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Review article

Understanding and addressing β-lactam resistance mechanisms in gram-negative bacteria in Lebanon: A scoping review

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ABSTRACT

Background: A growing threat to public health is the worldwide problem of antimicrobial resistance (AMR), in which gram-negative organisms are playing a significant role. Antibiotic abuse and misuse, together with inadequate monitoring and control protocols, have contributed to the emergence of resistant strains. This global scenario prepares us to look more closely at the situation in Lebanon. The aim of this review is to investigate in detail the resistance mechanisms and related genes that are displayed by gram-negative organisms in Lebanon.
Methods: A comprehensive analysis was carried out to pinpoint and gather information regarding gram-negative bacteria displaying resistance to antibiotics. To contribute to a complete understanding of the current state of antibiotic resistance in gram-negative strains, it was intended to collect and evaluate data on these organisms' resistance patterns in a comprehensive manner.
Results: Several studies have emphasized the prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) in Lebanon, specifically noting *Escherichia coli* and *Klebsiella pneumoniae* as the most frequent culprits, with OXA-48 and NDM-1 being the primary carbapenemases discovered. Furthermore, the TEM β-lactamase families are the primary source of extended-spectrum β-lactamases (ESBLs) in *Shigella* and *Salmonella*. Additionally, resistant strains of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have been linked to nosocomial infections in the country.
Conclusion: There is a considerable frequency of antibiotic overuse and misuse in Lebanon, based to the limited data available on antibiotic consumption. In conclusion, antibiotic stewardship initiatives and additional research beyond the confines of single-center studies in Lebanon are needed.

1. Introduction

Antibiotic resistance in bacteria poses serious problems that have a substantial influence on the economy and public health [1]. The diminishing effectiveness of antimicrobial agents against bacteria hampers our capacity to address bacterial infections [2]. This issue garners substantial attention in the media and politics, impacting individual health and placing financial strains on healthcare systems [2,3].

Despite the fact that modern media frequently emphasizes multidrug-resistant gram-positive bacteria, such as methicillin-resistant

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Staphylococcus aureus and vancomycin-resistant *Enterococcus*, the rise in resistance among gram-negative bacilli continues [4]. This trend occasionally leads to scenarios where limited or no effective antibiotics remain available for treatment [4,5].

The rise in infections attributed to drug-resistant Gram-negative organisms has triggered a global resurgence [6]. Out of all the families of enzymes that have been studied in detail, the β-lactamases have received nearly 28,900 citations in Medline alone. These enzymes have been the focus of academic research since the early 1940s, mainly because of their ability to deactivate β-lactam antibiotics [7,8]. Moreover, certain species have evolved resistance to several antimicrobial agents. These organisms fall under the category of multidrug resistant (MDR) if they exhibit resistance to more than three classes of antibacterial drugs. They are referred to as extensive drug resistant (XDR) if they are resistant to all but one or two kinds of antibiotics. When an organism exhibits resistance to every antibacterial agent, it is classified as pan-drug resistant (PDR) [9].

Numerous studies highlight a robust correlation between antimicrobial resistance and improper utilization and prolonged duration of antibiotic treatment [10,11]. The use of invasive medical devices and hospital environments aggravate this issue even more, raising the possibility of nosocomial transmission. Antimicrobial resistance is largely caused by increased exposure to healthcare environments and the use of medical interventions; this highlights the crucial role that responsible antibiotic use and infection control strategies play in tackling this worldwide health issue [11].

An increased rate of antibiotic consumption, combined with the absence of prudent and justified use, establishes conditions conducive to the emergence of resistance. Nevertheless, information on the dissemination of resistant Gram-Negative Bacteria (GNB) in Lebanon is relatively recent and limited in comparison to global data, primarily confined to studies conducted at individual healthcare centers [12].

Considering the substantial clinical risk posed by resistant GNB and the lack of a national surveillance center to furnish dependable data, our objective is to examine key studies about bacterial resistance in both *Enterobacteriaceae* and non-fermenters in Lebanon. This review aspires to deliver a reliable and thorough report outlining the present scenario and offering insights into bacterial resistance in Lebanon, where antibiotics are readily available and frequently misused.

2. Methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was adopted [13].

2.1. Literature search strategy

The main author along with the team members constructed an extensive search plan incorporating diverse keywords and connections associated with gram-negative bacteria and their resistance mechanisms. The objective was to pinpoint literature centered on recognizing these microorganisms while clarifying their resistance mechanisms and the genes linked to them. Subsequently, a search query tailored to the relevant database was built by identifying and extracting controlled vocabulary terms and synonymous expressions within the text that most accurately conveyed the research question and the elements of the search segments.

2.2. Databases

MEDLINE (PubMed) served as the primary database for sourcing pertinent literature due to its extensive coverage [14]. Grey literature exploration was omitted; however, some references were manually sourced from the bibliographies of identified articles.

2.3. Screening and study selection

Publications pertinent to the search method in MEDLINE were gathered. As the search relied solely on a single database, deduplication wasn't necessary. The first author initiated the selection process, reviewing titles and abstracts against predetermined criteria. Each paper was classified as "included," "excluded," or "maybe." Subsequently, the last author independently reviewed all references, resolving any conflicting assessments through consensus.

2.3.1. Inclusion criteria

The literature encompassed articles specifically addressing Gram-negative bacteria, detailing their resistance mechanisms and associated genes within the context of Lebanon.

2.3.2. Exclusion criteria

The reviewed literature deliberately excluded articles discussing bacterial instances in non-human contexts, topics associated with organisms other than bacteria or not related to Lebanon specifically, discussions about gram-positive bacteria, as well as any content deemed irrelevant to the study's focus.

2.4. Data extraction, synthesis, and abstraction

Following the initial screening and selection process of 91 articles, the assembled collection of studies was subsequently analyzed in full-text content, with systematic extraction of pertinent data. A primary in-depth perusal of the selected articles was performed.

During this thorough examination of full-text articles, an additional set of 9 articles were excised based on the predetermined

exclusion criteria. As a result of this iterative process, a finalized roster of 54 articles emerged (Fig. 1). In this review, two authors independently collected data from each report to ensure accuracy and reduce bias; no automation tools were used, and any discrepancies were resolved through discussion between the authors.

3. Results

3.1. *Escherichia coli and Klebsiella pneumoniae*

The global dissemination of multidrug-resistant bacteria, particularly *Escherichia coli* and *Klebsiella pneumoniae*, presents a significant challenge to the advancement of therapies targeting these resistant strains [15–17].

In Lebanon, a study carried out at Saint George Hospital in Beirut revealed a worrying increase in the number of diseases linked to Carbapenem-Resistant *Enterobacteriaceae* (CRE), which increased from 3 % in 2010 to 32 % in 2018 [18]. Additionally, a thorough examination of 6103 Gram-negative bacilli obtained from two North Lebanon hospitals between 2015 and 2017 revealed a significant rise in the prevalence of CRE, which increased from 1.7 % to 5.19 % [18,19].

In a study conducted in North Lebanon, a total of 290 Gram-negative bacteria resistant to carbapenems were isolated. *Escherichia coli* emerged as the predominant species, constituting 39.3 % of all isolates, followed by *Klebsiella* spp., which accounted for 8.6 % of the isolates [20].

Notably, *E. coli* and *K. pneumoniae* emerged as the most widespread CRE, with OXA-48 and NDM-1 being the predominant carbapenemases identified in the country [20].

Between 2008 and 2014, Kissoyan et al. studied the incidence of carbapenem resistance genes and how they affected the minimum inhibitory concentration (MIC90) needed to stop 90 % of the organisms in *Enterobacterales* from reproducing. To find resistance-associated genes, a collection of distinct CRE *E. coli* (n = 76) and *K. pneumoniae* (n = 54) were subjected to PCR analysis. The results showed that the prevalence of CRE in *K. pneumoniae* and *E. coli* increased from 0 % in 2008 to 1 % and 4 %, respectively, in 2014. PCR analysis showed that 18 % of isolates carried the *bla*NDM-1 gene and 36 % carried the *bla*OXA-48 gene, which is more common in *E. coli*. Among *E. coli* isolates, the majority had at least one porin-encoding gene, ompC or ompF (89 % among *bla*NDM-1-positive isolates and 96 % among *bla*OXA-48 isolates). In contrast, these genes were present in lower proportions among *K. pneumoniae* isolates

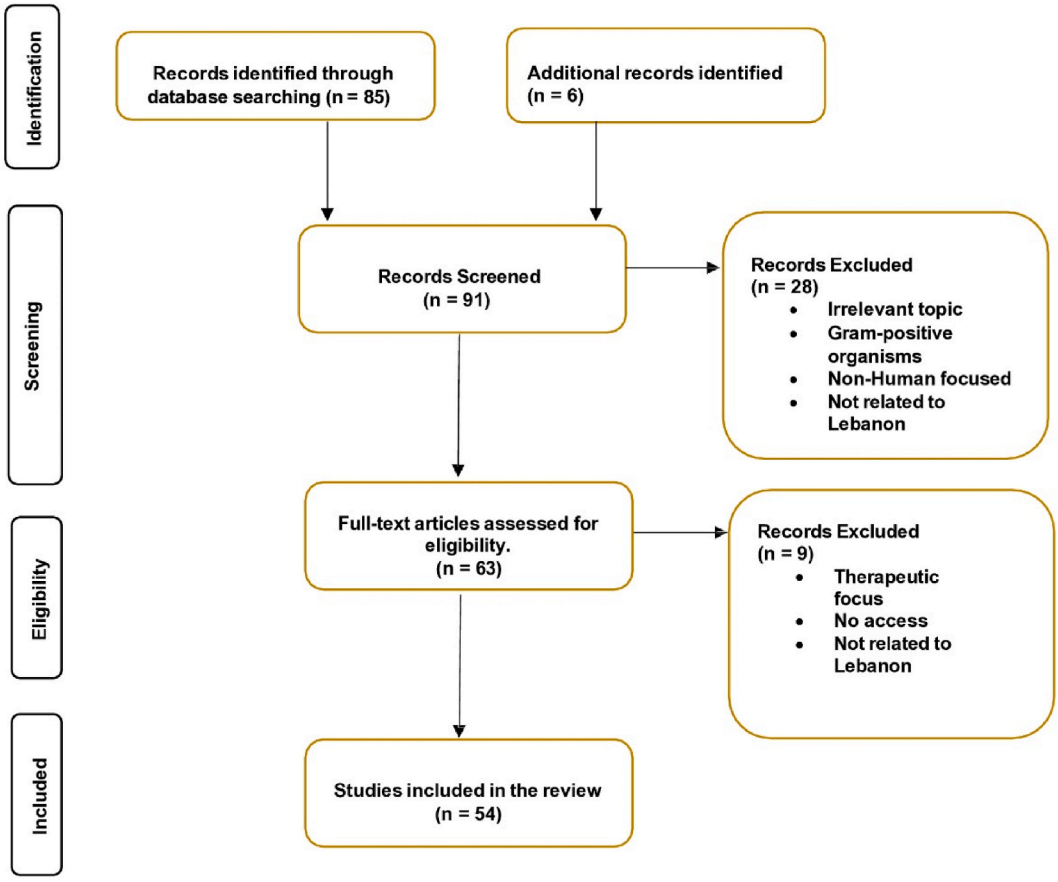

Fig. 1. PRISMA flow diagram of the search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(27 % among *bla*NDM-1-positive isolates and 65 % among *bla*OXA-48 isolates) [21,22].

On the other hand, a study undertaken subsequently involved the collection of 103 non-duplicated strains of *E. coli* and *K. pneumoniae* isolated from patients with wound infections in seven hospitals in North Lebanon. The identification of ESBL-producing isolates was accomplished through a double-disk synergy test, and the molecular detection of ESBL genes was conducted using multiplex polymerase chain reaction (PCR). *E. coli* emerged as the predominant bacterium, constituting 77.6 %, while *K. pneumoniae* represented 22.3 % of the strains. The overall prevalence of ESBL-producing organisms was 49 %, with a notably higher occurrence among female and elderly patients. *K. pneumoniae* exhibited a higher incidence of being both multidrug-resistant (86.95 %) and an ESBL producer (52.17 %), surpassing *E. coli* in both categories (77.5 % and 47.5 %, respectively). The majority of isolated ESBL producers carried multiple resistant genes (88 %), with *bla*CTX-M being the most prevalent (92 %), followed by *bla*TEM (86 %), *bla*SHV (64 %), and *bla*OXA genes (28 %) [23].

In summary, the Lebanese population is experiencing an increasing trend of resistance in *K. pneumoniae* and *E. coli* isolates. It's expected that the already high reported rate would become even higher unless antibiotic consumption is effectively controlled. The potential for these bacteria to render several antibiotics ineffective makes the advent of carbapenem and multidrug resistance a serious worry. Thus, it is essential that programs for antibiotic stewardship should be put into place as soon as possible to control the use of antibiotics, stop their widespread overuse, and deal with their misuse among Lebanese citizens. The goal of these programs is to lessen the increasing frequency of resistant strains [24].

3.2. *Salmonella species*

Foodborne illnesses can be due to a wide range of bacteria, one of the most common being *Salmonella* [25]. *Salmonella* infections are posing serious problems and can occasionally result in fatalities or severe consequences. The problem grows worse by the introduction of *Salmonella* species that are multidrug-resistant (MDR) to frequently recommended medications. Antimicrobial resistance has led to a reduction in the range of effective treatment choices, which has increased treatment costs and the likelihood of consequences [26].

The TEM and SHV β-lactamase families provide the majority of *Salmonella*'s extended-spectrum β-lactamases (ESBLs), however more recent studies have discovered other groups including PER and CTX-M [27].

Salmonella species exhibited an average susceptibility of 81.3 % to ampicillin and 95 % to ciprofloxacin. The susceptibility to trimethoprim–sulfamethoxazole slightly decreased to approximately 88 % in 2013, although this decline did not demonstrate statistical significance. Ceftriaxone susceptibility remained notably high at 97.3 %. Nalidixic acid susceptibility, reported from a single center, indicated rates of 75 % (n = 4) for *Salmonella* Typhi and 11 % for non-Typhi *Salmonella* (n = 28) [28].

3.3. *Shigella species*

Shigella, a Gram-negative bacterium belonging to the *Enterobacteriaceae* family, is a significant contributor to diarrheal diseases, resulting in approximately 210,000 deaths each year [29,30].

Antimicrobial therapy and supportive care are used in the treatment of shigellosis. However, there are now serious concerns due to the increasing incidence of antimicrobial resistance (AMR) in *Shigella* strains. The World Health Organization (WHO) designated *Shigella* as a priority pathogen due to this growing problem, highlighting the critical need for the development of new antimicrobial agents [31–33].

In a study assessing the susceptibility of *Shigella* isolates to a range of antimicrobial drugs, it was observed that 87 % of the isolates exhibited resistance to three or more classes of antimicrobial drugs, categorizing them as multidrug-resistant (MDR). Only three isolates demonstrated susceptibility to all tested drugs. The highest proportions of isolates displaying antimicrobial resistance (AMR) were noted for trimethoprim (85.2 %), followed by streptomycin (83.3 %), nalidixic acid (77.8 %), tetracycline (64.8 %), and sulfonamides (61.1 %). Lower resistance rates were recorded for ampicillin (38.9 %), cefotaxime (27.8 %), gentamicin (13 %), ceftazidime (11.1 %), chloramphenicol (11.1 %), and ciprofloxacin (1.9 %). Nevertheless, 55.6 % of the isolates displayed reduced susceptibility to ciprofloxacin. Notably, all isolates maintained susceptibility to ertapenem, amikacin, tigecycline, and azithromycin [34].

Certain isolates among these demonstrated the presence of the *bla*TEM1 gene, while others were found to harbor the plasmid-encoded *bla*CTX-M gene [24,34]. Additionally, in 2009, four instances of *Shigella sonnei* species producing extended-spectrum β-lactamases (ESBLs) and carrying the *bla*CTX-M-15 gene were identified in the stool samples of patients from a singular tertiary care center. This observation indicates a potential occurrence of the transfer of resistant genes through horizontal plasmid transfer [24].

3.4. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is among the most concerning nosocomial pathogens [35]. Infections caused by *Pseudomonas aeruginosa* are prevalent, linked to elevated mortality rates, and are progressively exhibiting resistance to carbapenems [36,37]. As a result, the World Health Organization (WHO) has identified carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) as one of the three Critical Priority pathogens [38].

The initial information regarding Antimicrobial Resistance (AMR) profiles of *Pseudomonas aeruginosa* in Lebanon was obtained from AUBMC and Makassed General Hospital in Beirut. During that period, 11 % of the clinical *P. aeruginosa* isolates circulating exhibited resistance to ceftazidime, and 8 % demonstrated resistance to imipenem [39].

During the initial years of the 21st century, there is noticeable evidence indicating a substantial decline in the susceptibility of

strains to ceftazidime and imipenem. To be precise, in an 11-year retrospective study conducted at AUBMC, the prevalence of resistance to both antimicrobials reached 17 % and 19 %, respectively [40].

Recent findings from three studies conducted between 2014 and 2018 at local tertiary care centers in Beirut, North, and Akkar governorates have raised concerns. The data revealed that 40–97.1 % of *Pseudomonas aeruginosa* infections were attributed to carbapenem-resistant isolates [41,42]. Additionally, resistance to other antimicrobials has been observed in clinical settings in Lebanon. For instance, at Hôtel-Dieu de France Hospital between 2005 and 2009, 26.4 % and 36.2 % of the isolates exhibited resistance to amikacin and levofloxacin, respectively [43].

Regrettably, there is a scarcity of studies addressing the presence of resistance genes in *Pseudomonas aeruginosa*. Despite the limited data available, it has been observed that carbapenem-resistant *P. aeruginosa* in Lebanon encompasses various factors, including carbapenem-hydrolyzing enzymes (such as *bla*VIM-2, *bla*GES-6, *bla*IMP-1, *bla*IMP-2, and *bla*IMP-15), non-enzymatic mechanisms (involving alterations in the outer membrane porin protein OprD and the overexpression of efflux pumps), and a combination of factors like reduced membrane permeability and/or drug efflux pumps along with enzyme inactivation mechanisms, such as Class C β-lactamase hyperproduction (e.g., PDC-13, AmpC) [44–46].

3.5. *Acinetobacter baumannii*

The frequency of hospital-acquired infections attributed to antimicrobial-resistant strains of *Acinetobacter baumannii* is consistently rising on a global scale, accompanied by elevated mortality rates. Due to the widespread occurrence of resistant isolates, the substantial risk of epidemics, and the existence of numerous virulence factors, *Acinetobacter baumannii* stands out as the most extensively researched species within the *Acinetobacter* genus [47].

In research conducted at Saint-George Hospital, a collection of 31 strains identified as *A. baumannii* exhibited notable resistance levels based on antibiotic susceptibility testing. The results indicated high resistance rates across all isolates to ticarcillin, ticarcillin-clavulanic acid, piperacillin-tazobactam, ceftazidime, cefepime, cefotaxime, imipenem, meropenem, ciprofloxacin, and levofloxacin. Moreover, a small percentage, 3.2 %, of the isolates displayed resistance to gentamicin, tobramycin, and amikacin. E-tests revealed a substantial resistance level to imipenem, with Minimum Inhibitory Concentration (MIC) exceeding 32 μg/ml for all isolates. Notably, none of the isolates exhibited resistance to colistin [48].

PCR results for carbapenemase-encoding genes indicated that 30 out of 31 isolates carried the acquired OXA carbapenemase gene

Table 1
Antimicrobial resistance profiles and mechanisms in common Gram-negative pathogens in Lebanon.

Organism	Key Findings	Resistance Mechanisms	References
Escherichia coli	Predominant CRE in North Lebanon, constituting 39.3 % of isolates. *bla*OXA-48 and *bla*NDM-1 identified as primary carbapenemases, with ompC and ompF genes prevalent. ESBL prevalence of 47.5 %, with *bla*CTX-M as the most common gene. Significant rise in carbapenem resistance from 0 % in 2008 to 4 % in 2014.	Porin loss (ompC, ompF). Carbapenemases (*bla*NDM-1, *bla*OXA-48). ESBLs (*bla*CTX-M, *bla*TEM, *bla*SHV, *bla*OXA).	[18,20,21]
Klebsiella pneumoniae	Represented 8.6 % of CRE in North Lebanon. *bla*OXA-48 and *bla*NDM-1 identified, with lower prevalence of porin-encoding genes than in *E. coli*. ESBL prevalence of 52.17 %, with *bla*CTX-M as the most frequent gene. Increase in carbapenem resistance from 0 % in 2008 to 1 % in 2014. Higher multidrug resistance (86.95 %) compared to *E. coli*.	Porin loss (ompC, ompF). Carbapenemases (*bla*NDM-1, *bla*OXA-48). ESBLs (*bla*CTX-M, *bla*TEM, *bla*SHV, *bla*OXA).	[18,21,23]
***Salmonella* spp.**	Multidrug Resistance: Increasing prevalence of MDR *Salmonella* strains, complicating treatment options. Nalidixic acid susceptibility showed significant differences between *Salmonella* Typhi (75 %) and non-Typhi *Salmonella* (11 %). β-Lactamase Production: Primarily TEM and SHV ESBLs, with emerging PER and CTX-M groups.	ESBLs (*bla*CTX-M, *bla*TEM, *bla*SHV).	[27,28]
***Shigella* spp.**	87 % of isolates are multidrug-resistant to three or more antimicrobial classes. High resistance to trimethoprim (85.2 %), streptomycin (83.3 %), and nalidixic acid (77.8 %). Retained susceptibility to ertapenem, amikacin, tigecycline, and azithromycin. Presence of *bla*TEM1 and *bla*CTX-M genes, with cases of ESBL-producing *Shigella sonnei*.	ESBLs (*bla*CTX-M, *bla*TEM).	[29,34]
Pseudomonas aeruginosa	A major nosocomial pathogen with increasing resistance to carbapenems, classified as a WHO Critical Priority pathogen. Carbapenem resistance rates in Lebanon have risen, with studies showing 40–97.1 % resistance between 2014 and 2018. Resistance to other antimicrobials is also significant, including 26.4 % for amikacin and 36.2 % for levofloxacin.	Carbapenemases (*bla*VIM-2, *bla*GES-6, *bla*IMP-1). Efflux pumps. Porin alterations (OprD). AmpC hyperproduction.	[38,41,44]
Acinetobacter baumannii	Rising hospital-acquired infections from antimicrobial-resistant *A. baumannii* with increased mortality. 31 hospital isolates showed resistance to multiple antibiotics (e.g., ticarcillin, imipenem, ciprofloxacin). Imipenem Resistance: All isolates had MIC >32 μg/ml, indicating high resistance. 30 isolates carried OXA-23-like, 1 carried OXA-24-like; all had the *bla*TEM gene.	Carbapenemases (*bla*OXA-23, *bla*OXA-24). ESBLs (*bla*TEM).	[47,48]

*bla*OXA-23-like, while one isolate expressed the *bla*OXA-24-like gene. Additionally, the β-lactamase gene *bla*TEM was detected in all isolates [48].

3.6. Other gram-negative species

In addition to the commonly discussed gram-negative pathogens, other species such as *Citrobacter* spp., *Enterobacter* spp., and *Providencia* spp. play a significant role in β-lactam resistance [49]. *Citrobacter* spp. are increasingly recognized for producing extended-spectrum β-lactamases such as TEM, SHV, and CTX-M, contributing to resistance against penicillins and cephalosporins [50]. Similarly, *Enterobacter* spp. frequently acquire AmpC β-lactamases, which can be inducible, rendering them resistant to third-generation cephalosporins [51]. Furthermore, plasmid-mediated carbapenemases like KPC and NDM-1 have been reported in *Enterobacter* species, posing a serious therapeutic challenge [52]. *Providencia* spp., often implicated in urinary tract infections, have shown resistance mediated by both ESBLs and carbapenemases, limiting the efficacy of β-lactam antibiotics. These species, along with others such as *Morganella* spp. and *Serratia* spp., demonstrate the ability to harbor and disseminate resistance genes [50], underscoring the importance of continued surveillance and targeted antimicrobial stewardship efforts to address their emerging threat.

Table 1 provides a summary of the main findings and resistance mechanisms discussed in the results section.

4. Antimicrobial consumption

In Lebanon, there has been a notable increase in the consumption of penicillin combinations, quinolones, third generation cephalosporins, tetracyclines, and carbapenems. This contrasts with a declining trend observed in the consumption of first-generation cephalosporins, sulfonamides and diaminopyrimidines, as well as beta-lactamase resistant penicillins [53].

In a study conducted at AUBMC, a discernible increase in Defined Daily Doses (DDD) was observed in conjunction with spikes in COVID-19 cases, notably during the fourth quarter of 2020 and the first quarter of 2021, with DDD rates of 142.8 and 135.4 per 100 patient days, respectively. Furthermore, there was a noticeable correlation between the escalation in antimicrobial consumption and the percentage of critically ill patients hospitalized, aligning with the surges in the pandemic across the country [54].

A proactive measure in curbing the rise of antibiotic-resistant bacterial strains involves urging hospitals to assess their antibiotic consumption and explore potential correlations with bacterial resistance. Various software solutions, such as "ABCcalc" and "WHO-net," are designed for this purpose. These applications are user-friendly, easily installable, and enable hospitals to monitor antibiotic consumption and the emergence of resistant strains over time. Such information holds significant value in the ongoing effort to mitigate the emergence of antibiotic resistance in Lebanon [24].

5. Limitations and future research Opportunities

This review extensively explored the resistance mechanisms of gram-negative organisms, aiming to encompass all crucial concepts. Despite efforts to include a wide range of information, there is still a lack of data on specific genes and additional factors that contribute to resistance. Continuous investigations are crucial to bridge these gaps and improve our comprehension of the resistance mechanisms in gram-negative organisms.

6. Conclusion

In conclusion, the overuse and misuse of antibiotics has led to the emergence of resistant gram-negative organisms, which pose a serious threat to human health. Programs for antibiotic stewardship must be implemented to stop the spread of resistance, highlighting the critical need for greater public awareness of this urgent problem. Furthermore, targeted investigations are required to find new compounds that could address the issues caused by resistant strains and help develop more effective treatments.

CRediT authorship contribution statement

Yara Khachab: Data curation, Formal analysis, Methodology, Writing – original draft. **Mohamad Hodroj:** Formal analysis, Methodology, Writing – original draft. **Elie Salem Sokhn:** Conceptualization, Project administration, Validation, Writing – review & editing.

Patient consent for publication

Not required.

Significance of the review

This review provides valuable insights into antibiotic resistance in gram-negative organisms in Lebanon, a region with limited data on this issue. By examining key resistance mechanisms and genes, our review contributes to a better understanding of the local AMR landscape and highlights the urgent need for enhanced surveillance and stewardship programs. The findings also serve as a foundation for future research and policy development in Lebanon and similar settings.

Data availability statement

All data relevant to the study is included in the article.

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Declaration of competing interest

None.

References

[1] A. Bravo, S. Ruiz-Cruz, I. Alkorta, M. Espinosa, When humans met superbugs: strategies to tackle bacterial resistances to antibiotics, Biomol. Concepts 9 (1) (Dec. 2018) 216–226, https://doi.org/10.1515/bmc-2018-0021.
[2] A. Walusansa, et al., Antibiotic-resistance in medically important bacteria isolated from commercial herbal medicines in Africa from 2000 to 2021: a systematic review and meta-analysis, Antimicrob. Resist. Infect. Control 11 (Jan. 2022) 11, https://doi.org/10.1186/s13756-022-01054-6.
[3] M. Massongo, et al., Trends of antibacterial resistance at the national reference laboratory in Cameroon: comparison of the situation between 2010 and 2017, BioMed Res. Int. 2021 (2021) 9957112, https://doi.org/10.1155/2021/9957112.
[4] M.-M. Osei, et al., Alarming levels of multidrug resistance in aerobic gram-negative bacilli isolated from the nasopharynx of healthy under-five children in accra, Ghana, Int J Environ Res Public Health 19 (17) (Sep. 2022) 10927, https://doi.org/10.3390/ijerph191710927.
[5] S.H. Haji, S.T.H. Aka, F.A. Ali, Prevalence and characterisation of carbapenemase encoding genes in multidrug-resistant Gram-negative bacilli, PLoS One 16 (11) (2021) e0259005, https://doi.org/10.1371/journal.pone.0259005.
[6] K. Aykac, et al., Current epidemiology of resistance among Gram-negative bacilli in paediatric patients in Turkey, J Glob Antimicrob Resist 11 (Dec. 2017) 140–144, https://doi.org/10.1016/j.jgar.2017.07.018.
[7] K. Bush, Past and present perspectives on β-lactamases, Antimicrob. Agents Chemother. 62 (10) (Sep. 2018) e01076, https://doi.org/10.1128/AAC.01076-18, 18.
[8] A. Tankeshwar, "Beta-Lactam Antibiotics: Mechanism of Action, Resistance • Microbe Online," Microbe Online. Accessed: January. 25, 2025. [Online]. Available: https://microbeonline.com/beta-lactam-antibiotics-mechanism-action-resistance/.
[9] I. Martin-Loeches, A.H. Rodriguez, A. Torres, New guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia: USA vs. Europe, Curr. Opin. Crit. Care 24 (5) (Oct. 2018) 347–352, https://doi.org/10.1097/MCC.0000000000000535.
[10] M.A. Caudell, et al., Risk factors for colonization with multidrug-resistant bacteria in urban and rural communities in Kenya: an antimicrobial resistance in communities and hospitals (ARCH) study, Clin. Infect. Dis. 77 (Suppl 1) (Jul. 2023) S104–S110, https://doi.org/10.1093/cid/ciad223.
[11] S. Omulo, et al., Risk factors for colonization with extended-spectrum cephalosporin-resistant and carbapenem-resistant Enterobacterales among hospitalized patients in Kenya: an antibiotic resistance in communities and hospitals (ARCH) study, Clin. Infect. Dis. 77 (Suppl 1) (Jul. 2023) S97–S103, https://doi.org/10.1093/cid/ciad258.
[12] M. Rima, et al., Prevalence and molecular mechanisms of carbapenem resistance among gram-negative bacilli in three hospitals of northern Lebanon, Antibiotics (Basel) 11 (10) (Sep. 2022) 1295, https://doi.org/10.3390/antibiotics11101295.
[13] M.J. Page, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (Mar. 2021) n71, https://doi.org/10.1136/bmj.n71.
[14] The contribution of databases to the results of systematic reviews: a cross-sectional study - PMC [Online]. Available, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037618/. (Accessed 30 October 2023).
[15] Y. Chong, S. Shimoda, N. Shimono, Current epidemiology, genetic evolution and clinical impact of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae, Infect. Genet. Evol. 61 (Jul. 2018) 185–188, https://doi.org/10.1016/j.meegid.2018.04.005.
[16] D. van Duin, D.L. Paterson, Multidrug-resistant bacteria in the community: an update, Infect Dis Clin North Am 34 (4) (Dec. 2020) 709–722, https://doi.org/10.1016/j.idc.2020.08.002.
[17] E.S. Sokhn, A. Salami, A. El Roz, L. Salloum, H.F. Bahmad, G. Ghssein, Antimicrobial susceptibilities and laboratory profiles of Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis isolates as agents of urinary tract infection in Lebanon: paving the way for better diagnostics, Med. Sci. 8 (3) (Aug. 2020) 32, https://doi.org/10.3390/medsci8030032.
[18] A. Chamieh, G. El-Hajj, O. Zmerli, C. Afif, E. Azar, Carbapenem resistant organisms: a 9-year surveillance and trends at Saint George university medical center, Journal of Infection and Public Health 13 (12) (Dec. 2020) 2101–2106, https://doi.org/10.1016/j.jiph.2019.02.019.
[19] J. Moussa, E. Nassour, E. Tahan, M. El Chaar, T. Jisr, S. Tokajian, Carbapenem resistance determinants and their transmissibility among clinically isolated Enterobacterales in Lebanon, Journal of Infection and Public Health 16 (12) (Dec. 2023) 1947–1953, https://doi.org/10.1016/j.jiph.2023.10.003.
[20] M. Hamze, Epidemiology and antibiotic susceptibility patterns of carbapenem resistant gram negative bacteria isolated from two tertiary care hospitals in NorthNorth Lebanon: carbapenem resistant gram negative bacteria in NorthNorth Lebanon, The International Arabic Journal of Antimicrobial Agents 8 (2) (Oct. 2018), https://doi.org/10.3823/823, 2.
[21] K.A. Kissoyan, G.F. Araj, G.M. Matar, Prevalence of carbapenem resistance genes and corresponding MIC90 in Enterobacteriaceae at a tertiary care center in Lebanon, J Infect Dev Ctries 12 (2.1) (Feb. 2018) 9S, https://doi.org/10.3855/jidc.10097.
[22] Retrospective case series of infections caused by carbapenem-resistant Enterobacteriaceae at a tertiary care centre in Lebanon - PubMed [Online]. Available, https://pubmed.ncbi.nlm.nih.gov/27155945/. (Accessed 13 January 2024).
[23] A.M. Hamwi, E. Salem-Sokhn, High frequency and molecular characterization of ESBL-producing Enterobacteriaceae isolated from wound infections in North Lebanon, Expert Review of Anti-infective Therapy 21 (8) (Aug. 2023) 901–909, https://doi.org/10.1080/14787210.2023.2234082.
[24] S.E. Salem, E. Dahdouh, Z. Daoud, Resistance of gram-negative bacilli in Lebanon, Int. Sch. Res. Notices 2013 (Jul. 2012) e759208, https://doi.org/10.5402/2013/759208.
[25] S.M. Fadlallah, et al., Molecular epidemiology and antimicrobial resistance of Salmonella species from clinical specimens and food Items in Lebanon, J Infect Dev Ctries 11 (1) (Jan. 2017) 19–27, https://doi.org/10.3855/jidc.7786.
[26] M. Malaeb, A.R. Bizri, N. Ghosn, A. Berry, U. Musharrafieh, Salmonella burden in Lebanon, Epidemiol. Infect. 144 (8) (Jun. 2016) 1761–1769, https://doi.org/10.1017/S0950268815003076.
[27] C. Moubareck, F. Doucet-Populaire, M. Hamze, Z. Daoud, F.-X. Weill, First extended-spectrum-β-lactamase (CTX-M-15)-Producing Salmonella enterica serotype typhimurium isolate identified in Lebanon, Antimicrob. Agents Chemother. 49 (2) (Feb. 2005) 864–865, https://doi.org/10.1128/AAC.49.2.864-865.2005.
[28] K. Chamoun, et al., Surveillance of antimicrobial resistance in Lebanese hospitals: retrospective nationwide compiled data, Int. J. Infect. Dis. 46 (May 2016) 64–70, https://doi.org/10.1016/j.ijid.2016.03.010.
[29] Morbidity and mortality due to shigella and enterotoxigenic Escherichia coli diarrhoea: the global burden of disease study 1990–2016 - PMC [Online]. Available, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202441/. (Accessed 13 January 2024).

[30] T. R. Connor et al., "Species-wide whole genome sequencing reveals historical global spread and recent local persistence in Shigella flexneri," Elife, vol. 4, p. e07335, doi: 10.7554/eLife.07335.
[31] S. Lefèvre, et al., Rapid emergence of extensively drug-resistant Shigella sonnei in France, Nat. Commun. 14 (Jan. 2023) 462, https://doi.org/10.1038/s41467-023-36222-8.
[32] H. Chung The, et al., Dissecting the molecular evolution of fluoroquinolone-resistant Shigella sonnei, Nat. Commun. 10 (Oct. 2019) 4828, https://doi.org/10.1038/s41467-019-12823-0.
[33] J. Hawkey, et al., Global population structure and genotyping framework for genomic surveillance of the major dysentery pathogen, Shigella sonnei, Nat. Commun. 12 (May 2021) 2684, https://doi.org/10.1038/s41467-021-22700-4.
[34] I. Yassine, et al., Genomic analysis of Shigella isolates from Lebanon reveals marked genetic diversity and antimicrobial resistance, Microb. Genom. 9 (12) (Dec. 2023) 001157, https://doi.org/10.1099/mgen.0.001157.
[35] D. Ibrahim, J.-F. Jabbour, S.S. Kanj, Current choices of antibiotic treatment for Pseudomonas aeruginosa infections, Curr. Opin. Infect. Dis. 33 (6) (Dec. 2020) 464–473, https://doi.org/10.1097/QCO.0000000000000677.
[36] J.T. Thaden, L.P. Park, S.A. Maskarinec, F. Ruffin, V.G. Fowler, D. van Duin, Results from a 13-year prospective cohort study show increased mortality associated with bloodstream infections caused by Pseudomonas aeruginosa compared to other bacteria, Antimicrob. Agents Chemother. 61 (6) (May 2017) e02671, https://doi.org/10.1128/AAC.02671-16, 16.
[37] B. Cai, et al., Prevalence of carbapenem-resistant gram-negative infections in the United States predominated by acinetobacter baumannii and Pseudomonas aeruginosa, Open Forum Infect. Dis. 4 (3) (Aug. 2017) ofx176, https://doi.org/10.1093/ofid/ofx176.
[38] WHO publishes list of bacteria for which new antibiotics are urgently needed." Accessed: January. 14, 2024. [Online]. Available: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.
[39] A.A. Dabbousi, F. Dabboussi, M. Hamze, M. Osman, I.I. Kassem, The emergence and dissemination of multidrug resistant Pseudomonas aeruginosa in Lebanon: current status and challenges during the economic crisis, Antibiotics (Basel) 11 (5) (May 2022) 687, https://doi.org/10.3390/antibiotics11050687.
[40] G.F. Araj, et al., A reflection on bacterial resistance to antimicrobial agents at a major tertiary care center in Lebanon over a decade, J. Med. Liban. 60 (3) (2012) 125–135.
[41] M. Osman, H. Mallat, M. Hamze, E. Raad, Prevalence and antibiotic susceptibility patterns of bacteria causing urinary tract infections in Youssef Hospital Center: first report from Akkar governorate, North Lebanon, International Arabic Journal of Antimicrobial Agents 7 (May 2017), https://doi.org/10.3823/802.
[42] M. Hamze, M. Osman, H. Mallat, M. Achkar, Prevalence and antibiotic susceptibility of ear pathogens isolated from patients in Tripoli, north of Lebanon, int. arab. j antimicrob. agents 7 (1) (May 2017), https://doi.org/10.3823/0801.
[43] E. Hamouche, D.K. Sarkis, "[Evolution of susceptibility to antibiotics of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumanii, in: A University Hospital Center of Beirut between 2005 and 2009], vol. 60, Jun. 2012 e15, https://doi.org/10.1016/j.patbio.2011.03.011. Pathol Biol (Paris).
[44] D. Hammoudi, C.A. Moubareck, A. Kanso, P. Nordmann, D.K. Sarkis, SURVEILLANCE of CARBAPENEM NON-SUSCEPTIBLE GRAM NEGATIVE STRAINS and CHARACTERIZATION of CARBAPENEMASES of CLASSES A, B and D in a LEBANESE HOSPITAL, J. Med. Liban. 63 (2) (2015) 66–73, https://doi.org/10.12816/0012553.
[45] J. Yaghi, N. Fattouh, C. Akkawi, L. El Chamy, R.G. Maroun, G. Khalil, Unusually high prevalence of cosecretion of ambler Class A and B carbapenemases and nonenzymatic mechanisms in multidrug-resistant clinical isolates of Pseudomonas aeruginosa in Lebanon, Microb. Drug Resist. 26 (2) (Feb. 2020) 150–159, https://doi.org/10.1089/mdr.2019.0040.
[46] T. Nawfal Dagher, C. Al-Bayssari, S.M. Diene, E. Azar, J.-M. Rolain, Emergence of plasmid-encoded VIM-2-producing Pseudomonas aeruginosa isolated from clinical samples in Lebanon, New Microbes New Infect 29 (May 2019) 100521, https://doi.org/10.1016/j.nmni.2019.100521.
[47] S. Jamal, A. Al Atrouni, R. Rafei, F. Dabboussi, M. Hamze, M. Osman, Molecular mechanisms of antimicrobial resistance in Acinetobacter baumannii, with a special focus on its epidemiology in Lebanon, Journal of Global Antimicrobial Resistance 15 (Dec. 2018) 154–163, https://doi.org/10.1016/j.jgar.2018.05.022.
[48] T. Nawfal Dagher, et al., Investigation of multidrug-resistant ST2 Acinetobacter baumannii isolated from Saint George hospital in Lebanon, BMC Microbiol. 19 (2019), https://doi.org/10.1186/s12866-019-1401-2, 29, Feb.
[49] M. El Khoury, T. Salloum, I. Al Kodsi, T. Jisr, M. El Chaar, S. Tokajian, Whole-genome sequence analysis of carbapenem-resistant Enterobacteriaceae recovered from hospitalized patients, Journal of Global Antimicrobial Resistance 34 (Sep. 2023) 150–160, https://doi.org/10.1016/j.jgar.2023.07.004.
[50] A.G. Stewart, P.N.A. Harris, M.D. Chatfield, R. Littleford, D.L. Paterson, Ceftolozane-tazobactam versus meropenem for definitive treatment of bloodstream infection due to extended-spectrum beta-lactamase (ESBL) and AmpC-producing Enterobacterales ('MERINO-3'): study protocol for a multicentre, open-label randomised non-inferiority trial, Trials 22 (Apr. 2021) 301, https://doi.org/10.1186/s13063-021-05206-8.
[51] A.G. Stewart, et al., Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections caused by AmpC β-lactamase–producing Enterobacter spp, Citrobacter freundii, Morganella morganii, Providencia spp, or Serratia marcescens: a pilot multicenter randomized controlled trial (MERINO-2), Open Forum Infect. Dis. 8 (8) (Aug. 2021) ofab387, https://doi.org/10.1093/ofid/ofab387.
[52] Gram-negative bacterial colonization in the gut: isolation, characterization, and identification of resistance mechanisms, Journal of Infection and Public Health 17 (10) (Oct. 2024) 102535, https://doi.org/10.1016/j.jiph.2024.102535.
[53] N. Lahoud, et al., Trends in the consumption of antibiotics in the Lebanese community between 2004 and 2016, Int. J. Clin. Pharm. 43 (4) (Aug. 2021) 1065–1073, https://doi.org/10.1007/s11096-020-01218-7.
[54] N. Haddad, et al., The experience of an antimicrobial stewardship program and antibiotic consumption and resistance trends during the COVID-19 pandemic at a tertiary care center in Beirut, J Infect Public Health 17 (2) (Dec. 2023) 254–262, https://doi.org/10.1016/j.jiph.2023.12.007.