JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Risk factors of multidrug-resistant bacterial infections among patients admitted in a tertiary care hospital of north India

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Abstract

Introduction: Infections with drug-resistant organisms (DRO) have been associated with poor patient outcomes. To tackle this global problem, it is necessary to understand the risk factors that predispose to infections with DRO.

Methodology: This was a prospective observational study conducted over a three-year period at a tertiary-care hospital. Bacterial culture isolates from patients admitted in medicine wards with community or hospital-acquired infections were included. Logistic regression analysis was used to determine risk factors for drug-resistant infections.

Results: Of the 295 patients with 323 isolates included, 40 (12.3%) had non-MDR (N-MDR) infections, 86 (26.6 %) had MDR infections and 197 (61%) had possible extensively drug-resistant (P-XDR) infections. History of previous admission in the preceding three months (Odds Ratio, OR = 4.53, 95% Confidence interval, CI = 1.8 – 11.42, p = -0.01), high SOFA score at admission (OR = 1.14, 95% CI = 1.0 – 1.290, p = -0.039) and prolonged duration of ventilation (OR = 1.25, 95% CI = 1.05 – 1.41, p = -0.012) were independently associated P-XDR infections when compared to patients with N-MDR.

Conclusions: High rate of multidrug-resistant infections in the studied area is alarming. In this single-centre study, we elicited various risk factors for drug-resistant bacterial infections ranging from patient characteristics to iatrogenic risk factors during the hospital stay. Infections with P-XDR and MDR isolates independently increased hospital and ICU stay duration and were associated with increased mortality.

Key words: Infectious disease; anti-microbial resistance; multidrug-resistant bacterial infection.

J Infect Dev Ctries 2021; 15(4):544-551. doi:10.3855/jidc.13963

(Received 20 September 2020 – Accepted 19 November 2020)

Introduction

The alarming rise in anti-microbial resistance (AMR) incidence is a paramount global health concern. Infections with drug-resistant organisms (DRO) have been consistently associated with poor patient outcomes. They also place a significant economic burden on the healthcare system [1,2]. To preserve the efficacy of currently available antibiotics without compromising patient care, it is necessary to understand the risk factors that predispose to infections with DRO.

Several studies from developed nations have tried to elucidate various risk factors for DRO acquisition [3,4]. Studies have shown that the risk of AMR depends on the inherent virulent potential of the microorganism, inappropriate antibiotic abuse, local environmental factors, and various patient-related factors [5]. However, due to regional differences in epidemiology, these results may not hold for developing countries like India [6]. Thus, regional and local data is essential for developing countries to understand the risk factors associated with infections due to DRO. Such data will facilitate the design and implementation of an effective anti-microbial stewardship program (ASP). It will also help select appropriate empirical antibiotic therapy in patients presenting with risk factors for infections with DRO.

This study has assessed the locally prevalent risk factors predisposing to drug-resistant infections and the clinical outcomes of patients admitted with these infections. The results of this study are intended to aid developing nations that are grappling with the problem of rising AMR by designing and implementing effective and targeted ASPs.

Methodology

Study Design

This is a prospective observational study conducted in the department of medicine at a tertiary care apex teaching institute in New Delhi, India. This study was conducted on patients admitted in the medicine wards

and intensive care unit (ICU) for 18 months after obtaining approval from the institute's ethics review board. Informed consent was taken from all participants before enrollment.

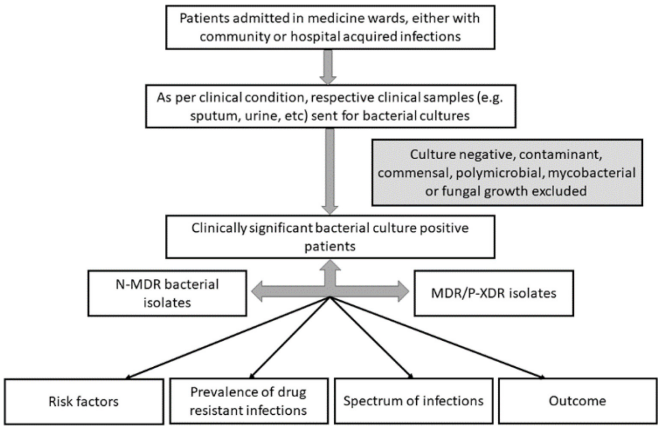
All patients admitted with a suspected infectious syndrome (community or hospital-acquired) whose body fluids were sent for microbiological cultures were assessed. Patients with any clinically significant culture growth were enrolled, and samples with at least one clinically significant culture isolate were included in the study. Clinically significant cultures were defined as microbial cultures with significant colony count as per infectious syndromes in question and without poly-microbial, contaminant, or commensal growth. Usually, a single sample was considered in each patient; however, multiple samples from the same patient were only considered from the same patient in the following scenario: 1. The samples were obtained from the same site (e.g., bronchoalveolar lavage) but with different clinical infectious episodes; 2. When samples were obtained from the same patients from two different sites (i.e. two different clinical infectious syndromes).

Cultures that showed fungal or mycobacterial growth were excluded from the study. Baseline patient data were collected from clinical records on the day of culture positivity and used for risk factor analysis. Recruited patients were followed up until discharge or death to evaluate clinical outcomes (Figure 1).

Sample collection and anti-microbial susceptibility testing

Clinically relevant samples included sputum, endotracheal aspirate, bronchoalveolar lavage, blood, urine, and other body fluids. Samples were sent to the microbiology laboratory in sterile containers, except blood, which was inoculated manually in culture bottles at the bedside. Sample processing, direct demonstration of organisms, inoculation on culture media, and identification were made per standard microbiological practices. Anti-microbial susceptibility testing was done using the disc diffusion method (Kirby-Bauer test), and interpretation was made following recent Clinical and Laboratory Standards Institute (CLSI) guidelines [7].

Figure 1. Workflow of the study.



Definitions

Various infectious syndromes were defined as per the CDC National Healthcare Safety Network surveillance guidelines, including ventilator-associated and hospital-acquired pneumonia (VAP, HAP), symptomatic and catheter-associated urinary tract infection (S-UTI, CA-UTI), primary and secondary bloodstream infections (BSI), skin/soft tissue infections (SSTI), etc. [8].

Culture isolates were then categorized based on the degree of drug resistance. A bacterial isolate was considered non-susceptible to an anti-microbial agent if tested resistant or intermediate when using clinical breakpoints as interpretive criteria, as provided by the CLSI guidelines [7]. Multi-drug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more anti-microbial categories. Pan drug resistance (PDR) was defined as non-susceptibility to all agents in all anti-microbial categories. Extensive drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer anti-microbial categories. However, in most microbiological laboratories in resource-limited settings, resistance testing is done only for commonly prescribed antibiotics. Hence, the terminology of "possible-XDR" (P-XDR) was coined. Bacterial isolates were defined as P-XDR when found resistant to most of the routinely tested classes of anti-microbials and susceptible to only one or two available categories of anti-microbials. P-XDR, however, should still be regarded as a marker of extensive resistance. All isolates which did not satisfy the criteria for MDR and P-XDR were classified as non-multidrug resistant (N-MDR) isolates (resistance to at least one agent in one or two different anti-microbial classes since the number of pan- susceptible isolates were few they were clubbed with N-MDR isolates [9].

Statistical analysis

The analysis was performed using STATA Version 12.1. Categorical variables were analyzed using the χ^2 test or Fisher's exact test and expressed as percentages. Continuous variables were analyzed using Student's t-test or Mann-Whitney U test and have been generally

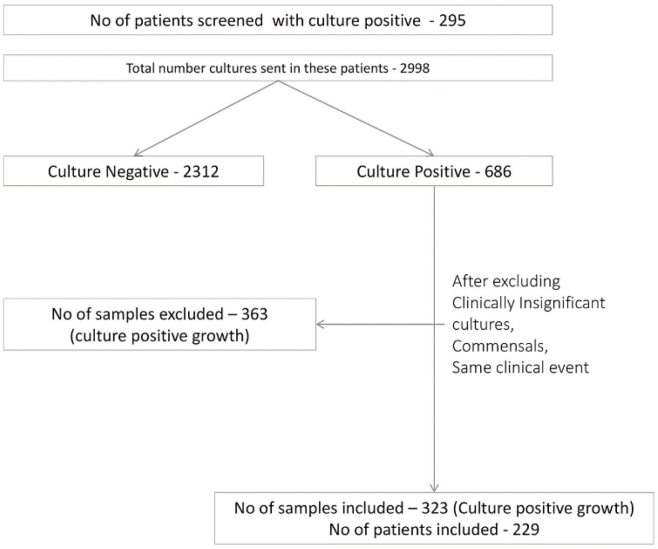
presented as means and standard deviation. Multivariate logistic regression analysis using the forward likelihood ratio selection method was done to identify independent risk factors of MDR/P-XDR infections and presented as odds ratios (95% confidence intervals, CI). All *p*-values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

During the study period, 295 patients with suspected infectious syndromes with 686 positive cultures were identified. After excluding cultures from the same clinical event as well as clinically insignificant cultures, 323 positive cultures from clinical samples belonging to 229 patients were included in the study (Figure 2).

These 323 culture isolates were further classified as per the spectrum of infections they caused and according to resistance pattern as N-MDR (40, 12.3%), MDR (86, 26.7%) P-XDR (197, 61%) (Table 1). The most common infection site with MDR and P-XDR organisms was the respiratory tract and urinary tract, respectively.

Figure 2. Flow chart showing inclusion and exclusion of culture isolates.



Patient characteristics

There was a preponderance of male patients (174, 54%) as compared to female patients (149, 46 %) included in this study. There was no significant difference in gender distribution between N-MDR,

Table 1. Classification of culture isolates from various clinical specimens based on the resistance pattern.

Resistance spectrum	Respiratory	Urinary	Blood	SSTI	Other body fluids	Total
NMDR (%)	8 (20)	11 (27.5)	12 (30)	5 (12.5)	4 (10)	40
MDR (%)	17 (20)	39 (45)	19 (22)	6 (7)	5 (6)	86
P-XDR (%)	106 (54)	28 (14)	42 (21)	9 (5)	12 (6)	197
Total (%)	131 (41)	78 (24)	73 (23)	20 (6)	21 (6)	323

Table 2. Baseline laboratory investigations on the day of culture isolation.

Baseline variable	N-MDR	MDR	P-XDR	p-value
Age	44.2 ±15.8	45.6±16.65	48.18±48.18	0.2751
Sex				
Female	14 (9.4)	45(30.2)	90(60.4)	0.188
Male	26(14.9)	41(23.6)	107(61.5)	
Hemoglobin	9.9 ± 2.7	8.74 ± 1.93	8.65 ± 2.24	0.0027
TLC	8.8 (5.3-13.7)	11.2 (7.56 -16.28)	13 (8.51-18.8)	0.0210
Platelet	156.5(99-223)	168(90 -258)	141(71 – 217)	0.0934
Urea	48(5.5-108)	62(26 -131)	89 (45 -155)	0.0032
Creatinine	1.15(0.9-3)	1.15(0.6 -3.7)	2.1(0.9 – 5)	0.0181
Bilirubin	0.5(0.3-0.8)	0.5 (0.4 -1)	0.6 (0.4 -1.2)	0.0490
Total protein	5.9 ± 1	5.99 ± 1.07	5.67 ± .85	0.022
Albumin	2.9 ± 0.8	2.63 ± 0.58	2.54 ±0.614	0.0025
AST	32 (20.5–65)	32.5(21-58)	44 (6 -27)	0.0244
ALT	32.5 (16–54.5)	20.5 (12 -43)	24 (11 -52)	0.3870
ALP	242.5 (194–309)	285(211- 444)	334(211-624)	0.0089

Parametric data has been expressed as mean ± standard deviation and non-parametric data as median (inter quartile range). TLC: Total leukocyte count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; N-MDR: Non-multidrug resistant; MDR: Multidrug resistant; P-XDR: Possibly extensively drug resistant.

MDR, and P-XDR groups. Most patients were found to be middle-aged with a mean age of 46 ± 17 years, whereas patients with P-XDR (48.18 ± 18.18) infections were slightly older than other groups, but this was not statistically significant. The baseline laboratory parameters of patients belonging to the three groups corresponding to the day of culture isolation have been shown in Table 2. Patients who had significant anaemia, leukocytosis, renal/hepatic dysfunction, and hypo-albuminemia had a higher risk of getting P-XDR than patients in the MDR and N-MDR groups.

Previous hospital stay

Univariate analysis showed that previous hospital admission within the three months, previous ICU admission, and previous intravenous antibiotic usage were significantly associated with P-XDR and MDR isolates compared with N-MDR isolates, whereas the duration of PHS did not (Table 3). The presence of co-morbidities and as well composite co-morbidity index like Charlson's co-morbidity index (CCI) did not significantly correlate with the occurrence of MDR, P-XDR compared to NMDR. Sick patients at admission with high clinical severity scores (APACHE II, SOFA)

Table 3. Univariate analysis of various risk factors for acquiring infection with MDR or P- XDR organism.

Risk Factors	N-MDR	MDR	P – XDR	p value
PHS				
PHS within three months	10 (6.2)	39 (24.2)	112 (69.6)	0.001
Duration of PHS	5 (3 -15)	7 (3 -14)	10 (4 -17)	0.3595
Previous ICU stay	2 (2.9)	16 (22.5)	53 (74.6)	0.006
Previous IV antibiotic use	6 (4.9)	25 (20.3)	92 (74.8)	0.0001
Referred from other hospitals	7 (6.8)	25 (24.3)	71 (68.9)	0.05
Co-morbidities				
DM	13 (11.7)	28 (25.2)	70 (63.1)	0.858
CKD	7 (8.1)	24 (27.9)	55 (64.0)	0.378
Outside dialysis	2 (5.6)	10 (27.8)	24 (66.6)	0.415
CVA	5 (11.1)	7 (15.6)	33 (73.3)	0.147
CLD	3 (8.11)	12 (32.4)	22 (59.5)	0.601
PLHIV	1 (16.7)	2 (33.3)	3 (50.0)	0.579
Immunosuppressive agent	7 (14.9)	12 (25.5)	28 (59.6)	0.851
Malignancy	4 (21.0)	7 (36.8)	8 (42.1)	0.151
CAD	4 (11.8)	5 (14.7)	25(73.5)	0.236
OAD	5 (13.5)	7 (18.9)	25 (67.6)	0.530
CCI (P25 – P 75)	2 (0-4)	3 (1-6)	4 (1-5)	0.2624
At admission				
APACHE II score	11.5 (3-21.5)	14 (9-21)	20 (15-27)	0.0001
SOFA Score	2 (0.5 -6.5)	4 (2-8)	6 (4-9)	0.0001
Shock at admission	36 (13.6)	77 (29.1)	152 (57.3)	0.018
During hospital stay				
More than 3 Antibiotic use for 48 hours	3 (3.0)	21 (21.2)	75 (75.8)	<0.0001
Antifungal use	3 (12.0)	5 (20.0)	17 (68.0)	0.754
ATT	2 (5.7)	11 (31.4)	22 (62.9)	0.441
Surgery	1 (4.8)	4 (19.1)	16 (76.2)	0.402
CPR	0 (0)	3 (15)	17 (85)	0.059
Re intubation	1 (7.1)	2 (14.3)	11 (78.6)	0.521
AKI	19 (9.1)	48 (23)	142 (67.9)	0.002
Dialysis	8 (7.5)	22 (20.6)	77 (72)	0.014
Duration of hospital stay/invasive catheters				
Hospital stay (in days)	2 (1- 4.5)	6 (2 -13)	8 (4 -14)	0.0001
ICU stay (in days)	0	0 (0-2)	3 (0-8)	0.0001
Ventilator stay (in days)	0 (0-2)	0 (0-6)	5 (2 -9)	0.0001
Central line in situ (in days)	0 (0 -1)	2 (0-7)	6 (2 -12)	0.0001
Urinary catheter in situ (in days)	0.5 (0-2)	4 (1-12)	8 (4 -13)	0.0001

Categorical variables are shown as frequency and row percentage, continuous variable are shown in median and IQR. N-MDR: Non-multidrug resistant; MDR: Multidrug resistant; P-XDR: Possibly extensively drug resistant; PHS: Previous hospital stay; ICU: Intensive care unit; IV: Intravenous; DM: Diabetes mellitus; CKD: Chronic kidney disease; CAD: Coronary artery disease; CLD: Chronic liver disease; PLHIV: Person living with HIV; OAD: Obstructive airway disease; CCI: Charleston comorbidity index; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; ATT: Anti-tubercular therapy; CPR: Cardiopulmonary resuscitation; AKI: Acute kidney injury.

and presence of shock at admission were more likely to have drug-resistant infections (Table 3).

Current hospital stay

Patients with acute kidney injury, undergoing renal replacement therapy, prolonged hospital stay/ICU stay, prolonged mechanical ventilation and prolonged duration of in-situ central venous catheters and urinary catheters had a significantly increased risk of infection with an MDR or P-XDR isolate ($p < 0.05$, Table 3).

Multivariate analysis of risk factors

The multi-nominal regression analysis showed that those who had P-XDR infections were more likely to have a previous admission in another hospital in the preceding three months (Odds ratio, OR = 4.53, 95% CI = 1.8 – 11.42, p = -0.01) and prolonged ventilator days duration (OR = 1.25, 95% CI = 1.05 – 1.41, p = 0.012) (Table 4).

Outcome analysis

Patients with P-XDR isolates require prolonged mechanical ventilation and ICU stay compared to patients with N-MDR and MDR isolates, as shown in Table 5. Also, patients with P-XDR isolates were more likely to die early, when compared with N-MDR and MDR patients. Logistic regression analysis with adjustment for significant confounders showed that duration of ICU stay and hospital stay was increased by 1.15 times (95% CI = -3.34 – 5.65, $p > 0.05$) and 8.09 times (95% CI = 0.1 – 16.07, $p < 0.05$) respectively in patients with MDR isolates as compared to those with N-MDR isolates, as shown in Table 6. Among patients with P-XDR infections, the total duration of ICU stay and hospital stay was increased by 6.87 times (95% CI = -2.79 – 10.9, p = 0.01) and 8.4 times (95% CI = 1.17 – 15.64, p = 0.023), respectively in patients with P-XDR isolates as compared to those with N-MDR isolates. Coefficient regression analysis showed mortality is 1.31 ($p < 0.05$) times higher with MDR and

Table 4. Multi nominal regression analysis of various risk factors for acquisition of infection with MDR or P- XDR organisms.

Risk factors	MDR		P-XDR	
	OR (95% CI)	p value	OR (95% CI)	p value
PHS in past 3 months	2.07(0.7, 5.4)	0.141	4.53(1.8,11.42)	0.001
SOFA score	0.97 (0.85,1.10)	0.664	1.14(1.0, 1.290)	0.039
Anemia	6.18(2.19, 17.43)	0.001	2.41(0.96, 6.06)	0.06
More than 3 antibiotics for 48 hours in current hospital stay	1.81(0.45,7.26)	0.398	3.3(0.87,12.77)	0.078
Ventilator stay (in days)	1.21(1.01,1.45)	0.032	1.25(1.05,1.41)	0.012

N-MDR: Non-multidrug resistant; MDR: Multidrug resistant; P-XDR: Possibly extensively drug resistant; RRR: Relative risk ratio; CI: Confidence interval; PHS: Previous hospital stay; SOFA: Sequential organ failure assessment.

Table 5. Comparison of outcome parameters among patients with NMDR, MDR, P-XDR isolates.

Outcome parameters	N-MDR	MDR	P- XDR	Overall P-value
Duration of hospital stay (days)	10 (6-15.5)	17 (9-23)	9 (2-17)	0.0001
Duration of ICU stay (days)	0 (0)	0 (0-8)	8 (0-20)	0.0001
Ventilator stay (days)	0 (0-4)	4 (0-13)	8 (0-19)	0.0001
Discharge	25 (62.5)	48 (55.8)	55 (27.9)	
Death	15 (37.5)	38 (42.4)	142 (72.1)	0.001

Parametric data has been summarized as mean ± standard deviation and non-parametric data as median (interquartile range). N-MDR: Non-multidrug resistant; MDR: Multidrug resistant; P-XDR: Possibly extensively drug resistant.

Table 6. Multi nominal regression analysis of outcome parameters in patients with MDR, P-XDR compared with NMDR infections.

Risk factors	MDR		P- XDR	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Duration of ICU Stay (in days)	1.15 (-3.34 – 5.65)	0.614	6.87 (2.79 – 10.9)	0.001
Duration of hospital stay (in days)	8.09 (0.1 – 16.07)	0.047	8.4 (1.17 – 15.64)	0.023
Death	1.31 (0.6 – 2.84)	0.480	4.3 (2.11 – 8.7)	0.0001

4.3 ($p < 0.05$) times higher with P-XDR isolates compared with patients with NMDR isolates.

Discussion

This large, prospective observational study of hospitalized patients with culture-proven infections was designed to identify risk factors for drug resistance in a developing country where such data has been historically sparse. In this present study, drug-resistant bacterial infections were classified as N-MDR, MDR, P-XDR, of which N-MDR culture isolates constituted only 12% of all culture isolates. Such a small proportion of isolates that were drug-sensitive/ resistant to less than two anti-microbial isolates are reflective of the current burden of AMR being faced in tertiary care hospitals [10,11].

Previous publications have implicated male gender and advanced age as risk factors for drug-resistant bacterial infections [12,13]. Although there is a similar trend, this association was not significant in our study. Similarly, various comorbidities are risk factors in other studies. Co-morbidities prolong the duration of hospital stay, thus increasing the period of exposure to drug-resistant flora. They also impair patients' defences and render them more susceptible to infections [3]. However, neither individual's co-morbid illness nor the Charlson Comorbidity Index was found to increase risk in this study [14]. This could be because the severity of acute illness and adequate treatment of comorbid conditions during the hospital stay may have nullified any association with the risk of drug-resistant infections.

Various guidelines recommend considering the history of previous hospital stay (PH) and prior antibiotic exposure when selecting appropriate empirical anti-microbial therapy [4,15]. Commensal floras in hospitals face constant selection pressure due to the use of broad-spectrum antibiotics. These selected drug-resistant organisms colonize and ultimately cause infections in susceptible hosts with impaired defences [16–18]. Thus, patients referred from other hospitals or have had recent hospital or ICU stay are more likely to harbour drug-resistant organisms requiring higher antibiotics at the outset. A similar association was apparent in this current study between PHS history for more than 48 hours within the preceding three months, the previous ICU stays, and previous intravenous antibiotic use with an increased risk of acquiring infections with MDR and P-XDR organisms. Among these, the history of PHS within the preceding three months was an independent risk factor for acquiring P-XDR infections compared to N-MDR infections (OR = 4.5, 95% CI = 1.8 – 11.42, p = -0.001).

Patients who are critically ill are highly susceptible to infections because of exposure to invasive procedures that compromise the anatomical barriers/defences, impairment of protective mechanisms such as airway protective reflex or gastric acid by sedative drugs or stress-ulcer prophylaxis and the frequent impairment of the immune response induced by trauma, surgery, and sepsis [19]. Further, these procedures and invasive lines disrupt the local protective immunity and allow pathogens to form bio-films into which antibiotic penetration is poor, leading to organisms' exposure to sub-therapeutic concentrations of antibiotics and selection of drug-resistant strains [20].

Our study found that patients who were sicker at admission were more likely to get infections with DRO, including those with shock, acute kidney injury, and higher clinical severity scores (APACHE II and SOFA). This is consistent with other published studies and supports higher antibiotics in sicker patients [21,22]. The risk of drug-resistant infections was found to increase in our study with invasive procedures during hospital stays like mechanical ventilation, urinary catheterization, and central venous catheter insertion. This association has been observed in previously published studies [23, 24]. This association reiterates the need to prevent VAP, CLABSI, and CAUTI by applying appropriate care bundles. Our study showed that only mechanical ventilation was independently associated with both MDR (RR = 1.21, 95% CI = 1.01 – 1.45, p = -0.032) and P-XDR (OR = 1.25, 95% CI = 1.05 – 1.41, p = -0.012) infections compared to N-MDR infections.

Infections with DRO are associated with increased mortality and morbidity in hospitalized patients in other studies [25]. We showed that mortality was significantly higher among patients with P-XDR infections (72%) as compared to MDR (42.4%) and N-MDR infections (37.5%). This may explain the shorter hospital stay duration (9 days in PXDR vs 10 days in NMDR) and the longer duration of ICU stay seen in patients with P-XDR infections. Logistic regression analysis showed that P-XDR infections increased mortality by 4.3 times (OR = 4.3, 95 % CI = 2.11 – 8.7, p = -0.0001) compared to N-MDR infections. However, the individual impact of isolation of a drug-resistant organism on mortality is difficult to accurately determine as patients with P-XDR isolates were critically ill, and their poor outcome may be attributable to other coexistent factors.

Our study has several significant limitations. Firstly, the risk factors selected for the study may not account for other unknown variables that may influence the risk of a drug-resistant infection. Secondly, antibiotic sensitivity testing in our laboratory was done by the disc diffusion method, whereas the broth dilution method is recommended. Thirdly, our study did not consider the choice and dose of antibiotics when considering the role of previous antibiotic exposure in the acquisition of drug-resistant infections. Finally, as per institutional policy, only antibiotics that are used in routine clinical practice were tested for sensitivity in culture isolates. Therefore, sensitivity testing for antibiotics from every class could not be done, thus preventing culture isolates from being classified as XDR or PDR. However, P-XDR was intended to describe culture isolates with drug resistance beyond what is considered MDR and should be considered a marker of extensive resistance.

Conclusions

This study has shown AMR's threat in patients with infectious syndromes in a developing country and its impact on patient outcomes. We identified the risk factors that could independently predict the acquisition of P-XDR infections that may help in early stratification/identification of patients and subsequent early initiation of antibiotics. The conclusions drawn from this robust dataset may provide the basis for future interventions to reduce AMR's burden by effective ASP.

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Conflict of interests: No conflict of interests is declared.