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SYSTEMATIC REVIEW

Current etiology and carbapenem resistance of bacteria causing spontaneous bacterial peritonitis: a systematic review

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Abstract

Spontaneous Bacterial Peritonitis (SBP) has traditionally been associated with Gram-negative Enterobacteriaceae. However, recent studies indicate a shift in the epidemiology, with Gram-positive bacteria now identified as major pathogens responsible for SBP. Furthermore, there is an increasing prevalence of bacteria resistant to carbapenems. Based on these developments, this systematic review aims to explore the epidemiology of SBP since the first report of Carbapenem-Resistant Enterobacterales (CRE) in 2012. This systematic review protocol was prospectively registered in PROSPERO (CRD42020173786). A comprehensive literature search was conducted, incorporating data available until 29 October 2023, from MEDLINE via PubMed, EMBASE and CENTRAL databases. A total of 1647 records were identified (EMBASE: 885; PubMed: 730; Cochrane: 32), among which 21 studies met the inclusion criteria for this review. In total, 2943 pathogens were isolated across these studies, and among them, 561 (19.02%) were identified as multidrug-resistant organisms (MDROs), resulting in an overall prevalence of MDROs of approximately one-fifth. Furthermore, a significant proportion of the isolates, specifically 1394 (47.27%), were classified as Gram-negative bacteria. Within this Gram-negative subset, 139 (9.97%) isolates exhibited resistance to carbapenem antibiotics, representing about one-tenth of the total. The data obtained from this systematic review indicate that Gram-negative bacteria account for slightly less than half of the isolates causing SBP. Within the Gram-negative category, approximately one-tenth of the isolates are resistant to carbapenems. Furthermore, the overall prevalence of MDROs responsible for SBP is about one-fifth of the isolates. These findings highlight the need for current guidelines on the empirical treatment of SBP to consider the prevailing etiology.

Keywords

Carbapenem resistance; Carbapenem-resistant enterobacterales; Multidrug resistance; β-lactamase inhibitors; Anti-infective agents; Spontaneous bacterial peritonitis; Sepsis; Infection; Systematic review

1. Introduction

The epidemiology of bacteria responsible for spontaneous bacterial peritonitis (SBP) has undergone rapid changes in recent years. Historically, Gram-negative bacteria have been recognized as the predominant pathogens causing SBP; however, recent studies indicate that Gram-positive bacteria are now the most prevalent pathogens associated with this condition [1, 2]. The latest guidelines from the American Association for the Study of Liver Diseases (AASLD), updated in August 2021, continue to classify Gram-negative bacteria as the primary causative agents of SBP [3].

In addition to the rising prevalence of Gram-positive bacteria, a significant increase in multidrug-resistant organisms (MDROs) has been observed. The first case of nosocomial SBP caused by Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) was reported in Italy over a decade ago (2012) [4]. Since that time, multiple global reports have documented the emergence of this concern [5–7]. The combination of SBP, which has mortality rates exceeding 80% when associated with septic shock [8], and CRKP infections, which carry a mortality rate greater than 50% in cases of bloodstream infections (CRKP-BSIs) [9], poses a significant risk to patient survival.

Given the limited therapeutic options [10, 11] and the urgent need for timely initiation of appropriate antimicrobial therapy (AAT)—with each hour of AAT delay associated with a 1.86-fold increase in in-hospital mortality [8]—CRKP-SBP infections represent a critical challenge for clinicians. Carbapenem

resistance is prevalent among *K. pneumoniae* isolates and other Carbapenem-Resistant Enterobacterales (CRE) [12]. Notably, the mortality rate among CRE cases mirrors the crude mortality rates observed in various infections caused by CRKP [13]. In this systematic review, we investigate the etiology and prevalence of Carbapenem resistance among the pathogens responsible for SBP.

2. Methods

The protocol for this systematic review was prospectively registered in PROSPERO (CRD42020173786) following a comprehensive search of key databases, including the Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, CENTRAL and PROSPERO, to eliminate duplicates. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, updated in 2020 [14].

2.1 Study search

The literature search was conducted using data available up to 29 October 2023, and included MEDLINE via PubMed, EMBASE and CENTRAL. The full search strategy is detailed in Table 1.

2.2 Study selection

We included both randomized controlled trials (RCTs) and non-randomized studies (both prospective and retrospective) published in peer-reviewed English-language journals, with no restrictions on publication dates. The inclusion and exclusion process is illustrated in Fig. 1, following the PRISMA flow diagram. After the search, duplicates were removed using citation management software (EndNote VX9, Clarivate Analytics, Philadelphia, PA, USA), and a comprehensive list of the included studies was compiled. Two authors (AA and SDF) independently screened the retrieved articles based on their titles and abstracts, followed by a full-text evaluation of selected articles for final inclusion. Standardized reasons for exclusion were recorded. Any discrepancies regarding study eligibility or data extraction were resolved by mutual consensus, involving a third reviewer (MF) when necessary.

2.3 Definition and outcomes

SBP is defined as an infection of ascitic fluid with a polymorphonuclear leukocyte (PMN) count exceeding 250 cells/mL. Culture-positive SBP refers to the identification of the etiological agent, which can be obtained through analysis of ascitic fluid or bloodstream cultures [8, 15].

The review focused on the following questions: (1) the epidemiology of SBP caused by CRE, (2) the prevalence of CRE among Gram-negative bacteria isolated from cultures, (3) the total number of Gram-positive and Gram-negative bacteria isolated, (4) the countries of origin of the isolates, and (5) the years during which the studies were conducted.

2.4 Data extraction and quality assessment

The methodological quality of the included studies was assessed using the Cochrane risk-of-bias tool for randomized controlled trials and the ROBINS tool for non-randomized studies [16]. Evaluations were conducted in duplicate by two reviewers (AA and SDF), with any disagreements resolved by a mutual consensus. When necessary, a third reviewer (MF) was involved in the resolution process.

2.5 Synthesis methods

A general summary of the characteristics and findings of the included studies was developed. Studies with incomplete data were excluded from the analysis. The results were synthesized using a table format to present the study findings effectively.

3. Results

A total of 1647 records were identified from the databases (EMBASE: 885; PubMed: 730; Cochrane: 32). After removing 305 duplicates, 1342 records were screened. Of these, 1154 were excluded based on title and abstract review. Among the remaining records, 188 articles were selected for further evaluation, from which five were again removed due to duplication. After assessing the eligibility of the final 183 articles, 21 studies were included in this systematic review (Fig. 1). Across the included studies, a total of 2949 pathogens were isolated. Notably, 561 of these were identified as MDROs, resulting in an overall prevalence of approximately 19% for MDROs. Additionally, a significant proportion of the isolates, accounting for 47% of the total, were classified as Gram-negative bacteria. Within this Gram-negative subset, 139 isolates, representing 10% of the total pathogens, exhibited resistance to carbapenem antibiotics (Fig. 2).

The collected data encompass a diverse range of countries and time periods, spanning from 1996 to 2022, and include both short-term and long-term studies. The details of the included studies are summarized in Table 2.

Analysis of carbapenem resistance among Gram-negative bacteria revealed significant variations in prevalence across different countries. Resistance rates varied widely, ranging from as low as 0.80% in Australia to as high as 38.46% in Greece. These findings should be interpreted with caution, as the studies may not fully represent the entire population of each country. Fig. 3 illustrates the absolute numbers of MDROs and carbapenem-resistant (CR) pathogens in different nations.

A comprehensive analysis of resistance patterns among various pathogens further highlights these discrepancies. Among the Gram-negative pathogens, Escherichia coli exhibited a relatively low resistance rate, with only 14 out of 235 isolates (5.96%) demonstrating resistance. In contrast, Klebsiella pneumoniae showed a higher resistance rate, with 24 out of 98 isolates (24.49%) resistant to antibiotics. Pseudomonas aeruginosa also demonstrated a resistance rate of 25%, with 5 out of 20 isolates being resistant, emphasizing its well-documented ability to resist multiple antibiotics. Acinetobacter baumannii stood out with a notably high resistance rate of 61.54%, as 8 out of 13 isolates demonstrated resistance, reflecting a serious issue with multidrug resistance. Citrobacter species also ex-

TABLE 1. Search strategies for different databases.

Database	Search String
EMBASE	(“primary peritonitis”/exp OR “spontaneous peritonitis” OR “primary peritonitis” OR “peritonitis”/exp/mj) AND (“carbapenem-resistant enterobacteriaceae”/exp OR “cnse (enterobacteriaceae)” OR “cr enterobacteriaceae” OR “cre (enterobacteriaceae)” OR “carbapenem non-susceptible enterobacteriaceae” OR “carbapenem nonsusceptible enterobacterial isolate” OR “carbapenem resistant enterobacteriaceae” OR “carbapenem-nonsusceptible enterobacteriaceae” OR “carbapenem-resistant enterobacteriaceae” OR “carbapenems-resistant enterobacteriaceae” OR “carbapenem resistance”/exp/mj OR “carbapenem resistance” OR “carbapenems resistance” OR “enterobacteriaceae”/mj OR “enterobacteriaceae” OR “enteric bacteria” OR “enterobacteria” OR “enterobacteriacea“ OR “enterobacterium” OR ((“end stage liver disease”/exp/mj OR “end stage hepatic disease” OR “end stage hepatic dysfunction” OR “end stage hepatic failure” OR “end stage hepatic insufficiency” OR “end stage liver disease” OR “end stage liver dysfunction” OR “end stage liver failure” OR “end stage liver insufficiency” OR “liver cirrhosis”/exp/mj OR “cirrhosis” OR “cirrhosis hepatis” OR “cirrhosis, liver” OR “cryptogenic liver cirrhosis” OR “dietary cirrhosis” OR “dietary liver cirrhosis” OR “hepatic cirrhosis” OR “liver cirrhosis” OR “postnecrotic liver cirrhosis”) AND infectio*)) AND (2013–2023)/py
PubMed	((“intraperitoneal infection”(All Fields) OR “peritoneal infection”(All Fields) OR “peritonism”(All Fields) OR “peritonitis”(MeSH Terms) OR “spontaneous peritonitis”(All Fields)) AND (“Enterobacteriaceae”(MeSH Terms) OR “carbapenem-resistant Enterobacteriaceae”(All Fields) OR “cr Enterobacteriaceae”(All Fields) OR “carbapenem non-susceptible Enterobacteriaceae”(All Fields)) OR “carbapenem-resistant Enterobacteriaceae”(All Fields) OR “carbapenem-nonsusceptible Enterobacteriaceae”(All Fields) OR “carbapenem-resistant Enterobacteriaceae”(All Fields) OR “carbapenems-resistant Enterobacteriaceae”(All Fields) OR “Enterobacteriaceae”(All Fields) OR “Enterobacteriaceae”(All Fields) OR “enteric bacteria”(All Fields) OR “enterobacteria”(All Fields) OR “enterobacteriacea”(All Fields) OR “enterobacterium”(All Fields) OR “carbapenem resistance”(All Fields) OR “carbapenem resistance”(All Fields) OR “carbapenems resistance”(All Fields) OR ((“end stage liver disease”(All Fields) OR “end stage hepatic disease”(All Fields) OR “end stage hepatic dysfunction”(All Fields) OR “end stage hepatic failure”(All Fields) OR “end stage liver disease”(All Fields) OR “end stage liver dysfunction”(All Fields) OR “end stage liver failure”(All Fields) OR “liver cirrhosis”(All Fields) OR “cirrhosis”(All Fields) OR “cirrhosis hepatis”(All Fields) OR “cirrhosis liver”(All Fields) OR “cryptogenic liver cirrhosis”(All Fields) OR “hepatic cirrhosis”(All Fields) OR “liver cirrhosis”(All Fields) OR “postnecrotic liver cirrhosis”(All Fields)) AND “infectio*”(All Fields))) AND (2013:2023(pdat))
Cochrane	(“intraperitoneal infection” OR “peritoneal infection” OR “peritonism” OR “peritonitis” OR “spontaneous peritonitis”) AND (“enterobacteriaceae” OR “carbapenem-resistant enterobacteriaceae” OR “cr enterobacteriaceae” OR “carbapenem non-susceptible enterobacteriaceae” OR “carbapenem-resistant enterobacteriaceae” OR “carbapenem-nonsusceptible enterobacteriaceae” OR “carbapenem-resistant enterobacteriaceae” OR “carbapenems-resistant enterobacteriaceae” OR “enterobacteriaceae” OR “enterobacteriaceae” OR “enteric bacteria” OR “enterobacteria” OR “enterobacteriacea” OR “enterobacterium” OR “carbapenem resistance” OR “carbapenem resistance” OR “carbapenems resistance” OR ((“end stage liver disease” OR “end stage hepatic disease” OR “end stage hepatic dysfunction” OR “end stage hepatic failure” OR “end stage liver disease” OR “end stage liver dysfunction” OR “end stage liver failure” OR “liver cirrhosis” OR “cirrhosis” OR “cirrhosis hepatis” OR “cirrhosis liver” OR “cryptogenic liver cirrhosis” OR “hepatic cirrhosis” OR “liver cirrhosis” OR “postnecrotic liver cirrhosis”) AND “infectio*”))

*: *part of search-string (wildcard).*

hibited significant resistance, with 1 out of 4 isolates (25%) resistant, despite the smaller sample size.

Interestingly, the percentage of infections caused by Gram-positive bacteria was approximately 52.73%, which exceeds traditional expectations based on previous literature that primarily associates SBP with Gram-negative bacteria.

4. Discussion

This present systematic review has several limitations. For instance, many of the included studies encompassed extended enrollment periods, some starting before 2012, the year of the first report on CRE [4], which might have led to an underestimation of the incidence of CRE. Additionally, some studies were conducted in different centers within the same country that exhibited considerable variability in characteristics. For instance, in the studies by Friedrich and Quickert, both conducted in Germany, the incidence of carbapenem resistance was reported as 44.26 % and 0%, respectively [24, 32].

SBP has predominantly been associated with Gram-negative bacteria, particularly Enterobacteriaceae [37, 38]. However, our review indicates a significant shift in the epidemiology of SBP, with an increasing incidence of Gram-positive bacterial infections [39, 40]. The findings suggest an evolution in the bacterial landscape, as the percentage of infections caused by Gram-positive bacteria was found to be approximately 52.73%, surpassing traditional expectations based on previ-

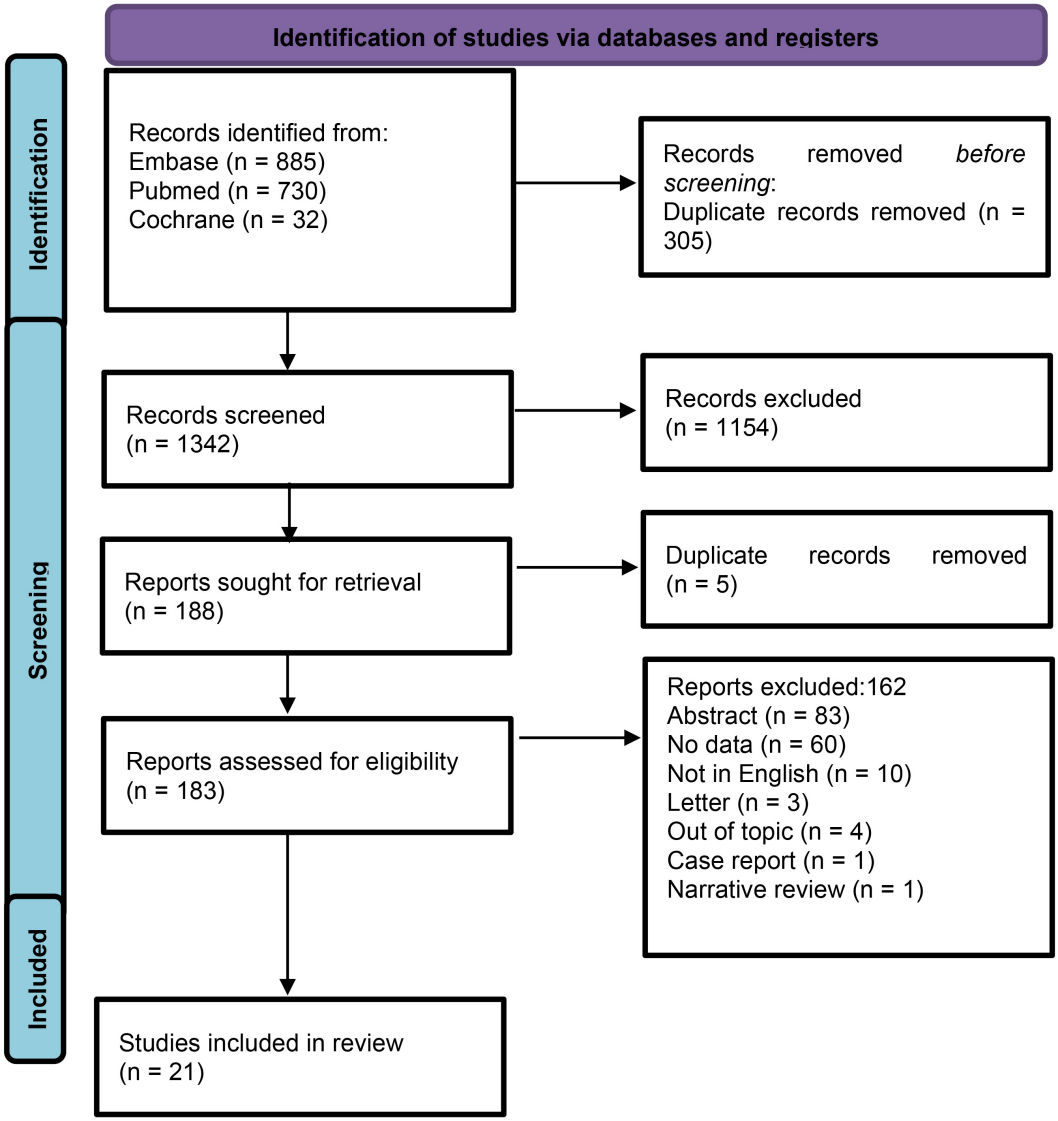

FIGURE 1. PRISMA flow diagram.

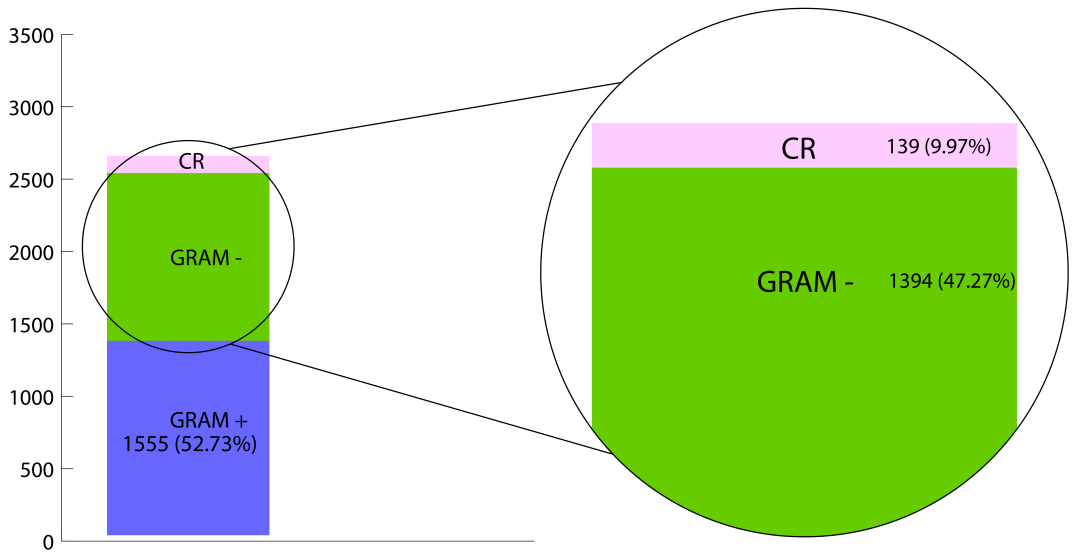

FIGURE 2. Proportions between Gram-positive (GRAM +) and Gram-negative (GRAM −) bacteria, as well as the proportion of carbapenem-resistant (CR) strains among Gram-negative bacteria in the analyzed isolates.

TABLE 2. Details of the included studies.

First Author [Ref.]	Journal	Pub Year	Country	Start year	End year	Centre(s) involved	Total	GRAM –	MDROs	CR
Zhu [17]	Medicine (Baltimore)	2022	China	2013	2019	Single center	32	19 (59.38)	15 (46.88)	0 (0.00)
Abu-Freha [18]	J Clin Med	2022	Israel	1996	2020	Single center	77	43 (55.84)	12 (15.58)	3 (6.98)
Alelign [19]	Infect Drug Resist	2021	Ethiopia	2019	2019	Single center	30	23 (76.67)	13 (43.33)	6 (26.09)
Alexopoulou [20]	World J Gastroenterol	2016	Greece	2012	2014	Single center	128	65 (50.78)	27 (21.09)	25 (38.46)
Bhat [21]	Indian J Gastroenterol	2013	India	2007	2011	Single center	30	28 (93.33)	7 (23.33)	1 (3.57)
Bhattacharya [22]	Annals Hepat	2019	India	2013	2015	Single center	78	78 (100.00)	62 (79.49)	16 (20.51)
Falleti [23]	J Clin Exp Hepatol	2021	Italy	2012	2016	Single center	15	10 (66.67)	4 (26.67)	0 (0.00)
Friedrich [24]	J of Gastr and Hep	2016	Germany	2007	2013	Single center	128	61 (47.66)	6 (4.69)	27 (44.26)
Guo [25]	Experimental and Therapeutic Medicine	2019	China	2011	2016	Single center	139	73 (52.52)	28 (20.14)	2 (2.74)
Kim [26]	Medicine (Baltimore)	2016	Korea Rep	2006	2013	Single center	77	50 (64.94)	10 (12.99)	0 (0.00)
Li [27]	Peritoneal Dialysis International	2017	China	2000	2015	Single center	66	66 (100.00)	12 (18.18)	5 (7.58)
Li [28]	World J Gastroenterol	2015	China	2011	2013	Single center	297	178 (59.93)	46 (15.49)	25 (14.04)
Mahajan [29]	Indian J Gastroenterol	2020	India	2011	2019	Single center	23	15 (65.22)	10 (43.48)	4 (26.67)
Oliveira [6]	Canadian J Gastr Hep	2019	Brazil	2010	2017	Single center	113	53 (46.90)	45 (39.82)	5 (9.43)
Öztoprak [30]	J Infect Microb Antimicrob	2019	Turkey	2011	2014	Single center	57	33 (57.89)	10 (17.54)	7 (21.21)
Pérez-Cameo [31]	Liver transpl	2014	Spain	2009	2011	Single center	57	31 (0.00)	1 (1.96)	0 (0.00)
Quickert [32]	Dig Dis	2022	Germany	2021	2022	Two centers	49	21 (42.86)	3 (6.12)	0 (0.00)
Ratnasekera [33]	Medicine (Baltimore)	2022	Australia	2008	2017	Multicenter	985	249 (25.28)	34 (3.45)	2 (0.80)
Al-Ghamdi [34]	Acta Gastroenterol Belg	2019	Saudi Arabia	2010	2016	Single center	103	64 (62.14)	12 (11.65)	0 (0.00)
Furey [35]	Dig Dis and Sci	2023	US	2015	2021	Two centers	88	56 (63.64)	18 (20.45)	0 (0.00)
Zhang [36]	Dig Liver Dis	2023	China	2015	2020	Single center	377	178 (47.21)	186 (49.34)	11 (6.18)
Total							2949	1394 (47.27)	561 (19.02)	139 (9.97)

MDROs: multidrug-resistant organisms; CR: carbapenem-resistant bacteria; GRAM −: Gram negative; MDROs: n (% of the total. GRAM −: n (% of the total). CR: n (% of GRAM −).

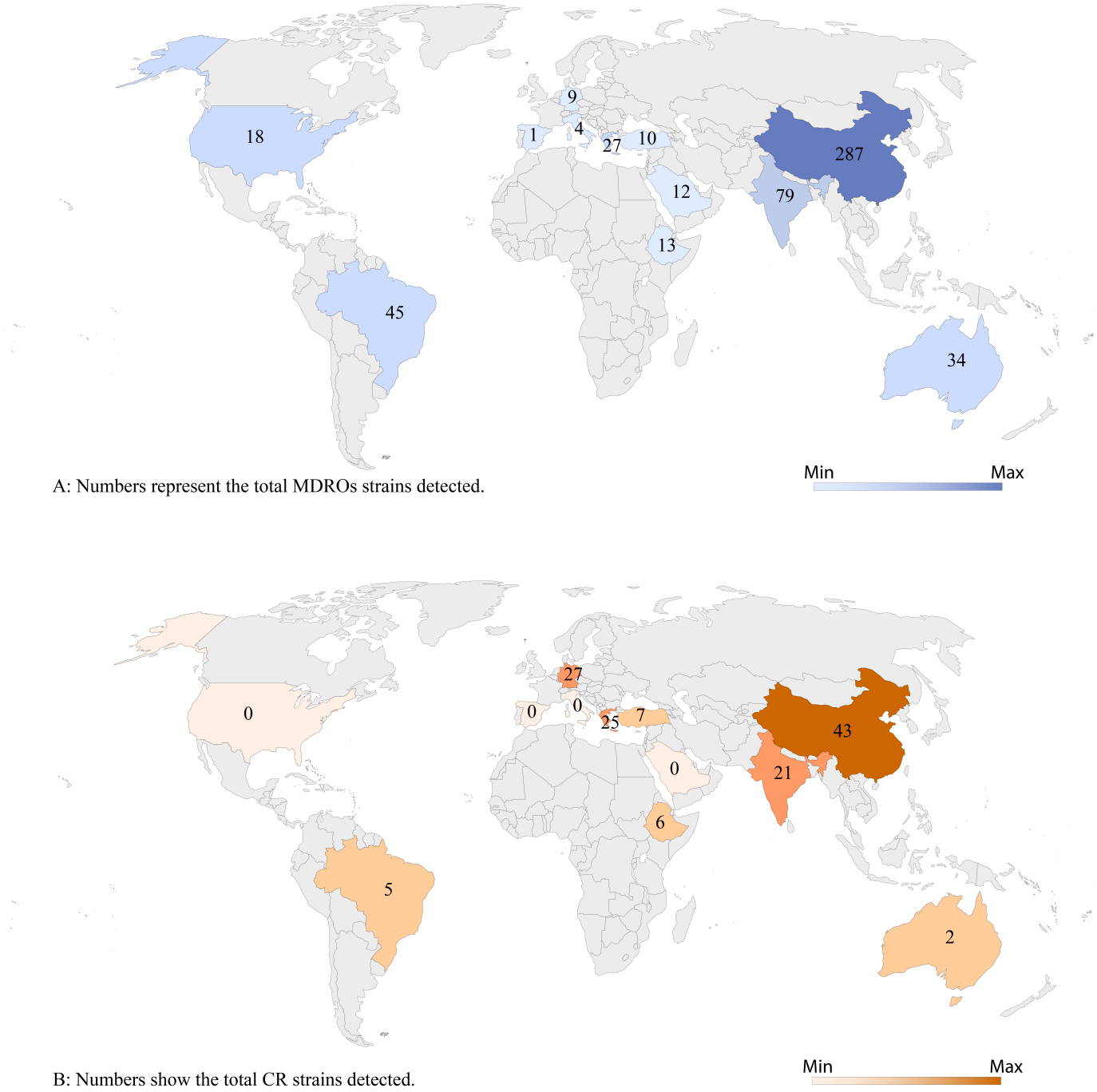

FIGURE 3. The geographical map of studies reported in Table 2, with the frequency of MDROs (Fig. 3A) and CR bacteria (Fig. 3B). MDROs: multidrug-resistant organisms; CR: carbapenem-resistant bacteria.

ous literature that primarily attributed SBP to Gram-negative pathogens. This shift possibly necessitates a reevaluation of empirical antibiotic regimens to address the changing patterns of bacterial resistance and infections in cirrhotic patients [41]. The alarming prevalence of Gram-positive bacterial infections, affecting 52.73% of subjects, stands in stark contrast to the literature that frequently cites Gram-negative bacteria as the primary cause of SBP. The latest guidelines from the AASLD, updated in August 2021, continue to designate Gram-negative bacteria as the most prevalent pathogens in SBP and recommend third-generation cephalosporins as first-line empirical therapy for community-acquired SBP. In cases of treatment failure, consideration should be given to broadening antibiotic coverage [3].

Specifically, carbapenem resistance among Gram-negative bacteria, particularly in pathogens such as Acinetobacter and Citrobacter, has shown significant increases. This trend underscores the need for focused surveillance and targeted antimicrobial strategies to effectively combat these resistant strains [42, 43]. The variation in resistance rates observed across different countries further highlights the importance of regional and global cooperation in monitoring and controlling the spread of MDROs [44]. Continuous studies on the etiology are essential for the prevention and control of carbapenem

resistance [45].

MDROs have a significant correlation with nosocomial SBP [46]. A recent meta-analysis of studies conducted over the past decade supports the differentiation between community-acquired and nosocomial SBP, revealing increased mortality rates and antibiotic resistance in patients with nosocomial infections [47]. The higher rates of MDROs observed in nosocomial SBP compared to community-acquired SBP may contribute to the elevated mortality associated with these cases [48]. In centers where third-generation cephalosporin resistance is prevalent, these antibiotics should not be used as a first-line treatment, even for managing community-acquired SBP [49].

Another important consideration is whether to broaden antibiotic coverage in cases of inadequate treatment response [50]. An antibiotic de-escalation strategy is widely practiced in critically ill patients to mitigate the emergence of antibiotic resistance [51]. This strategy involves initiating broad-spectrum antibiotic therapy and subsequently narrowing the coverage upon the availability of culture results. This approach is generally preferred over an escalation strategy, which would start with cephalosporins and switch to broader-spectrum antibiotics only after culture results or treatment failure indicate the need for a change.

In a prospective study enrolling 101 patients with SBP—31 with community-acquired infections and 70 with nosocomial infections—Umgelter *et al.* [52] investigated the rate of treatment failure associated with recommended empirical therapies and their impact on mortality on 17 patients who received a broad-spectrum antibiotic regimen without modification and 84 patients who were treated with one of the published first-line therapies (cefotaxime, ampicillin/clavulanate or ciprofloxacin). An escalation strategy was necessary for 24 of the 84 patients who received these first-line therapies. Notably, mortality was significantly higher in the escalation strategy group compared to those whose treatment was not changed (66.7% *vs.* 30%, $p = 0.002$). In multivariable analysis, modification of antibiotic treatment emerged as an independent risk factor for mortality, with an odds ratio of 5.876 (95% confidence interval 1.826–18.910, $p = 0.003$) [52]. In another randomized open-label study involving 175 patients, Jindal *et al.* [53] initiated empirical antibiotic treatment with third-generation cephalosporins. Patients exhibiting microbial resistance to third-generation cephalosporins or no resolution of infection at 48 hours were randomized to escalate their antibiotic therapy to either a fourth-generation cephalosporin (cefepime) or a carbapenem (imipenem). The mortality rate at two weeks showed no statistically significant difference between the two treatment groups (25.3% *vs.* 25%) [53]. A subsequent randomized controlled trial by Piano *et al.* [54] compared the efficacy of *ab initio* third-generation cephalosporins (ceftazidime) and carbapenems (meropenem), with the addition of daptomycin. The combination of a carbapenem and daptomycin demonstrated significantly greater effectiveness than third-generation cephalosporins for the treatment of nosocomial SBP (86.7% *vs.* 25%; $p < 0.001$) [54].

Overall, our study highlights that while Escherichia coli remains largely susceptible to antibiotics, pathogens such as Klebsiella, Pseudomonas, Acinetobacter, and Citrobacter exhibit significant resistance rates, posing serious challenges for antibiotic management [55]. The exceptionally high resistance rate observed in Acinetobacter necessitates urgent intervention, including the development of new treatments and the implementation of stringent infection control practices [56]. To effectively manage and mitigate the impact of resistant infections, it is crucial to understand real-time, pathogen-specific resistance patterns [57].

5. Conclusions

SBP has predominantly been caused by Gram-negative bacteria, particularly within the Enterobacteriaceae family, and in this systematic review, we investigated the incidence of both Gram-negative and Gram-positive bacteria, along with the rates of MDROs and CR bacteria. The findings indicate a significant increase in Gram-positive bacterial infections, with Gram-positive pathogens now showing a prevalence comparable to that of Gram-negative bacteria as causative agents of SBP. The overall prevalence of MDROs among the identified causative agents was approximately 20%, while infections due to Enterobacteriaceae with carbapenem resistance accounted for about 10%, suggesting that the currently recommended empirical antibiotic regimens may not achieve the desired treatment outcomes in a significant number of patients with SBP, potentially contributing to increased mortality rates.

AVAILABILITY OF DATA AND MATERIALS

The data of this systematic review are available from the corresponding author, upon reasonable request.

AUTHOR CONTRIBUTIONS

MF and AA—contributed to the writing of the main review. AA and SDF—collected the data. MBO, MCP and PS added significant intellectual content to the manuscript by critically revising it. All authors approved the final version to be published.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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