




Review

Can risk factors and risk scores help predict colonization and infection in multidrug-resistant gram-negative bacteria?

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Abstract

Antimicrobial resistance (AMR) is positioning as one of the most relevant threats to global public health and threatens the effective treatment of an ever-growing number of bacterial infections in various healthcare settings, particularly in acute care and surgical units, as well as in the community. Among multidrug-resistant (MDR) gram-negative bacteria (MDRGNB), *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* require special attention, since they account for most of the mortality associated with bacterial infections and are often MDR. It is clear that there is an important global variation in antibiotic resistance profiles among MDRGNB species. Extended-spectrum β -lactamase-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales*, DTR-*P. aeruginosa*, and MDR-*A. baumannii* are the focus of this review. Here, we summarize a series of relevant studies on risk factors associated with colonization and infection with these MDRGNB. Likewise, we offer a comparative overview of those studies providing scoring systems to predict the risk of infection with these MDR pathogens, and their pros and cons. Despite the variable accuracy of published risk factors for predicting colonization or infection with MDRGNB, these scores are valuable tools that may help anticipate colonization and infection among those colonized. More importantly, they may help reduce unnecessary use of broad-spectrum antimicrobials and guiding the selection of an optimal treatment.

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Introduction

The prevalence of multidrug-resistant gram-negative bacteria (MDRGNB) is increasing worldwide and is of particular concern in vulnerable populations in acute care settings.^{1–5} Although multiple mechanisms confer β -lactam resistance, β -lactamase production remains the most common mechanism of resistance.⁶ *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are identified as some of the most relevant pathogens with high rates of resistance to several classes of antibiotics, limiting treatment options for infections caused by these organisms.^{4,7–10}

The rise in MDRGNB poses an increasing problem in acute care, surgery, hospital wards, intensive care units (ICUs), and within the community.^{3,8,11–13} It is important to quantify the burden to have a clear understanding of the epidemiology of MDRGNB, including its regional variability.^{4,14–16} Likewise, it is equally important to understand risk factors for MDRGNB infection to ensure appropriate steps are taken to mitigate their spread and to ensure that appropriate empiric antibiotic therapy is

started as early as possible.^{17–20} Not only does delayed appropriate therapy increase the risk of death,²¹ but studies have also shown that it also prolongs hospitalization.²² Moreover, prolonged hospitalization places patients at risk for developing subsequent antibiotic-resistant infections,²³ which can ultimately lead to further antibiotic usage²⁴ and exacerbate institutional antimicrobial resistance (AMR) patterns.²⁵ Therefore, it is important to investigate whether published current risk factor associations and their related scoring systems accurately identify patients at risk particularly for MDRGNB infections.^{26,27}

This review aims to provide an overview of relevant studies on risk factors for colonization and/or infection with MDRGNB, as well as evaluate scoring systems, focusing on those aiming to determine the risk of MDRGNB infection, colonization and/or mortality. We conducted a search for data published in international public databases (PubMed, Scopus, Google Scholar, SciELO—for Latin American and the Caribbean (LAC)—studies and LILACS) dating from January 2014 to June 2023, using as search criteria within the title section and within the abstract section [Title/Abstract] the following terms: “antimicrobial resistance,” “Gram-negative bacteria,” “extended spectrum β -lactamase,” “carbapenem-resistant,” together with [AND/OR] “*Enterobacterales*,” “*Klebsiella pneumoniae*,” “*Escherichia coli*,” “*Pseudomonas aeruginosa*,” “*Acinetobacter baumannii*,” together with [AND/OR] “risk factors,” “risk assessment,” “scoring system,” and “score.” The quality of the studies was

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not formally evaluated but we have excluded publications not considered as peer reviewed. Duplicates were deleted before screening. Selected documents were reviewed for full-text eligibility and furthermore, we manually selected all those publications reporting a risk score and/or risk assessment to determine the risk of MDRGNB infection and/or mortality. Discrepancies were solved among all authors. During this search, a final number of 81 published studies were finally included in this review and, 23 were used to build the comparative assessment analysis presented particularly in Table 2, as well as in Table 3.

Global burden of bacterial AMR

One of the most comprehensive studies evaluating AMR burden was published in 2022.²⁸ The study assessed estimated deaths and disability-adjusted life-years (DALYs) directly attributed to bacterial AMR. It examined the deaths and DALYS associated with 23 different pathogens and multiple pathogen–drug combinations in 204 countries in 2019.²⁸ The researchers used systematic literature reviews, hospital systems, surveillance systems, and other sources to obtain a wide range of data.²⁸ Furthermore, they employed predictive statistical modeling to estimate AMR burden, even in locations lacking specific data.²⁸ In summary, three infectious syndromes were associated with the highest AMR burden in 2019: (i) lower respiratory infections, (ii) bloodstream infections, and (iii) intra-abdominal infections.²⁸ These three syndromes accounted for 79% of deaths attributed to AMR in 2019. Notably, six pathogens were responsible for more than 250,000 deaths associated with AMR; those pathogens were: *E. coli*, *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae*, *A. baumannii*, and *P. aeruginosa*. Although the order of attributable mortality of the pathogens varied depending on the world's region, together, these six pathogens were responsible for a calculated 929,000 deaths attributed to AMR, and 3.57 million deaths associated with AMR globally in 2019.²⁸

As the prevalence of MDR organisms is constantly increasing, along with its associated mortality, identifying risk factors for developing an MDRGNB infection could greatly affect patient care and infection management.^{20,29}

The increase in AMR is a global concern; the World Health Organization's (WHO) in its most recent Global Antimicrobial Resistance and Use Surveillance System (GLASS) report from 2022, involving surveillance data from 109 countries collected during 2017–2020, revealed multiple concerning findings including, increased rates of MDR *E. coli* from blood isolates by more than 15% in 2020 when compared to the rates of 2017, particularly for meropenem (0.5% [in 2017]–0.9% [in 2020]) and third generation cephalosporins (20.2% [in 2017]–24.0 [in 2020]). Similarly, they reported high levels of resistance in *K. pneumoniae* to third-generation cephalosporins (59%–64.7%) and to fourth-generation cephalosporins (57.4%), with isolates often showing multidrug resistance. Also, a high percentage of resistance to carbapenems in *Acinetobacter* spp. (> 50%), 73.1% (in 2017) and 72.9% (in 2020).³⁰

Overview of AMR in GNB: regional dissemination

Multiple antibiotic-resistant organisms have spread worldwide; particularly extended-spectrum β -lactamase (ESBL)-producing *E. coli*. In India and Latin America, this group represents up to 40% of the worldwide burden of clinical isolates of ESBL-producing *E. coli*.^{31,32} CR-*K. pneumoniae* is common (6%–28%) in China, the US, and Latin America. New Delhi metallo- β -lactamase (NDM)-producing *Enterobacterales* have been increasingly observed over

the past 15 years in South Asia, China, the USA, and Europe.^{31,33–35} Variants of several β -lactamase genes, particularly ESBLs, such as *bla*_{CTX-M}, *bla*_{TEM}, *bla*_{SHV}, *bla*_{PER}, *bla*_{VEB} and *bla*_{TLA} variants, are reported worldwide, among which *bla*_{CTX-M} group is the most prevalent group.³⁶ Carbapenem-hydrolyzing enzymes such as *K. pneumoniae* carbapenemases (KPC), NDM-1, the imipenemases (IMP), Verona integron-encoded metallo- β -lactamases (VIM) and OXA (oxacillinase)-48 have become widely disseminated. However, there are important differences in the prevalence of these enzymes across countries and particular geographical regions.^{37,38} The successful global dissemination of these carbapenemases is primarily attributed to the presence of their genes on mobile genetic elements, most commonly plasmids. These elements often co-harbor resistance to multiple classes of antibiotics, leading to the emergence of pan-drug-resistant organisms.^{39,40}

The regional and national variations, whether in terms of ESBLs or carbapenemases, are mainly due to variations in population density, hygiene and integrity of the country's infrastructure, use of antibiotics, and infection control practices.⁴¹ As for its international spread, it was attributed largely to international travel, including globalized medical tourism.⁴²

Globalization, along with the increase in antibiotic use worldwide, has significantly affected the evolution and spread of antibiotic-resistance genes over the past 25 years. Studies have shown that 8% of *E. coli* isolates in the US produce ESBL, while in Latin America and South Asia the percentage may reach 32% and 33%, respectively.^{43,44} In 2019, more than half of *E. coli* isolates reported to EARS-Net and more than a third of *K. pneumoniae* isolates were resistant to at least one antimicrobial group of interest, and combined resistance to multiple antimicrobial groups was common.⁴⁵ While carbapenem resistance remained rare in *E. coli*, in contrast, several countries reported carbapenem resistance percentages above 10% for *K. pneumoniae*. In this report, carbapenem resistance was also common in *P. aeruginosa* and *Acinetobacter* spp.⁴⁵ A summary of this international report, covering more than 30 countries, is given in Table 1.

Risk factors and risk assessment scores for colonization and infection by MDRGNB

Infections caused by MDRGNB mainly involve carbapenem-resistant (CR) and ESBL-producing pathogens. Most of these infections are healthcare-acquired; however, some originate in the community.^{46,47} Multiple publications have addressed risk assessment for ESBL-producing and CR-related infection and colonization. Table 2 describes and compares studies that identified risk factors associated with these conditions and their corresponding odds ratio.

It is currently uncertain whether it is necessary to conduct active fecal screening for ESBLs at hospital admission.⁴⁸ The prevalence of ESBL-producing *Enterobacterales* (ESBL-PE) infections among carriers at ICU admission was reported with a rate of 15% in a recent 7-year study.⁴⁹ From this study, a clinical risk score designed to predict ESBL-PE infection was derived from five independent risk factors associated with ESBL-PE infection in carriers (ie, age >60 years, cirrhosis, broad-spectrum antibiotic treatment within the previous 3 months, urinary or intra-abdominal infection, and absence of chronic pulmonary disease). Based on these variables, an ESBL risk score was created to guide empirical carbapenem therapy against ESBL-producing *Enterobacterales* infections, scores of 4–5, and 6–7 had a prevalence of 26%, and 49%, respectively.⁴⁹ Based on a systematic review and

Table 1. Single and MDR percentage in isolates of *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp. reported by EARS-NET in EU/EEA countries during 2015–2019

	<i>E. coli</i> (n = 118,399) (57.1% resistant isolates), combinations used	<i>K. pneumoniae</i> (n = 39,025) (36.6% resistant isolates) combinations used	<i>P. aeruginosa</i> (n = 18,416) (30.8% resistant isolates) combinations used	<i>Acinetobacter</i> spp. (n = 5,696) (53.4% resistant isolates) combinations used
Resistance to one antimicrobial	34.8% Aminopenicillins; fluoroquinolones; other antimicrobial groups	8.0% Fluoroquinolones; third- generation cephalosporins; other antimicrobial groups	13.2% Fluoroquinolones; carbapenems; piperacillin- tazobactam; aminoglycosides; ceftazidime	4.8% Fluoroquinolones; aminoglycosides; carbapenems
Resistance to two antimicrobials	10.5% Aminopenicillins + fluoroquinolones; aminopenicillins + third-generation cephalosporins; aminopenicillins + aminoglycosides; other antimicrobial group combinations	8.1% Third-generation cephalosporins + fluoroquinolones; third-generation cephalosporins + aminoglycosides; fluoroquinolones + aminoglycosides; other antimicrobial group combinations	7.6% Piperacillin-tazobactam + ceftazidime; fluoroquinolones + carbapenems; other antimicrobial group combinations	5.0% Fluoroquinolones + carbapenems; fluoroquinolones + aminoglycosides; aminoglycosides + carbapenems
Resistance to three antimicrobials	7.3% Aminopenicillins + third- generation cephalosporins + fluoroquinolones; aminopenicillins + fluoroquinolones + aminoglycosides; other antimicrobial group combinations	15.6% Third-generation cephalosporins + fluoroquinolones + aminoglycosides; third-generation cephalosporins + fluoroquinolones + carbapenems; other antimicrobial group combinations	3.9% Piperacillin-tazobactam + ceftazidime + carbapenems; other antimicrobial group combinations	43.6% Fluoroquinolones + aminoglycosides + carbapenems
Resistance to four antimicrobials	4.5% Aminopenicillins + third- generation cephalosporins + fluoroquinolones + aminoglycosides; other antimicrobial group combinations	4.9% Third-generation cephalosporins + fluoroquinolones + aminoglycosides + carbapenems	2.8% Piperacillin-tazobactam + fluoroquinolones + ceftazidime + carbapenems; other antimicrobial group combinations	– Data not available
Resistance to five antimicrobials	<0.1% Aminopenicillins + third- generation cephalosporins + fluoroquinolones + aminoglycosides + carbapenems	– Data not available	3.4% Piperacillin-tazobactam + fluoroquinolones + ceftazidime + aminoglycosides + carbapenems	– Data not available

Data source: EARS-Net, European Antimicrobial Resistance Surveillance Network; EU/EEA, European Union/European Economic Area.⁴⁵

meta-analysis, ESBL colonizers were more likely to have a history of recent antibiotic treatments or healthcare facility utilization.⁵⁰ However, predicting colonization is not easy; many risk factors are nonspecific and are also common to all MDRGNB.⁵¹ Nevertheless, some scores of risk stratification reliably identify colonization by resistant bacteria. An example is a scoring system devised by Tumbarello *et al.*, which is used to identify ESBL colonization in patients with GNB infections (*E. coli*, *Klebsiella* spp. or *Proteus mirabilis*) at hospital admission.⁵²

Conversely, CRE infections have become an urgent public health threat with higher morbidity and mortality, as well as limited antibiotic treatments available.⁵³ Although the CDC does recommend surveillance for CR gram-negative pathogens for infection control purposes, some studies also have shown that the detection of colonization by a CR organism (CRO) could guide empirical therapy in certain populations such as hematology patients or kidney transplant recipients.⁴⁸ The primary risk factors for developing CRE infections include longer hospital stays, ICU admission, invasive procedures, recent surgery, recent immunosuppression/immunodeficiency, severe underlying comorbidities, prior antibiotic exposure, and colonization/carriage with CRE.^{27,54} Additional studies indicate that ICU admission, transfer between wards, prolonged hospital stay and sharing a room with known carriers are predominant factors related to CRE colonization.^{55,56} There is also evidence showing high rates of CRE infections up to 45% in critically ill individuals among patients who were previously colonized but asymptomatic.^{57,58} A systematic review of 92 studies found that the most important risk factors for CR-GNB include previous antibiotic

use (especially carbapenems), previous colonization, mechanical ventilation, previous ICU stay, dialysis, catheter use, length of hospital stay, comorbidities and, an increase in Acute Physiology and Chronic Health Evaluation (APACHE) II score.¹⁹ To better predict the development of infections, risk factors have been evaluated and scored for carriers of these CR bacteria.

The Giannella risk score (GRS) has been used to identify the risk of KPC-producing *K. pneumoniae* bloodstream infection (BSI) among rectal carriers.⁵⁴ Notably, multi-site colonization was considered the most reliable predictor.⁵⁴ Further cohort studies have measured the utility of the GRS and determined a cutoff point (of 7) to discriminate between low and high risk of all KPC-producing *K. pneumoniae* infection.²⁷

Lastly, the acquisition of MDR *P. aeruginosa* is significantly related to ICU admission but is also related to other factors including prior use of broad-spectrum (cephalosporins, aminoglycosides, quinolones, carbapenems) high invasive-device scores and prior hospital stays, advanced age, and human immunodeficiency virus infection.^{9,52,59–61} In the case of MDR *A. baumannii* infections, prior colonization plays an important role as a risk factor; as well as, previous antibiotic use, prolonged or prior hospitalization, previous ICU stay, or invasive procedures and repeated skin grafts.^{62–65}

Based on previous studies and the fact that previous colonization with a MDRGN can lead to an infection, rectal surveillance in patients hospitalized in critical care areas in hospitals with high prevalence of MDRGN is suggested, as this practice can help guide treatment for critically ill patients.^{66–68}

Table 2. Comparative analysis of risks factors for MDR-GNB infections or colonization on evaluation studies

Ref.	Type of study	Population	Defined case or event	Risk factor ¹ (for infection or for colonization)												
				Previous use of antibiotics	History of previous hospitalization	Invasive procedures or surgeries	Urinary catheterization	Referral from another hospital	Previous colonization	Immunosuppression	Advanced age	Diabetes mellitus	Previous history of infection	Type of infection	Other	
89	Case-control	110 cases: 338 controls	ESBL Infection: <i>E. coli</i> and <i>K. pneumoniae</i>	3.8 ²⁴ (2.1–6.9)	3.2 ¹² (1.6–6.5)		5.9 ⁴ (3.1–11.6)	4.3 (2.1–8.8)								
				3.5 ²⁴ (1.9–6.4)	2.6 ¹² (1.3–5.4)		6.9 ⁴ (3.6–13.4)	5.3 (2.7–10.7)		2.3 ⁸ (1.1–4.8)						
90	Cohort	184 participants (76 events)	Colonization: <i>P. aeruginosa</i> carbapenem-resistant	9.9 ²⁵ (1.9–51.4) 2.5 ^{3,26} (1.1–5.5)								3.9 (1.5–10.2)				
84	Cohort	11502 participants with infection (2324 events carbapenem-resistant and 1033 BRE ²)	Infection: <i>P. aeruginosa</i> susceptible, carbapenem-resistant and EBR	4.2 ^{4,5,26} (3.3–5.3)										8.8 ⁵ (6.7–11.5)	5.0 ⁶ (3.9–6.5)	
				2.3 ^{4,6,26} (1.7–2.9)												
91	Case-control	192 cases/432 controls	Infection by MDRGNB ⁷									1.9 ⁹ (1.1–3.2)				23.5 ¹⁰ (7.0–79.1)
68	Cohort	334 participants (UCI)	Infection by CRE ¹¹		6.6 ¹³ (1.3–34.3)	3.7 ¹⁴ (1.2–11.1)				10.8 ¹⁵ (2.8–41.9)						
92	Case-control	91 cases: 1376 controls	Colonization MDRGNB ⁷		1.01 ¹² (1.00–1.03)	2.8 ¹⁶ (1.3–5.9) 2.0 ¹⁴ (0.9–4.0)				5.3 ⁷ (1.5–16.6)						6.5 (2.2–19.2)
54	Case-control	143 cases: 572 controls	Infection CR-KPE ¹⁸			1.9 ¹⁶ (1.2–3.0)				3.4 ¹⁸ (2.5–4.4)	3.1 ⁸ (1.8–5.3)					1.6 ²⁹ (1.1–2.6)
52	Case-control	113 cases: 339 controls	Infection ESBL-EKP ¹⁹	3.7 ²⁴ (2.0–6.9)	5.7 ¹² (2.9–11.0)		3.5 (2.0–6.9)	5.6 (1.6–19.1)				3.2 ²⁰ (1.8–5.7)				
82	Cohort	1141 participants (65 events)	Infection ESBL: <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>K. oxytoca</i>	15.3 (7.7–61.4)	3.7 (1.6–9.00) 10.0 ²¹ (5.0–20.1) 27.8 ²² (12.6–61.3)	12.3 ¹⁴ (5.6–27.2)	3.4 (1.1–10.2)					2.1 (1.1–4.1)				
83	Case-control	443 cases: 367 controls	Infection by <i>E. coli</i> ESBL	2.1 (1.4–3.2) 12.9 ³² (4.4–37.8)								1.5 ²⁷ (1.0–2.2)		7.9 ³¹ (2.2–27.7)	2.3 ²⁸ (1.5–3.5)	1.9 ³⁰ (1.1–3.2)
49	Cohort	336 cases: 59 controls	Infection ESBL-EKP ¹⁹	3.2 (1.7–6.2)								2.4 ³⁴ (1.2–4.9)			5.4 ^{10,36} (2.9–10.2)	6.9 ³⁵ (1.6–31.0) 3.1 ³³ (1.2–8.0)

¹ Risk factors are expressed in the association measure Odds Ratio (OR) with 95% confidence intervals, ² BRE: resistant to carbapenems, ceftazidime and piperacillin/tazobactam, ³ within the last 3 months, ⁴ within the last 30 days, ⁵ *P. aeruginosa* carbapenem-resistant infection, ⁶ *P. aeruginosa* BRE infection, ⁷ gram-negative bacilli resistant to 3 different antibiotic families, ⁸ immunosuppressive therapy with steroids, tacrolimus, sirolimus, cyclosporine, mycophenolate, antithymocyte globulin, or chemotherapy (with alkylating agents) within the past 3 months, ⁹ Steroids within the past 3 months, ¹⁰ urinary tract infection, ¹¹ carbapenem-resistant *Enterobacteriaceae*, ¹² within the last year, ¹³ within the last 6 months, ¹⁴ Esophagus-gastro-duodenoscopy or colonoscopy within the past 6 months, ¹⁵ previous colonization by CRE, ¹⁶ abdominal surgery a year or less ago, ¹⁷ hospital stay longer than 5 days, ¹⁸ carbapenem-resistant *Klebsiella pneumoniae*, ¹⁹ ESBL *E. coli*, *K. pneumoniae* and *P. mirabilis*, ²⁰ age ≥ 70 years, ²¹ emergency room consult within the last 4 weeks, ²² nursing home resident, ²⁴ β-lactams or quinolones within the past 3 months, ²⁵ aminoglycosides in the last 3 months, ²⁶ carbapenems, ²⁷ age ≥ 55 years, ²⁸ hospital-acquired infection, ²⁹ hospitalization in ICU, ³⁰ prolonged hospitalization, ³¹ previous infection with *E. coli* ESBL, ³² 3rd or 4th generation cephalosporins, ³³ liver cirrhosis, ³⁴ age > 60 years, ³⁵ chronic obstructive pulmonary disease, ³⁶ intra-abdominal infection.

Risk factors and risk scores for mortality in MDRGNB

Data from the WHO confirms that the risk of death attributable to infection by antibiotic-resistant microorganisms is twice that of non-resistant bacteria.⁶⁹ Falagas *et al.* published a meta-analysis of nine studies on mortality following CRE infections in 2012, reporting that 26%–44% of deaths in seven studies were attributable to carbapenem resistance.⁶⁹ A recent multinational prospective cohort study that looked at the effect of carbapenem resistance on outcomes of BSI caused by *Enterobacterales* in low- and middle-income countries (LMICs) showed that carbapenem resistance was associated with increased length of hospital stay and mortality.⁷⁰ In Latin American countries, BSI by CRE has been shown to increase in-hospital mortality four times, compared to non-CRE infection (OR = 4.0 CI 95% (1.7–9.5)).⁷¹ However, an analysis of 24 studies on infections caused by MDRGNB in ICUs published in 2016, did not confirm a direct association between infections due to MDRGNB and mortality in ICU patients.⁷²

Many factors confound the identification of main risk predictors for mortality in MDRGNB-associated infections, including variability in patient populations, late onset of appropriate initial antibiotic therapy, lack of appropriate antibiotic therapy on site in everyday practice, heterogeneity in the outcomes of each study, and the lack of availability of a quick and specific diagnostic test to identify MDR bacteria.³ Despite inconsistencies in studies defining risk factors, here we point out studies with common risk factors reported to be associated with higher risk for mortality in MDRGNB.

Patolia *et al.* conducted a retrospective observational cohort study and used data collected over a 13-month period from the electronic health records of patients with gram-negative bacteremia at a single university medical center; 177 patients were included in the analysis, 46 of which (26%) had MDRGNB bacteremia with a mortality rate of 34.8%, compared to 13.7% in the non-MDR-gram-negative bacteremia group ($P = 0.002$). In particular, inappropriate empiric antibiotics (OR: 7.59, 95% CI: 1.68–34.34), urinary catheter as a source of infection (OR: 5.68, 95% CI: 1.37–23.5), intra-abdominal source of infection (OR: 3.66, 95% CI: 1.14–11.73), end-stage liver disease (OR: 3.64, 95% CI: 1.07–12.3) and solid organ malignancy (OR: 3.64, 95% CI: 1.25–10.56) were significant independent risk factors for mortality in patients with MDRGNB. Additional risk factors were identified in the multivariate analysis as significant for the development of a MDRGNB infection: diabetes mellitus (OR: 2.8, 95% CI: 1.00–4.88), previous antibiotic use (OR: 2.93, 95% CI: 1.25–6.87), and urinary catheter as a source of infection (OR: 5.96, 95% CI: 1.78–19.94).²⁰

For *A. baumannii*, significant mortality has been reported with CR-*Acinetobacter baumannii* (CRAB) infection although limited data on contributing microbiological factors have been published. In a retrospective study of 164 patients, Hyo-Ju Son *et al.* found that 90 (55%) of the 164 patients died within 30 days.⁷³ In the multivariate analysis of study findings, independent risk factors for mortality were a non-eradicated focus, septic shock, and inappropriate antimicrobial therapy.⁷³ A recent meta-analysis evaluating the predictors of mortality in patients infected with CRAB identified that the most relevant risk factors for mortality were inappropriate empirical antimicrobial treatment (OR, 5.04; 95%), septic shock (OR, 5.65; 95%), chronic liver (OR, 2.36; 95%), and chronic renal disease (OR, 2.02; 95%).⁷⁴

Infection with MDR *P. aeruginosa* is also associated with high mortality. In a retrospective study of patients diagnosed with *P. aeruginosa* BSIs in two Italian university hospitals, Tumbarello

*et al.*⁷⁵ compared risk factors for isolation of MDR or non-MDR *P. aeruginosa* in blood cultures. Presentation with septic shock, infection due to MDR *P. aeruginosa* and inadequate initial antimicrobial therapy were the variables independently associated with 21-day mortality.⁷⁵

For CP-CRE, Tamma *et al.* conducted an observational study that compared 14-day mortality in patients with CP-CRE and non-CP-CRE bacteremia. After adjusting for severity of illness on day 1 of bacteremia, underlying medical conditions, and differences in the antibiotic treatment administered, the odds of dying within 14 days was more than four times greater for CP-CRE compared with non-CP-CRE bacteremia patients (aOR, 4.92; 95% CI: 1.01–24.81).⁷⁶

The INCREMENT CPE score was developed, and subsequently validated, to assess mortality risk – and subsequently guide the initiation of empiric therapy – using objective clinical criteria in CPE-colonized patients, including KPC-producing *K. pneumoniae*. The underlying logistic regression model identified the following variables in BSIs and assigned a point-based weighting, to which a threshold was applied.^{27,77} INCREMENT-CPE has been externally validated in further studies.^{78,79}

Finally, a meta-analysis published by Vardakas *et al.* included 30 studies, 25 of which were retrospective, nine provided data on predictors of mortality for MDRGNB infections only, and 21 provided data for MDRGN versus non-MDRGNB infections.⁸⁰ Within the studies, *Acinetobacter* spp., *P. aeruginosa* and *Enterobacterales* were the most studied bacteria. There was significant diversity among studies regarding evaluated predictors of mortality. Nevertheless, the most reported independent predictors of mortality were infection severity and underlying diseases, followed by multidrug resistance, inappropriate treatment and increasing age. In the studies that included only patients with MDRGNB infections, cancer (RR: 1.65, 95% CI: 1.13–2.39) and prior or current ICU stay (RR: 1.27, 95% CI: 1.02–1.56) were the risk factors associated with mortality.⁸⁰

Author's opinion: advantages and disadvantages of risk scores

There are multiple advantages of the scoring systems; they are simple to calculate and are based on readily available data at hospital admission.^{54,75,81,82} Such scores can shorten the time to initiate appropriate empiric therapy, help optimize therapy and avoid inappropriate and potentially toxic therapies.^{27,54,83,84} Such scoring systems also help de-escalate therapies, avoiding toxicity and costs associated with extended antibiotic use.^{52,54} In studies evaluating these scoring systems, those assessing MDRGNB risk performed well, providing significant and accurate predictions of infection or mortality with good powers of prediction.^{27,52,54,83} Table 3 summarizes the different studies evaluated for this review and compare the different risk scores for the prediction of infection or mortality by resistant bacteria. We found that the sensitivity of scores ranges between 74%–96%, the specificity from 42%–91%, and the negative predictive values from 68%–99%.^{27,52,54,82,83,85}

Despite the advantages of using risk scores, we found that one of the major disadvantages with MDRGNB risk scoring systems is that multiple methods have not been externally validated in wider populations and may not be generalizable to patient cohorts in different regions.^{27,54,81–83,86,87} In addition, it was not clear which sub-populations would benefit most from this risk assessment, as some studies evaluated specific populations^{21,43,73,76} or specific sites of infection.^{43,70,76} The utility of a scoring system depends on the intended application and its ultimate value. Moreover, many of the

Table 3. Performance of risk scores predicting infection, colonization, or mortality by MDR bacteria

Score reference	Sensitivity	Specificity	Negative predictive value
Giannella, <i>et al.</i> 2014 ⁵⁴ GRS	93%	42%	96%
Cano <i>et al.</i> 2018 ²⁷ GRS & ICS	93%	87%	94%
Tumbarello <i>et al.</i> 2011 ⁵²	93%	62%	97%
Johnson <i>et al.</i> 2013 ⁸⁵	87%	69%	94%
Kengkla <i>et al.</i> 2016 ⁸³	74%	66%	68%
Lee <i>et al.</i> 2017 ⁸²	85%	93%	99%
Henderson <i>et al.</i> 2020 PBS* and qPitt** ⁸⁶	95%	65%	n.d.***
Henderson <i>et al.</i> 2020 PBS and qPitt ⁸⁶	93%	60%	n.d.
Teyseyre <i>et al.</i> 2019 ⁸⁷ CarbaSCORE	96%	91%	n.d.

*PBS score.

**qPitt score.⁸⁶

***n.d. = no data.

studies assessing these scores have been retrospective, and do not consider the different methods and patient populations involved.^{82,86,88} It is also worth noting that the quality of data and medical practice may not be consistent across all sites.^{82,86,88} Moreover, scoring systems are unable to determine the duration of carrier status prior to the development of an infection.⁵⁴ In some scoring systems, the cutoff value for the score that represents a risk is critical and can change the indicated outcome, and more data is needed to determine the reliability of risk prediction. Due to the difference in rates of resistance at various locations, some scoring systems may also require local adaptation of the test parameters or changes in cutoff values.⁸⁵ Another limitation is that most risk scoring systems are intended for use with specific pathogens/resistance mechanisms rather than multiple different mechanisms of resistance of GNB, and this may restrict their usefulness and widespread use, or dictate that multiple different scores may need to be used.^{81,85–87} Nonetheless, examples like the INCREMENT-ESBL scoring system, which has been evaluated at multiple different locations internationally, has more reliable evidence-based data to support its use. Despite these current drawbacks, risk scoring systems show promise and have the potential to expedite appropriate treatment and substantially improve outcomes in serious MDRGNB infections.

Conclusions

This review underscores the concerning prevalence of antibiotic resistance in MDRGNB, specifically focusing on the clinically relevant *Enterobacteriales*, *P. aeruginosa*, and *A. baumannii*. The escalating global presence of these bacteria emphasizes the critical need to identify colonization and infection risk factors which are significantly linked to mortality. Selecting multiple publications which reported risk factors with association measures and compared the different OR values that might aid when assessing risk factors to predict colonization and/or infection with MDR bacteria may help the selection of empiric treatment in a more appropriate way. Although the accuracy of published risk factor scores and assessments varies, it is imperative to consider these

factors and utilize available tools judiciously. We found that most risk scores have a high sensitivity, while most of them are not specific. Nonetheless, we believe that used in a judicious and individualized way in each clinical situation, these tools can aid healthcare workers in expediting appropriate empiric therapy, guiding the selection of optimal treatment, applying necessary infection control and prevention measures and thereby improve the overall clinical outcomes for patients. In the future, machine learning, as well as AI, could revolutionize the prediction of colonization and infection risk. By combining patient-specific risk factors with dynamic, machine-learning-driven approaches, these advanced models have the potential to significantly enhance predictive accuracy. Unlike traditional methods, machine learning models and AI can integrate vast amounts of data, including clinical, microbiological, and demographic information, in real time. This allows for the generation of personalized risk assessments tailored to each patient's unique profile, enabling earlier and more targeted interventions.

However, it is important to note that while these risk assessment tools can be valuable in initiating empirical therapy for at-risk patients, they should not supersede clinical judgment or the availability of clinical data to prevent the overuse of broad-spectrum antibiotics.

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Ethical standard. None.

References

1. Abayneh M, Worku T. Prevalence of multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli: a meta-analysis report in Ethiopia. *Drug Target Insights* 2020;14:16–25.
2. Breijyeh Z, Jubeh B, Karaman R. Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules* 2020;25:1340.
3. Exner M, Bhattacharya S, Christiansen B, *et al.* Antibiotic resistance: what is so special about multidrug-resistant gram-negative bacteria? *GMS Hyg Infect Control* 2017;12:Doc05.
4. Morris S, Cerceo E. Trends, epidemiology, and management of multi-drug resistant gram-negative bacterial infections in the hospitalized setting. *Antibiotics (Basel)* 2020;9:196.
5. Santoro A, Franceschini E, Meschiari M, *et al.* Epidemiology and risk factors associated with mortality in consecutive patients with bacterial bloodstream

- infection: impact of MDR and XDR bacteria. *Open Forum Infect Dis* 2020;7: ofaa461.
6. De Angelis G, Giacomo PD, Posteraro B, *et al.* Molecular mechanisms, epidemiology, and clinical importance of β -lactam resistance in enterobacteriaceae. *Int J Mol Sci* 2020;21:1–22.
 7. Bassetti M, Peghin M, Vena A, *et al.* Treatment of infections due to MDR gram-negative bacteria. *Front Med (Lausanne)* 2019;6:74.
 8. Cerceo E, Deitelzweig SB, Sherman BM, *et al.* Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. *Microb Drug Resist* 2016;22:412–431.
 9. Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. *Pharmacotherapy* 2015;35:949–962.
 10. Oliveira J, Reygaert WC. Gram-Negative Bacteria. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. <https://www.ncbi.nlm.nih.gov/books/NBK538213/>.
 11. Gandra S, Tseng KK, Arora A, *et al.* The mortality burden of multidrug-resistant pathogens in india: a retrospective, observational study. *Clin Infect Dis* 2019;69:563–570.
 12. MacVane SH. Antimicrobial resistance in the intensive care unit: a focus on gram-negative bacterial infections. *J Intensive Care Med* 2017;32:25–37.
 13. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant gram-negative bacilli in Europe. *Euro Surveill* 2008;13.
 14. Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. *Clin Infect Dis* 2019;69:S521–S528.
 15. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health* 2015;109:309–318.
 16. Tang SS, Apisarnthanarak A, Hsu LY. Mechanisms of beta-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug-resistant bacteria. *Adv Drug Deliv Rev* 2014;78:3–13.
 17. Bassetti M, Carnelutti A, Peghin M. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in gram-negative bacterial infections. *Expert Rev Anti Infect Ther* 2017;15:55–65.
 18. Hawkey PM, Warren RE, Livermore DM, *et al.* Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British society for antimicrobial chemotherapy/healthcare infection society/British infection association joint working party. *J Antimicrob Chemother* 2018;73: iii2–iii78.
 19. Palacios-Baena ZR, Giannella M, Manissero D, *et al.* Risk factors for carbapenem-resistant gram-negative bacterial infections: a systematic review. *Clin Microbiol Infect* 2021;27:228–235.
 20. Patolia S, Abate G, Patel N, *et al.* Risk factors and outcomes for multidrug-resistant Gram-negative bacilli bacteremia. *Ther Adv Infect Dis* 2018;5:11–18.
 21. Lodise TP, Patel N, Kwa A, *et al.* Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. *Antimicrob Agents Chemother* 2007;51:3510–3515.
 22. Raman G, Avendano E, Berger S, *et al.* Appropriate initial antibiotic therapy in hospitalized patients with gram-negative infections: systematic review and meta-analysis. *BMC Infect Dis* 2015;15:1–11.
 23. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect* 2016;22:416–422.
 24. Tellado JM, Sen SS, Caloto MT, *et al.* Consequences of inappropriate initial empiric parenteral antibiotic therapy among patients with community-acquired intra-abdominal infections in Spain. *Scand J Infect Dis* 2007;39:947–955.
 25. Dellit TH, Owens RC, McGowan JE Jr, *et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44:159–177.
 26. Aliberti S, Di Pasquale M, Zanaboni AM, *et al.* Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012;54:470–478.
 27. Cano A, Gutiérrez-Gutiérrez B, Machuca I, *et al.* Risks of infection and mortality among patients colonized with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: validation of scores and proposal for management. *Clin Infect Dis* 2018;66:1204–1210.
 28. Murray CJ, Ikuta KS, Sharara F, *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;399:629–655.
 29. Anaya-Baz B, Maldonado N, Palacios-Baena ZR, *et al.* Systematic literature review of the burden and outcomes of infections due to multidrug-resistant organisms in Europe: the ABOUT-MDRO project protocol. *BMJ Open* 2020;10:e030608.
 30. Achmad Ali Fikri, Syamsul Arifin MFF. Global antimicrobial resistance and use surveillance system (GLASS) Report 2022. *World Health Organiz* 2022;2:2003–2005.
 31. OneHealthTrust. ResistanceMap: Antibiotic resistance. <https://resistance.map.onehealthtrust.org/AntibioticResistance.php>. Published 2024. Accessed June 29, 2024.
 32. Center for Disease Dynamics, Economics & Policy. *State of the World's Antibiotics*. Washington, DC: CDDEP; 2015.
 33. Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-beta-lactamase (NDM)-mediated carbapenem resistance. *J Med Microbiol* 2013;62:499–513.
 34. Moellering RC Jr. NDM-1—a cause for worldwide concern. *N Engl J Med* 2010;363:2377–2379.
 35. Pillai DR, McGeer A, Low DE. New Delhi metallo-beta-lactamase-1 in enterobacteriaceae: emerging resistance. *CMAJ* 2011;183:59–64.
 36. Abrar S, Ain NU, Liaqat H, *et al.* Distribution of bla CTX - M, bla TEM, bla SHV and bla OXA genes in extended-spectrum-beta-lactamase-producing clinical isolates: a three-year multi-center study from Lahore, Pakistan. *Antimicrob Resist Infect Control* 2019;8:80.
 37. Ageevets VA, Partina I V, Lisitsyna ES, *et al.* Emergence of carbapenemase-producing gram-negative bacteria in Saint Petersburg, Russia. *Int J Antimicrob Agents* 2014;44:152–155.
 38. van Duijn D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence* 2017;19:460–469.
 39. Hawkey PM. Multidrug-resistant gram-negative bacteria: a product of globalization. *J Hosp Infect* 2015;89:241–247.
 40. Weingarten RA, Johnson RC, Conlan S, *et al.* Genomic analysis of hospital plumbing reveals diverse reservoir of bacterial plasmids conferring carbapenem resistance. *mBio* 2018;9:e02011–7.
 41. Bush K, Bradford PA. Epidemiology of β -Lactamase-producing pathogens. *Clin Microbiol Rev*. 2020;33:e00047-19.
 42. Ahammad ZS, Sreekrishnan TR, Hands CL, *et al.* Increased waterborne blaNDM-1 resistance gene abundances associated with seasonal human pilgrimages to the upper ganges river. *Environ Sci Technol* 2014;48:3014–3020.
 43. Guzmán-Blanco M, Labarca JA, Villegas MV, *et al.* Extended spectrum β -lactamase producers among nosocomial Enterobacteriaceae in Latin America. *Braz J Infect Dis* 2014;18:421–433.
 44. Islam K, Heffernan AJ, Naicker S, *et al.* Epidemiology of extended-spectrum β -lactamase and metallo- β -lactamase-producing *Escherichia coli* in South Asia. *Future Microbiol* 2021;16:521–535.
 45. Ecdc. Antimicrobial resistance in the EU/EEA (EARS-Net) - AER for 2019, <https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019>. Accessed September 6, 2023.
 46. Maechler F, Pena Diaz LA, Schroder C, *et al.* Prevalence of carbapenem-resistant organisms and other gram-negative MDRO in German ICUs: first results from the national nosocomial infection surveillance system (KISS). *Infection* 2015;43:163–168.
 47. Poulou A, Spanakis N, Pournaras S, *et al.* Recurrent healthcare-associated community-onset infections due to *Klebsiella pneumoniae* producing VIM-1 metallo-beta-lactamase. *J Antimicrob Chemother* 2010;65:2538–2542.
 48. Tenover FC, Goff DA. Surveillance and stewardship: where infection prevention and antimicrobial stewardship intersect. *Open Forum Infect Dis* 2023;10:ofad176.
 49. Razazi K, Rosman J, Phan AD, *et al.* Quantifying risk of disease due to extended-spectrum beta-lactamase producing Enterobacteriaceae in patients who are colonized at ICU admission. *J Infect* 2020;80: 504–510.

50. Flokas ME, Alevizakos M, Shehadeh F, *et al.* Extended-spectrum beta-lactamase-producing Enterobacteriaceae colonisation in long-term care facilities: a systematic review and meta-analysis. *Int J Antimicrob Agents* 2017;50:649–656.
51. Burillo A, Muñoz P, Bouza E. Risk stratification for multidrug-resistant Gram-negative infections in ICU patients. *Curr Opin Infect Dis* 2019;32:626–637.
52. Tumbarello M, Trecarichi EM, Bassetti M, *et al.* Identifying patients harboring extended-spectrum- β -lactamase-producing enterobacteriaceae on hospital admission: derivation and validation of a scoring system. *Antimicrob Agents Chemother* 2011;55:3485–3490.
53. Salomao MC, Guimaraes T, Duailibi DF, *et al.* Carbapenem-resistant Enterobacteriaceae in patients admitted to the emergency department: prevalence, risk factors, and acquisition rate. *J Hosp Infect* 2017;97:241–246.
54. Giannella M, Trecarichi EM, De Rosa FG, *et al.* Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. *Clin Microbiol Infect* 2014;20:1357–1362.
55. Pano Pardo JR, Serrano Villar S, Ramos Ramos JC, *et al.* Infections caused by carbapenemase-producing Enterobacteriaceae: risk factors, clinical features and prognosis. *Enferm Infecc Microbiol Clin* 2014;32:41–48.
56. Torres-Gonzalez P, Cervera-Hernandez ME, Niembro-Ortega MD, *et al.* Factors associated to prevalence and incidence of carbapenem-resistant enterobacteriaceae fecal carriage: a cohort study in a Mexican tertiary care hospital. *PLoS One* 2015;10:e0139883.
57. Kontopoulou K, Iosifidis E, Antoniadou E, *et al.* The clinical significance of carbapenem-resistant *Klebsiella pneumoniae* rectal colonization in critically ill patients: from colonization to bloodstream infection. *J Med Microbiol* 2019;68:326–335.
58. Zarakolu P, Eser OK, Aladag E, *et al.* Epidemiology of carbapenem-resistant *Klebsiella pneumoniae* colonization: a surveillance study at a Turkish university hospital from 2009 to 2013. *Diagn Microbiol Infect Dis* 2016;85:466–470.
59. Aloush V, Navon-Venezia S, Seigman-Igra Y, *et al.* Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. *Antimicrob Agents Chemother* 2006;50:43–48.
60. Raman G, Avendano EE, Chan J, *et al.* Risk factors for hospitalized patients with resistant or multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 2018;7:79.
61. Tacconelli E, Tumbarello M, Bertagnolio S, *et al.* Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: analysis of trends in prevalence and epidemiology. *Emerg Infect Dis* 2002;8:220–221.
62. Blanco N, Harris AD, Rock C, *et al.* Risk factors and outcomes associated with multidrug-resistant *Acinetobacter baumannii* upon Intensive Care Unit Admission. *Antimicrob Agents Chemother* 2018;62:1–7.
63. Munier AL, Biard L, Legrand M, *et al.* Incidence, risk factors and outcome of multi-drug resistant *Acinetobacter baumannii* nosocomial infections during an outbreak in a burn unit. *Int J Infect Dis* 2019;79:179–184.
64. Munier AL, Biard L, Rousseau C, *et al.* Incidence, risk factors, and outcome of multidrug-resistant *Acinetobacter baumannii* acquisition during an outbreak in a burns unit. *J Hosp Infect* 2017;97:226–233.
65. Sheng WH, Liao CH, Lauderdale TL, *et al.* A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. *Int J Infect Dis* 2010;14:e764–9.
66. Jaiswal SR, Gupta S, Kumar RS, *et al.* Gut colonization with carbapenem-resistant enterobacteriaceae adversely impacts the outcome in patients with hematological malignancies: results of a prospective surveillance study. *Mediterr J Hematol Infect Dis* 2018;10:e2018025.
67. Cohen R, Babushkin F, Cohen S, *et al.* A prospective survey of *Pseudomonas aeruginosa* colonization and infection in the intensive care unit. *Antimicrob Resist Infect Control* 2017;6:7.
68. McConville TH, Sullivan SB, Gomez-Simmonds A, *et al.* Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study. *PLoS One* 2017;12:e0186195.
69. Falagas ME, Tansarli GS, Karageorgopoulos DE, *et al.* Deaths attributable to carbapenem-resistant enterobacteriaceae infections. *Emerg Infect Dis* 2014;20:1170–1175.
70. Stewardson AJ, Marimuthu K, Sengupta S, *et al.* Effect of carbapenem resistance on outcomes of bloodstream infection caused by enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. *Lancet Infect Dis* 2019;19:601–610.
71. Villegas MV, Pallares CJ, Escandón-Vargas K, *et al.* Characterization and clinical impact of bloodstream infection caused by carbapenemase-producing enterobacteriaceae in seven latin American countries. *PLoS One* 2016;11:e0154092. DOI: [10.1371/JOURNAL.PONE.0154092](https://doi.org/10.1371/JOURNAL.PONE.0154092).
72. Paramythiotou E, Routsis C. Association between infections caused by multidrug-resistant gram-negative bacteria and mortality in critically ill patients. *World J Crit Care Med* 2016;5:111–120.
73. Son HJ, Cho EB, Bae M, *et al.* Clinical and microbiological analysis of risk factors for mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. *Open Forum Infect Dis* 2020;7:ofaa378.
74. Du X, Xu X, Yao J, *et al.* Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: a systematic review and meta-analysis. *Am J Infect Control* 2019;47:1140–1145.
75. Tumbarello M, Repetto E, Trecarichi EM, *et al.* Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. *Epidemiol Infect* 2011;139:1740–1749.
76. Tamma PD, Goodman KE, Harris AD, *et al.* Comparing the outcomes of patients with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant enterobacteriaceae bacteremia. *Clin Infect Dis* 2017;64:257–264.
77. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, *et al.* Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017;17:726–734.
78. Papadimitriou-Olivgeris M, Bartzavali C, Georgakopoulou A, *et al.* External validation of INCREMENT-CPE score in a retrospective cohort of carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections in critically ill patients. *Clinical Microbiology and Infection* 2021;27:915.e1–915.e3.
79. Machuca I, Gutiérrez-Gutiérrez B, Rivera-Espinar F, *et al.* External validation of the INCREMENT-CPE mortality score in a carbapenem-resistant *Klebsiella pneumoniae* bacteraemia cohort: the prognostic significance of colistin resistance. *Int J Antimicrob Agents* 2019;54:442–448.
80. Vardakas KZ, Rafailidis PI, Konstantelias AA, *et al.* Predictors of mortality in patients with infections due to multi-drug resistant gram negative bacteria: the study, the patient, the bug or the drug? *J Infect* 2013;66:401–414.
81. Boyd SE, Vasudevan A, Moore LSP, *et al.* Validating a prediction tool to determine the risk of nosocomial multidrug-resistant gram-negative bacilli infection in critically ill patients: a retrospective case-control study. *J Glob Antimicrob Resist* 2020;22:826–831.
82. Lee CH, Chu FY, Hsieh CC, *et al.* A simple scoring algorithm predicting extended-spectrum beta-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia: matters of frequent emergency department users. *Medicine (Baltimore)* 2017;96:e6648.
83. Kengkla K, Charoensuk N, Chaichana M, *et al.* Clinical risk scoring system for predicting extended-spectrum beta-lactamase-producing *Escherichia coli* infection in hospitalized patients. *J Hosp Infect* 2016;93:49–56.
84. Tartof SY, Kuntz JL, Chen LH, *et al.* Development and assessment of risk scores for carbapenem and extensive beta-lactam resistance among adult hospitalized patients with *Pseudomonas aeruginosa* infection. *JAMA Netw Open* 2018;1:e183927.
85. Johnson SW, Anderson DJ, May DB, *et al.* Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum beta-lactamase-producing enterobacteriaceae on hospital admission. *Infect Control Hosp Epidemiol* 2013;34:385–392.
86. Henderson H, Luterbach CL, Cober E, *et al.* The pitt bacteremia score predicts mortality in nonbacteremic infections. *Clin Infect Dis* 2020;70:1826–1833.
87. Teyssyre L, Ferdynus C, Miltgen G, *et al.* Derivation and validation of a simple score to predict the presence of bacteria requiring carbapenem

- treatment in ICU-acquired bloodstream infection and pneumonia: CarbaSCORE. *Antimicrob Resist Infect Control* 2019;8:78.
88. Palacios-Baena ZR, Gutierrez-Gutierrez B, De Cueto M, *et al.* Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-beta-lactamase-producing enterobacteriaceae. *J Antimicrob Chemother* 2017;72:906–913.
89. Johnson SW, Anderson DJ, May DB, *et al.* Utility of a clinical risk factor scoring model in predicting infection with extended-spectrum beta-lactamase-producing enterobacteriaceae on hospital admission. *Infect Control Hosp Epidemiol* 2013;34:385–392.
90. Hu Y, Qing Y, Chen J, *et al.* Prevalence, risk factors, and molecular epidemiology of intestinal carbapenem-resistant pseudomonas aeruginosa. *Microbiol Spectr* 2021;9:e0134421.
91. 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.
92. Fernández-Martínez NF, Cárcel-Fernández S, De la Fuente-Martos C, *et al.* Risk factors for multidrug-resistant gram-negative bacteria carriage upon admission to the intensive care unit. *Int J Environ Res Public Health* 2022;19:1039.