an MIC threshold to identify resistance based on the Clinical & Laboratory Standards Institute (CLSI) standards.

The outcomes of interest were death, length of stay (LOS) in the hospital and the duration of antibiotic use. Survival analysis and adjustment for confounders were performed using multivariate Cox regression while negative binomial regression (NBR) was used for the other two outcomes. NBR was used instead of Cox regression to analyze length of stay since several studies have shown that the proportional hazard model has insufficient power and high prediction error with an elevated bias when comparing LOS, partly due to the highly skewed data and the heavy tail in the distribution (1-3). Other studies have found logistic regression, linear regression and NBR are good statistical techniques to examine LOS as opposed to Cox regression (4-6). The per-protocol analysis required adjustment for age, gender and Sequential Organ Failure Assessment (SOFA) score. A Bonferroni correction was utilized whereby a p-value of less than 0.0083 was considered statistically significant (0.05 divided by 6 given the possible associations with the 6 families of hypotheses linked to the variables MDRO, ESBL, CRAB, CRE, CRP and MRSA).

Time to event analysis is often performed using Cox or proportional hazards regression. This method assumes that the effects of predictor variables upon survival are constant over time. The model utilized was as follows (λ is the hazard function, t is time and β_1, β_2 and β_3 are constants):

$$\lambda(t) = \lambda_0(t)e^{\beta_1<Age>+\beta_2<SOFA>+\beta_3<Gender>}$$

NBR is commonly used to model over-dispersed count data, especially when the variance and the mean are markedly different from each other. In this study, the model for NBR was the following (μ is the mean length of stay or duration of antibiotic use and β_0, β1, β2 and β3 are constants):

$$ln(\mu) = \beta_0 + \beta_1 < Age > + \beta_2 < SOFA > + \beta_3 < Gender >$$

All statistical analyses were done using Excel version 1904 (Microsoft office 365) and R version 3.3.1. Categorical variables were compared using Fisher's exact test. Ethical approval for carrying out this study was granted by the Ethics Committee of the Ministry of Health and Wellness.

Results

Table 1 lists out the basic characteristics of the patients. While cases and controls mostly shared similar baseline characteristics, it should be noted that patients with MDRO were more likely to have Foley catheters (85% vs 69%) and central lines (62% vs 38%). There were no missing data among the included patients.

347 cultures were ordered out of which 130 (37%) were blood cultures and 117 were urine cultures (34%). 32% of patients had chest infections, 17% had skin and soft tissue infections and 14% had urogenital infections.

Of note, of 229 organisms, 79 were gram positives (34%) out of which 40 were coagulase negative staphylococcus (51%), 20 were *Enterococcus* spp. (25%) and 15 were *Staphylococcus aureus* (19%). Of the gram negatives, 37 were *Acinetobacter baumannii* (25%), 24 were *Klebsiella* spp. (16%), 23 were *Escherichia coli* (15%) and 21 were *Pseudomonas* spp. (14%).

Out of 82 organisms isolated from blood cultures, 24 were coagulase negative staphylococcus (29%), 14 were *Acinetobacter baumannii* (17%) and 10 were *Klebsiella* spp. (12%).

Of the 214 organisms that were isolated and whose susceptibilities were available, 146 (68%) were MDRO, 59 out of 76 *Enterobacteriaceae* were ESBL (78%), 32 out of 37 *Acinetobacter baumannii* were CRAB (86%), 23 out of 76 *Enterobacteriaceae* were CRE (30%), 16 out of 20 *Pseudomonas* spp. were CRP (80%) and 8 out of 15 *Staphylococcus aureus* were MRSA (53%). One *Serratia marcescens* was resistant to all antibiotics to which it was tested. 60 patients (76%) out of 79 whose cultures were positive, had an MDRO.

Adjustment using Cox regression and NBR was performed for standard healthcare variables (age and gender) and a theoretically plausible biological confounder (the SOFA score). Due to the small sample size, it was unwise to adjust for a large number of variables; furthermore, the SOFA score already incorporates multiple important data points like mechanical ventilation and kidney injury.

Unadjusted and adjusted analyses showed no association of MDRO (P = .18; adjusted P = .056), ESBL (P = .16; adjusted P = .043), CRAB (P = .50; adjusted P = .71), CRE (P = .61; adjusted P = .99), CRP (P = .89; adjusted P = .19) or MRSA (P = .89; adjusted P = .93) with mortality. The corresponding Kaplan-Meier curve is shown in figure 2. The mortality rates of patients with MDRO, ESBL, CRAB, CRE, CRP and MRSA were 72%, 67%, 87%, 80%, 83% and 60% respectively.

Regarding length of stay in the hospital, MDRO was associated with an increased duration with an adjusted p-value of 0.0013 (adjusted odds ratio (aOR) = 1.1-2.1). Antibiotic use was

increased when either MDRO or ESBL was present (adjusted *P* = 1.3E-10 with aOR = 1.7-3.0, and adjusted *P* = 2.7E-5 with aOR = 1.3-2.9 respectively).

Discussion

We deduce from this study that, in our ICU, gram negative organisms are more commonly isolated than gram positives, contaminants are frequently present in cultures, and the rate of antimicrobial resistance, in particular to carbapenems, is very elevated. Moreover, while patients infected with MDRO had a 72% chance of dying and controls had only a 59% chance of death, this 13% difference was not statistically significant. However, this study was under-powered, and a larger sample size is required to demonstrate statistical significance. Patients afflicted with MDRO stayed in the hospital longer (mean duration of 29 days vs 19 days) and used antibiotics for a longer period (mean duration of 24 days vs 11 days).

Previous authors reported rates of antimicrobial resistance within the general hospital setting in Mauritius: by 2014, the prevalence of MRSA was 39%, CRP was 40%, CRAB was 68% and CRE was only 5% (7-10). Unsurprisingly, the corresponding rates in the ICU are higher. In addition, we noted that the mortality rate of ventilated patients was very high at 86% (59 out of 69 patients died) and patients with SOFA scores greater than 3 had 85% chance of dying (66 deaths out of 78 patients), even though the analogous values in other countries are much lower at 25-28% and 27-32% respectively (11-14); figure 3 illustrates the elevated death rate using bar charts.

This study has multiple limitations including its small sample size and the fact that it is a single-center study; despite all the efforts to adjust for confounders, bias from residual confounding may still be present. Nonetheless, we performed multiple other adjustments in a post-hoc analysis – confounders were identified through the use of direct acyclic graphs, when their p-

values were less than 0.20, their change in estimate criterion was more than 10% and there were at least 10 participants per variable. Thereafter, additional adjustments were done for various types of MDRO on variables like “surgery within the past 30 days”, “peripheral arterial disease” and “diabetes mellitus”; these did not alter our findings, implying that the results are robust.

Conclusion

Proper infection prevention and control measures and antibiotic stewardship should be put in place in Mauritius in order to reduce the rate of antibiotic resistance, to ensure that less cultures are contaminated, and to ascertain that less money is wasted on prolonged hospital stay and antibiotic use. Empiric treatment of patients with septic shock in our ICU should cover carbapenem resistant organisms. The cause of high mortality rates within our ICU should be investigated in order to improve the management of sepsis and save lives. This study has implications for surrounding countries since patients who travel from our island after having been in our ICU, and who need admission in another hospital, should be considered at high risk of being colonized with MDRO, a point that was already noted by Angue et al and Holman et al (15, 16).

Disclaimer: *The opinions expressed in this publication are those of the authors. They do not purport to reflect the opinions or views of the Ministry of Health and Wellness of Mauritius.*

Consent

Patient consent was not necessary since this is a retrospective study.

Ethical approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Figure 1: Flow chart illustrating study population based on culture results

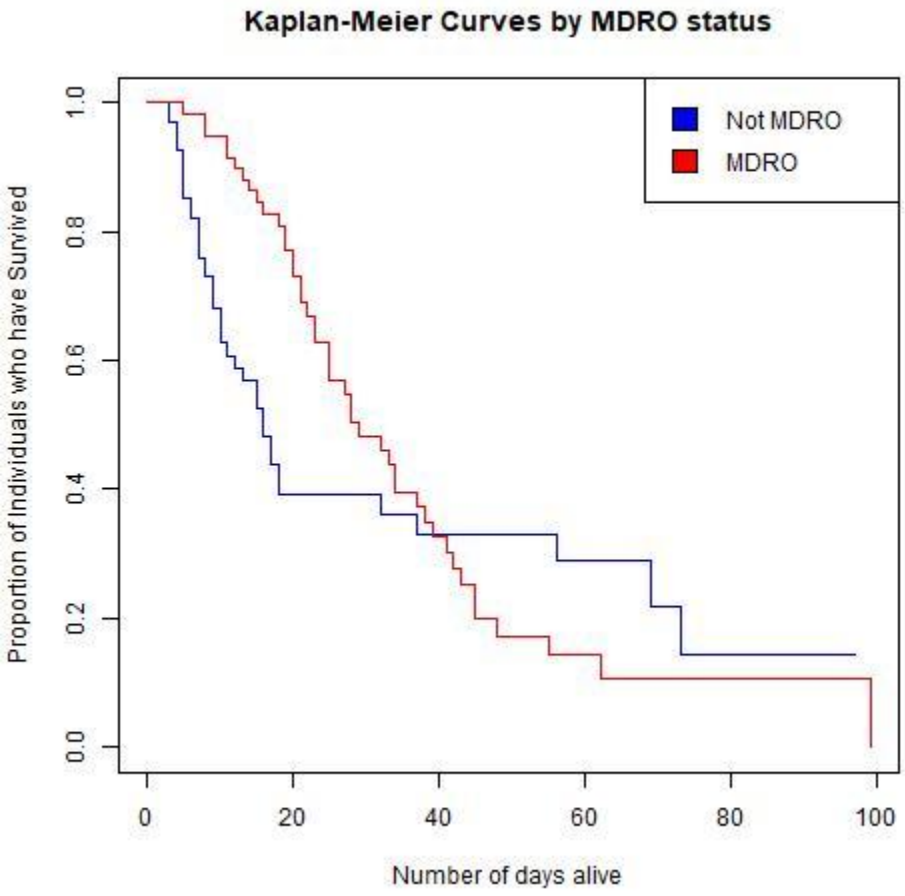

Figure 2: Survival curves of patients with and without multi-drug resistant organisms

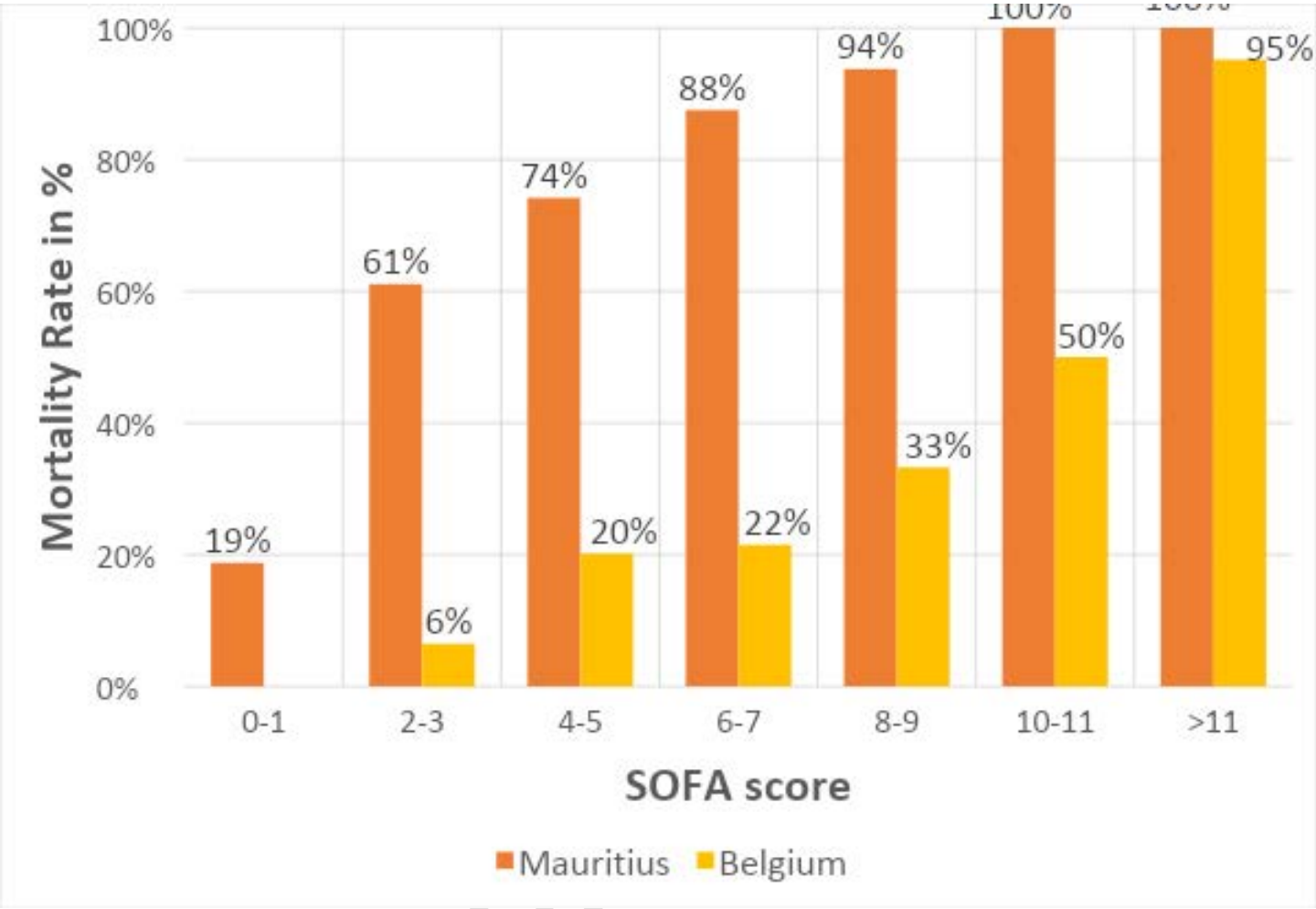

Figure 3: This bar chart compares the mortality rate adjusted by SOFA score of patients in the ICU in Mauritius and in Belgium. Data are taken from Ferreira et al. (13).

Characteristic	No. of patients with MDRO (%): N = 60	No. of controls (%): N = 68	P value
Males	38 (63%)	44 (65%)	1.0
Diabetes mellitus	34 (57%)	44 (65%)	.37
Acute renal failure	10 (17%)	10 (15%)	.81
Chronic renal failure	4 (6.7%)	8 (12%)	.38
Hemodialysis before transfer to ICU	2 (3.3%)	3 (4.4%)	1.0
Lung fibrosis	0 (0%)	3 (4.4%)	.25
COPD	0 (0%)	0 (0%)	1.0
Asthma	0 (0%)	4 (5.9%)	.12
Cirrhosis	0 (0%)	1 (1.5%)	1.0
Heart failure	1 (1.7%)	1 (1.5%)	1.0
Coronary artery disease	10 (17%)	17 (25%)	.28
Peripheral arterial disease	10 (17%)	8 (12%)	.46
Cancer	6 (10%)	7 (10%)	1.0
Mechanical ventilation	31 (52%)	38 (56%)	.72
Foley catheter	51 (85%)	47 (69%)	.039
Central line	37 (62%)	26 (38%)	.013
Hemodialysis line	4 (6.7%)	8 (12%)	.38
Arterial line	13 (22%)	8 (12%)	.16
Surgery within past 30 days	20 (33%)	13 (19%)	.073
Pressure ulcers	5 (8.3%)	6 (8.8%)	1.0
Presence of wounds	13 (22%)	7 (10%)	.091
Dementia	3 (5.0%)	1 (1.5%)	.34
Previous hospitalizations	14 (23%)	19 (28%)	.69
History of infection / colonisation with MDRO	0 (0%)	1 (1.5%)	1.0
Immunosuppressed	33 (55%)	29 (43%)	.21
Age < 60	29 (48%)	32 (47%)	1.0
SOFA ≤ 2	15 (25%)	24 (35%)	.25

Table 1: Basic characteristics of patients