Risk Factors and Outcomes for Multidrug-resistant Gram-negative Bacterial Infection in Adult Patients with Abdominal Surgery Requiring Intensive Care

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Abstract

Background: Multidrug-resistant (MDR) gram-negative bacterial (GNB) infections remain a significant cause of morbidity and mortality among surgical patients. The objective of our study was to recognize the risk factors for MDR GNB infection in surgical intensive care unit (SICU) patients with abdominal surgery and determine the predictors independently associated with death.

Methods: From 2010 to 2017, a retrospective cohort study was conducted among patients with abdominal surgery admitted in SICU. Patients with GNB (MDR and non-MDR) infections were included for analyses.

Results: A total of 364 patients with abdominal surgery experienced GNB infections, among them, 117 (32.1%) were MDR GNB infections. Of 133 MDR GNB isolates, the most frequent isolate was *Escherichia coli* (45.1%). Patients with MDR GNB infection had significantly longer ventilator days and hospital stay, as well as higher 30-day and in-hospital mortality compared to non-MDR GNB patients. Multivariable analysis showed longer length of pre-ICU stay, surgical re-exploration, received anti-pseudo carbapenems and fluoroquinolones, and higher total bilirubin were independent risk factors for the acquisition of MDR GNB infection. Predictors for 30-day mortality among patients with MDR GNB infection were chronic kidney disease, received anti-pseudo carbapenems and inappropriate empirical antimicrobial therapy.

Conclusions: This study provides important information about the risk factors for subsequent MDR GNB infection and 30-day mortality among the patients with abdominal surgery. Given the increasingly MDR GNB infection and mortality, implementation of antimicrobial stewardship programs in critical care unit is crucial to reduce MDR pathogens and optimize antimicrobial therapies.

Introduction

Despite the advances in infection control and postoperative care, bacterial infections remain a major problem after surgery and contribute significantly to the rate of morbidity and mortality[1–3]. Besides, postsurgical infection leads to increased length of hospital stay, higher rates of hospital readmission and higher healthcare costs [4–6]. While gram-negative bacteria (GNB) are becoming more common pathogens of postoperative infections, multidrug-resistance (MDR) strains among GNB were more prevalent substantially [7, 8] with the incidence up to 48–65% in critically ill patients [9, 10]. Previous studies have identified risk factors for acquiring MDR GNB infection [11, 12]. Identifying a subgroup of critically ill patients who have a high risk of harboring MDR GNB infection after abdominal surgery would have important implications for patient care and outcomes. Meanwhile, antimicrobial stewardship is particularly important for intensive care unit (ICU) settings due to increasing trends in antimicrobial resistance of bacterial pathogens. The online antimicrobial-stewardship program has been implemented in the ICUs of the Kaohsiung Chang Gung Memorial Hospital, as previously reported [13, 14]. Briefly, all antimicrobial agents prescribed to ICU patients required approval from infectious diseases physicians. If a prescription was disapproved, the antimicrobial would be discontinued within 48 hours, and the

prescriber would be notified to modify the regimen [13, 14]. In the present study, we sought to recognize the risk factors for the development of infection caused by MDR GNB in surgical ICU (SICU) patients who underwent abdominal surgery and determine the predictors independently associated with death.

Methods

Study design, setting and participants

From January 2010 to December 2017, all consecutive adult patients (≥ 18 years old) who underwent abdominal surgery and admission to SICU, at the Kaohsiung Chang Gung Memorial Hospital, a 2,600-bed primary care and tertiary referral medical center in Taiwan, were retrospectively included. The SICU is a 23-bed multispecialty intensive care center for critically ill patients who receive surgery including severe trauma and acute abdomen surgery (stomach, intestine/colon, appendix, rectum, liver, biliary system, pancreas, spleen and kidney), or those experiencing shock, cardiac arrest or sepsis after major surgery.

Patients were categorized as those either with MDR or non-MDR GNB infections. A comparison was made between MDR and non-MDR GNB patients to determine the independent risk factors for the acquisition of MDR GNB. To analyze the predictors of 30-day mortality among MDR GNB patients, we further compared clinical characteristics and laboratory findings as well as complications of survivors and non-survivors.

Definitions

The surgical site was divided into (1) digestive system (includes esophagus, stomach, duodenal, small intestinal, colon, appendix and rectum) and (2) hepatobiliary/pancreas/spleen and kidney. If a patient had multiple episodes of GNB (MDR and non-MDR) infection during the study period, only the first episode was included for analyses. In cases of polymicrobial infections, the episode was defined as an MDR GNB case if one of the isolates was an MDR GNB strain. Chronic kidney disease is defined as kidney damage or glomerular filtration rate < 60 mL/min/1.73 m2 for 3 months or more, irrespective of cause [15]. MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories according to the consensus definition proposed by the Centers for Disease Control and Prevention [16]. The non-susceptibility refers to either a resistant, intermediate or non-susceptible result obtained from in vitro antimicrobial susceptibility testing [16]. Empiric antibiotic therapy was considered inappropriate if it did not include at least one antibiotic active against the GNB in vitro.

Data collection

The data were mainly retrieved from the Chang Gung Research Database, the largest multi-institutional electronic medical records collection in Taiwan [17], and were supplemented by a secondary manual search. The Chang Gung Research Database is a de-identified database derived from original medical records of Kaohsiung Chang Gung Memorial Hospital, with large volumes of database for research studies and analysis. We collected patient demographics and characteristics, Charlson Comorbidity Index, American Society of Anesthesiologists Classification, surgical wound classification [18], operative time, surgical sites, and number of re-explorations. We also retrieved the information regarding of

invasive procedures and management including blood transfusion, surgical drainage (including pigtail, chest tube, Jackson-Pratt drains, abdominal open drains, and percutaneous transhepatic cholangiography and drainage), enteral tube (including nasogastric tube, nasoduodenal tube, jejunostomy tube, and gastrostomy tube), mechanical ventilation, invasive vascular access (including arterial lines, central venous catheters, Swan-Ganz catheters, large-bore catheters, and Hickman lines), foley catheter and hemodialysis. A medication information prescribed within 30 days before the onset of GNB infection was extracted including antibiotics, steroid, inotropic agents, chemotherapy and immunosuppressive agents.

Laboratory parameters included white cell blood□platelet count□hemoglobin□creatinine□C-reactive protein□ albumin□alanine aminotransferase and total bilirubin levels were obtained. Microbiology specimens (including blood, ascites, bile, abscess, excision tissue, surgical wound and body fluid) collection from different anatomical sites were obtained. The culture results of urine specimen and central venous catheter tip were excluded from the study. The length of stay prior to ICU admission, duration of mechanical ventilation, 30-day fatality after the onset of GNB infection and in-hospital mortality were record for analyses.

Antimicrobial susceptibility testing

Microbiology laboratories performed antimicrobial susceptibility testing of isolates using disk diffusion or automated testing methods according to guidelines and breakpoints established by the Clinical Laboratory and Standards Institute [19].

Statistical analysis

Values for continuous and categorical variables are expressed as means ± standard deviations (SD) and the number and percentage of the group from which they are derived. The ANOVA Wilcoxon test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables, as appropriate. The logistic regression model with a stepwise procedure was used for multivariate analysis. Kaplan-Meier was used for 30-day survival analysis. All tests of significance used a 2-sided $P < .05$. Statistical analyses were conducted using SAS EG version 5.1.

Results

Patients characteristics

A study flow-chart is shown in Fig. 1. A total of 6720 surgical patients were found during the study period, and among them, 364 patients underwent abdominal surgery (283 [77.7%] patients received digestive system surgery and 81 [22.3%] received hepatobiliary/pancreas/spleen or kidney surgery) and experienced GNB infections were included. Among 364 (247 [67.9%] were non-MDR GNB and 117 [32.1%] MDR GNB) patients, 106 (29%) admitted directly from the emergency department to the SICU, and 258 (71%) patients were scheduled admissions subsequently required ICU care after surgery. Totally, 228 (62.6%) patients managed with emergency surgical intervention. Surgical re-exploration was found in 124

(34%) patients. The characteristic of the 364 patients with GNB (MDR and non-MDR) infection is summarized in Table 1.

Table 1
Demographic, clinical and laboratory characteristics of 364 patients with abdominal surgery experienced MDR and non-MDR GNB infections.

Variable	Non-MDR GNB group (n = 247)	MDR GNB group (n = 117)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Male	147 (59.5)	70 (59.8)	-		
Age ≧ 65 years	160 (64.8)	73 (62.4)	-		
Charlson score > 3 points	140 (56.7)	65 (55.6)	-		
Ischemic heart disease	7 (2.8)	3 (2.6)	-		
Congestive heart failure	24 (9.7)	14 (12.0)	-		
Peripheral vascular disease	19 (7.7)	16 (13.7)	-		
Cerebrovascular disease	39 (15.8)	13 (11.1)	-		
Chronic pulmonary obstructive disease	48 (19.4)	25 (21.4)	-		
Type 2 diabetes mellitus	61 (24.7)	23 (19.7)	-		
Malignancy	127 (51.4)	55 (47.0)	-		
Chronic kidney disease	55 (22.3)	35 (29.9)	-		
Length of stay prior to ICU admission, mean (SD) (days)	4.4 (6.8)	8.6 (10.5)	< .001	1.05 (1.02–1.08)	< .001
Requiring emergency surgery	153 (61.9)	75 (64.1)			
ASA score ≦ 3	203 (82.2)	88 (75.2)	-		
Surgical wound classification < 3	183 (74.1)	81 (69.2)	-		
Operative time, mean (SD) (mins)	305.9 (176.1)	288.1 (140.1)	-		
Surgical site					
Digestive system*	192 (77.7)	91 (77.8)	-		

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CT chemotherapy; CRP C-reactive protein; GI gastrointestinal; GNB gram-negative bacteria; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

*Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

Variable	Non-MDR GNB group (n = 247)	MDR GNB group (n = 117)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Hepatobiliary/pancreas/spleen and kidney	55 (22.3)	26 (22.2)	-		
Re-exploration	74 (30.0)	50 (42.7)	.015	1.73 (1.05–2.84)	.031
Blood transfusion	87 (35.2)	66 (56.4)	< .001	-	-
Surgical drainage	89 (36.0)	45 (38.5)	-		
Mechanical ventilation	148 (59.9)	74 (63.2)	-		
Invasive vascular access	162 (65.6)	88 (75.2)	-		
Foley indwelling	163 (66.0)	88 (75.2)	-		
Antimicrobial therapy < 30 days before onset of GNB infection					
Penicillin ± β-lactamase	23 (9.3)	19 (16.2)	-		
Anti-pseudo penicillin	29 (11.7)	31 (26.5)	< .001	-	-
1’ or 2’ cephalosporin	67 (27.1)	37 (31.6)	-		
3’ cephalosporin	110 (44.5)	50 (42.7)	-		
Anti-pseudo cephalosporins	11 (4.5)	14 (12.0)	.008	-	-
Carbapenem group 1	77 (31.2)	34 (29.1)	-		
Anti-pseudo carbapenems	90 (36.4)	67 (57.3)	< .001	2.10 (1.29–3.41)	.003
Fluoroquinolones	12 (4.9)	23 (19.7)	< .001	3.65 (1.64–8.09)	.002
Use of steroid > 2 weeks	136 (55.1)	67 (57.3)	-		

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CT chemotherapy; CRP C-reactive protein; GI gastrointestinal; GNB gram-negative bacteria; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

*Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

Variable	Non-MDR GNB group (n = 247)	MDR GNB group (n = 117)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Use of inotropic agents > 2 days	94 (38.1)	67 (57.3)	< .001	-	-
Use of CT or ISx	13 (5.3)	3 (2.6)	-		
Albumin, mean (SD) (g/dL)	2.9 (0.7) (n = 236)	2.7(0.5) (n = 113)	.027	-	-
WBC, mean (SD) (1000/μL)	10.0 (6.3) (n = 185)	11.6 (8.1) (n = 91)	-		
Hemoglobin < 8 (g/dL)	17 (6.9)	6 (5.1)	-		
Platelet count < 150 (1000/μL)	107 (43.3)	58 (49.6)	-		
CRP, mean (SD) (mg/L)	154.6 (120.9) (n = 140)	129.9 (115.3) (n = 80)	-		
Creatinine > 1.2 (mg/dL)	115 (46.6)	63 (53.8)	-		
ALT > 80 (U/L)	31 (12.6)	17 (14.5)	-		
Total-Bili > 1.4 (mg/dL)	80 (32.4)	64 (54.7)	< .001	2.15 (1.32–3.48)	.002

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CT chemotherapy; CRP C-reactive protein; GI gastrointestinal; GNB gram-negative bacteria; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

*Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

An individual patient might have more than one sample collected from different sites of body. Ascitic fluid (n = 214, 55.6%) was the most common sample cultures positive for GNB, followed by abscess (n = 46, 11.9%), bile aspirate fluid (n = 44, 11.4%) and surgical wound (n = 43, 11.2%). Table 2 shows the distribution of gram-negative bacteria isolates obtained from the 364 patients based on surgical sites and clinical sample sources. A total of 594 (461 [77.6%] isolates in non-MDR and 133 [22.4%] in MDR GNB groups) GNB isolates were isolated. Of 594 GNB isolates, *Escherichia coli* (n = 176, 29.6%) was the most common isolate, followed by Enterobacter sp. (n = 140, 23.6%) and *Klebsiella pneumoniae* (n = 114,19.2%) (Table 3). Among the 133 MDR GNB isolates, the most frequent isolates were *Escherichia coli* (n = 60, 45.1%), *Klebsiella pneumoniae* (n = 23, 17.3%) and Acinetobacter sp. (n = 19, 14.3%) (Table 3). All carbapenem resistant GNB isolates were MDR strain. Carbapenem resistant was found in 47.6% of

acinetobacter spp. and 25% of pseudomonas spp. Thirty-four (8.8%) patients experienced MDR GNB bacteremia.

Table 2
Distribution of gram-negative bacteria isolates obtained from the 364 patients based on surgical sites and clinical sample sources*

Variable	Total isolates (n = 594)	Non-MDR isolates (n = 461)	MDR isolates (n = 133)
Received digestive system surgery†	451 (75.9)	346 (75.1)	105 (78.9)
Abscess			
Escherichia coli	14 (2.4)	10 (2.2)	4 (3.0)
Enterobacter sp.	11 (1.9)	11 (2.4)	0
Klebsiella pneumoniae	9 (1.5)	9 (2.0)	0
Pseudomonas sp.	7 (1.2)	5 (1.1)	2 (1.5)
Non-fermenting GNB	2 (0.3)	1 (0.2)	1 (0.5)
Ascites			
Escherichia coli	108 (18.2)	75 (16.3)	33 (24.8)
Klebsiella pneumoniae	73 (12.3)	61 (13.2)	12 (9.0)
Enterobacter sp.	62 (10.4)	60 (13.0)	2 (1.5)
Pseudomonas sp.	32 (5.4)	30 (6.5)	2 (1.5)
Acinetobacter sp.	19 (3.2)	10 (2.2)	9 (6.8)
Non-fermenting GNB	10 (17.2)	8 (1.7)	2 (1.5)
Haemophilus influenzae	1 (0.2)	1 (0.2)	0
Blood			
Escherichia coli	8 (1.3)	5 (1.1)	3 (2.3)
Enterobacter sp.	8 (1.3)	5 (1.1)	3 (2.3)
Pseudomonas sp.	6 (1.0)	5 (1.1)	1 (0.8)
Acinetobacter sp.	5 (0.8)	2 (0.4)	3 (2.3)
Klebsiella pneumoniae	3 (0.5)	1 (0.2)	2 (1.5)

Data were no. (%). MDR multidrug-resistant; GNB gram-negative bacteria.

*An individual patient might have more than one sample obtained from different sites of body.
†Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

Variable	Total isolates (n = 594)	Non-MDR isolates (n = 461)	MDR isolates (n = 133)
Non-fermenting GNB	3 (0.5)	1 (0.2)	2 (1.5)
Body fluid			
Enterobacter sp.	1 (0.2)	1 (0.2)	0
Klebsiella pneumoniae	1 (0.2)	1 (0.2)	0
Dialysate			
Pseudomonas sp.	1 (0.2)	1 (0.2)	0
Tissue			
Escherichia coli	2 (0.3)	0	2 (1.5)
Enterobacter sp.	1 (0.2)	0	1 (0.8)
Non-fermenting GNB	1 (0.2)	1 (0.2)	0
Wound			
Pseudomonas sp.	19 (3.2)	18 (3.9)	1 (0.8)
Escherichia coli	16 (2.7)	9 (2.0)	7 (5.3)
Enterobacter sp.	11 (1.9)	8 (1.7)	3 (2.3)
Acinetobacter sp.	7 (1.2)	2 (0.4)	5 (3.8)
Klebsiella pneumoniae	5 (0.8)	2 (0.4)	3 (2.3)
Non-fermenting GNB	5 (0.8)	3 (0.7)	2 (1.5)
Received hepatobiliary/pancreas/spleen and kidney surgery	143 (24.1)	115 (24.9)	28 (21.1)
Abscess			
Pseudomonas sp.	8 (1.3)	7 (1.5)	1 (0.8)
Escherichia coli	5 (0.8)	3 (0.7)	2 (1.5)
Klebsiella pneumoniae	5 (0.8)	4 (0.9)	1 (0.8)
Enterobacter sp.	3 (0.5)	3 (0.7)	0

Data were no. (%). MDR multidrug-resistant; GNB gram-negative bacteria.

*An individual patient might have more than one sample obtained from different sites of body.
†Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

Variable	Total isolates (n = 594)	Non-MDR isolates (n = 461)	MDR isolates (n = 133)
Non-fermenting GNB	1 (0.2)	1 (0.2)	0
Ascites			
Escherichia coli	9 (1.5)	3 (0.7)	6 (4.5)
Enterobacter sp.	8 (1.3)	7 (1.5)	1 (0.8)
Klebsiella pneumoniae	6 (1.0)	6 (1.3)	0
Pseudomonas sp.	5 (0.8)	4 (0.9)	1 (0.8)
Acinetobacter sp.	3 (0.5)	2 (0.4)	1 (0.8)
Bile			
Enterobacter sp.	29 (4.8)	28 (6.1)	1 (0.8)
Pseudomonas sp.	15 (2.5)	13 (2.8)	2 (1.5)
Escherichia coli	11 (1.9)	9 (2.0)	2 (1.5)
Klebsiella pneumoniae	9 (1.5)	5 (1.1)	4 (3.0)
Acinetobacter sp.	7 (1.2)	6 (1.3)	1 (0.8)
Non-fermenting GNB	3 (0.5)	2 (0.4)	1 (0.8)
Blood			
Klebsiella pneumoniae	2 (0.3)	2 (0.4)	0
Enterobacter sp.	2 (0.3)	2 (0.4)	0
Escherichia coli	2 (0.3)	2 (0.4)	0
Acinetobacter sp.	1 (0.2)	1 (0.2)	0
Wound			
Enterobacter sp.	4 (0.7)	3 (0.7)	1 (0.8)
Pseudomonas sp.	3 (0.5)	2 (0.4)	1 (0.8)
Klebsiella pneumoniae	1 (0.2)	0	1 (0.8)

Data were no. (%). MDR multidrug-resistant; GNB gram-negative bacteria.

*An individual patient might have more than one sample obtained from different sites of body.
[†]Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

Variable	Total isolates (n = 594)	Non-MDR isolates (n = 461)	MDR isolates (n = 133)
Escherichia coli	1 (0.2)	0	1 (0.8)
Data were no. (%). MDR multidrug-resistant; GNB gram-negative bacteria.			
*An individual patient might have more than one sample obtained from different sites of body. †Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.			

Table 3
Gram-negative bacteria isolated from the 364 patients*.

Isolates	Total isolates (n = 594)	Non-MDR GNB isolates (n = 461)	MDR GNB isolates (n = 133)
Escherichia coli	176 (29.6)	116 (25.2)	60 (45.1)
Enterobacter sp.	140 (23.6)	128 (27.8)	12 (9.0)
Klebsiella pneumoniae	114 (19.2)	91 (19.7)	23 (17.3)
Pseudomonas sp.	96 (16.2)	85 (18.4)	11 (8.3)
Acinetobacter sp.	42 (7.1)	23 (5.0)	19 (14.3)
Non-fermenting gram-negative bacteria	25 (4.2)	17 (3.7)	8 (6.2)
Haemophilus influenzae	1 (0.2)	1 (0.2)	0 (0)
Data were no. (%). MDR multidrug-resistant; GNB gram-negative bacteria.			
*An individual patient might have more than one sample obtained from different sites of body.			

Analysis of risk factors for acquisition of MDR GNB infection (Table 1)

Compared to the patients with non-MDR infection, patients with MDR GNB infection had significantly longer length of stay prior to ICU admission (4.4 vs 8.6 days, p < .001), higher frequencies of re-exploration (30.0% vs 42.7%, p = .015), blood transfusion (35.2% vs 56.4%, p < .001), received anti-pseudo penicillin (11.7% vs 26.5%, p < .001), anti-pseudo cephalosporins (4.5% vs 12.0%, p = .008), anti-pseudo carbapenems (36.4% vs 57.3%, p < .001), fluoroquinolones (4.9% vs 19.7%, p < .001) and inotropic agent (38.1% vs 57.3%, p < .001) in addition to higher total bilirubin level (32.4% vs 54.7%, p < .001). Multivariate analysis revealed that length of stay prior to ICU admission (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.02–1.08; p < .001), re-exploration (OR 1.73; 95% CI 1.05–2.84; p = .031), received anti-pseudo carbapenems (OR 2.10; 95% CI 1.29–3.41; p = .003) and fluoroquinolones (OR 3.65; 95% CI 1.64–8.09; p

= .002), as well as high total bilirubin level (OR 2.15; 95% CI 1.32–3.48; p = .002) were independent risk factors for acquisition of MDR GNB infection in SICU patients with abdominal surgery.

Comparisons of length of mechanical ventilation, hospital stay and survival between MDR and non-MDR patients

Patients with MDR GNB infection had significantly longer ventilator days (17.9 vs 10.6 days; p < .001), higher 30-day mortality (43% vs 21%; p < .001) and in-hospital mortality (56% vs 26%; p < .001) in addition to longer hospital stay (41.3 vs 34.1 days; p < .001) compared to patients with non-MDR GNB infection (Table 4). Kaplan-Meier analysis showed significantly lower 30-day survival in the MDR GNB group (p < .001) (Fig. 2).

Table 4
Outcomes of 364 patients with MDR and non-MDR GNB infections.

Variable	Non-MDR GNB group (n = 247)	MDR GNB group (n = 117)	p
Duration of mechanical ventilation after onset of GNB infection, mean ± SD (days)	10.6 ± 13.1	17.9 ± 14.2	< .001
Length of stay in hospital, mean ± SD (days)	34.1 ± 16.9	41.3 ± 17.9	< .001
30-day mortality after onset of GNB infection, no (%)	53 (21)	50 (43)	< .001
In-hospital mortality, no (%)	65 (26)	65 (56)	< .001
GNB gram-negative bacteria; MDR multidrug-resistant.			

Risk factors associated with 30-day mortality among the MDR GNB patients

Among 117 patients with MDR GNB infection, 50 died within 30-day after onset of MDR GNB infection, giving a 30-day mortality rate of 43%. As shown in Table 5, univariate analyses revealed that the following factors were significantly associated with 30-day mortality: high Charlson score (p = .050), had chronic kidney disease (p = .004), received anti-pseudo carbapenems (p = .002) and inotropic agent (p = .002), presence of thrombocytopenia (p = .007), experienced MDR non-fermenting GNB infection (p = .014) and inappropriate empirical antimicrobial therapy (p = .015). Multivariate analysis revealed chronic kidney disease (OR 3.02; 95% CI 1.19–7.65; p = .020), received anti-pseudo carbapenems (OR 4.05; 95% CI:1.67–9.80; p = .002) and inappropriate empirical antimicrobial therapy (OR 3.22; 95% CI:1.36–7.62, p = .008) as independent risk factors for 30-day mortality in patients with abdominal surgery and experienced MDR GNB infection (Table 5).

Table 5
Risk factors for 30-day mortality in 117 patients with MDR GNB infection.

Variable	Survivors (n = 67)	Non-survivors (n = 50)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Male	45 (67.2)	25 (50.0)	-		
Age ≧ 65 years	38 (56.7)	35 (70.0)	-		
Charlson score > 3 points	32 (47.8)	33 (66.0)	.050	-	-
Ischemic heart disease	2 (3.0)	1 (2.0)			
Congestive heart failure	5 (7.5)	9 (18.0)			
Peripheral vascular disease	7 (10.4)	9 (18.0)			
Cerebrovascular disease	8 (11.9)	5 (10.0)			
Chronic obstructive pulmonary disease	12 (17.9)	13 (26.0)			
Type 2 diabetes mellitus	13 (19.4)	10 (20.0)	-		
Malignancy	32 (47.8)	23 (46.0)	-		
Chronic kidney disease	13 (19.4)	22 (44.0)	.004	3.02 (1.19–7.65)	.020
Requiring emergency surgery	40 (59.7)	38 (70.0)			
Length of pre-ICU stay, mean (SD) (days)	8.4 (9.7)	8.9 (11.5)	-		
ASA score ≦ 3	53 (79.1)	35 (70.0)	-		
Surgical wound classification < 3	42 (62.7)	39 (78.0)	-		
Operative time, mean (SD) (mins)	286.9 (145.2)	289.8 (134.3)	-		
Surgical site					

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CRP C-reactive protein; CT chemotherapy; GI gastrointestinal; GNB gram-negative bacteria; ICU intensive care unit; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

* Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

**Non-fermenting GNB included Pseudomonas sp, Acinetobacter sp and other non-fermenting GNB.

Variable	Survivors (n = 67)	Non-survivors (n = 50)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Digestive system*	48 (72.0)	43 (86.0)	-		
Hepatobiliary/pancreas/spleen and kidney	19 (28.4)	7 (14.0)	-		
Re-exploration	28 (41.8)	22 (44.0)	-		
Blood transfusion	33 (49.3)	33 (66.0)	-		
Surgical drainage	23 (34.3)	22 (44.0)	-		
Mechanical ventilation	44 (65.7)	30 (60.0)	-		
Invasive vascular access	46 (68.7)	42 (84.0)	-		
Foley indwelling	51 (76.1)	37 (74.0)	-		
Antimicrobial therapy < 30 days before onset of GNB infection					
Penicillin ± β-lactamase	12 (17.9)	7 (14.0)	-		
Anti-pseudo Penicillin	15 (22.4)	16 (32.0)	-		
1’ or 2’ cephalosporin	25 (37.3)	12 (24.0)	-		
3’ cephalosporin	30 (44.8)	20 (40.0)	-		
Anti-pseudo cephalosporin	6 (9.0)	8 (16.0)	-		
Carbapenem group 1	23 (34.3)	11 (22.0)	-		
Anti-pseudo carbapenems	30 (44.8)	37 (74.0)	.002	4.05 (1.67–9.80)	.002
Fluoroquinolones	11 (16.4)	12 (24.0)	-		
Others	8 (11.9)	10 (20.0)	-		

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CRP C-reactive protein; CT chemotherapy; GI gastrointestinal; GNB gram-negative bacteria; ICU intensive care unit; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

* Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

**Non-fermenting GNB included Pseudomonas sp, Acinetobacter sp and other non-fermenting GNB.

Variable	Survivors (n = 67)	Non-survivors (n = 50)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Use of steroid > 2 weeks	34 (50.7)	33 (66.0)	-		
Use of inotropic agents > 2 days	30 (44.8)	37 (74.0)	.002	-	-
Use of CT or ISx	1 (1.5)	2 (4.0)	-		
Albumin, mean (SD) (g/dL)	2.8 (0.5) (n = 476)	2.7 (0.5) (n = 33)			
WBC, mean (SD) (1000/μL)	11.1 (8.0) (n = 60)	12.3 (8.3) (n = 47)			
Hemoglobin < 8 (g/dL)	4 (6.0)	2 (4.0)	-		
Platelet count < 150 (1000/μL)	26 (38.8)	32 (64.0)	.007	-	-
CRP, mean (SD) (mg/L)	112.2 (109.2) (n = 50)	151.3 (120.3) (n = 41)	-		
Creatinine > 1.2 (mg/dL)	34 (50.7)	29 (58.0)	-		
ALT > 80 (U/L)	7 (10.4)	10 (20.0)	-		
Total Bili > 1.4 (mg/dL)	35 (52.2)	29 (58.0)	-		
MDR species					
E. coli	38 (56.7)	20 (40.0)	-		
Klebsiella pneumoniae	14 (20.9)	8 (16.0)	-		
Enterobacter *sp*	5 (7.5)	7 (14.0)	-		
Non-fermenting GNB**	14 (20.9)	21 (42.0)	.014	-	-

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CRP C-reactive protein; CT chemotherapy; GI gastrointestinal; GNB gram-negative bacteria; ICU intensive care unit; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

* Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

**Non-fermenting GNB included Pseudomonas sp, Acinetobacter sp and other non-fermenting GNB.

Variable	Survivors (n = 67)	Non-survivors (n = 50)	p	Multivariate analysis	
				Odds ratio (95% CI)	p
Inappropriate empirical antimicrobial therapy	29 (43.2)	33 (66)	.015	3.22 (1.36–7.62)	.008
Interval between positive culture results and antibiotic therapy, mean (SD) (hours)	88.3 (28.9)	91.7 (33.8)	-		

Data were no (%) unless otherwise indicated. ALT alanine aminotransferase; ASA American Society of Anesthesiologists; CI confidence interval; CRP C-reactive protein; CT chemotherapy; GI gastrointestinal; GNB gram-negative bacteria; ICU intensive care unit; ISx immunosuppressant; MDR multidrug-resistant; WBC white blood cell.

* Digestive system included esophagus, stomach, duodenum, small intestinal, colon, appendix and rectum.

**Non-fermenting GNB included Pseudomonas sp, Acinetobacter sp and other non-fermenting GNB.

Discussion

Bacterial Infection represent the most important cause of morbidity after major abdominal surgery [20, 21]. Notable, GNB was the predominant pathogens seen in patients who undergoing abdominal surgery. In the era of increasing prevalence of MDR bacterial infections, MDR GNB is strongly associated with mortality in critically ill surgical patients [22]. Our study investigated the independent risk factors associated with MDR GNB infection after abdominal surgery and highlights MDR GNB infection is associated with a lower 30-day survival compared to non-MDR GNB infection. Our findings are valuable for clinicians working in highly stressful environment such as SICU and provides useful practical information on prevention and early intervention of MDR GNB infection in SICU patients who received abdominal surgery.

Hasanin et al. [10] analyzed SICU patients who underwent various types of surgery found that 65% of 234 samples showing growth of GNB were MDR strains. In the study of Alexiou et al [9], 48% of 100 SICU patients who underwent gastrointestinal surgery were found to have MDR GNB infection. In our series, the incidence of MDR GNB among SICU patients with GNB infection was 32.1%. Furthermore, once developed MDR GNB infection, the 30-day mortality rate can be as high as 43% compared to non-MDR GNB infection. Our study highlights the urgent need for improving clinicians' awareness and early recognition as well as aggressive management of this potentially fatal MDR GNB infection in patients with abdominal surgery.

Several studies have been done to determine the risk factors for acquisition of carbapenem-resistant GNB infection [23–25]. Longer hospital stay, previous exposure to anti-pseudomonal penicillin, anti-

pseudomonal cephalosporins and carbapenems have been reported to be independent risk factors for acquiring carbapenem-resistant GNB (70% cases were glucose non-fermenting GNB) infection [14]. Nevertheless, enterobacteriaceae are the culprit pathogens involved in complicated intra-abdominal infection. This study focuses on MDR GNB infection including carbapenem-resistant strains in SICU patients who received abdominal surgery. In fact, carbapenem-resistant isolates were entirely belonging to MDR strain in our series. Our results showed that longer length of stay prior to ICU admission, re-exploration, received anti-pseudo carbapenems and fluoroquinolones, as well as hyperbilirubinemia were independent risk factors for MDR GNB infection in SICU patients with abdominal surgery. Our study differs from previous studies in that 71% of cases with MDR GNB infections were caused by enterobacteriaceae. The findings of this study can truly reflect the risk factors for the development of MDR GNB infection in SICU patients who underwent abdominal surgery.

In our study, 71% of patients was transferred from general wards to SICU for critical care. Our analysis disclosed that longer length of stay prior to admission to the SICU was independently associated with MDR GNB infection. Previous studies have suggested that a longer length of hospital stay prior to ICU admission is associated with a higher mortality [26, 27]. Prior antibiotic use and duration of antibiotic treatment is a concern for those patients before admission to SICU. Likewise, the increase in the pre-ICU length of stay might, however, suggest delay in ICU referral. These scenarios pose the emerging for development of MDR GNB infection.

Previous studies have showed that hyperbilirubinemia is associated with greater severity of illness and poor outcome [28, 29]. Fleid et al reported that hyperbilirubinemia in the SICU patients predisposes to infection [30]. Elevation of bilirubin level in ICU patients is usually associated with severe infections such as GNB sepsis or septic shock [31, 32]. An observational study conducted in 283 critically ill patients exposed sepsis is one of the most important factors of hyperbilirubinemia [32]. Our study was the first analysis conducted in critically ill abdominal surgery patients unveiled that hyperbilirubinemia is associated with MDR GNB infection. We believe that hyperbilirubinemia in this series is due to severe MDR GNB sepsis rather than anatomic biliary abnormality. Accordingly, it should judiciously take into account the threat and potential MDR bacterial infection when elevated bilirubin level was found in SICU patients. Further studies to elucidate more information on this respect are warranted.

Several studies have demonstrated that re-exploration of abdomen after the first operation was associated with prolonged length of ICU stay, higher mortality rate and more frequent wound infections [33–35]. The most common complications requiring re-laparotomy were bleeding, sepsis, anastomotic leaks, bowel obstruction and wound dehiscence. We have no information concerning whether the patients received urgent or elective re-operation, but our finding shown that re-exploration is an important risk factor for acquiring MDR bacterial infection. This result is undoubtedly emphasizing the importance of thoroughness at the first laparotomy.

An important key finding in our study is exposure to anti-pseudo carbapenems and fluoroquinolones is associated with the acquisition of MDR bacterial infection. Fluoroquinolones, which are associated with

MDR *Pseudomonas aeruginosa* have also been identified as a risk factor for carbapenem-resistant *Klebsiella pneumoniae* infection [36, 37]. Prior carbapenems use also have been identified as significant independent risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection [38]. Consistent with our study, antibiotic exposure was associated with an increased risk of developing MDR bacteria but the relationship is a multifaceted issue such as intra- and inter-hospital transmission and antimicrobial resistance in community level. Given the increasingly MDR GNB infections, implementation of antimicrobial stewardship programs in critical care unit is crucial to reduce and optimize antimicrobial therapies.

In our series, the in-hospital mortality rate was as high as 56% in patients with MDR GNB infection. Our findings exposed the independent risk factors for 30-day mortality after onset of MDR GNB infection were chronic kidney disease, anti-pseudo carbapenems, and inappropriate empirical antimicrobial therapy. Undoubtedly, delay in starting appropriate treatment is associated with increased morbidity and mortality [39, 40]. Mosdell et al. shown 480 patients with secondary bacterial peritonitis, patients who received empirical treatment with an appropriate antimicrobial agent had fewer wound infections, abscesses, re-operations, and lower mortality when compared to patients who received inappropriate therapy [39]. While inappropriate therapy certainly has an important impact on clinical outcomes, our series emphasized needs to be considered in the context of other patient risk-factors such as co-morbid conditions. Our study not only highlights the importance of appropriate antimicrobial therapy in improving outcomes, but also underscores that chronic kidney disease is one of key factors that influence outcomes. Previous studies underscore patients with chronic kidney disease had exceedingly high mortality rates compared with patients without chronic kidney disease in the clinical course of sepsis [41, 42]. Our study results emphasize efforts are needed to reduce the negative effects of infections in patients with chronic kidney disease.

In addition, this study illustrating use of anti-pseudo carbapenems is risk factor for subsequent MDR GNB infection and increase 30-day mortality after developed MDR GNB infection. The risk of acquisition of carbapenem-resistant GNB increases with carbapenem exposure [43]. As a result, the emergence of resistant to carbapenems GNB has severely challenged antimicrobial therapy. This indicates the limitation of using anti-pseudo carbapenems as empirical therapeutic options in critically ill surgical patients. The agents of last resort against MDR organisms include the tigecycline, aminoglycosides and polymyxins particularly carbapenem-resistant isolates, but it can be also associated with more significant adverse effects (i.e., nephrotoxicity, ototoxicity, and neurotoxicity) [44–50]. Consideration of therapeutic effectiveness and adverse effects, combination therapy, at least in the empirical phase of treatment, is the higher probability that a MDR isolate will be susceptible to at least one agent in combination regimens and minimize the adverse effects [51, 52]. Before the development of novel antimicrobials that could provide clinical efficacy towards MDR organisms, multiple interventions should be employed to control the spreading of MDR organisms including antimicrobial stewardship policies and appropriate infection control measures [13, 14]. Implementation of online antimicrobial-stewardship program has been significantly reduced antimicrobial consumption and expenditure in the ICU setting [13]. Further

study is essential to investigate the effects on reducing the incidence of antimicrobial resistant before and after implementation of antimicrobial-stewardship program.

Several limitations of our study should be noted. First, this study was conducted at a single medical center which might be biased by patient referral patterns. Second, being a retrospective study, power calculation to determine the sample size was not performed, and unavoidable that some data are missing included the interval between time elapsed from diagnosis to surgery and information regarding the treatment of open surgical wound. Further, information about adequate source control was not available. Nevertheless, our study assessed patient who requiring drainage and surgical re-exploration, as source control generally involves drainage of abscesses or infected fluid, and debridement of necrotic or infected tissues.

Conclusion

This study has underscored the high prevalence rate of MDR GNB infection and provides important information about the risk factors for the development of MDR GNB infection in patients with abdominal surgery. Risk factors like chronic kidney disease, anti-pseudo carbapenems and inappropriate antibiotics therapy were associated with increased 30-day mortality. Our study highlights the alarming need of multidisciplinary efforts to define the optimal strategy for the empirical treatment of patients at the risk for MDR GNB infection.

Abbreviations

MDR, multidrug-resistant, GNB, gram-negative bacteria, SICU, surgical intensive care unit

Declarations

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Author contributions

Ting-Lung Lin and Ing-Kit Lee designed the study, collected, analyzed data and wrote the manuscript. Po-Hsun Chang developed the theory and performed the computations. I-Ling Chen and Po-Hsun Chang contributed to analysis and interpretation of data. Wei-Hung Lai, Ying-Ju Chen and Wei-Feng Li assisted in preparation of the article. Ing-Kit Lee and Chih-Chi Wang supervised the project and revised the draft. All authors have critically reviewed the manuscript and approved the final version.

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Availability of data and materials

The dataset supporting the conclusions of this article is included within the

article and additional file.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (Document no. 201702053B0C502), Taiwan. Informed consent was not required as the data were analyzed anonymously.

Consent for publication

Each author agrees to the publication of the present study.

Competing interests

The authors declare that they have no competing interests.

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Figures

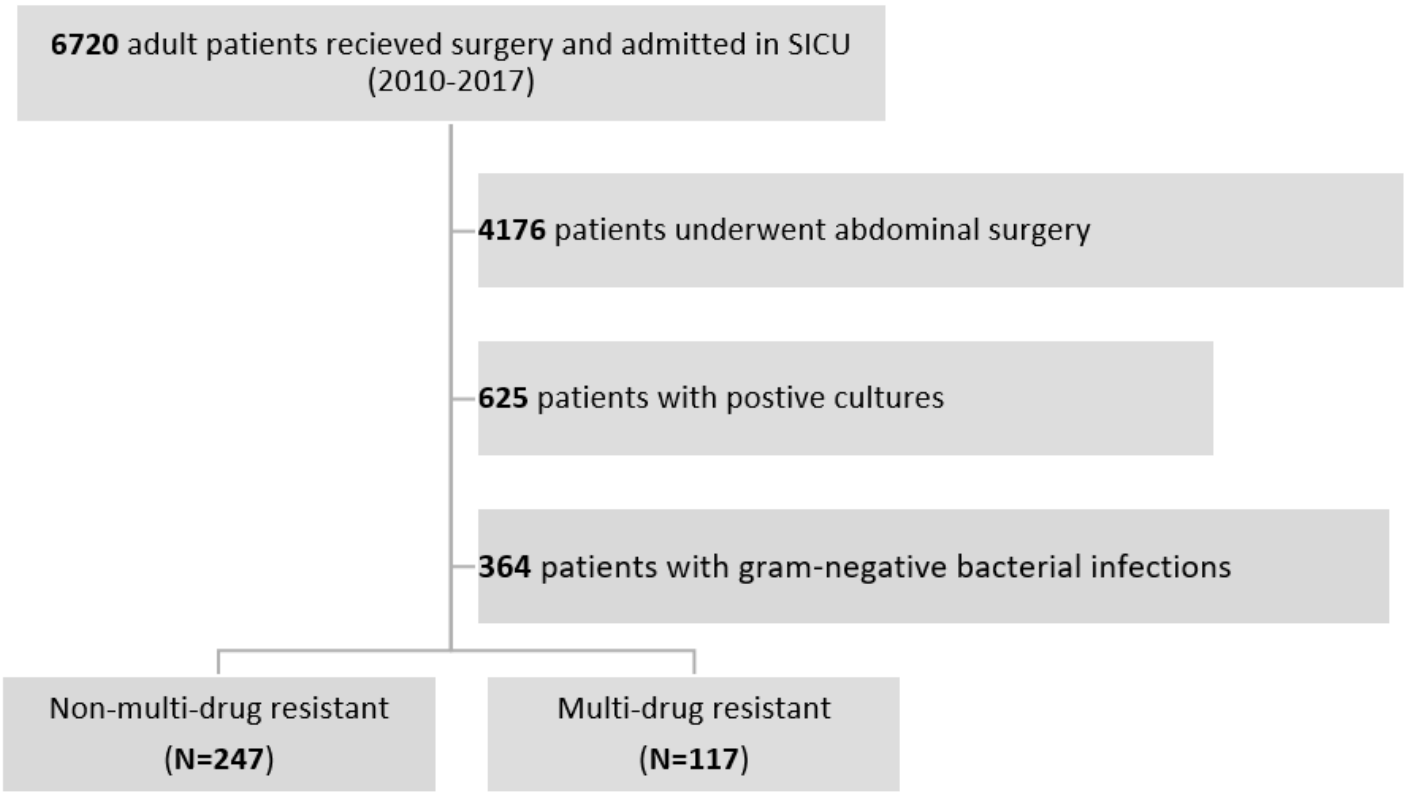

Figure 1

The study flow-chart.

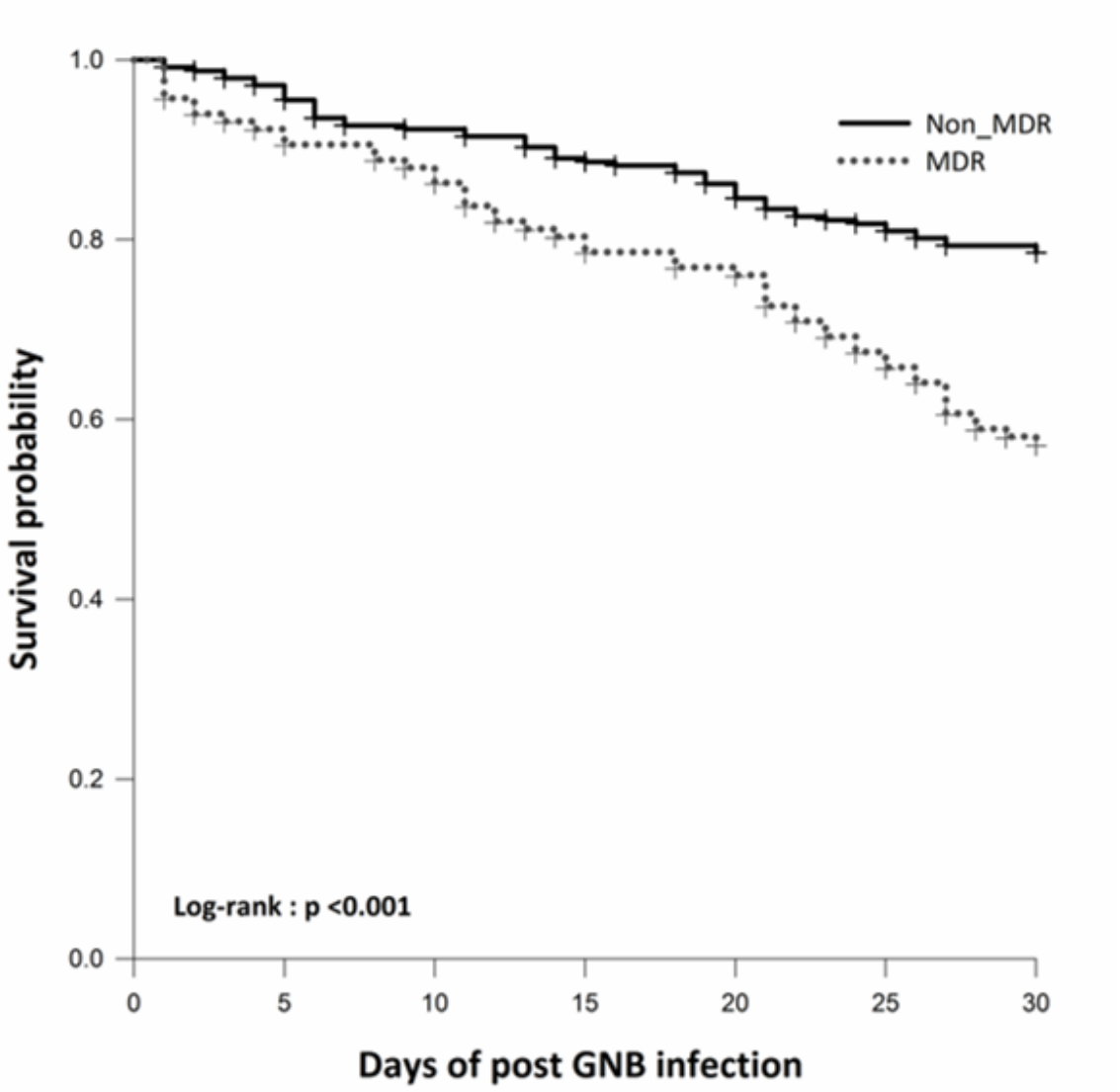

Figure 2

Kaplan-Meier curves for 30-day survival of patients with MDR and non-MDR GNB infections. Note: Patients in the non-MDR GNB group have a significantly lower 30-day mortality rate after onset of GNB infection (p <0.001). GNB gram-negative bacteria; MDR multi-drug resistant.