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The epidemiology of gram-negative bacteremia in Lebanon: a study in four hospitals

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Abstract

Introduction Gram-negative bacteremia is a life-threatening infection with high morbidity and mortality. Its incidence is rising worldwide, and treatment has become more challenging due to emerging bacterial resistance. Little data is available on the burden and outcome of such infections in Lebanon.

Methods We conducted this retrospective study in four Lebanese hospitals. Data on medical conditions and demographics of 2400 patients diagnosed with a bloodstream infection based on a positive blood culture were collected between January 2014 and December 2020.

Results Most bacteremias were caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, with the more resistant organisms being hospital-acquired. Third-generation cephalosporin and quinolone resistance was steady throughout the study, but carbapenem resistance increased. Mortality with such infections is high, but carbapenem resistance or infection with *Pseudomonas* or *Acinetobacter* species were significant risk factors for poor outcomes.

Conclusion This is the first multi-center study from Lebanon on gram-negative bacteremia, resistance patterns, and factors associated with a poor outcome. More surveillance is needed to provide data to guide empirical treatment for bacteremia in Lebanon.

Keywords Gram-negative, Bacteremia, Multicentric, Mortality, Lebanon

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Introduction

Bloodstream infections (BSIs) have recently become a pressing public health concern. BSIs strain patients, healthcare systems, and economies worldwide, especially with the increase in antimicrobial resistance (AMR) [1]. Sepsis-induced organ dysfunction can cause permanent and irreversible cognitive impairment and organ failure and is associated with markedly high mortality rates [2, 3]. In the last couple of decades, BSIs have increased substantially, driven mainly by a surge in gram-negative bacterial infections [4]. In many settings, the rates of these bacteremia cases have overtaken those caused by gram-positive pathogens [5]. BSIs exert a heavy toll on patients and healthcare systems alike and are a growing cause of morbidity and mortality across the world [6, 7]. In the United States of America alone, an estimated two million patients suffer from antibiotic-resistant gram-negative or gram-positive bacteremia, with an associated 23,000 deaths [8]. While primary bacteremia is expected, with no identified origin of infection, secondary bacteremia spreads from a preexisting source of infection, most commonly urinary tract infection (UTI) and pneumonia [9]. Gram-negative pathogens gain entry into the body via several routes and can take place in the hospital or be community-acquired. The environment, gastrointestinal colonization, and contaminated medical devices are also sources of infection which disseminate to the blood [9].

The global emergence of antimicrobial resistance compounds the mounting risk of gram-negative BSIs. There are several mechanisms by which resistance spreads, and there is a rapidly depleting pool of available treatments [8]. Gram-negative infections are the primary culprits in BSI mortality, mainly third-generation cephalosporin-resistant (3GCR)-Enterobacterales, carbapenem-resistant Enterobacter ales (CRE), multidrug-resistant (MDR), *Acinetobacter baumanni*i, and MDR *Pseudomonas aeruginosa*, all of which are acquired in the healthcare setting [8]. Similar trends regarding antimicrobial resistance are seen worldwide. Middle Eastern countries are especially vulnerable to rampant MDR pathogens stemming from unchecked dissemination and use of antibiotics, combined with years of political unrest and conflict causing the relocation of many immigrants and refugees. Lebanon exemplifies these conditions, having always been a hub of shuffling populations for touristic, religious and geo-political reasons [10]; this has increased in recent years. This has hampered monitoring shifts in gram-negative bacteria epidemiological and resistance trends and allowed for faster spread of resistance. Hence, the present study is the only large-scale study in recent years. The data from hundreds of patients diagnosed with bacteremia on admission or during hospitalization in four different centers in Lebanon has been compiled. Gram-negative epidemiology and resistance patterns have been carefully documented and grouped to better profile gram-negative BSIs in Lebanon.

Methods

This retrospective study was conducted between January 2014 and December 2020 in 4 Lebanese Hospitals. We reviewed 2400 charts of patients with BSIs. The data collected included demographics (age and sex), hospital admission and discharge dates, whether community-acquired or hospital-acquired infections, ICU-acquired infections, infection site, gram-negative pathogen isolated and its antibiotic resistance pattern (antibiogram), and status on discharge.

Definitions

Any patient with a positive blood culture that was not considered to be contaminated was included in this study. Contamination was defined as coagulase-negative staphylococci in 1 out of 2 blood culture specimens. A failure to respond to treatment was considered a clinically confirmed treatment failure in the patient charts, whether there was further deterioration or persistent fever.

Community-acquired bacteremia: Bacteremia documented outside of the hospital setting or within 48 h of hospitalization.

Hospital-acquired bacteremia: Bacteremia documented more than 48 h after hospitalization or bacteremia that can be linked to a prior hospitalization within 30 days, according to the primary physician.

Statistical analysis

Data were coded, validated and analyzed using SPSS (version 28.0. IBM Corporation, Armonk, NY, USA). Descriptive statistics were reported using frequencies and percentages for the categorical variables. The chi-square test (χ^2) assessed the correlation between categorical variables. *Post-hoc* analysis using the Bonferroni correction test was performed to reduce the instances of false positive significance. We considered a p-value < 0.05 as statistically significant.

Ethics and funding

The Lebanese American University Institutional Review Board (IRB) approved the study. No funding was received for this study.

The work conducted was in accordance with the Declaration of Helsinki.

Table 1 Resistance pattern for *E. coli* species

***E. coli* (%–n): total**	**100%–900**			
Classes				
Non-3GCR	53.2%–476			
3GCR	42.2%–377			
CRE	4.6%–41			
Unknown (excluded)	0.7%–6			
Quinolone resistance				
Quinolone sensitive	40.2%–360			
Quinolone resistant	59.8%–535			
Unknown (excluded)	0.6%–5			
Important associations:				
Infection source	Non-3GCR	3GCR	CRE	P-value
Community-acquired	63.6%–342	33.5%–180	3.0%–16	< 0.001
Hospital-acquired	37.6%–134	55.3%–197	7.0%–25	

Table 2 Resistance pattern for all *Klebsiella* species

***Klebsiella* (%–n): total**	**100%–192**	
Classes		
Non-3GCR	55.5%–106	
3GCR	36.6%–70	
CRE	7.9%–15	
Unknown (excluded)	0.5%–1	
Quinolone resistance		
Quinolone sensitive	65.3%–124	
Quinolone resistant	34.7%–66	
Unknown (excluded)	1.0%–2	
Important associations:		
Infection source		P-value
Community-acquired	40.1%–77	< 0.05
Hospital-acquired	59.9%–115	

Results

Of the 2400 collected results, 1668 (69.5%) infections were attributed to gram-negative bacteria. Of these, 900 (54%) were *Escherichia coli* (Table 1), 192 (11.5%) were *Klebsiella pneumoniae* (Table 2), 160 (9.6%) were *Pseudomonas aeruginosa*, and 108 (6.5%) were *Acinetobacter* species.

The most common source of bacteremia was urine tract infection (UTI), followed by pneumonia and intra-abdominal infection (Fig. 1). Of all *E. coli* bacteremia, third-generation cephalosporin resistance (3GCR) was documented in 42%, and carbapenem resistance in 4.6%; 3GCR and carbapenem resistance (CR) was detected in 33.5% and 3%, respectively, of community-acquired *E. coli*, vs 55.3% and 7%, of hospital-acquired *E.coli*. A similar pattern was observed with *Klebsiella* species and all other Enterobacteriaceae, where 3GCR and carbapenem-resistant Enterobacterales (CRE) rates were higher in the hospital setting (Table 3). In the community, rates of 3GCR and CR were 29.87% and 6.5%, respectively, while 29.8% and 8.8% were in the hospital setting. Notably, the 3GCR production rates remained stable from 2013 to 2020, whereas CRE rates increased yearly, rising from 0.3% in 2013 to 13% in 2020. Figure 2 shows the bacterial species' resistance trends during the study.

Regarding *Pseudomonas* species (Table 4), our data shows that the community-acquired infections were more sensitive to all antipseudomonal agents. In contrast, hospital-acquired infections showed up to 40% resistance rate to any drug, with quinolone resistance of 25.7%, ceftazidime and cefepime resistance of 20.2%, carbapenem resistance approaching 31.2% and extensive drug resistance (all mentioned antibiotics and colistin) around 1.2%. Conversely, infections of *Acinetobacter* species (Table 5) were more often hospital-acquired and much more resistant, particularly to carbapenems, approaching 80% resistance rates. For

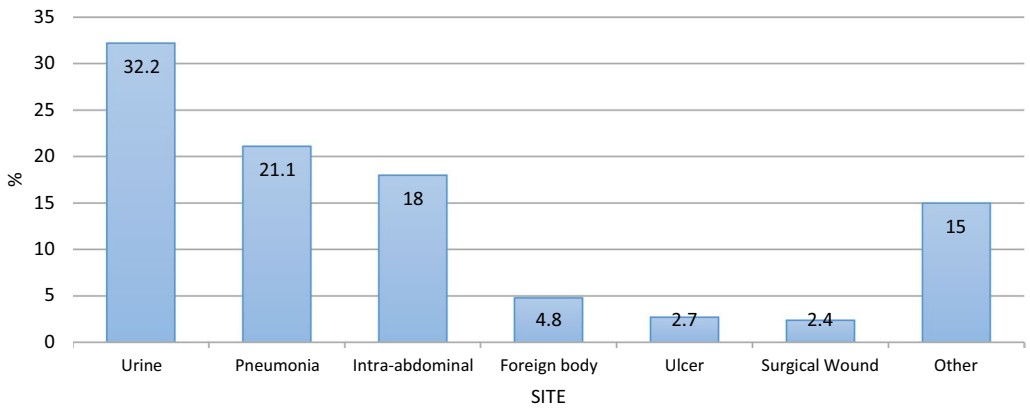

Fig. 1 Bacteremia percentages according to the identified source

Table 3 Resistance pattern for all Enterobacterales species

Enterobacterales (%–n): total	**100%–1201**			
Classes				
Non-3GCR	55.6%–661			
3GCR	39.0%–464			
CRE	5.4%–64			
Unknown (excluded)	1%–12			
Quinolone resistance				
Quinolone sensitive	47.4%–565			
Quinolone resistant	52.6%–628			
Unknown (excluded)	0.7%–8			
Change of resistance with time	Non-3GCR		3GCR	CRE
2013	60%–3		40%–2	0%- 0
2014	57.8%–67		39.7%–46	2.6%–3
2015	57.9%–77		36.8%–49	5.3%–7
2016	60%–126		36.2%–76	3.8%–8
2017	54.3%–82		41.7%–63	4.0%–6
2018	49.2%–123		43.2%–108	7.6%–19
2019	56.3%–103		38.3%–70	5.5%–10
2020	55.9%–80		35%–50	9.1%–13
Important associations:				
Infection source	Non-3GCR	3GCR	CRE	P-value
Community-acquired	64.8%–423	31.7% -207	3.5%–23	< 0.001
Hospital-acquired	44.4%–238	47.9%–257	7.6%–41	

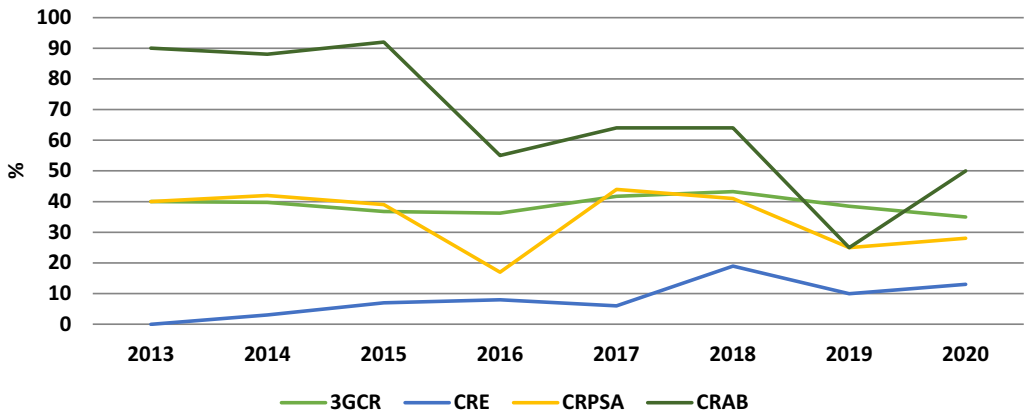

Fig. 2 Resistance pattern variations of different bacteria between 2013 and 2020

both *Pseudomonas* and *Acinetobacter* species, resistance rates were higher in the hospital than in the community setting. *Stenotrophomonas maltophilia* were generally sensitive to trimethoprim-sulfamethoxazole (TMP-SMX) (79.3%) and resistant to cefepime (78.6%). *Stenotrophomonas* species showed only 15% resistance to fluoroquinolones.

55.2% of 3GCR-producing GNB, 64.1% of CREs, 86.8% of *Acinetobacter* species, 79.2% of carbapenem-resistant *Pseudomonas* (CRPS) and 62.4% of carbapenem-sensitive *Pseudomonas* (CSPS) were hospital-acquired ($p < 0.01$).

Regarding the association of the infectious source and outcomes, community-acquired bacteremia was associated with an 80% clinical cure rate, 11.3% death rate and 8.8% treatment failure. At the same time, hospital-acquired bacteremia was associated with a 65.7% cure rate, 29.3% death rate and 4.9% no response, defined as

Table 4 Resistance pattern for *Pseudomonas* species (*aeruginosa* and non-*aeruginosa*)

Pseudomonas (%–n): total	**100%–170**		
Quinolone resistance			
Quinolone sensitive	74.3%–124		
Quinolone resistant	25.7%–43		
Unknown (excluded)	1.8%–3		
Carbapenem resistance			
Carbapenem-sensitive	68.8%–117		
Carbapenem-resistant	31.2%–53		
Ceftazidime/cefepime resistance			
Ceftazidime/cefepime sensitive	79.8–130		
Ceftazidime/cefepime resistant	20.2%–33		
Unknown (excluded)	4.1%–7		
Resistance classes			
Sensitive to all quinolones, carbapenems and ceftazidime/cefepime	61.8%–105		
Resistant to either class (quinolones, carbapenems or ceftazidime/cefepime)	12.4%–21		
Resistant to only two classes (quinolones, carbapenems or ceftazidime/cefepime)	14.1%–24		
Difficult-to-treat Resistance (DTR): Resistant to quinolones, carbapenems and ceftazidime/cefepime but colistin sensitive	10.6%–18		
Multi-Drug Resistant (MDR): Resistant to quinolones, carbapenems, ceftazidime/cefepime and colistin	1.2%–2		
Important associations:			
Infection source	Pan-sensitive	Resistant to any drug	p-value
Community-acquired	72.7%–40	27.3%—15	0.042
Hospital-acquired	56.5%–65	43.5%—50	

Table 5 Resistance pattern for *Acinetobacter* species

***Acinetobacter* (%–n): total**	**100%–108**		
Imipenem resistance			
Imipenem-sensitive	29.5%–31		
Imipenem-resistant	70.5%–74		
Unknown (excluded)	2.8%–3		
Colistin resistance			
Colistin sensitive	99.1%–103		
Colistin resistant	0.9%–1		
Unknown (excluded)	3.7%–4		
Important associations:			
Infection source	Imipenem-sensitive	Imipenem-resistant	P-value
Community-acquired	85.7%–12	14.3%–2	< 0.01
Hospital-acquired	20.9%–19	79.1%–72	

persistence of blood culture positivity ($p < 0.01$). The rate ratio of death between hospital and community-acquired bacteremia was calculated to be 2.59. Therefore, the rate of death in gram-negative bacteremia in this study was 2.59 times higher in hospital-acquired infections.

Regarding the cultured organisms, our study showed that having a CRPS was associated with a 68.4% death rate, compared to CSPS, which had a 16% death rate ($p < 0.01$). The rate ratio of death between CRPS and CSPS bacteremia in this study was 4.25 times higher in CRPS. Similarly, post-hoc analysis showed a statistically significantly lower death rate with 3GC and carbapenem-sensitive gram-negative enterobacterales (12.4% vs 18.6% overall, $p < 0.01$). The odds ratio

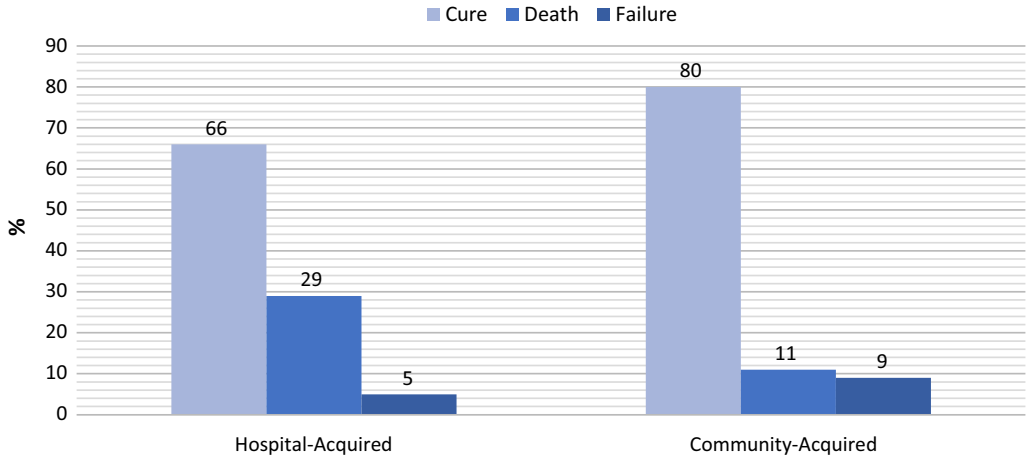

Fig. 3 Mortality, failure and cure rates between hospital and community-acquired pathogens

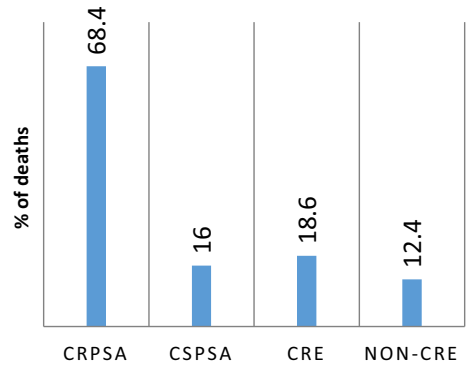

Fig. 4 Differences in mortality based on carbapenem resistance for *Pseudomonas* species and Enterobacterales

calculated was 0.2, a 20% lower death rate than 3GC-sensitive enterobacterales.

When the bacteremia source was the urinary system (UTI), *E. coli* showed a sensitivity of 96.1% to fosfomycin, 85.7% to nitrofurantoin, 52.7% to TMP-SMX, 42.3% to quinolones, and 22.7% to ampicillin. Figure 3 shows the mortality rates according to infection source. Figure 4 shows the difference regarding carbapenem resistance in the enterobacterales and *Pseudomonas*. Figure 5 shows the percentages of gram-negative bacteria species involved in BSIs, and Table 1 shows details of the most common agent, *E. coli*.

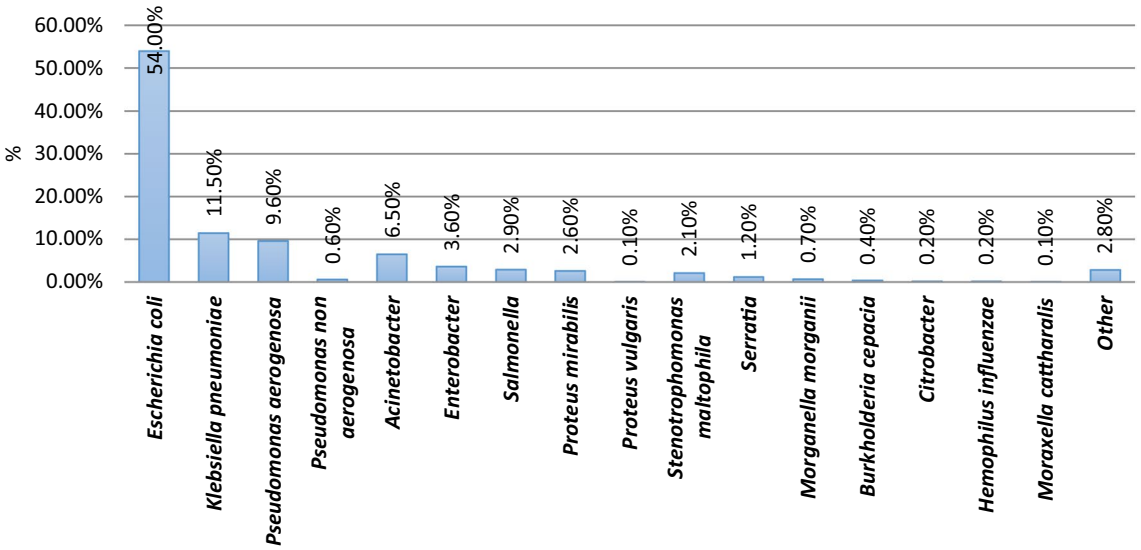

Fig. 5 Pathogens involved in Gram-negative bloodstream infections

Discussion

The five most common gram-negative bacteria responsible for BSIs in the present study were *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii and S. maltophilia. E. coli* BSIs were more prevalent in the community setting. Whether community or hospital-acquired, they had a relatively high rate of 3GCR resistance, while carbapenem resistance was seen mainly in in-patients and was usually associated with higher mortality.

Our findings matched other BSI studies when comparing our data with the literature. Data on BSI organisms collected from over 200 medical centers in 45 nations showed the prevalent organisms were *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* between 1997 and 2016, with *E. coli* supplanting S. aureus as of 2005 [11]. Simultaneously, other gram-negative bacteria such as *K. pneumonia*, *P. aeruginosa* and *A. baumannii* also became prominent causative agents in BSI [12]. Similar results were seen in the Far East, Sub-Saharan Africa and Europe [13–16]. *Acinetobacter* bacteremia in Lebanon is far more prevalent than in Europe, China and Japan [17]. A similar trend is also seen in South Korea [18]. This is mainly related to outbreaks in specific regions, hospitals and specific intensive care units (ICUs), and they are usually related to less effective infection control measures, highlighting the importance of prevention in the control of *Acinetobacter* spread [19]. Regionally, a similar trend was seen in Qatar in 2019 [20], but the data from Saudi Arabia in 2015 shows a higher prevalence of *Klebsiella* (21%), *Acinetobacter* (15.6%), *Stenotrophomonas*, *Proteus* and *Serratia* [21]. Figure 6 shows the different organisms involved in gram-negative bacteremias across different countries.

Most gram-negative pathogens, with the main exceptions of *E. coli* and *Salmonella*, were more prevalent in the hospital than in the community setting in the present study. Proportions vary among studies and regions; *E. coli* was the most common species isolated from community-acquired cases, and the healthcare-associated bacteremia in the SENTRY study was responsible for 26% and 15.6% of the cases, respectively [11]. *K. pneumoniae* was the second most prevalent gram-negative species for both community- and hospital-acquired bacteremia, followed by *P. aeruginosa*. *A. baumannii* was also a frequent cause of hospital-acquired bacteremia, accounting for 3.2% of cases [11]. In addition, a study of over one thousand hospitalized patients with BSIs at or during admission in northern Italy found that *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were the most prominent gram-negative BSIs, whether community or hospital-associated [1]. Older age and UTIs are known risk factors for *E. coli* BSIs, which could explain the predominance of *E. coli* BSIs in the community setting. In Lebanon, the prominent elderly population struggles with access to adequate healthcare and proper follow-up. There is also increasing antimicrobial resistance to commonly prescribed drugs and inconsistent infection control practices among healthcare centers [22].

As the most common gastrointestinal bacteria, *E. coli* and *K. pneumoniae* are the agents most commonly involved in UTIs, possibly explaining their high prevalence in Gram-Negative Bacilli Bacteremias (GNBBs) [23]. BSIs secondary to UTIs are a rising threat worldwide. In the UK, Lishman et al. found that urogenital infections accounted for over half of all *E. coli* bacteremia episodes. Other sources of infection included biliary (11–27%) and other intra-abdominal infections (4–48%) [24].

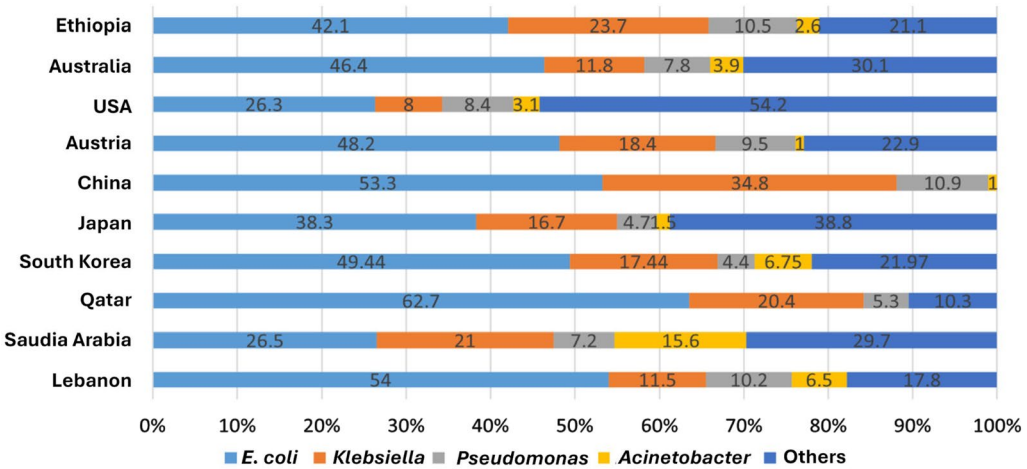

Fig. 6 Percentage of each organism's involvement in total Gram-negative bacteremias across different countries

In Lebanon, similar to data from the Middle East and North Africa (MENA) [25], UTI remains one of the major driving forces of BSIs and antimicrobial resistance (particularly 3GCR and CRE). The increased prevalence of UTIs with poor access to proper prevention and treatment measures has exacerbated local bacterial resistance [26]. The proportion of BSIs attributed to UTIs in the present study (32%) points to the significant burden and rising threat of UTIs, whose treatment is an essential driver for resistance, and the presence of other significant causes behind bacteremia cases.

Collapsed, inadequate or non-maintained infrastructure and water piping and treatment are primary factors behind the spread of GNBs, especially in the developing Arab countries of the Middle East [27]. Water systems are essential in spreading *Pseudomonas* and enterobacterales in the community or hospital setting [28]. While the enterobacterales come primarily from the gastrointestinal (GI) tract, Pseudomonas species are more water-related pathogens [9]. In a 2021 Canadian study, upper UTIs were the most common source of infection (40%), followed by bloodstream infections of unknown source (24%) and infection of the hepatobiliary tract (12%) [29]. Other causes of gram-negative organisms spread in hospitals include pillows, linen, dispensers, blood pressure cuffs, skin and ultra-filtrate bags [32].

Resistance trends vary worldwide based on a variety of factors, including antibiotic misuse, their use in plantations and livestock, injection drug use, poor infection control measures and inappropriate infrastructure [30, 31]. Natural or man-made disasters also play a role in antibiotic resistance spread [32]. Specific populations and their contemporary problems can majorly influence resistance trends [33]. For example, the ongoing crises in the Arab world, the ensuing economic and political issues, and poor hygiene may have caused a surge in gram-negative bacterial infections and facilitated the spread of resistance genes from nearby countries in the MENA region [27, 34]. Therefore, approaches such as the "One Health Approach" that emphasises the inter-species exchange of resistance and microbiota become important to mitigate these challenges [31]. Lebanon has been affected by such challenges since 2010, fueling the spread of resistant gram-negative bacteria across the Lebanese population [35].

Our data shows a stable pattern of *E. coli* resistance to fluoroquinolones and 3GCs over the years, maintained at around 60% and 40%, respectively, while there was a steady rise in CRE rates from 0.2 to 13%. This might be explained by the ease of access to over-the-counter antimicrobials maintained over the years and the increased use of carbapenems [36]. This is different to other areas of the world. A Korean study between 2019 and 2020 comparing resistance patterns of *E. coli* isolated from either the blood or urine of hospitalized patients found that ampicillin/sulbactam resistance was approximately 40% in blood and 45% in urine, whereas 20.0% of blood isolates and 27.5% of urine isolates showed 3GC resistance. The fluoroquinolone resistance rate was 33.8% [37]. In a Canadian study comparing different *E. coli* subtypes, cefotaxime, ceftazidime, aztreonam, and cefepime resistance rates (78.9%) of specific isolates (ST131) were higher than those of others (0–12% for non-ST131 isolates). Other significant antimicrobial resistance rates for blood vs urine isolates in Korea between 2020 and 2021 were Ciprofloxacin, 30.0% vs 37.5% and Tetracycline, 30.0% vs 35.0%, respectively [35]. In Lebanon, *E. coli* has a variety of ST genes, with ST131 being the most prevalent, followed by ST10 and ST69 [38]. In our study, the resistance rates for *E. coli* in urine are comparable to those in primary bacteremia. In addition, fluoroquinolone and 3GC resistance are similar to that in UTIs, whether in the community or hospital-acquired setting.

A Canadian study examining the epidemiology of extra-intestinal pathogenic *E. coli* between 2019 and 2020 found high resistance rates to most antibiotics, specifically detecting 3GC resistance in 14.3% of isolates and fluoroquinolone resistance in 28.6% of them [29]. There was an increase in *E. coli* BSI incidence rates in the population area studied from 2006 to 2016, which coincides with increased resistance rates to antimicrobials, most prominently ceftriaxone (4.2-fold increase) and ciprofloxacin (2.4-fold increase). This correlation could explain the rise of resistance in BSIs [29].

Our data regarding enterobacterales resistance is similar to worldwide trends, showing a growing resistance pattern to various antibiotic classes [39]. Of 103 g-negative isolates in a regional Saudi-Arabian study in 2019, 23.3% were 3GCR. *Klebsiella pneumoniae* and *E. coli* were reported as major 3GCR bacteria in hospital settings within and outside Saudi Arabia, with varying rates from 20 to 70% [39]. The tendency of such resistance patterns to spread in some geographical regions and across different hospitals is concerning and warrants quick intervention and continuous surveillance to avoid outbreaks. In this study, over 70% of *E. coli* were resistant to 2nd to 4th generation cephalosporins. Fluoroquinolone resistance was also found to be highly elevated [39].

In the same study, *E. coli* resistance to carbapenems was below 10%; it was 18% to piperacillin/tazobactam, 5% to nitrofurantoin and 4.3% to amikacin [39]. These findings were similar in other studies in the same region and further afield [14, 40]. This can be explained by the overuse of antibiotics purchased over the counter in Saudi Arabia despite attempts to restrict their use. This highlights

the need for more robust implementation of regulations to restrict the prescription of antibiotics in humans and animals [41]. The high CRE rates can also be attributed to outbreaks in a single institution from the studied region. These data are alarming and show the potential for the spread of drug resistance across the MENA region.

Our data are similar to those from Turkey, where, despite local efforts at antimicrobial stewardship [42], there are similar problems with the OTC dispensing of antibiotics and their availability in tablet forms.

Similar to *E. coli*, our data showed *K. pneumoniae* maintained a 36.6% resistance rate to 3GCs and a 34% resistance rate to quinolones throughout the study. These bacteria can spread and cause multiple infections, leading to sepsis [43]. In the Saudi-Arabian gram-negative BSI study, around 15% of isolates of *K. pneumoniae* were 3GCR. All of the CR *K. pneumoniae* in the study were taken from ICU patients. ICU *Klebsiella* isolates showed 80% resistance to 3GCs, 60% to carbapenems, 65% to fluoroquinolones and 22.6% to amikacin [39]. This sheds light on the frequent outbreaks of KPC *K. pneumoniae* in ICU settings, leading to high CR trends.

Our study further shows the steady increase in CRE rates in BSIs, highlighting the ease of transfer of resistance genes. Among the proposed mechanisms is the spread of these genes via plasmids by contact. This emphasizes the need for more robust antimicrobial stewardship and infection control measures [44]. This is especially important in the Arab world, where ineffective or non-antimicrobial stewardship programs continue to be a problem driving AMR [41]. For instance, CRE *K. pneumoniae* has been well-documented in Gulf countries and is a rising global threat [45]. A Chinese surveillance study spanning 20 years also showed an increase in CRE *K. pneumoniae* prevalence [14]. In contrast, a Brazilian study of BSIs showed *K. pneumoniae* as the most common pathogen among enterobacterales, with 3GC resistance rates of 95.6% and CRE rates of 13.6% [46]. Similar to the findings in our study in the ICU setting, antibiotic failure and higher disease severity translated to poorer outcomes in patients with CR *Klebsiella pneumoniae* [47].

Pseudomonas aeruginosa is a gram-negative aerobic bacterium typically found in intestinal flora [48]. However, this pathogen is a dangerous opportunist that targets critically ill or immune-deficient patients [49]. It is consistently among the top four most common pathogens in hospital-acquired BSIs and the three most common pathogens detected in the ICU [50].

Our study shows that *Pseudomonas* species have a 74% resistance rate to fluoroquinolones in BSIs and a 68% resistance rate to carbapenems. Regarding global spread, *P. aeruginosa* resistant to carbapenems has been frequently reported from some of the Levant and North African Arab countries (>50% resistance) [10]. Metallo-β-lactamase production has been its primary mechanism of carbapenem resistance in Lebanon [51]. The Asia Pacific (17–50%) and Latin America (64.6%) regions also exhibit high rates of carbapenem resistance compared with Europe (0–35.6%) and North America (10.3–19.4%) [52]. The Japan Nosocomial Infections Surveillance (JANIS) 2016 report, compiling data from 1653 facilities, found that the rates of imipenem and meropenem resistance according to CLSI 2012 breakpoints were 12.3% for *P. aeruginosa* [53]. In China, the average carbapenem resistance rates range between 9 and 24%, while Extended drug-resistant (XDR) *P. aeruginosa* proportions were between 1 and 8% [54, 55]. This shows that the resistance trends of *Pseudomonas* tend to be regional, dictating a possible spread of resistance patterns across countries nearby.

Carbapenemases, porin channel manipulation, and efflux pumps all contribute to the increasing challenges when treating *P. aeruginosa* [52, 56]. The different resistance mechanisms it possesses give it a versatile pattern of resistance [57]. Its natural reservoir being water makes it easy to infiltrate communities with poor water infrastructure. Its colonization of water supplies in hospitals makes it an exceptionally successful hospital-acquired pathogen [58]. Globally, different clones predominate in each region [59]. ST235, ST654 and ST233 are the most prevalent strains in the MENA region [60]. Genotypic analyses and genome-wide virulence profiling were done in Lebanon, where multiple drug-resistance genes were found, especially in ST235. Resistance mechanisms were mostly enzymatic, efflux pumps and biofilm-producing genes [61, 62]. Porin regulation seems to be slower than other resistance mechanisms, often taking more time to develop after prolonged periods of antibiotic exposure. This makes it a significant mechanism in chronic infections needing long courses of treatment, leading to a poorer response to treatment [63]. Thus, antimicrobial stewardship and adequately treated water systems are essential in controlling resistant *Pseudomonas*.

Acinetobacter baumannii is an increasingly concerning gram-negative bacterium mainly responsible for hospital-acquired BSIs [11]. Its non-motile characteristic makes it exceptionally resilient, able to recur several months after cleaning [64]. Its prevalence and resistance profiles depend highly on the regional and local institutional epidemiology. It can vary depending on differences in infection control measures [65]. Outbreaks of MDR *A. baumannii* have been reported in countries during economic crises, which might explain their increased burden in recent years in Lebanon [66]. In addition, MDR *A. baumanii* outbreaks have also

been reported in war and conflict-affected areas. This possibly added to the burden in Lebanon, where ongoing conflicts were occurring during the study period [66]. Most *A. baumannii* infections (75%) and antimicrobial resistance (86%) are found in the healthcare setting [67]. Pneumonia and UTIs are common sources of *A. baumannii* infections in the community setting. At the same time, invasive medical procedures and more extended hospital stays are potential sources of infection in the hospital setting [68, 69]. Its nasal colonization rates were between 72 and 90% in Taiwan and 63% in the USA in long-term inpatients [70]. *A. baumannii*'s ability to create biofilms to survive on most hospital equipment and expanding resistance profile highlights the need for urgent infection control measures to control its spread [71].

XDR *A. baumannii* may arise through various mechanisms similar to those of *P. aeruginosa*. In the last few years, *A. baumannii* has also been labelled a difficult-to-treat (DTR) organism, resistant to all first-line antimicrobial drugs [72]. A 2016 US-based study from the Premier Healthcare Database showed that 44.8% of *A. baumannii* were carbapenem-resistant, compared with only 1% of Enterobacterales [73].

A nationwide Korean database study discovered that the two most common DTR organisms were *Acinetobacter* species (79.6%) and *P. aeruginosa* (17.7%) in 2020 [72]. Prior antibiotic consumption, healthcare contact, mechanical ventilation, and lower respiratory tract infections were all factors linked to DTR infections [72]. These infections are more associated with poor compliance with hospital infection control policies and procedures, leading to frequent outbreaks [74].

Our study shows a 70% rate of Acinetobacter resistance to carbapenems and only a 0.9% resistance rate to colistin. Most of the outbreaks of *A. baumannii* occurred in two hospitals, and the carbapenem resistance trends of Acinetobacter in Lebanon decreased from 88% in 2014 to 50% in 2020 [19]. Despite high CR rates, some European countries continue to have Acinetobacter outbreaks, ranging from 0% (Belgium) to 95% (Greece) [75]. The China Antimicrobial Surveillance Program noted a sharp increase in CR from 13% in 2004 to 70% in 2014, and that of XDR *A. baumannii* increased from 11% in 2004 to 60% in 2014 [55]. A Saudi-Arabian BSI study found *A baumannii* resistant to gentamicin, cephalosporins and carbapenems. A 70.6% resistance rate to trimethoprim-sulfamethoxazole was observed; however, all isolates were sensitive to colistin [39]. In some hospitals, introducing more meticulous infection control and cleaning methods with robust staff training decreased MDR Acinetobacter incidence, as was the case with a Lebanese tertiary care hospital between 2017 and 2019, highlighting the importance of infection control in mitigating the burden of these MDR GNBs [19].

GNBBs have high mortality rates, reaching up to a 15% case fatality rate. GNBB with resistant organisms has an even higher mortality rate with fewer treatment options and a higher rate of treatment failure [76]. Our data shows that carbapenem resistance is usually associated with the highest mortality; CRE bacteremia had a 25.6% mortality rate, compared to 19.6% with 3GCR enterobacterales. In addition, Carbapenem-Resistant *Pseudomonas Aeruginosa* (CRPSA) infections had the highest odds of death, with a statistically significant odds ratio of 4.25 compared to Carbapenem Sensitive *Pseudomonas Aeruginosa* (CSPSA), confirming its virulence in BSIs. Our data also shows that *Pseudomonas and Acinetobacter* were associated with higher mortality than enterobacterales and nosocomial infections, which have higher mortality than community-acquired infections.

Pseudomonas bacteremia is an independent risk factor for mortality, ranging from 18 to 61%, regardless of the resistance profile, mainly due to its ability to cause multi-site infection [77]. In addition, carbapenem resistance increases the risk of death (OR 4.485) recorded with CRPSA in comparison with CSPSA [77]. CRPSA and CRE organisms should be regarded as high-risk organisms for mortality, as reflected in multiple studies, and similar to what was found in our study [78, 79]. Therefore, carbapenem resistance should be considered an essential risk factor leading to mortality. Controlling these types of resistant bacteria should be prioritized through antimicrobial stewardship and infection control programs.

The literature corroborates these findings, where CRE infections have very high mortality risks in any infection, especially in BSIs [80]. Taye et al. showed that having a CRE bacteremia by itself had 2.47 times increased odds of death and 3.35 times increased odds of ICU admission compared with carbapenem-sensitive bacteria [81]. In addition, another study documented higher mortality rates with hospital-acquired CRE infections [82].

Failure to treat UTIs increases the likelihood of *E. coli*-related bacteremia, causing higher mortality [83]. A 2015 UK study looking at 30-day all-cause mortality in *E. coli* bacteremia found that while UTI-related bacteremia had a lower case fatality rate than other secondary bacteremia, the high numbers of untreated UTIs at the population level indicate that they still account for the highest crude number of deaths [84]. Our data shows that CR prevalence is rising, especially in *E. coli,* which is linked to higher mortality, probably because such infections are more complicated to treat.

Regarding *Acinetobacter* infections, especially carbapenem-resistant *A. baumannii* (CRAB), mortality is very high, approaching 33% [85]. An Acinetobacter BSI

quadruples the odds of death [86]. In our study, the data demonstrated a 33% mortality with Acinetobacter. This is important in the setting of hard-to-control outbreaks reported in multiple hospitals in Lebanon in the past [17, 19]. These outbreaks had high levels of extensive drug resistance [87]. This has been further confirmed by plasmid gene analysis to reveal multiple beta-lactam genes, specifically carbapenems [88].

We ended in 2020, the year of the onset of the Coronavirus Infectious Disease (COVID-19) pandemic in Lebanon. During the pandemic, antibiotic prescriptions increased dramatically, which might have affected the patterns of antimicrobial resistance [89]. Future studies are needed.

Conclusions

GNBBs are community or hospital-acquired infections. They are usually severe and have a high mortality. While CRE are on the rise, the presence of a Pseudomonas or an Acinetobacter bacteremia is linked to higher mortality rates. Carbapenem resistance explicitly increases the mortality rate in almost all patients with GNBBs. While most GNBBs originate from inadequately treated UTIs, several other driving forces may exist in Lebanon, whether location-related or socioeconomic. The increasing prevalence of various primary infections leading to bacteremia with inadequate infection control and antimicrobial stewardship has led to bacterial resistance, translating to more difficult-to-treat bacteremia and higher mortality. This multicenter study provides a detailed view of the nature and resistance profiles of GNBBs and outcomes and may help guide the empirical treatment of such infections.

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Author contributions
Conceived and designed the study and experiments: JN, HA, JM, TH, YJ, EA, AM, RA, RAA, DA, AB, MM, RA, ST, HEA, JEM, RM, AJRM, RH. Performed the experiments: JN, HA, JM, TH, YJ, EA, AM, RA, RAA, DA, AB, MM, RA, ST, HEA, JEM, RM. Contributed reagents/materials/analysis tools: JN, HA, JM, TH, YJ, EA, AM, RA, RAA, DA, AB, MM, RA, ST, HEA, JEM, WA, RM. Wrote the paper: JN, HA, JM, TH, YJ, EA, AM, RA, RAA, DA, AB, MM, RA, ST, HEA, JEM, RM. All authors reviewed the paper.

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Availability of data and materials
Available upon reasonable request. No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Lebanese American University Institutional Review Board (IRB) approved the study. As this study exclusively involved the analysis of pre-existing, anonymised records and did not include any direct human intervention or contact, it was exempt from the requirement for ethical approval typically necessary for research involving human subjects. In addition, the study's methodology did not involve any interaction with patients, nor did it influence patient care or treatment outcomes. As such, the informed consent requirement was irrelevant to our research framework.

Competing interests
The authors declare no competing interests.

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