ORIGINAL ARTICLE

# Outcomes and Associated Factors Among Patients with Multidrug-Resistant Gram-Negative Bacilli Bacteremia at a Tertiary Care Hospital in Thailand

Tanatorn Soravipukuntorn, MD[1], Arsa Thammahong, MD, PhD[2], Lantharita Charoenpong, MD[3], Patama Suttha, MD[3], Weerawat Manosuthi, MD[3]

[1] Department of Anatomy, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2] Center of Excellence in Antimicrobial Resistance and Stewardship, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [3] Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, Thailand

**Objective:** Multidrug-resistant (MDR) Gram-negative bacilli (GNB) bacteremia is a major problem worldwide, including in Thailand. The present study aimed to determine the outcomes and associated factors of MDR GNB bacteremia among adult patients at a tertiary care hospital in Thailand.

**Materials and Methods:** A retrospective cohort study was conducted between January 1, 2017 and December 31, 2020 among patients older than 15 years with laboratory-confirmed GNB bacteremia. Univariate and multivariate logistic regression analyses were used to determine factors significantly associated with MDR bacteremia.

**Results:** Three hundred sixty-four subjects were included in the present study. The most common source of GNB bacteremia was genitourinary tract infection, in 49.2%, and 33.8% of all GNB bacteremia was MDR. The most common causative pathogen was *Escherichia coli*. The factors significantly positively associated with MDR infection were residing in a long-term care facility (adjusted odds ratio [aOR] 4.25, 95% confidence interval [CI] 1.47 to 12.29, p=0.008), previous hospitalization within 90 days (aOR 3.40, 95% CI 1.62 to 7.16, p=0.010), and having a genitourinary tract infection (aOR 2.33, 95% CI 1.04 to 5.20, p=0.040). There was no significant difference in mortality between the two groups. The median duration of hospital stay among the MDR group was longer compared to that of the non-MDR group in 11 (interquartile range [IQR] 7 to 21.5) versus 10 (IQR 5 to 18) days (p=0.020). The median duration of fever in the MDR group was also longer than that in the non-MDR group at 3 (IQR 2 to 5) versus 3 (IQR 1 to 5) days (p=0.041). The factor significantly associated with survival in the MDR group was having an appropriate empiric antibiotic (aOR 0.07, 95% CI 0.12 to 0.43, p=0.004).

**Conclusion:** Patients admitted to hospital from a long-term care facility, had prior hospitalization within 90 days, or had genitourinary tract infection should receive empiric antibiotics covering MDR GNB pathogens. Further studies are needed to determine whether making these changes will result in improving survival among the study population.

**Keywords:** Associated factor; Outcomes; Multidrug resistance; Gram-negative bacilli; Bacteremia, Thailand

Received 10 July 2024 | Revised 12 November 2024 | Accepted 9 December 2024

**J Med Assoc Thai 2025;108(1):30-41**

**Website:** http://www.jmatonline.com

Antimicrobial resistance (AMR) poses a significant public health threat worldwide. The presence of AMR infection results in high morbidity and mortality, prolonged hospitalization, increased healthcare expenditures, and treatment failure[1-3]. An assessment of the global burden of AMR in 204 countries in 2019 estimated that 4.95 million deaths were associated with AMR bacteria, including 1.27 million deaths were attributable to bacterial AMR, which was much larger than death from HIV and malaria[2]. According to the 2016 AMR Review, the annual death toll from AMR could reach up to 10 million by 2050, surpassing the death toll from cancer and road traffic accidents[4]. In Thailand, AMR resulted in approximately 88,000 infections, causing 38,000 fatalities and at least 3.24 million extra hospital days[5]. The direct expenses of antibiotics for treating AMR infections ranged from $70 million to $170 million. The indirect expenses associated with illness and premature mortality due to AMR amounted to at least $1.1 billion[5]. A report by the World Health Organization's Global Antimicrobial

**Correspondence to:**

Charoenpong L.

Department of Medicine, Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, 38 Tiwanon Road, Talat Khwan Subdistrict, Mueang Nonthaburi, Nonthaburi 11000, Thailand.

**Phone:** +66-2-5903408, Fax: +66-2-5903411

**Email:** iamtum_154@yahoo.co.th

**How to cite this article:**

Soravipukuntorn T, Thammahong A, Charoenpong L, Suttha P, Manosuthi W. Outcomes and Associated Factors Among Patients with Multidrug-Resistant Gram-Negative Bacilli Bacteremia at a Tertiary Care Hospital in Thailand. J Med Assoc Thai 2025;108:30-41.

DOI: 10.35755/jmedassocthai.2025.1.30-41-01303

Resistance and Use Surveillance System in 2021 revealed an increase in multidrug-resistant (MDR) Gram-negative bacilli (GNB), especially carbapenem-resistant (CR) Enterobacterales, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*[6]. This finding aligned with a recent large-scale surveillance of 47 hospitals in Thailand, which revealed a high prevalence of AMR[7]. The prevalence of extended-spectrum cephalosporin resistant (ESCR) was greater in *Escherichia coli*, at 42.5%, compared to *Klebsiella pneumoniae*, which is at 32%, whereas CR-*K. pneumoniae*, at 17.2%, was higher than CR-*E. coli* at 3.8%[7]. Among the *A. baumannii* complex isolates, a considerable proportion of up to 77.6% exhibited extensively drug-resistant (XDR) or MDR[7]. In contrast, *P. aeruginosa* demonstrated XDR or MDR at a lower rate of 22.8%[7]. The study site is a tertiary hospital that has had a significant increase in CR-*K. pneumoniae*, rising from 4% in 2013 to 11.6% in 2023. The prevalence of MDR/XDR *A. baumannii* complex also escalated with time, rising from 71% in 2013 to 81% in 2023.

MDR infections and associated risk factors vary among hospitals according to local patterns of use. It is essential to observe the epidemiology at both a regional and a facility level. Under-recognition of the potential of MDR pathogens to cause infections leads to inappropriate empirical antibiotic use. The delayed administration of antibiotics against susceptible pathogens increases the length of hospital stays, hospitalization expenditures, and mortality rates[8]. Previous studies have reported associations between MDR GNB infections and several factors, including previous use of antibiotics, inappropriate antibiotic therapy, prior MDR infection or colonization, recent hospitalization, longer hospitalization, catheter-associated urinary tract infection (UTI), endotracheal intubation, mechanical ventilation, nursing home residence, and higher disease severity score[9-13]. Therefore, epidemiological data regarding AMR in every hospital and individual risk stratification approaches can be utilized to select appropriate antibiotics and improve treatment outcomes and mortality.

In the present study, the authors aimed to determine the incidence of MDR GNB infections among patients with bloodstream infections at the study hospital and determine the factors significantly associated with MDR GNB bacteremia and treatment outcomes.

## Materials and Methods

### Study design and population

The authors conducted a single-center retrospective observational cohort study at the Bamrasnaradura Infectious Diseases Institute, a 230-bed tertiary care hospital in Thailand, between January 1, 2017 and December 31, 2020. The inclusion criteria for study subjects were older than 15 years and laboratory-confirmed GNB bacteremia, including Enterobacterales, *Pseudomonas* spp., and *Acinetobacter* spp. Subjects admitted with GNB bacteremia multiple times during the study period were included in the present study for only the last admission. Subjects with more than one episode of GNB bacteremia during the same admission were considered as having a single episode. The exclusion criteria were positive specimen for GNB considered to be laboratory contamination and treatment begun or completed at another hospital where data were missing. Subjects were identified by searching the laboratory database. Each subject's electronic and hard copy medical records were reviewed, and demographic characteristics, clinical course, severity of infection, antimicrobials used for treatment, case outcome, and any complications were recorded.

### Definitions

For the purposes of this present, the authors defined MDR as the ability to resist at least one antimicrobial agent in three or more antimicrobial categories[14]. The criteria for diagnosing systemic inflammatory response syndrome (SIRS) included satisfying any two of the following conditions, temperature greater than 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 per minute or $PaCO_2$ of less than 32 mmHg, and white blood cell count of more than 12,000 per $mm^3$ or less than 4,000 per $mm^3$ or more than 10% immature bands[15]. Sepsis was defined as a severe condition when the body's reaction to infection became uncontrolled, leading to life-threatening organ dysfunction[16]. Subjects with septic shock were selected based on a clinical definition of sepsis characterized by ongoing hypotension that necessitate the use of vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg or more and had a serum lactate level of more than 2 mmol/L despite receiving sufficient fluid resuscitation[16]. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated based on the most abnormal data recorded within 24 hours after sepsis[17]. Community-acquired infection refers to an

infection that was acquired outside the hospital or within 48 hours after admission. Hospital-associated infection was defined as an infection that occurred more than 48 hours after a patient was admitted to the hospital[18]. Inappropriate antibiotic treatment could be classified into two categories, undertreatment and overtreatment. Undertreatment was defined as the act of administering an antibiotic that the organism was resistant to. Overtreatment was the act of administering more antibiotics than necessary. The appropriateness of empirical antibiotics was defined based on the isolated bacteria being susceptible to at least one of the antibiotics administered within 24 hours of the patient being diagnosed with bacteremia. The appropriateness of specific antibiotics was defined based on the isolated bacteria being susceptible to the antibiotics without excessive treatment. The appropriateness of antibiotic treatment was reviewed and evaluated by an infectious disease specialist. The time to initiation of the first dose of antibiotics was measured from the time blood cultures were taken until the time antibiotics were begun.

### Outcomes and complications

Improvement of infection was defined as complete resolution or reduction of the symptoms and signs of infection. An adverse effect of an antibiotic was defined as an allergic reaction or side effect, including reactions such as nephrotoxicity, hepatotoxicity, leukopenia, thrombocytopenia, and drug fever. Antibiotic-associated diarrhea was classified as diarrhea occurring after antibiotic treatment with or without confirmed *Clostridium difficile* toxin, after other causes of diarrhea were excluded.

### Statistical analysis

The sample size was calculated based on the finding of Chaisathaphol & Chayakulkeeree[10] that the prevalence of overall MDR Gram-negative bacteria infection was 48.8%. With alpha=0.05 and d=0.055, the sample size needed was 318 subjects. The continuous data were reported as mean and standard deviation (SD) and median and interquartile range (IQR) and analyzed them using either a Student's t-test for normal distribution data or a Mann-Whitney U test for non-normal distribution data. The categorical data were presented as numbers and percentages and analyzed using the chi-square test. Univariate and multivariate logistic regression analyses were conducted to determine the relationships between MDR GNB infections and selected factors. Odds ratios (OR) and 95% confidence interval (CI) were used to quantify these associations. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA).

### Ethical approval

The present study was approved by the Ethics Review Board of the Bamrasnaradura Infectious Diseases Institute (S004h/64_ExPD). The institution's Institutional Review Board waived the informed consent due to de-identification of patient data. The confidentiality and privacy of the information were assured by removing the identity of the individuals and replacing it with a new anonymous code given by the authors prior to being used in the present retrospective study.

## Results

### Patients and clinical characteristics of infection

The authors had 364 subjects that had 373 episodes of GNB bacteremia in the present study. Two hundred eleven (58%) were female. The mean (±SD) age of study subjects was 67.4±17.7 years, with a range of 17 to 100 years (Table 1). Of the 364 subjects, 123 (33.8%) had MDR GNB infections. The percentage of MDR GNB organisms was highest in 2017 at 41.1%, and lowest in 2018 at 30.2%. The percentage of MDR GNB organisms was 32.1% in 2019 and 31.4% in 2020. Out of the 364 patients, 325 (89.3%) had comorbidities and 64 (17.6%) had invasive medical devices. Subjects with MDR GNB were significantly more likely than those with non-MDR GNB to have a long-term urinary catheter, which is more than seven days (p=0.005), resided in a long-term care facility (p<0.001), had been hospitalized in the previous 90 days (p<0.001), had received an antibiotic in the previous 90 days (p<0.001), had a hospital wound dressing (p<0.001), and had MDR GNB colonization or infection in the previous 90 days (p<0.001) (Table 1). In the previous 90 days, subjects with MDR GNB received more of the following antibiotics than subjects with non-MDR GNB, which are penicillin (p=0.017), third-generation cephalosporins (p<0.001), carbapenems (p=0.004), and fluoroquinolone (p=0.03) (Table 1).

The most common causative pathogens of GNB bacteremia were *E. coli*, at 66.2%, followed by *Klebsiella* spp., at 16.2%, and *A. baumannii*, at 4.9% (Table 2). MDR strains were identified in 39% of

**Table 1.** Demographic and clinical characteristics of subjects with Gram-negative bacilli bacteremia (n=364)

| Demographic and clinical characteristics | Total (n=364) | Non-MDR Gram-negative bacteremia (n=241) | MDR Gram-negative bacteremia (n=123) | p-value |
|---|---|---|---|---|
| Average age (years); mean±SD | 67.4±17.7 | 65.8±18.2 | 70.5±16.2 | 0.956 |
| Sex; n (%) | | | | 0.234 |
| Male | 153 (42.0) | 96 (39.8) | 57 (46.3) | |
| Female | 211 (58.0) | 145 (60.2) | 66 (53.7) | |
| Ward; n (%) | | | | 0.059 |
| General ward | 285 (78.3) | 184 (76.4) | 101 (82.1) | |
| ICU | 46 (12.6) | 29 (12.0) | 17 (13.8) | |
| OPD | 33 (9.1) | 28 (11.6) | 5 (4.1) | |
| Department; n (%) | | | | 0.128 |
| Medicine | 296 (81.3) | 188 (78) | 108 (87.8) | |
| Surgery | 37 (10.2) | 28 (11.6) | 9 (7.3) | |
| OPD GP | 29 (8.0) | 23 (9.5) | 6 (4.9) | |
| Comorbidity; n (%) | | | | |
| DM | 134 (36.8) | 83 (34.4) | 51 (41.5) | 0.189 |
| CVA | 50 (13.7) | 29 (12.0) | 21 (17.1) | 0.186 |
| Cirrhosis | 29 (8.0) | 21 (8.7) | 8 (6.5) | 0.461 |
| HIV infection | 39 (10.7) | 28 (11.6) | 11 (8.9) | 0.435 |
| CKD | 64 (17.6) | 37 (15.4) | 27 (22.0) | 0.118 |
| ESRD on HD | 10 (2.8) | 9 (3.7) | 1 (0.8) | 0.107 |
| Solid cancer | 39 (10.7) | 26 (10.8) | 13 (10.6) | 0.949 |
| Bed-ridden status | 95 (26.1) | 56 (23.2) | 39 (31.7) | 0.082 |
| None | 39 (10.7) | 29 (12.0) | 10 (8.1) | 0.255 |
| Receiving invasive medical device; n (%) | 64 (17.6) | 38 (15.8) | 26 (21.1) | 0.203 |
| Central venous catheter | 16 (4.4) | 13 (5.4) | 3 (2.4) | 0.193 |
| Long-term urinary catheter | 39 (10.7) | 18 (7.5) | 21 (17.1) | 0.005 |
| Endotracheal tube | 29 (8.0) | 17 (7.1) | 12 (9.8) | 0.368 |
| Residence in long-term care facility; n (%) | 26 (7.1) | 9 (3.7) | 17 (13.8) | <0.001 |
| Previous admission within 90 days; n (%) | 105 (28.9) | 42 (17.4) | 63 (51.2) | <0.001 |
| Previous antibiotic used within 90 days; n (%) | 139 (38.2) | 66 (27.8) | 73 (59.4) | <0.001 |
| Type of ATB exposure; n (%) | | | | |
| Penicillin | 23 (6.3) | 10 (4.2) | 13 (10.6) | 0.017 |
| Third-generation cephalosporin | 58 (15.9) | 25 (10.4) | 33 (26.8) | <0.001 |
| Carbapenem | 55 (15.1) | 27 (11.2) | 28 (22.8) | 0.004 |
| Piperacillin/ tazobactam | 15 (4.1) | 7 (2.9) | 8 (6.5) | 0.102 |
| Aminoglycoside | 6 (1.7) | 3 (1.2) | 3 (2.4) | 0.397 |
| Fluoroquinolone | 9 (2.5) | 12 (5.0) | 17 (13.8) | 0.03 |
| Prior MDR colonization/infection; n (%) | 57 (15.7) | 22 (9.1) | 35 (28.5) | <0.001 |
| Wound dressing at the hospital; n (%) | 32 (8.8) | 12 (5.0) | 20 (16.3) | <0.001 |

ATB=antibiotic; CKD=chronic kidney disease; CVA=cerebrovascular accident; DM=diabetes mellitus; ESRD=end-stage renal disease; GP=general practitioner; HD=hemodialysis; HIV=human immunodeficiency virus; ICU=intensive care unit; MDR=multidrug resistant; OPD=outpatient department; SD=standard deviation

*E. coli*, 38.9% of *A. baumannii*, 23.7% of *Klebsiella* spp., and 12.5% of *P. aeruginosa* (Table 2). Eighty of the 289 isolates (27.7%) were obtained from subjects with community-acquired Enterobacterales bacteremia and were MDR/ESCR/CR strains. Community-acquired MDR/ESCR *E. coli* accounted for 24.1% of all *E. coli* isolates (58 out of the 241 subjects). Community-acquired MDR/ESCR *K. pneumoniae* accounted for 2.5% of all *K. pneumoniae* isolates (one out of the 40 subjects).

Of the subjects with GNB infections, 85.2% had community-acquired infections. The most common sites of infection were genitourinary tract in 49.2%, followed by respiratory tract in 6.3%, and intra-

**Table 2.** Organisms of interest by the number of episodes of infection

| Organism | Total (n=364); n (%) | Non-MDR Gram-negative bacteremia (n=241); n (%) | MDR Gram-negative bacteremia (n=123); n (%) | p-value |
|---|---|---|---|---|
| Enterobacterales | | | | <0.001 |
| *Escherichia coli* | 241 (66.2) | 147 (61) | 94 (76.4) | |
| *Klebsiella* spp. | 59 (16.2) | 45 (18.7) | 14 (11.4) | |
| *Enterobacter* spp. | 8 (2.2) | 4 (1.7) | 4 (3.3) | |
| *Proteus* spp. | 10 (2.7) | 9 (3.7) | 1 (0.8) | |
| *Citrobacter* spp. | 2 (0.5) | 2 (0.8) | 0 (0.0) | |
| Others | 10 (2.7) | 9 (3.7) | 1 (0.8) | |
| *Pseudomonas aeruginosa* | 16 (4.4) | 14 (5.8) | 2 (1.6) | |
| *Acinetobacter baumannii* | 18 (4.9) | 11 (4.6) | 7 (5.7) | |

MDR=multidrug resistant

**Table 3.** Characteristics and severity of infection

| Characteristics and severity of infection | Total (n=364) | Non-MDR Gram-negative bacteremia (n=241) | MDR Gram-negative bacteremia (n=123) | p-value |
|---|---|---|---|---|
| Community-acquired infection; n (%) | 310 (85.2) | 206 (85.5) | 104 (84.6) | 0.814 |
| Healthcare-associated infection; n (%) | 54 (14.8) | 35 (14.5) | 19 (15.5) | |
| Primary bacteremia; n (%) | 149 (40.9) | 112 (46.5) | 37 (30.1) | 0.003 |
| Respiratory tract | 23 (6.3) | 15 (6.2) | 8 (6.5) | 0.917 |
| Genitourinary tract | 179 (49.2) | 101 (41.9) | 78 (63.4) | <0.001 |
| Intraabdominal | 20 (5.5) | 15 (6.2) | 5 (4.1) | 0.393 |
| Wound and soft tissue | 4 (1.1) | 3 (1.2) | 1 (0.8) | 0.709 |
| Catheter-related infection | 9 (2.5) | 8 (3.3) | 1 (0.8) | 0.145 |
| Severity of infection; n (%) | | | | 0.206 |
| SIRS | 213 (58.5) | 148 (61.4) | 65 (52.9) | |
| Sepsis | 74 (20.3) | 48 (19.9) | 26 (21.1) | |
| Septic shock | 77 (21.2) | 45 (18.7) | 32 (26.0) | |
| Organ dysfunction; n (%) | 215 (59.1) | 133 (55.2) | 82 (66.7) | 0.035 |
| Respiratory | 60 (16.5) | 37 (15.4) | 23 (18.7) | 0.416 |
| Renal | 127 (34.9) | 82 (34.0) | 45 (36.6) | 0.628 |
| Cardiovascular | 85 (23.4) | 58 (24.1) | 27 (22.0) | 0.652 |
| CNS | 92 (25.3) | 52 (21.6) | 40 (32.5) | 0.023 |
| Hematologic | 29 (8.0) | 18 (7.5) | 11 (8.9) | 0.623 |
| GI | 47 (12.9) | 35 (14.5) | 12 (9.8) | 0.200 |
| Metabolic acidosis | 39 (10.7) | 19 (7.9) | 20 (16.3) | 0.015 |
| APACHE II score; median (IQR) | 22 (17 to 27) (n=37) | 21 (15.5 to 24.75) (n=26) | 25 (21.5 to 29) (n=11) | 0.051 |

APACHE=acute physiology and chronic health evaluation; CNS=central nervous system; GI=gastrointestinal; IQR=interquartile range; MDR=multidrug resistant; SD=standard deviation; SIRS=systemic inflammatory response syndrome

abdominal region in 5.5%. The prevalence of GNB bacteremia with an unidentified source of infection was found to be 40.9% (Table 3). The incidence of organ dysfunction was determined to be significantly higher in subjects with MDR infection, which was 66.7%, compared to those with non-MDR infection at 55.2% (p=0.035). The prevalence of central nervous system dysfunction (p=0.023) and metabolic acidosis (p=0.015) was higher in subjects with MDR infection than those with non-MDR infection (Table 3).

### Factors associated with MDR Gram-negative bacteria infection

The factors significantly positively associated with MDR GNB infection compared to non-MDR GNB infection were previous stay in a long-term care facility (adjusted OR [aOR] 4.25, 95% CI 1.47 to 12.29, p=0.008), hospitalization in the previous 90 days (aOR 3.40, 95% CI 1.62 to 7.16, p=0.01), and infection of the genitourinary tract (aOR 2.33, 95% CI 1.04 to 5.20, p=0.040) (Table 4).

**Table 4.** Univariate and multivariate analysis of risk factors for MDR Gram-negative bacilli bacteremia

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | cOR (95% CI) | p-value | aOR (95% CI) | p-value |
| Long-term urinary catheter | 2.55 (1.30 to 4.99) | 0.006 | 0.80 (0.33 to 1.92) | 0.616 |
| Residence in long-term care facility | 4.13 (1.78 to 9.58) | 0.001 | 4.25 (1.47 to 12.29) | 0.008 |
| Previous admission within 90 days | 4.96 (3.06 to 8.08) | <0.001 | 3.40 (1.62 to 7.16) | 0.01 |
| Previous antibiotic use within 90 days | 3.87 (2.45 to 6.12) | <0.001 | 1.79 (0.74 to 4.34) | 0.196 |
| Type of ATB exposure: Penicillin | 2.73 (1.16 to 6.42) | 0.021 | 1.15 (0.41 to 3.28) | 0.790 |
| Type of ATB exposure: Third-generation cephalosporin | 3.17 (1.78 to 5.63) | <0.001 | 1.18 (0.54 to 2.59) | 0.683 |
| Type of ATB exposure: Carbapenem | 2.34 (1.31 to 4.18) | 0.004 | 0.73 (0.30 to 1.75) | 0.477 |
| Type of ATB exposure: Fluoroquinolone | 3.06 (1.41 to 6.64) | 0.005 | 1.25 (0.48 to 3.25) | 0.640 |
| Prior MDR colonization/infection | 3.96 (2.20 to 7.13) | <0.001 | 1.59 (0.71 to 3.56) | 0.259 |
| Wound dressing at the hospital | 3.71 (1.75 to 7.86) | 0.001 | 1.83 (0.71 to 4.67) | 0.209 |
| Type of organism | 0.99 (0.97 to 1.01) | 0.230 | 0.99 (0.97 to 1.01) | 0.193 |
| Primary bacteremia | 0.50 (0.31 to 0.79) | 0.003 | 1.04 (0.47 to 2.33) | 0.916 |
| Site of infection: Genitourinary | 2.40 (1.54 to 3.76) | <0.001 | 2.33 (1.04 to 5.19) | 0.040 |
| Having organ dysfunction | 1.62 (1.03 to 2.55) | 0.036 | 1.17 (0.64 to 2.13) | 0.614 |
| Organ dysfunction: CNS | 1.75 (1.08 to 2.85) | 0.024 | 0.76 (0.38 to 1.52) | 0.430 |
| Organ dysfunction: Metabolic acidosis | 2.27 (1.16 to 4.43) | 0.017 | 2.38 (0.99 to 5.74) | 0.053 |
| APACHE II score | 1.13 (1.00 to 1.27) | 0.05 | 0.99 (0.95 to 1.03) | 0.471 |

aOR=adjusted odds ratio; APACHE=acute physiology and chronic health evaluation; ATB=antibiotic; CI=confidence interval; CNS=central nervous system; cOR=crude odds ratio; MDR=multidrug resistant

### Characteristics of antimicrobial treatment

Among the subjects with GNB infection, 211 (58.2%) received their first dose of antibiotics within one hour of being diagnosed with sepsis. Subjects in the non-MDR group were prescribed significantly more third-generation cephalosporins as initial antibiotics (p=0.018), whereas subjects in the MDR group were prescribed significantly more carbapenems (p=0.016). It is notable that 78% of the subjects with GNB bacteremia received antibiotics against susceptible organisms within 24 hours of being diagnosed with bacteremia. Susceptibility to antimicrobial therapy within 24 hours was lower in the MDR group, at 46.3%, than in the non-MDR group, at 94.2%, (p<0.001) (Table 5).

The antibiotic regimens for 184 subjects with GNB bacteremia (50.6%) were adjusted by the attending physicians over the therapy period. The antibiotic regimen that was altered was characterized as specific antimicrobial therapy. Among the non-MDR group, 129 subjects, or 53%, continued to receive empirical antibiotics as part of their ongoing therapy. Seventy-one subjects, or 58%, in the MDR group received specific antibiotic therapy, which enhanced coverage compared to empirical antibiotics (Table 5).

Although 80.8% of subjects with GNB received appropriate specific antibiotic treatment, 19.9% of subjects in the non-MDR group were overtreated compared with the MDR group, which was 0.8%, while 10.6% of subjects in the MDR group were undertreated compared with the non-MDR group, which was 2.9% (p<0.001). Subjects in the MDR group received significantly more carbapenems as specific antibiotics (p<0.001), whereas subjects in the non-MDR group received more third-generation cephalosporins (p<0.001) (Table 5).

### Outcomes and complications of infection

Subjects in the MDR and non-MDR groups did not significantly differ in terms of mortality at the end of the antibiotic course (p=0.737). Subjects in the MDR group did not have a significantly lower survival rate than subjects in non-MDR group (p=0.976). The median duration of hospital stay for the MDR group was 11 days (IQR 7 to 21.5), longer than the non-MDR group's median of 10 days (IQR 5 to 18), with a p-value of 0.020. The median duration of fever in the MDR group was three days (IQR 2 to 5), longer than the non-MDR group, which had a median of three days (IQR 1 to 5) (p=0.041). There was no significant difference between the groups in evidence of superinfection (p=0.420) and evidence of reinfection (p=0.371). There was also no significant difference between groups in the incidence of complications such as antibiotic-associated diarrhea

**Table 5.** Characteristics of antimicrobial administration

| Characteristics of antimicrobial administration | Total (n=364); n (%) | Non-MDR Gram-negative bacteremia (n=241); n (%) | MDR Gram-negative bacteremia (n=123); n (%) | p-value |
|---|---|---|---|---|
| Time to initiate the first dose of ATB | | | | 0.076 |
| Within 1 hour | 212 (58.2) | 148 (61.5) | 64 (52.0) | |
| 1 to 2 hours | 78 (21.4) | 43 (17.8) | 35 (28.5) | |
| 2 to 3 hours | 28 (7.7) | 17 (7.1) | 11 (8.9) | |
| 3 to 6 hours | 16 (4.4) | 13 (5.4) | 3 (2.4) | |
| >6 hours | 30 (8.2) | 20 (8.3) | 10 (8.1) | |
| Received full-loading dose | 347 (95.3) | 227 (94.2) | 120 (97.6) | 0.149 |
| Appropriate dose and dosing interval within 48 hours | 347 (95.3) | 230 (95.4) | 117 (95.1) | 0.893 |
| Susceptible of ATB within 24 hours | 284 (78.0) | 227 (94.2) | 57 (46.3) | <0.001 |
| Type of empirical antibiotic | | | | 0.743 |
| Monotherapy | 301 (82.7) | 196 (81.3) | 105 (85.4) | |
| Combined therapy | 61 (16.8) | 44 (18.3) | 17 (13.8) | |
| Empirical ATB treatment | | | | |
| Third-generation cephalosporin | 206 (56.6) | 147 (61.0) | 59 (48.0) | 0.018 |
| Carbapenem | 115 (31.6) | 66 (27.4) | 49 (39.8) | 0.016 |
| BL/BI | 26 (7.1) | 14 (5.8) | 12 (9.8) | 0.167 |
| Aminoglycoside | 21 (5.8) | 12 (5.0) | 9 (7.3) | 0.366 |
| Fluoroquinolone | 19 (5.2) | 15 (6.2) | 4 (3.3) | 0.228 |
| Colistin | 1 (0.3) | 1 (0.4) | 0 (0.0) | 0.474 |
| Fosfomycin | 4 (1.1) | 2 (0.8) | 2 (1.6) | 0.491 |
| Specific ATB treatment | | | | <0.001 |
| De-escalated | 57 (15.6) | 54 (22.4) | 3 (2.4) | |
| Continued | 177 (48.6) | 129 (53.5) | 48 (39.0) | |
| Escalated | 127 (34.8) | 56 (23.2) | 71 (57.7) | |
| Appropriateness of specific ATB | | | | <0.001 |
| Appropriate | 294 (80.8) | 185 (76.8) | 109 (88.6) | |
| Overtreatment | 49 (13.5) | 48 (19.9) | 1 (0.8) | |
| Undertreatment | 20 (5.5) | 7 (2.9) | 13 (10.6) | |
| Specific ATB treatment | | | | |
| Third-generation cephalosporin | 138 (37.9) | 132 (54.8) | 6 (4.9) | <0.001 |
| Carbapenem | 182 (50.0) | 80 (33.2) | 102 (82.9) | <0.001 |
| BL/BI | 22 (6.0) | 14 (5.8) | 8 (6.5) | 0.792 |
| Aminoglycoside | 18 (5.0) | 13 (5.4) | 5 (4.1) | 0.580 |
| Fluoroquinolone | 24 (6.6) | 19 (7.9) | 5 (4.1) | 0.165 |
| Colistin | 7 (1.9) | 1 (0.4) | 6 (4.9) | 0.003 |
| Fosfomycin | 16 (4.4) | 5 (2.1) | 11 (8.9) | 0.002 |

ATB=antibiotic; BL/BI=beta-lactam/beta-lactamase inhibitors; MDR=multidrug resistant

(p=0.397) and acute kidney injury requiring renal replacement therapy (p=0.768) (Table 6).

### Association between appropriateness of antibiotic treatment and mortality among subjects with MDR GNB bacteremia

Univariate and multivariate analyses were conducted to assess the association between the suitability of antibiotic treatment and mortality among subjects with MDR GNB infection. The findings revealed a significant association between the appropriateness of empirical antibiotics and survival in the MDR group (crude OR [cOR] 0.09, 95% CI 0.02 to 0.53, p=0.008; aOR 0.07, 95% CI 0.12 to 0.43, p=0.004). Univariate analysis showed no significant association between the appropriateness of specific antibiotics and mortality among subjects with MDR infection (cOR 1.81, 95% CI 0.98 to 3.35, p=0.059; aOR 2.05, 95% CI 1.09 to 3.86, p=0.025).

**Table 6.** Outcomes and complications of infection

| Outcomes and complications of infection | Total (n=364) | Non-MDR Gram-negative bacteremia (n=241) | MDR Gram-negative bacteremia (n=123) | p-value |
|---|---|---|---|---|
| Clinical outcome at the end of antibiotic treatment | | | | 0.737 |
| Infection improved | 316 (86.8) | 210 (87.1) | 106 (86.2) | |
| Infection worsened | 8 (2.2) | 4 (1.7) | 4 (3.3) | |
| Death from infection | 38 (10.4) | 26 (10.8) | 12 (9.8) | |
| Death from other causes | 2 (0.6) | 1 (0.4) | 1 (0.8) | |
| Hospital outcome | | | | 0.976 |
| Cured/improved | 301 (82.7) | 200 (83) | 101 (82.1) | |
| Death from infection | 49 (13.5) | 32 (13.3) | 17 (13.8) | |
| Death from other causes | 14 (3.9) | 9 (3.7) | 5 (4.1) | |
| Evidence of superinfection | 23 (6.3) | 17 (7.1) | 6 (4.9) | 0.420 |
| Evidence of reinfection | 6 (1.7) | 5 (2.1) | 1 (0.8) | 0.371 |
| Antibiotic-associated diarrhea | 6 (1.7) | 3 (1.2) | 3 (2.4) | 0.397 |
| Acute kidney injury needs RRT | 5 (1.4) | 3 (1.2) | 2 (1.6) | 0.768 |
| Length of fever in days; median (IQR) | 3 (1 to 5) | 3 (1 to 5) | 3 (2 to 5) | 0.041 |
| Length of hospital stay in days; median (IQR) | 11 (5 to 19) | 10 (5 to 18) | 11 (7 to 21.5) | 0.020 |

IQR=interquartile range; GI=gastrointestinal; MDR=multidrug resistant; RRT=renal replacement therapy; SD=standard deviation

## Discussion

The prevalence of MDR GNB bacteremia in this present was 33.8%, which was slightly higher than the 30.8% prevalence data recently reported at a community hospital between January 2016 and December 2020[19], yet lower than the 48.8% documented at an academic tertiary hospital in Thailand in 2012[10]. This could be due to greater disease complexity in the academic tertiary hospital. In 2016, Thailand approved the first five-year National Strategic Plan on AMR for 2017 to 2021, emphasizing the reduction of AMR morbidity in hospitals, the decrease of antimicrobial consumption in human and animal sectors, and the enhancement of public awareness. The strategies to attain the objectives of the national plan encompass regulating antimicrobial distribution, prevention, and control of hospital-acquired infections, and enhancing antimicrobial stewardship to encourage the judicious use of antimicrobials in hospitals, clinics, and pharmacies[20]. These national strategic initiatives may aid in diminishing the incidence of AMR in facilities. *E. coli* and *K. pneumoniae* remained the most common pathogens among non-MDR and MDR Gram-negative bacteria, with proportions of MDR infection of 39% and 23.7%, respectively, compared with previous reports[2,10,19]. The proportion of resistant isolates varied by country and territory[2,6]. The current study could not determine the difference in mortality between the two groups. However, the duration of hospitalization and fever was much greater in the MDR group. These findings were consistent with other investigations[5,8,9].

The present study identified three variables significantly associated with MDR GNB bacteremia, which were residence in a long-term care facility, previous hospitalization within 90 days, and genito-urinary tract infection.

Studies indicate that residing in long-term care facility is a risk factor for multidrug-resistant organism (MDRO) colonization, which can then be transmitted and lead to infections[9,11,21]. The overall prevalence of colonization with MDROs in long-term care facility worldwide varies by continents. The median global prevalence for extended-spectrum β-lactamase (ESBL) Enterobacteralses, CR-Enterobacterales, and methicillin-resistant *Staphylococcus aureus* (MRSA) reported was 11.6%, 0.8%, and 13.2%, respectively[22]. The highest prevalence of these pathogens was observed in Asia, with ESBL-Enterobacterales, CR-Enterobacterales, and MRSA at 71.6%, 6.9%, and 25.6%, respectively[22]. This finding aligns with the outcome of a recent prospective cohort conducted in a nursing home in Thailand. The present study revealed that 38% of residents exhibited ESCR-Enterobacterales colonization, with an all-cause mortality rate of 18%[23]. In this study, 13.8% of patients with MDR GNB bacteremia were residents of long-term care facilities, compared to 3.7% in the non-MDR cohort. This finding is consistent with a large cohort of patients from Singapore's tertiary referral hospitals that indicates that the risk of MDR

Gram-negative bacteremia is over five times higher in residents living in long-term care facility compared to those not residing in such facility[11].

Factors contributing to the acquisition of resistant pathogens as a resident of a long-term care facility are divided into resident-related and facility-related factors. Resident-related factors included previous antibiotic use, use of invasive devices such as urinary catheters and feeding tubes, lower functional status, previous colonization with MDR organisms, and physical condition, including decubitus ulcers, wounds, urinary incontinence, and comorbidities[21]. Facility-related factors included higher patient-to-staff ratios and a lack of infection control measures, such as hand hygiene, cough etiquette, and barrier precautions[21].

Hospitalized patients have an increased risk of being colonized by resistant pathogens as a result of the extensive use of antibiotics, and cross-transmission between healthcare personnel, patients, and the environment that can increase the risk of MDR infection[24,25]. A prospective surveillance study conducted at a Thai academic tertiary hospital revealed an increasing trend of MDR bacterial colonization among hospitalized patients following admission(24). This trend was most pronounced for ESCR *Klebsiella* spp. and CR *A. baumannii* and *P. aeruginosa*[24]. The observational study from the university hospital in Taiwan demonstrated the occurrence of MDR bacterial colonization in hospitalized patients increased the risk of subsequent MDR infection and mortality during 12 months after discharge[26].

Genitourinary tract infections showed a stronger association with MDR GNB than other infections in this study. Urinary tract infections (UTIs) are common bacterial infections in both community and hospital settings, and an increasing burden of bacterial AMR in UTI has also been observed[27]. A recent study in East Africa had estimated that the proportion of MDR uropathogens was as high as 51%[28]. A recent study conducted in northern Thailand reported that the incidence of community-acquired UTIs caused by MDR-Enterobacterales was 25.7%[29]. The National Antimicrobial Resistance Surveillance Center of Thailand reported in 2021 that up to 55% of urine samples from 83 hospitals throughout the country contained higher concentration of Enterobacterales that were resistant to third-generation cephalosporins[30]. This implied that a higher proportion of secondary bacteremia resulting from UTI would be MDR. A retrospective cohort study conducted at University Hospital in Missouri, USA, revealed that the urinary catheter served as a source of infection, promoting the development of MDR-GNB and increasing the mortality rate in patients with MDR-GNB bacteremia by approximately five times[13]. The result of this study, consistent with a case-control study conducted in a rural community hospital in Thailand, revealed that UTI increase the risk of MDR-GNB infections twofold[19]. Furthermore, UTI is a common infection for which people frequently purchase antibiotics from pharmacies, which are occasionally used inappropriately, contributing to the development of drug resistance.

In this study, 87% of patients received the first dose of antibiotics within three hours. Studies have shown that a delay in starting antibiotic treatment increases the likelihood of death in people with sepsis. Therefore, antibiotic administration is crucial for the treatment of sepsis and septic shock[31]. For adults with suspected septic shock or a high probability of sepsis, the Surviving Sepsis Campaign 2021 strongly recommends promptly delivering antimicrobials, ideally within one hour after recognition[32].

The appropriateness of empirical antibiotics was significantly associated with survival in the MDR bacteremia group in the present study. This result is consistent with previous research reporting that the improper use of empirical antibiotics increases mortality[8,10-12,33]. In this study, only 57 patients (46.3%) in the MDR bacteremia group received an antibiotic against susceptible organisms within 24 hours. A lack of awareness of the potential for MDR organisms to cause infections contributes to inappropriate initial empirical antibiotic use[34,35]. Additionally, the prescriber's knowledge or institutional policies regarding local guideline for empirical antibiotics could potentially contribute to inappropriate empirical antibiotic use. Therefore, individual risk factors, the severity of infection, and local epidemiological data should be considered when selecting empirical antibiotics to reduce mortality. To optimize antimicrobial utilization, it is important to precisely diagnose clinical syndrome before starting antibiotics and implement and adhere to local guidelines for empirical antibiotics[36].

Most of the 66 individuals in the MDR group given improper empirical antibiotic therapy had their therapy modified to a specific antibiotic regimen. As a result, the proportion of inappropriate antibiotic therapy decreased from 46.3% to 11.4%. In the non-MDR group, 19.9% of specific antibiotics were

considered inappropriate due to overtreatment, which was a result of not de-escalating to narrower-spectrum antibiotics. The authors could not establish a correlation between previous use of broad-spectrum antimicrobials and subsequent infections caused by MDR organisms. Nevertheless, the key aspect of an antibiotic stewardship program to further decrease MDR infections is de-escalation of antimicrobial therapy based on susceptibility results[37]. In this study, 10.6% of the specific antibiotics in the MDR group were considered to be an undertreatment. This might have been due to the physician's inability to keep updated on the susceptibility results of these organisms, resulting in a failure to adjust the antimicrobials according to the susceptibility data.

This 4-year retrospective cohort study is the first to investigate factors and outcomes associated with MDR GNB bacteremia at the present study facility. Epidemiological data and associated factors can be applied to manage at-risk patients and achieve favorable outcomes. This study has limitations. First, some variables were not included in the data records, such as socioeconomic factors, co-morbidities beyond those recorded, patient compliance with treatment, the patient's history of previous antibiotic use or hospitalization if they were admitted to this facility for the first time, the reason for inappropriate specific antibiotic use, reports of reinfection or superinfection, and consequent MDR infection. Second, the present study was conducted at a single-center tertiary care hospital. This limits the adaptability of the findings to different hospital types or geographic locations. Third, owing to its retrospective nature, this study limits the ability to establish causation. Multi-center prospective studies are essential to further investigate risk factors associated with MDRO infection that cannot be gathered from retrospective studies. The factors of inappropriate empirical and specific antibiotic use, as well as the outcomes and burden of MDR infections need to be included. This will facilitate the development of local guidelines for empirical antibiotic use in patients at risk of MDR infections.

## Conclusion

Residence in a long-term care facility, previous hospitalization within 90 days, and genitourinary tract infection were factors associated with MDR GNB bacteremia. Therefore, patients whose disease course includes these factors should receive empiric antibiotics covering MDR GNB bacteremia. Nonetheless, any facility can determine this result based on regional variations in AMR patterns and practices. Further studies are needed to determine whether making these changes will result in improved survival of the study population.

## What is already known on this topic?

The number of MDR infections is constantly increasing globally. The incidence of MDR infections and associated risk factors vary across hospitals. Early administration of antibiotics covering MDR pathogens based on risk assessment enhances treatment outcomes and reduces mortality.

## What does this study add?

MDR GNB bacteremia was associated with residing in a long-term care facility, previous hospitalization within 90 days, and genitourinary tract infection. Consequently, patients whose disease course comprised these factors should be administered empiric antibiotics that respond to MDR GNB bacteremia.


## Acknowledgment

The authors thank Unchana Thawornwan and Ponnapa Phoonlapphon, medical technologists at the Clinical Microbiology Laboratory, Bamrasnaradura Infectious Diseases Institute, Thailand, for providing laboratory data support for the present study.


## Authors' contributions

TS and AT provide substantial contributions to the study concept and design, data collecting, data analysis and interpretation, and drafting of the manuscript. LC, PS, and WM significantly contributed to the conceptualization and design of the study, the interpretation of data, and the critical revision of the manuscript. All authors made significant contributions to the critical revisions and gave their approval to the final manuscript.


## Funding disclosure

The present research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.


## Conflicts of interest

The authors declare that there are no competing interests.

## References


1. Dadgostar P. Antimicrobial resistance: Implications and costs. Infect Drug Resist 2019;12:3903-10.

2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399:629-55.
3. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019 [Internet]. Atlanta, GA: CDC; 2019 [cited 2022 Oct 16]. Available from: https://ndc.services.cdc.gov/wp-content/uploads/Antibiotic-Resistance-Threats-in-the-United-States-2019.pdf.
4. O'Neill J, Review on Antimicrobial Resistance (London). Antimicrobial resistance: Tackling a crisis for the health and wealth of nations [Internet]. 2014 [cited 2022 Oct 16]. Available from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.
5. Pumart P, Phodha T, Thamlikitkul V, Riewpaiboon A, Prakongsai P, Limwattananon S. Health and economic impacts of antimicrobial resistance in Thailand: a preliminary study. J Health Serv Res Policy 2012;6:352-60.
6. Global antimicrobial resistance and use surveillance system (GLASS) Report 2021 [Internet]. Geneva: WHO; 2021 [cited 2022 Oct 16]. Available from: https://www.who.int/publications/i/item/9789240027336.
7. Yungyuen T, Chatsuwan T, Plongla R, Kanthawong S, Yordpratum U, Voravuthikunchai SP, et al. Nationwide surveillance and molecular characterization of critically drug-resistant gram-negative bacteria: Results of the research university network Thailand study. Antimicrob Agents Chemother 2021;65:e0067521.
8. Bonine NG, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, et al. Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious gram-negative bacterial infections. Am J Med Sci 2019;357:103-10.
9. Chen G, Xu K, Sun F, Sun Y, Kong Z, Fang B. Risk factors of multidrug-resistant bacteria in lower respiratory tract infections: A systematic review and meta-analysis. Can J Infect Dis Med Microbiol 2020;2020:7268519. doi: 10.1155/2020/7268519.
10. Chaisathaphol T, Chayakulkeeree M. Epidemiology of infections caused by multidrug-resistant gram-negative bacteria in adult hospitalized patients at Siriraj Hospital. J Med Assoc Thai 2014;97 Suppl 3:S35-45.
11. Venkatachalam I, Yang HL, Fisher D, Lye DC, Moi Lin L, Tambyah P, et al. Multidrug-resistant gram-negative bloodstream infections among residents of long-term care facilities. Infect Control Hosp Epidemiol 2014;35:519-26.
12. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Multidrug resistance, inappropriate empiric therapy, and hospital mortality in Acinetobacter baumannii pneumonia and sepsis. Crit Care 2016;20:221. doi: 10.1186/s13054-016-1392-4.
13. Patolia S, Abate G, Patel N, Patolia S, Frey S. Risk factors and outcomes for multidrug-resistant Gram-negative bacilli bacteremia. Ther Adv Infect Dis 2018;5:11-8.
14. Strich JR, Kadri SS. Difficult-to-treat antibiotic-resistant gram-negative pathogens in the intensive care unit: Epidemiology, outcomes, and treatment. Semin Respir Crit Care Med 2019;40:419-34.
15. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
16. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
18. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
19. Ponyon J, Kerdsin A, Preeprem T, Ungcharoen R. Risk Factors of Infections Due to Multidrug-Resistant Gram-Negative Bacteria in a Community Hospital in Rural Thailand. Trop Med Infect Dis 2022;7:328. doi: 10.3390/tropicalmed7110328.
20. Sumpradit N, Wongkongkathep S, Poonpolsup S, Janejai N, Paveenkittiporn W, Boonyarit P, et al. New chapter in tackling antimicrobial resistance in Thailand. BMJ 2017;358:j3415. doi: 10.1136/bmj.j2423.
21. van Buul LW, van der Steen JT, Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, et al. Antibiotic use and resistance in long term care facilities. J Am Med Dir Assoc 2012;13:568.e1-13.
22. Rodríguez-Villodres Á, Martín-Gandul C, Peñalva G, Guisado-Gil AB, Crespo-Rivas JC, Pachón-Ibáñez ME, et al. Prevalence and risk factors for multidrug-resistant organisms colonization in long-term care facilities around the world: A review. Antibiotics (Basel) 2021;10:680. doi: 10.3390/antibiotics10060680.
23. Ngamprasertchai T, Vanaporn M, Muangnoicharoen S, Pan-Ngum W, Ruenroengbun N, Piroonamornpun P, et al. Mortality in thai nursing homes based on antimicrobial-resistant enterobacterales carriage and COVID-19 lockdown timing: A prospective cohort study. Antibiotics (Basel) 2022;11:762. doi: 10.3390/antibiotics11060762.
24. Rattanaumpawan P, Choorat C, Takonkitsakul K, Tangkoskul T, Seenama C, Thamlikitkul V. A prospective surveillance study for multidrug-resistant bacteria colonization in hospitalized patients at a Thai University Hospital. Antimicrob Resist Infect Control 2018;7:102. doi: 10.1186/s13756-018-0393-2.

25. Capsoni N, Bellone P, Aliberti S, Sotgiu G, Pavanello D, Visintin B, et al. Prevalence, risk factors and outcomes of patients coming from the community with sepsis due to multidrug resistant bacteria. Multidiscip Respir Med 2019;14:23. doi: 10.1186/s40248-019-0185-4.
26. Tseng WP, Chen YC, Chen SY, Chen SY, Chang SC. Risk for subsequent infection and mortality after hospitalization among patients with multidrug-resistant gram-negative bacteria colonization or infection. Antimicrob Resist Infect Control 2018;7:93. doi: 10.1186/s13756-018-0388-z.
27. Li X, Fan H, Zi H, Hu H, Li B, Huang J, et al. Global and Regional Burden of Bacterial Antimicrobial Resistance in Urinary Tract Infections in 2019. J Clin Med 2022;11:2817. doi: 10.3390/jcm11102817.
28. Mlugu EM, Mohamedi JA, Sangeda RZ, Mwambete KD. Prevalence of urinary tract infection and antimicrobial resistance patterns of uropathogens with biofilm forming capacity among outpatients in morogoro, Tanzania: a cross-sectional study. BMC Infect Dis 2023;23:660. doi: 10.1186/s12879-023-08641-x.
29. Assawatheptawee K, Treebupachatsakul P, Luangtongkum T, Niumsup PR. Risk factors for community-acquired urinary tract infections caused by multidrug-resistant enterobacterales in Thailand. Antibiotics (Basel) 2022;11:1039. doi: 10.3390/antibiotics11081039.
30. National Antimicrobial Resistant Surveillance Center, Thailand (NARST). Antibiogram [Internet]. 2021 [cited 2022 Sep 8]. Available from: http://narst.dmsc.moph.go.th/.
31. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749-55.
32. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
33. Lueangarun S, Leelarasamee A. Impact of inappropriate empiric antimicrobial therapy on mortality of septic patients with bacteremia: a retrospective study. Interdiscip Perspect Infect Dis 2012;2012:765205. doi: 10.1155/2012/765205.
34. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237-48.
35. Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranellou K, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. Clin Microbiol Infect 2011;17:1798-803.
36. Wisutep P, Thamlikitkul V, Sirijatuphat R. Effectiveness of implementing a locally-developed guideline for antibiotic treatment of lower urinary tract infection in adults in Thailand. Sci Rep 2023;13:18013. doi: 10.1038/s41598-023-5299-6.
37. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs [Internet]. Atlanta, GA: US Department of Health and Human Services, CDC; 2019 [cited 2022 Oct 16]. Available from: https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.