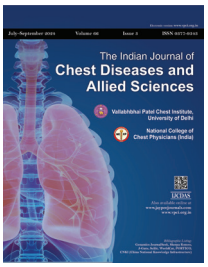
ORIGINAL RESEARCH

# Incidence and Clinical Outcomes of Multidrug-resistant Respiratory Infection in the Intensive Care Units of a Tertiary Care Hospital: A Prospective, Observational Study

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Meghana Sanil[1], Pratibha Todur[2], Varun R Nayak[3], Souvik Chaudhuri[4]

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## Abstract

**Background:** The surge in income levels coupled with reduced drug costs has contributed to a notable escalation in the utilization of antibiotics among individuals, consequently fostering the emergence of antibiotic resistance. Despite the detrimental effects of antibiotic resistance on patient outcomes, there exists a significant gap in global research, particularly in middle- and low-income countries. Hence, we aimed to evaluate the burden of gram-negative multidrug-resistant (GNB-MDR) respiratory infections in mechanically ventilated patients.

**Materials and methods:** A single center, prospective-observational study was performed in the intensive care units (ICU) of a Tertiary Care Hospital in Southern India from September 2021 to May 2022. Endotracheal aspirates were collected as per the physician's order and using the standard microbiological methods, gram-negative bacteria were identified, and their antibiotic susceptibility patterns were obtained. Demographic data of patients, clinical profile of the organism and clinical outcomes including the hospital stay, ICU stay and weaning from mechanical ventilation were documented.

**Results:** Among the 418 admitted patients, the incidence of gram-negative bacteria was 21.5%, among which the occurrence of multidrug-resistant gram-negative bacteria (MDR-GNB) was 16.26%. *Acinetobacter baumannii* (57.7%) was the most commonly found species, followed by *Klebsiella pneumoniae* (38.8%) and *Escherichia coli* (6.6%). About 77.7% of the cohort were carbapenem resistant, of which 90% cases were multidrug resistant. Significantly more MDR-GNB patients have undergone simple and difficult weaning compared to non-multidrug-resistant gram-negative bacteria (NMDR-GNB) infected patients ($p = 0.026$).

**Interpretation and conclusion:** The rising prevalence of antibiotic resistance, notably carbapenem resistance, emphasizes the importance of observing the trends in the resistance pattern and conducting routine surveillance in critical care settings to alleviate the associated mortality and morbidity.

**Keywords:** Gram-negative bacteria, Incidence, Intensive care unit, Multidrug resistance.

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## Abbreviations Used in this Article

APACHE II = Acute physiology chronic health evaluation II; CCI = Charlson comorbidity index; GNB-MDR = Gram-negative multidrug-resistant; HAIs = Healthcare-associated infections; HAP = Hospital-acquired pneumonia; ICU = Intensive care units; MDR = Multidrug-resistant; NMDR-GNB = Non-multidrug-resistant gram-negative bacteria; PDR = Pan-drug resistant; SBT = Spontaneous breathing trial; VAP = ventilator-associated pneumonia; XDR = Extensively drug resist.

## Introduction

Healthcare-associated infections (HAIs) present a critical challenge within the healthcare sector, especially in intensive care units (ICU). The escalating threat of antibiotic resistance further compounds this issue, described as a silent tsunami confronting modern medicine.[1] Specifically, the prevalence of infections linked to multidrug-resistant gram-negative bacteria (MDR-GNB) has seen a concerning rise in recent years.[2,3] Multidrug-resistant (MDR) bacteria pose a significant risk, rendering conventional treatments ineffective and leading to an alarming increase in mortality rates. Multidrug-resistant bacteria are predicted to cause 10 million fatalities by 2050, with substantial economic consequences, contributing to approximately 7,00,000 deaths annually worldwide.[4] The global

[1,2]Department of Respiratory Therapy, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, Karnataka, India

[3]Department of Respiratory Therapy, Hamad Medical Corporation, Doha, Qatar

[4]Department of Critical Care Medicine, Kasturba Medical College Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

**Corresponding Author:** Meghana Sanil, Department of Respiratory Therapy, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, Karnataka, India, Phone: +91 9972046949, e-mail: meghanasanil456@gmail.com

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situation reveals that even though in the ICUs of developed countries, infections due to gram-positive bacteria are prevalent, MDR-GNB infections are more widespread in the Pacific region of Asia, including India.[5–7]

According to the World Health Organization, antimicrobial resistance ranks among the top ten global threats to public health.[8] The most common problem faced by critically ill patients due to underlying disease, weakened immunity and exposure to various invasive devices is infection, and it is significantly associated with cost, mortality, and morbidity.[9,10] The prevalence of hospital-acquired pneumonia (HAP) due to specific MDR-GNB can vary depending on various factors such as the hospital, total patients, antibiotic use, and illness of the patient. Understanding that this prevalence can change over time is essential, highlighting the need for timed, local surveillance data.[11]

Multiple studies have stated a direct association, while others have revealed that MDR-GNB infections do not prolong the hospital stay and increase mortality rates.[12–15] The impact of respiratory infections caused by MDR-GNB on the length of hospital stay, in-hospital mortality, mechanical ventilator days, and weaning from mechanical ventilation, is still not established. Hence, our objective was to estimate the incidence of MDR-GNB respiratory infection and to determine the clinical outcomes. This contributes to a better comprehension of MDR-GNB infection, facilitating more effective approaches to treatment and prevention.

## Materials and Methods

It was an observational study conducted prospectively in the ICUs of a tertiary care hospital. The study was performed from September 2021 to May 2022 following the Institutional Ethical Committee clearance (IEC 341-2021) and registration in the Clinical Trial Registry of India (CTRI) - CTRI/2021/09/036756. Before enrolling in the study, written informed consent was obtained from the participant's legally authorized representatives.

### Study Population

Inclusion criteria included patients aged above 18 years infected with gram-negative bacteria in endotracheal aspirate culture specimens. Patients were excluded from the study if their ICU admission lasted less than 48 hours. By considering the sample proportion from the previous study with a power of 80% and $p$-value $< 0.05$, a sample size of 90 was determined, and a convenience sampling method was opted.[16]

### Data Collection

Patient demographics, comorbidities, and causes for hospital admission were collected at the time of admission. Acute physiology chronic health evaluation II (APACHE II) score and the Charlson comorbidity index (CCI) score were used to assess the severity of illness at baseline. Additionally, the data were collected on clinical outcomes, which included the duration of the ICU stay, hospital stay, successful weaning from mechanical ventilation, and in-hospital mortality. The presence of MDR, extensively drug resistant (XDR), and pan-drug resistant (PDR) infections was identified with sensitivity reports.

### Definitions

For the analysis of data, multidrug resistance (MDR) was determined as, "non-susceptibility to at least one agent in three or more antimicrobial categories", XDR was described as, "non-susceptibility to at least one agent in all except in two or fewer antimicrobial categories" and pan-drug resistance (PDR) was defined as, "non-susceptibility to all agents in all antimicrobial categories".[17,18]

Weaning was classified as simple, defined as, "the patient effectively passes the initial spontaneous breathing trial (SBT) and is successfully extubated on the initial attempt". Difficult weaning was defined as, "patients needing three SBT or 7 days from the initial SBT to attain effective weaning" and prolonged weaning was defined as, "comprises patients requiring more than three SBT or >7 days of weaning following the first SBT".[19]

### Statistical Analysis

Data were analyzed using v 4.2.2 and presented as categorical data in frequencies and percentages and continuous data in means and medians. The student's $t$-test was used to evaluate the differences in age and trends in variables between the survivors and those who expired. The comparison of baseline characteristics between MDR-GNB and NMDR-GNB bacterial infections was conducted using the Mann-Whitney $U$ test. Clinical outcomes between MDR-GNB and NMDR-GNB were analyzed with the Wilcoxon signed rank test. A $p$-value $< 0.05$ was considered statistically significant.

## Results

During the study period, 418 patients underwent intubation. The incidence rate of gram-negative bacteria was 21%. Among the 90 included patients, 68 (75.5%) exhibited growth of MDR-GNB, resulting in an incidence rate of 16.26% with a mean age of 55.9 ± 17 years. In contrast, 22 (24.4%) patients had NMDR-GNB growth, with a mean age of 57.5 ± 16.15 years. The incidence of PDR-GNB was identified in two patients, representing 0.48%, while one patient was infected with XDR-GNB (Figs 1 and 2).

In the overall cohort, the most common species was *Acinetobacter baumannii* (57.7%), followed by *Klebsiella pneumoniae* (38.8%) and *Escherichia coli* (6.66%). The same trend followed in patients with MDR infection with 70.6, 30.8 and 5.88%, respectively. However, in non-MDR patients, *Klebsiella pneumoniae* was the pathogen most identified, followed by *A. baumannii* and *Pseudomonas aeruginosa*. Notably, a high proportion of the cohort, accounting for 77.7%, exhibited carbapenem resistance, and 63 cases were multidrug resistant.

Our study revealed that out of the 90 patients with gram-negative bacterial infections, 39 (43.3%) recovered from the

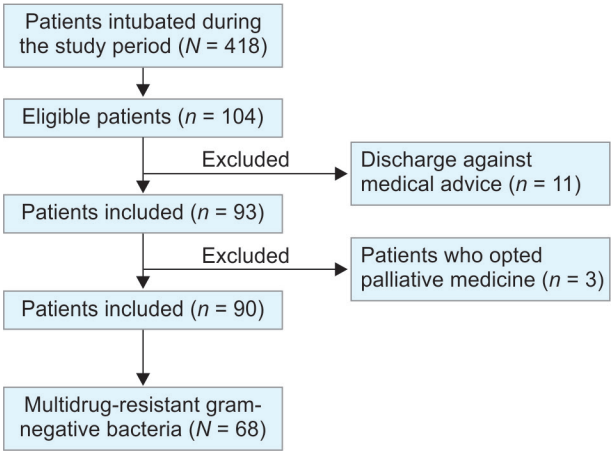


**Fig. 1:** Flow diagram of the study population

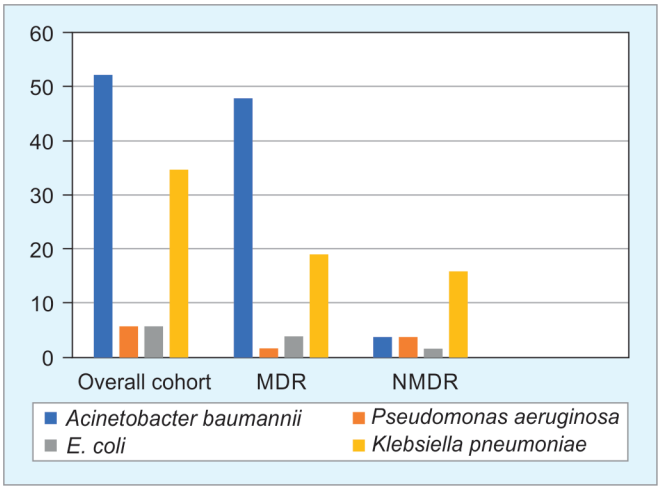


**Fig. 2:** Organism profile in the intensive care unit

**Table 1:** Baseline and clinical characteristics of patients

| *Demographic data* | *Overall cohort (n = 90)* | *Multidrug resistant (n = 68)* | *Nonmultidrug resistant (n = 22)* |
|---|---|---|---|
| Age (years) | 56.3 ± 16.9 | 55.9 ± 17.2 | 57.5 ± 16.1 |
| Gender, male (*n*, %) | 69 (76.6) | 50 (55.5) | 19 (21.1) |
| *Reason for admission (n, %)* | | | |
| Respiratory | 36 (40) | 29 (42.6) | 7 (31.8) |
| Neurological | 27 (30) | 16 (23.5) | 11 (50) |
| Digestive/liver | 16 (17.8) | 13 (19.1) | 3 (13.6) |
| Surgical | 7 (7.8) | 6 (8.8) | 1 (4.5) |
| Cardiovascular | 3 (3.3) | 3 (4.4) | 0 |
| APACHE score at 48 h Mean ± SD | 15.9 ± 7.19 | 15.79 ± 7.64 | 16.22 ± 5.71 |
| Charlson comorbidity index Median (IQR) | 3 (1–6) | 3 (1–5) | 4 (2–7) |
| Mortality (*n*, %) | 52 (57.7) | 43 (63.2) | 9 (40.9) |

infection. Surprisingly, only 10 (25.6%) recovered patients survived. The antibiotic of choice for most of the patients was Tigecycline. Among the 29 patients who did not recover, 23 (79.3%) were infected by carbapenem-resistant GNB.

The baseline and clinical characteristics of patients are depicted in Table 1. The median hospital stay was higher in NMDR patients compared to MDR patients, i.e., (19.5) vs (16). Intensive Care Unit duration and mechanical ventilation (MV) days for both groups were identical. 38 patients were eligible for weaning as depicted in Table 2. The majority of patients with MDR-GNB underwent simple weaning (12%) and difficult weaning (48%) compared to the patients with NMDR-GNB ($p = 0.026$).

## Discussion

The current study aimed at determining the incidence of gram-negative bacterial respiratory infection and determining the clinical outcomes of these affected patients. In the ICU, the occurrence of

**Table 2:** Clinical outcomes of multidrug resistant and non-multidrug resistant bacteria

| *Parameters* | *Multidrug resistant bacteria (MDR) (n = 68)* | *Nonmultidrug resistant bacteria (NMDR) (n = 22)* | *p-value* |
|---|---|---|---|
| Hospital stay (days) | 16.0 (15.3) | 19.5 (11.5) | 0.281 |
| ICU duration (Days) | 9 (8.5) | 9 (7.75) | 0.825 |
| Mechanical ventilation days | 7.50 (5.25) | 7.50 (8.50) | 0.731 |
| *Weaning classification (n, %)* | *Multidrug resistant bacteria (MDR) (n = 25)* | *Nonmultidrug resistant bacteria (NMDR) (n = 13)* | 0.026*** |
| Prolonged weaning | 10 (40) | 10 (76.9) | |
| Difficult weaning | 12 (48) | 2 (15.38) | |
| Simple weaning | 3 (12) | 1 (7.69) | |

****p–value* is 0.026 between the MDR and NMDR groups measured for the prolonged, difficult, and simple weaning

GNB was 21 per 100 patients, of which 75.55% were infected with MDR-GNB. The overall incidence of MDR-GNB was 16.26%, which aligns with a study on MDR-GNB isolated from intubated ICU patients. The study findings indicate that 88% of the total isolates were GNB, with 72% of them being MDR.[19] The biofilm that forms in the endotracheal tube and the colonization of the oropharynx are crucial reservoirs for infectious microorganisms. In critically ill patients in the ICU, the risk of developing ventilator-associated pneumonia (VAP) is increased by the use of mechanical ventilation and aspiration of secretions into the lower airway.[20,21] In contrast to our findings, Jatan B Sherchan and Humagain[22] reported that the growth of gram-negative bacteria was only 6.17%.

A systematic review describing the burden of MDR - Healthcare-associated infections revealed an incidence of MDR *A. baumannii* of 58%.[23] Even in our study, in the overall cohort, *A. baumannii* (53.9%) and *Klebsiella pneumoniae* (41%) were the predominant specie found, which is similar to the previous findings.[3,16,24] However, *K. pneumoniae* (72.7%) was the major culprit among NMDR-GNB infected patients. Carbapenem resistance was found in all the *A. baumannii* isolates. This finding is in accordance with Priya Kannian et al.[25] The majority of carbapenem resistance was observed in MDR, and the highest was in *A. baumannii*. The most relevant reason for increasing resistance towards carbapenem by *A. baumannii* species is the acquisition of carbapenem-coding genes.[26]

The overall, in-hospital mortality was 57.7%. Mortality in MDR patients was 63.2% and NMDR was 40.9%, indicating the chance of survival to be higher in the NMDR-GNB patients. The mortality rate in patients with *A. baumannii* was 34.6%, which is similar to the study done by Brotfain et al.,[27] where they found that the presence of MDR-*A. baumannii* was not an independent risk factor for mortality.

Our study reveals that, although not statistically significant, in patients infected with MDR-GNB, the duration of hospital stay is less compared to those infected with NMDR-GNB. This is contrary to the results of a study by Siwakoti et al.,[3] where the patients infected with

MDR-GNB had a longer duration of hospital stay than the patients infected with NMDR-GNB isolates. This finding could be due to the high mortality associated with MDR-GNB infections. The number of patients undergoing prolonged ventilation is higher in the MDR-GNB group compared to the NMDR-GNB. However, in a study by Johannes Bickenbach et al.,[28] patients undergoing prolonged ventilation were higher in the NMDR-GNB group. Significantly more MDR-GNB patients have undergone simple and difficult weaning compared to NMDR-GNB infected patients ($p = 0.026$).

The rising prevalence of antibiotic resistance, notably carbapenem resistance, emphasizes the importance of observing the trends in the resistance pattern and conducting routine surveillance. Infection control practices should be strictly implemented and monitored to curb the rapid spread of GNB infections in the ICUs.

The major limitation of our study is that it was a single-center study, which restricts the generalizability of the study results. Additionally, there was insufficient data on appropriate empiric antibiotic therapy, which could potentially impact in-hospital mortality. Furthermore, procalcitonin level as a bacterial biomarker was obtained only during day 1 of infection; consequent procalcitonin values were not obtained in most patients.

### Future Directive

To comprehensively understand the clinical outcomes and trends associated with MDR, PDR, and XDR bacterial infections in this region, it is imperative to conduct a multicenter study that incorporates a variety of infection biomarkers.

## Conclusion

The study provides insights into the incidence and clinical outcomes of MDR-GNB infections. Monitoring the resistance patterns and implementing effective infection control measures are imperative to curb the rising trend of antibiotic resistance and improve patient outcomes in critical care settings.

### Clinical Significance

Even though significant research has been conducted in the field of antibiotics, there is a significant surge in carbapenem-resistant *A. baumannii*. Antimicrobial Stewardship programs should be implemented in the critical care units.

## Orcid

*Meghana Sanil* https://orcid.org/0009-0009-7598-5741
*Pratibha Todur* https://orcid.org/0000-0003-0967-2252
*Varun R Nayak* https://orcid.org/0000-0003-2206-0461
*Souvik Chaudhuri* https://orcid.org/0000-0001-8392-2366

## References

1. Cox D. Antibiotic resistance: The race to stop the silent tsunami facing modern medicine. The Guardian 2015;41(5):320–327. [online]. Available from: https://www.theguardian.com/society/blog/2015/aug/21/antibiotic-resistance-the-race-to-stop-the-silent-tsunami-facing-modern-medicine. [Last accessed October, 2024].
2. Rodrigo-troyano A, Sibila O. The respiratory threat posed by multidrug resistant G ram-negative bacteria. Respirology 2017;22(7):1288–1299. DOI: 10.1111/resp.13115.
3. Siwakoti S, Subedi A, Sharma A, et al. Incidence and outcomes of multidrug-resistant gram-negative bacteria infections in intensive care unit from Nepal-a prospective cohort study. Antimicrobial Resist Infect Control 2018;7(1):114.
4. Reale M, Strazzulla A, Quirino A, et al. Patterns of multi-drug resistant bacteria at first culture from patients admitted to a third level University hospital in Calabria from 2011 to 2014: Implications for empirical therapy and infection control. Infez Med 2017;25(2):98–107. PMID: 28603227.
5. Chaudhry D, Prajapat B. Intensive care unit bugs in India: How do they differ from the Western world? J Assoc Chest Physicians 2017;5(1):10–17. DOI: 10.4103/2320-8775.196645.
6. Mendes RE, Mendoza M, Banga Singh KK, et al. Regional resistance surveillance program results for 12 Asia Pacific nations (2011). Antimicrob Agents Chemother 2013;57(11):5721–5726. DOI: 10.1128/AAC.01121-13.
7. Ghanshani R, Gupta R, Gupta BS, et al. Epidemiological study of prevalence, determinants, and outcomes of infections in medical ICU at a tertiary care hospital in India. Lung India 2015;32(5):441–448. DOI: 10.4103/0970-2113.164155.
8. World Health Organization. Antimicrobial resistance. [online]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. [Last accessed October, 2024].
9. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302(21):2323–2229. DOI: 10.1001/jama.2009.1754.
10. Blot S, Ruppé E, Harbarth S, et al. Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies. Intensive Crit Care Nurs 2022;70:103227. DOI: 10.1016/j.iccn.2022.103227.
11. Seligman R, Ramos-Lima LF, Oliveira VD, et al. Risk factors for infection with multidrug-resistant bacteria in non-ventilated patients with hospital-acquired pneumonia. J Bras Pneumol 2013;39(3):339–348. DOI: 10.1590/S1806-37132013000300011.
12. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. Clin Infect Dis 2006;42(Suppl 2):S82–S89. DOI: 10.1086/499406.
13. Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. Clin Microbiol Infect 2012;18(1):54–60. DOI: 10.1111/j.1469-0691.2011.03478.x.
14. Blot S, Vandewoude K, De Bacquer D, et al. Nosocomial bacteremia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: Clinical outcome and length of hospitalization. Clin Infect Dis 2002;34(12):1600–1606. DOI: 10.1086/340616.
15. Menashe G, Borer A, Yagupsky P, et al. Clinical significance and impact on mortality of ESBL-producing gram-negative isolates in nosocomial bacteremia. Scand J Infect Dis 2001;33(3):188–193 PMID: 11303808
16. Vishwanath S, Chawla K, Gopinathan A. Multidrug resistant Gram-negative bacilli in lower respiratory tract infections. Iran J Microbiol 2013;5(4):323–327. PMID: 25848499.
17. Gandra S, Tseng KK, Arora A, et al. The mortality burden of multidrug-resistant pathogens in India: A retrospective, observational study. Clin Infect Dis 2019;69(4):563–570. DOI: 10.1093/cid/ciy955.
18. Basak S, Singh P, and Rajurkar M. Multidrug-resistant and extensively drug-resistant bacteria: A study. J Pathog 2016;2016:4065603. DOI: 10.1155/2016/4065603.
19. Gupta R, Malik A, Rizvi M, et al. Epidemiology of multidrug-resistant Gram-negative pathogens isolated from ventilator-associated pneumonia in ICU patients. J Glob Antimicrob Resist 2017;9:47–50. DOI: 10.1016/j.jgar.2016.12.016.
20. Coudron PE. Inhibitor-based methods for detection of plasmid-mediated AmpC β-lactamases in Klebsiella spp., Escherichia coli, and Proteus mirabilis. JClin Microbiol 2005;43(8):4163–4167. DOI: 10.1128/JCM.43.8.4163-4167.2005.
21. Picao RC, Andrade SS, Nicoletti AG, et al. Metallo-β-lactamase detection: Comparative evaluation of double-disk synergy versus combined disk tests for IMP-, GIM-, SIM-, SPM-, or VIM-producing

isolates. J Clin Microbiol 2008;46(6):2028–2037. DOI: 10.1128/JCM.00818-07.
22. Sherchan JB, Humagain S. Antimicrobial susceptibility pattern of gram-negative bacteria causing lower respiratory tract infections in Kathmandu university hospital. J Nepal Health Res Counc 2021;18(4):661–666. DOI: 10.33314/jnhrc.v18i4.2566.
23. Teerawattanapong N, Panich P, Kulpokin D, et al. A systematic review of the burden of multidrug-resistant healthcare-associated infections among intensive care unit patients in Southeast Asia: The rise of multidrug-resistant Acinetobacter baumannii. Infect Control Hosp Epidemiol 2018;39(5):525–533. DOI: 10.1017/ice.2018.58.
24. Guclu AU, Kocak AA, Ok MA, et al. Antibacterial resistance in lower respiratory tract bacterial pathogens: A multicenter analysis from turkey. J Infect Dev Ctries 2021;15(02):254–262. DOI: 10.3855/jidc.12599.
25. Kannian P, Mahanathi P, Ashwini V, et al. Carbapenem-resistant gram negative bacilli are predominantly multidrug or pan-drug resistant. Microb Drug Resist 2021;27(8):1057–1062. DOI: 10.1089/mdr.2020.0294.
26. Ramirez MS, Bonomo RA, Tolmasky ME. Carbapenemases: Transforming Acinetobacter baumannii into a yet more dangerous menace. Biomolecules 2020;10(5):720. DOI: 10.3390/biom10050720.
27. Brotfain E, Borer A, Koyfman L, et al. Multidrug resistance acinetobacter bacteremia secondary to ventilator-associated pneumonia: Risk factors and outcome. J Intensive Care Med 2017;32(9):528–534. DOI: 10.1177/0885066616632193.
28. Bickenbach J, Schöneis D, Marx G, et al. Impact of multidrug-resistant bacteria on outcome in patients with prolonged weaning. BMC Pulm Med 2018;18(1):141. DOI: 10.1186/s12890-018-0708-3.