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RESEARCH ARTICLE

Magnitude and outcomes of lower respiratory tract infections attributed to multi-drug resistant bacteria among critically ill patients at a tertiary center in Jordan.

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ABSTRACT

Objectives: Lower respiratory tract infections related to multidrug-resistant organisms carry a significant morbidity and mortality. In this study we are trying to find the magnitude of this problem among intensive care unit patients admitted to a tertiary university hospital in Jordan and highlight potential associated factors.

Methods: We conducted an observational retrospective study in which we reviewed respiratory and blood cultures of all patients treated in the intensive care unit for a lower respiratory tract infection between January 1, 2021, and October 1, 2022. We investigated all culture positive cases, we investigated the prevalence of multi-drug resistant organisms among culture positive cases, predominating organisms, and compared different groups to look for potential associations and outcomes related to multidrug-resistant organisms.

Results: Out of the 563 patients with lower respiratory tract infections, 208 (37%) were culture positive. A multi-drug resistant organism was isolated from around 81% of the cases (168 out of the 208 patients with positive culture). Multi-drug resistant Acinetobacter baumanii was the predominating organism (isolated from 106 patients, 51% of the culture positive study population and 63% of the MDRO sub-population). The presence of a multi-drug resistant organism was significantly associated with the diagnosis of hospital-acquired pneumonia (P <0.01), use of mechanical ventilation (P <0.01), increased length of hospital stays (P 0.02), and was associated with increased mortality (P <0.01). A. baumannii was also significantly associated with the diagnosis of hospital-acquired pneumonia (P <0.01), use of mechanical ventilation (P <0.01), and increased mortality (P <0.01). Those associations were still significant after conducting multivariate logistic regression.

Conclusions: Our study revealed a significantly high prevalence of multi-drug resistant organism in lower respiratory tract infections among intensive care unit patients at a tertiary center in Jordan. Multi-drug resistant A. baumannii was the most frequently isolated pathogen. It was significantly associated with the diagnosis of hospital-acquired pneumonia, use of mechanical ventilation, and increased mortality. Those findings are alarming and signal the urgent need for implementation of effective infection prevention mechanisms and improved antimicrobial stewardship programs.

Keywords: Multidrug-resistant organism (MDRO), Lower respiratory tract infection (LRTI), Acinetobacter baumannii, Hospital acquired pneumonia (HAP).

Introduction

Infections related to multi-drug resistant organisms (MDRO) have become an emerging health concern as the number of infections related to MDRO have been on the rise in healthcare facilities across the world [1, 2]. The definition of multi-drug resistant organism (MDRO) depends on the organism in question, but it generally refers to an organism that is non-susceptible to traditional anti-microbials [3]. Resistance to the traditional first line antimicrobial drugs along with the potential lack of effective alternatives poses a major challenge for hospitals and long-term care facilities, especially in developing countries, as it creates pressure on the resources of the health care facilities, which are already struggling after the COVID-19 pandemic. Intensive care unit patients are at increased risk for contracting multi-drug resistant organisms (MDROs), lower respiratory tract infections (LRTIs) are the most common nosocomial infection in intensive care units and one of the leading causes for prolonging the stay [4]. Contracting multi-drug resistant organism (MDRO) in this subset population will only complicate the picture, as the delay in initiating appropriate treatment is associated with increased risk of morbidity and mortality [5].

Acinetobacter baumannii is an opportunistic bacterial pathogen primarily associated with hospital-acquired infections, it is commonly linked to aquatic environments, and as a pathogen, A. baumannii specifically targets moist tissues such as mucous membranes [6, 7]. It can form biofilms on the surface of the endotracheal tubes [8, 9, 10] and poses a significant risk for patients requiring mechanical ventilation in the intensive care unit settings [11]. Acinetobacter baumannii is one of the organisms that has the potential to develop extensive antibiotic resistance [12]. In fact, Multidrug-resistant (MDR) Acinetobacter baumannii infections are considered as emerging nosocomial infections particularly in patients hospitalized in intensive care units [13, 14, 15, 16]. The organism was designated as a "red alert" human pathogen [17] especially in developing countries in South America, Asia, and the Middle East [18]. MDR A. baumannii is defined by non-susceptibility to at least one agent in at least three antimicrobial classes [3, 19]. LRTIs related to *A. baumannii* have been associated with increased mortality [20, 21, 22].

The scope of LRTI related to MDRO among ICU patients is not well known in Jordan. To our knowledge, no previous studies were conducted to study this phenomenon and better understand the risk factors behind increasing rates of MDRO in LRTIs, especially those related to A. baumannii, along with the outcomes related to those infections.

In this study we are trying to describe the magnitude, characteristics, and outcomes of respiratory tract infections (LRTIs) related to multi-drug resistant organisms (MDROs), especially A. baumannii, at a tertiary hospital intensive care unit in Jordan.

Methods

STUDY, DESIGN, SETTINGS, AND PARTICIPANTS.

This is an observational, retrospective cohort study at a tertiary university hospital in Jordan. The study was approved by the Research Committee and Deanship of Research at Jordan University of Science and Technology (Proposal Number: 518-2022). Medical records of all patients admitted to the medical intensive care unit with lower respiratory tract infection (LRTI) between January 1, 2021, and October 1, 2022, were investigated. All patients with positive respiratory cultures or blood cultures were included. Inclusion criteria were age of 16 years or above, diagnosis of lower respiratory tract infection (LRTI), need for intensive care unit stay, and microbiological diagnosis with positive respiratory culture, blood culture, or both. Diagnosis of lower respiratory tract infection (LRTI) was based on treating physician clinical judgment with compatible radiological features.

Regarding multi-drug resistant organism (MDRO) definitions. We adopted the definitions outlined by the Centers for Disease Control and Prevention's National Healthcare Safety (CDC's NHSN) [3, 19].

- Carbamepenase positive Enterobacteriaceae (CRE): Any Enterobacteriaceae spp. testing resistant to any carbapenem using the current the Clinical and Laboratory Standards Institute (CLSI) breakpoints; or by a positive result for any Food and Drug Administration (FDA) approved method for carapenemase detection.
- Extended-spectrum beta-lactamase (ESBL): Enterobacteriaceae spp. non-susceptible to ceftazidime, cefepime, ceftriaxone, or cefotaxime.
- Multi-drug resistant (MDR) Acinetobacter: Non-susceptibility to at least one agent in at least three antimicrobial classes.
- Multi-drug resistant (MDR) Pseudomonas: Non-susceptibility to at least one agent in at least three antimicrobial classes.
- Multi-drug resistant (MDR) Stenotrophomonas: Non-susceptibility to at least one agent in at least three antimicrobial classes.
- Methicillin Resistant Staphylococcus Aureus (MRSA): oxacillin-resistant, ceoxitin-resistant, or methicillin-resistant by standard susceptibility testing methods.

DATA COLLECTION

Demographic data including sex, age, and baseline characteristics such as body mass index (BMI) and co-morbid conditions of diabetes mellitus (DM), congestive heart failure (CHF), hypertension (HTN), coronary artery disease (CAD), chronic kidney disease (CKD), history of hospital admission within the last 90 days, and history of COVID-19 infection within the last 90 days were collected. Clinical data regarding onset of pneumonia after admission to the hospital, source of positive culture, type of bacteria isolated and its antimicrobial susceptibilities, need for mechanical ventilation, length of hospital stay after lower respiratory tract infection (LRTI) diagnosis, and the outcome on discharge (survival versus death) were also collected.

STATISTICAL ANALYSIS

Statistical analysis was performed on SPSS (Statistical Package for the Social Sciences) version 12.0. Descriptive statistics were reported as frequencies with percentages for categorical variables like gender, prior hospitalization, etc., and mean ± SD (standard deviation)

for continuous variables like age, body mass index BMI, length of stay. Categorical variables were analyzed using the Chi-Square test, and the T test was used for continuous variables. P-value ≤0.05 was considered significant. A multiple logistic regression analysis was conducted to identify the variables that are independently associated with MDRO and MDR A. baumannii. The magnitude of association was also described by Wald test and 95% confidence intervals (CIs).

Results

A total of 563 patients were admitted to intensive care unit (ICU) with pneumonia during this 16-month period. Patients' respiratory and blood cultures were reviewed.

Out of the 563 patients diagnosed with lower respiratory tract infection (LRTI), 208 (37%) had either a positive respiratory culture, blood culture or both. 168 patients (80.8%) had positive respiratory culture, and 67 patients (32.2%) had positive blood culture. 27 patients (13%) had both positive respiratory and blood cultures.

The bacteria isolated were:

- Acinetobacter baumanii in 112 cultures
- Staphylococcus aureus in 35 cultures
- Pseudomonas aeruginosa in 32 cultures
- Klebsiella Pneumoniae in 28 cultures
- Escherichia coli in 11 cultures
- Serratia marcescens in 4 cultures
- Stenotrophomonas maltophilia in 3 cultures
- Haemophiles influenza in 2 cultures
- Mycobacteria tuberculosis in 2 cultures
- Others: 6 (one culture of each of Enterobacter cloacae, Achromobacter species, actinomyces species, Exophiala species, Raoultella species, and Apergillus species).

Figure 1 shows the proportions of non-MDRO to MDRO from blood culture isolates, while figure 2 shows those proportions from respiratory culture isolates.

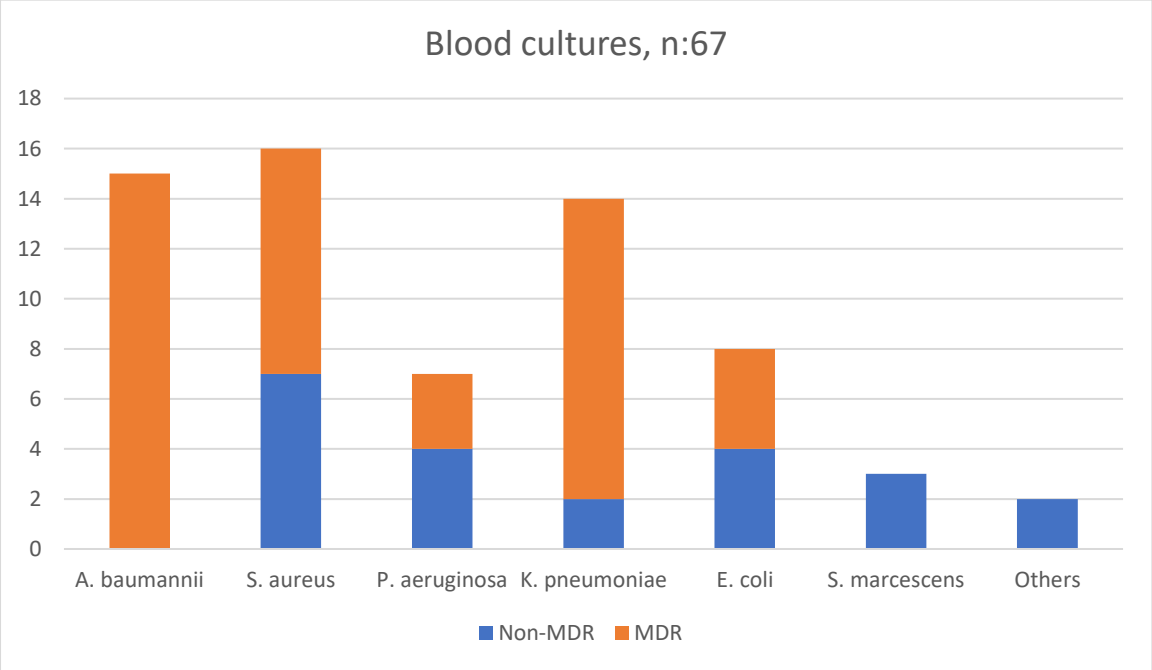

Figure 1, blood cultures isolates.

The proportion of MDRO to non-MDRO isolates from each bacterial species was highlighted by the proportion of the orange color to the blue color of each bar.

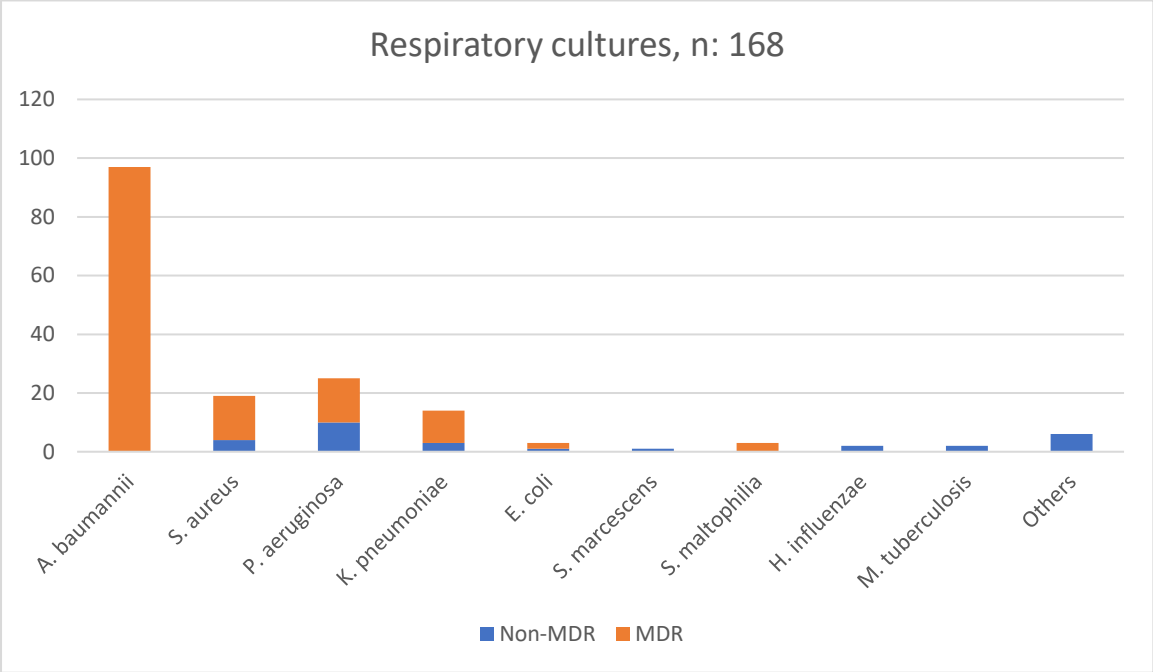

Figure 2, respiratory cultures isolates.

Out of the 208 patients with positive cultures, 168 had multi-drug resistant organism MDRO (around 81%).
The order of multi-drug resistant (MDR) bacterial species identified as the primary pathogen for LRTI were:

- Multi-drug resistant (MDR) Acinetobacter baumannii: isolated from 106 patients (Sputum: 97, blood: 15, both: 6).
- Methicillin resistant Staphylococcus aureus (MRSA): isolated from 24 patients.
- Carbamepenase positive Enterobacteriaceae (CRE) Klebsiella pneumonia: isolated from 22 patients.
- Multi-drug resistant (MDR Pseudomonas aeruginosa: isolated from 12 patients.
- Extended-spectrum beta-lactamase (ESBL) Escherichia coli: isolated from 5 patients.
- Multi-drug resistant (MDR) Stenotrophomonas maltophilia: isolated from 3 patients.
- Extended-spectrum beta-lactamase (ESBL) Klebsiella pneumonia: isolated in 2 patients.

Of note, different MDR organisms were isolated from blood and respiratory cultures in 6 of the study group.
Figure 3 shows the proportions of LRTIs attributed to each multi-drug resistant pathogen.

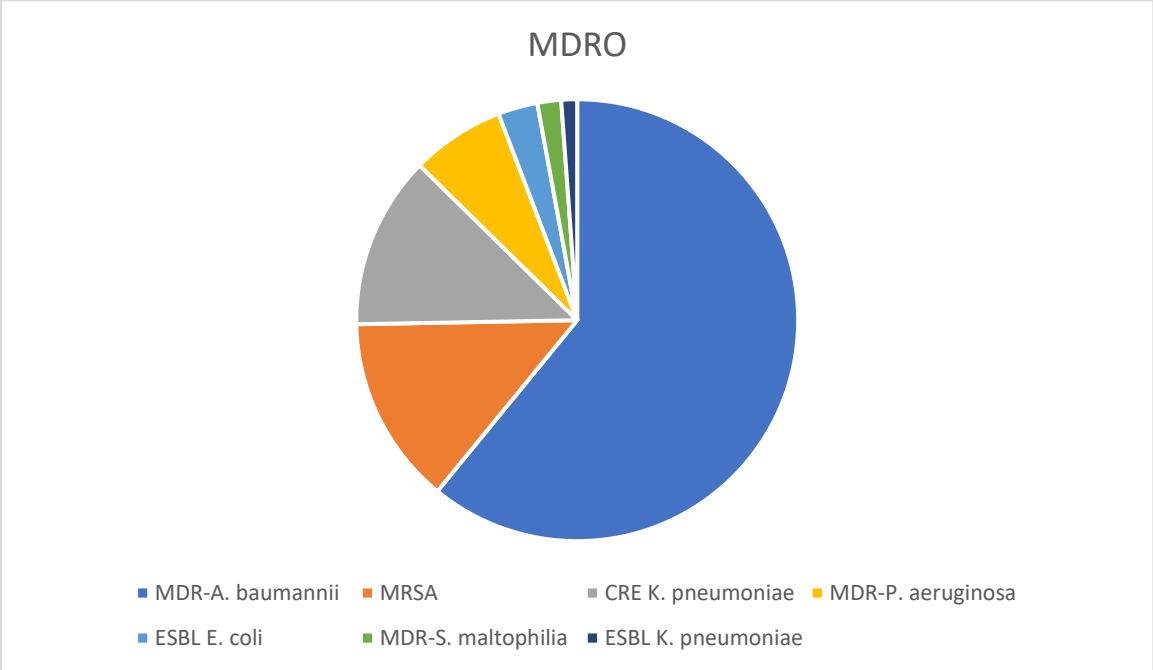

Figure 3, proportions of LRTIs attributed to each multi-drug resistant pathogen.

What striking was that patients with MDR-Acinetobacter accounted for 51% of the culture positive study population and 63% of the patient population with MDRO.

Table 1 shows the characteristics of the study population and compares the group with MDRO to non-MDRO group.

Table 1, characteristics of the study population, MDRO group, and non-MDRO group.

Characteristics	Total	Groups		P
		MDRO	*Non-MDRO*	
	208	168 (80.8%)	40 (19.2%)	
Male sex	136 (65.4%)	112 (66.7%)	24 (60%)	0.462
Age	62.35 (+- 17.66)	62.51 (+- 18.06)	61.65 (+- 16.07)	0.782
Body mass index (BMI)	27.13 (+- 6.88)	27.15 (+- 6.66)	27.03 (+- 7.82)	0.915
Hypertension (HTN)	123 (59.1%)	101 (60.1%)	22 (55%)	0.594
Diabetes mellitus (DM)	90 (43.3%)	76 (45.2%)	14 (35%)	0.288
Coronary artery disease (CAD)	60 (28.8%)	46 (27.4%)	14 (35%)	0.338
Congestive heart failure (CHF)	47 (22.6%)	41 (24.4%)	6 (15%)	0.292
Chronic kidney disease (CKD)	45 (21.6%)	37 (22%)	8 (20%)	1.000
Recent COVID	39 (18.8%)	33 (19.6%)	6 (15%)	0.653
Hospital acquired pneumonia	55 (26.4%)	52 (31%)	3 (7.5%)	0.002
Healthcare associated pneumonia	81 (38.9%)	64 (38.1%)	17 (42.5%)	0.719
Need for mechanical ventilation	151 (72.6%)	133 (79.2%)	18 (45%)	<0.001
Length of stay	21.90 (+- 22.07)	23.68 (+- 23.13)	14.45 (+- 14.97)	0.017
Outcome (Death)	148 (71.2%)	130 (77.4%)	18 (45%)	<0.001

The total group of culture positive lower respiratory tract infections (LRTIs) constitutes of 208 patients, 65.4% (136 patients) were males, mean age was 62.4 years (SD 17.7), Body mass index (BMI) 27.1 kg/m2 (SD 6.9). Co-morbidities in descending order were hypertension (HTN) 123 patients (59.1%), diabetes mellitus (DM) 90 patients (43.3%), coronary artery disease (CAD) 60 patients (28.8%), congestive heart failure (CHF) 47 patients (22.6%), and chronic kidney disease (CKD) 45 (21.6%). Only 39 patients (18.8%) had COVID-19 positive test over the past 3 months. 55 patients (26.4%) developed pneumonia after 48 hours of hospital admission and were considered hospital acquired pneumonia (HAP), and 81 patients (38.9%) had recent admission, over past 3 months, and were considered healthcare associated pneumonia (HCAP). The rest, 72 patients (34.6%) were community acquired pneumonia (CAP). 72.6% of the study population, 151 patients, required mechanical ventilation (MV). The study population had relatively prolonged hospital stay, 21.9 days (SD 22.1), and had a poor outcome with mortality rate of 71.2% (only 60 patients out of the 208 patients were able to make it out of the hospital alive).

MDRO Group Versus Non-MDRO Group

Patients with LRTI related to MDR organism were more likely to have hospital acquired pneumonia (31% vs. 7.5%, P: 0.002), need for mechanical ventilation (79.2% vs. 45%, P:<0.001), longer hospital stay (mean of 23.7 days vs. 14.5 days, P: 0.017), and mortality (77.4% vs. 45%, P: <0.001).

There was no statistical difference between the two groups regarding the gender, age, BMI, recent COVID infection, HCAP, and co-morbid conditions of HTN, DM, CHF, CAD, and CKD.

We conducted a multiple logistic regression using a stepwise selection method. All variables with P value < 0.3 were included (HAP, need for MV, CHF, DM. Length of stay, and mortality), HAP, mortality, length of stay, and need for mechanical ventilation were again significant, though need for mechanical ventilation did not reach the cutoff P value equal to or < 0.05 (0.06).

	Wald	95% CI	P
Hospital acquired pneumonia	7.4	0.05 – 0.6	<0.01
Mortality	6.1	0.15 – 0.8	0.01
Length of stay	3.8	0.05 - 1.0	0.05
Need for mechanical ventilation	3.5	0.18 – 1.0	0.06

A baumannii infected group versus others

A baumannii was by far the most common organism recovered from our study population, it was isolated from 106 patients (51%). We compared patients whose LRTI was attributed to A. baumannii with the rest of the study population. We found that the group with A baumannii positive culture were more likely to have HAP (35.8% vs. 17.6%, P: 0.003), need MV (81.1% vs. 63.7%, P:<0.005), and mortality (80.2% vs. 61.8%, P: <0.004).

Characteristics	A. baumannii group 106 (51%)	Another pathogen 102 (49%)	P
Male sex	64 (60.4%)	72 (70.6%)	0.145
Age	63.16 (+- 18.43)	61.50 (+- 16.87)	0.499
BMI	27.16 (+- 6.59)	27.10 (+- 7.20)	0.948
HTN	58 (54.7%)	65 (63.7%)	0.206
DM	48 (45.3%)	42 (41.2%)	0.578
CAD	26 (24.5%)	34 (33.3%)	0.172
CHF	27 (25.5%)	20 (19.6%)	0.325
CKD	26 (24.5%)	19 (18.6%)	0.317
Recent COVID	22 (20.8%)	17 (16.7%)	0.482

Characteristics	A. baumannii group 106 (51%)	Another pathogen 102 (49%)	P
HAP	38 (35.8%)	17 (16.7%)	0.003
HCAP	38 (35.8%)	43 (42.2%)	0.394
Need for MV	86 (81.1%)	65 (63.7%)	0.005
Length of stay	22.07 (+- 15.58)	21.74 (+- 27.31)	0.914
Outcome (Death)	85 (80.2%)	63 (61.8%)	0.004

We also conducted a multiple logistic regression using a stepwise selection method. All variables with P value < 0.3 were included (gender, HAP, need for mechanical ventilation, Mortality, HTN, and CAD). HAP, need for mechanical ventilation, and mortality were again significant with P values of 0.007, 0.05, and 0.05 respectively).

	Wald	95% CI	P
HAP	7.3	1.3 – 5.1	<0.01
Need for MV	3.9	1.0 – 4.2	0.05
Mortality	3.8	1.0 – 4.1	0.05

Discussion

Multidrug resistant organisms, particularly MDR Acinetobacter baumannii, have become a major threat to many intensive care facilities and healthcare organization. Many recent publications are uncovering the alarming magnitude of this problem as well as the bad consequences related to infections caused by these organisms [23, 24, 25, 26, 27]. Lower respiratory tract infections remain the most common infection acquired in the ICU settings [28]. In this study, the sample was predominated by older males (63%) with multiple comorbidities. Most of the LRTI cases were attributed to healthcare associated pneumonia (HCAP), 38.9%, or hospital acquired pneumonia (HAP), 26.4%. The study period coincided with COVID-19 pandemic. Almost 19% of the study population had a recent positive COVID-19 PCR test. Recent COVID-19 test positivity didn't seem to be associated with MDRO LRTI risk.

The findings of this study demonstrate the high prevalence of MDRO LRTIs in ICU settings at a tertiary center in a Middle East developing country. 81% of the ICU population with a culture positive LRTI had a multi-drug resistant organism isolated from a respiratory culture, a blood culture, or both.

A buamanii was by far the most common organism responsible for LRTIs in our study population. All A. baumannii isolates recovered from our patients' population were multi-drug resistant (MDR). Hospital acquired pneumonia, increased length of hospital stay, and need for MV were independent factors associated with MDRO related LRTIs. Our study also demonstrates the high mortality rate of LRTIs related to MDRO, 77.4%. Many other studies have also pointed to this trend of escalating MDRO prevalence in healthcare facilities of developing countries and the high mortality rate attributed to those organisms [1, 2, 29].

In this study group, A. baumannii. accounted for almost half, 51%, of the LRTIs and 63% of LRTIs attributed to MDROs. Hospital acquired pneumonia (HAP) and the need for mechanical ventilation (MV) were independent factors associated with A. baumannii infection. LRTI due to MDR-A. baumannii was associated with poor outcomes with a mortality rate of around 80%.

The high prevalence of LRTI related to A. baumannii seems to be shared by other similar institutions in other developing countries. For example, a study done at a tertiary-care university hospital in Brazil between 2015 – 2019 showed that A. baumannii accounted for a round 45% of culture confirmed LRTIs in ICU population [30].

Those findings are alarming and mandate immediate attention and quick actions to curb the trend. Virtually all MDRO are spread by contact [31]. Contact can be direct, e.g., by actual touching, or indirect, by contact with objects or the environment. A. baumannii is known to be responsible for nosocomial infections. It usually spreads via cross transmission among patients and environment. The ability of this bacteria to form biofilms is likely responsible for its ability to persist in the ICU environment [32]. The surge in A. baumannii related LRTIs could reflect poor infection control mechanisms implementation among facilities or poor compliance among health-care workers [33]. It could also reflect antibiotic overuse and poor antibiotic stewardship protocols. Prior exposure to broad spectrum antibiotic, especially carbapenem, has been associated increased risk for colonization and infection with MDR Acinetobacter [20].

Proper implementation and adherence to infection prevention mechanisms and through search for potential microbial reservoirs such as shared patient's devices, water sources, or even sinks could also help eliminate common sources [34].

LIMITATIONS

This study has many limitations, to count, it is a one center university hospital settings, which limits generalization. Developing countries may vary regarding availability of resources, local infection control mechanism implemented, national and local antibiotic stewardship implemented.

We hope that the findings of this study will increase the awareness of the rising proportion of LRTI related to MDRO among intensive care unit patients, especially the finding of high prevalence of MDR A. baumannii. Implementing effective infection prevention mechanisms will likely decrease the burden of this problem, preserve resources and save lives.

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