ECRONICON OPEN ACCESS

EC GYNAECOLOGY
Review Article

# Prevalence of Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae* Rectovaginal Colonization among Healthy Pregnant Women: A Comprehensive Review

**Nicholas A Kerna[1,2]*, Joseph Anderson II[3], John V Flores[4,5], Hilary M Holets[4,5], Sudeep Chawla[6], ND Victor Carsrud[7], Kevin D Pruitt[8,9] and Dabeluchi C Ngwu[10,11]**

[1]*Independent Global Medical Research Consortium, USA*

[2]*First InterHealth Group, Thailand*

[3]*International Institute of Original Medicine, USA*

[4]*Beverly Hills Wellness Surgical Institute, USA*

[5]*Orange Partners Surgicenter, USA*

[6]*Chawla Health & Research, USA*

[7]*Lakeline Wellness Center, USA*

[8]*Kemet Medical Consultants, USA*

[9]*PBJ Medical Associates, LLC, USA*

[10]*Cardiovascular and Thoracic Surgery Unit, Department of Surgery, Federal Medical Center, Umuahia, Nigeria*

[11]*Earthwide Surgical Missions, Nigeria*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com.

**Received:** October 30, 2022; **Published:** November 28, 2022

**DOI:** 10.31080/ecgy.2022.11.00817

## Abstract

Several members of the *Enterobacteriaceae* family produce extended-spectrum β-*lactamases* (ESBL), which hydrolyze extended-spectrum cephalosporins. Clavulanic acid has been effective in inhibiting ESBL. Since their discovery in the early 1980s, ESBL producers are increasingly being found in patients with hospital-associated and community-acquired infections. CTX-M enzymes replace SHV and TEM enzymes as the most common ESBLs, mainly in community-acquired *Escherichia coli* infections. The most common infections requiring hospitalization are urinary tract infections (UTIs), pneumonia (*Klebsiella pneumoniae*), endocarditis, peritonitis, birth problems in neonates, bloodstream infections (BSI), and intra-abdominal infections (IAI).

Affected patients often have several underlying risk factors. Antibiotic misuse or overuse of antibiotics is a well-recognized key contributor to the emergence of new diseases, the development of resistant bacteria in individual patients, and the global spread of antimicrobial resistance. Therefore, antibiotics must be used with caution. The obstruction of drugs imparted by ESBL and co-resistance to different antimicrobial families—such as fluoroquinolones, aminoglycosides, cephalosporins, and trimethoprim with sulfamethoxazole—limit treatment decisions for ESBL-associated infections. Clinical evidence on the efficacy of drugs to manage ESBL-associated infections is insufficient. Although several cephalosporins appear to be active *in vitro*, their clinical effects are poor in clinical settings.

This review discusses therapeutic options for ESBL-E with a focus on rectovaginal colonization among healthy pregnant women. Combinations of β-lactam/β-lactamase inhibitors may be effective. Carbapenems are preferred to fluoroquinolones for treating severe infections, as they are more effective. Pivmecillinam, nitrofurantoin, and tigecycline demonstrate significant antibacterial action against ESBL-E. Imipenem/cilastatin, relebactam, nacubactam, and enmetazobactam are newer medications that have shown *in vivo* effectiveness against ESBL-producing bacteria.

***Keywords:*** *Bacteria Resistance; Infectious Disease; Hospital-Acquired Disease; Multidrug Resistance; Novel Antibiotics; UTI*

## Abbreviations

BLBLI: β-Lactam-β-Lactamase Inhibitor; BSI: Bloodstream Infection; cIAI: Complicated Intra-Abdominal Infection; CLSI: Clinical and Laboratory Standards Institute; cUTI: Complicated Urinary Tract Infection; EMA: European Medicines Agency; ESBL: Extended-Spectrum β-Lactamase; EUCAST: European Committee on Antimicrobial Susceptibility Testing; FDA: Food and Drug Administration; GIT: Gastrointestinal Tract; HAP: Hospital-Acquired Pneumonia; HGT: Horizontal Gene Transfer; ICU: Intensive Care Unit; MBL: Metallo-β-Lactamase; MDR: Multidrug-Resistant; MIC: Minimum Inhibitory Concentration; TEST: Tigecycline Evaluation and Surveillance Trial; UTI: Urinary Tract Infection

## Introduction

*Enterobacteriaceae* comprise one of the most significant families of gram-negative bacteria. They include the plague-causing bacillus, *Yersinia pestis*, and the typhoid-causing bacillus, *Salmonella serotype typhi*—two of the most prominent bacterial diseases in human history [1]. This genus has had significant morphogenetic alterations in its 85-year lifespan, particularly from 2000 to 2020 [2]. Although Rahn first proposed the genus in 1937, many of its members date considerably back [3]. *Enterobacteriaceae* differ from other gram-negative rod-shaped bacteria in cell shape and size, flagellar organization, oxidase production, sodium requirements, and the presence of enterobacterial common antigen. Members of *Enterobacteriaceae*, commonly called enteric bacteria, are typically found in the gastrointestinal tract (GIT) of humans and animals [4-6].

The taxonomy of *Enterobacteriaceae* has become sophisticated and is rapidly evolving due to the emergence of techniques such as nucleic acid hybridization and sequencing. Approximately 63 genera have been recognized in the Internet Taxonomy database of the National Library of Medicine; however, only 20 – 25 species of *Enterobacteriaceae* are clinically significant [6]. These bacteria have peritrichous flagella, and they oxidize nitrates and ferment glucose. However, the *Shigella* and *Klebsiella* members are devoid of peritrichous flagella.

The members of the *Enterobacteriaceae* family use aerobic respiration. These designations, however, are not interchangeable since some species do not live in the GIT, and many GIT species do not match the same *Enterobacteriaceae*. The genera and subgroups of the most common human pathogenic *Enterobacteriaceae* are listed in Figure 1 [7].

*Enterobacteriaceae* are rod-shaped, 1 to 3 μm long, 0.5 μm wide, with abundant surface appendages, such as pili and flagella. The genome is scattered across the cytoplasm and typically consists of a set of circular chromosomes with several plasmids of varying sizes. Breathing occurs in the cytoplasmic membrane. These gram-negative organisms also have inner and outer phospholipid membranes surrounding a periplasmic space containing the peptidoglycan cell membrane [6].

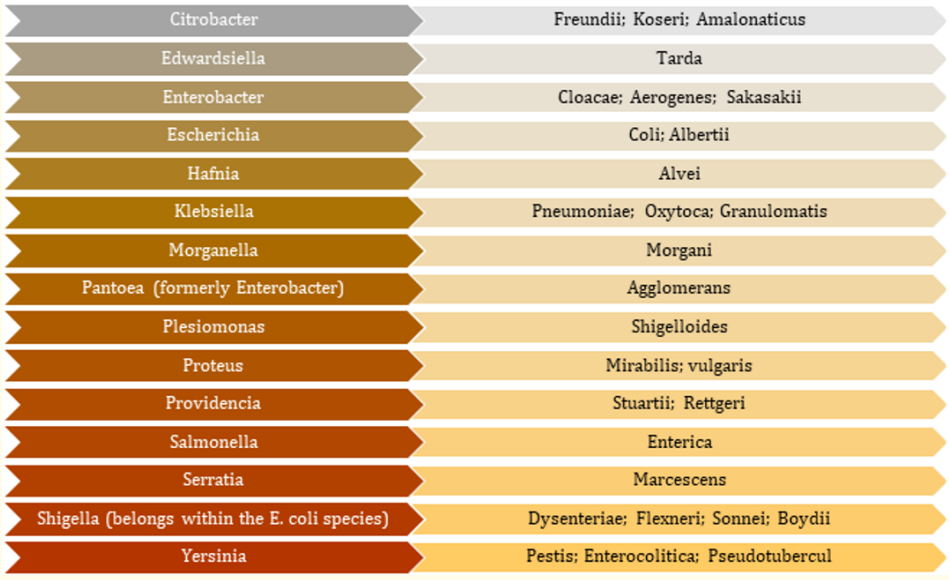


***Figure 1:*** *Enterobacteriaceae commonly found in humans [6].*

*Non-Enterobacteriaceae* aerobic gram-negative rods (non-gut bacteria) are classified based on their fermentation processes. Fermentative gram-negative rods include *Aeromonas, Pasteurella, Plesiomonas*, and *Vibrio*, while non-fermentative gram-negative rods include *Acinetobacter and Alcaligenes Burkholderia*, *Flavobacterium*, *Pseudomonas*, and *Stenotrophomonas* [8]. Non-fermentative bacteria are aerobic, non-spore-forming bacilli that do not use carbohydrates for energy [9].

Important publications by Edwards and Ewing (1972), Ewing (1986), and Kauffmann (1969) provide helpful fundamental information on the isolation, identification, and serotyping of *Enterobacteriaceae*, along with a historical perspective. *Enterobacteria* by Janda and Abbott (1998) and Topley and Wilson, 10th edition (1998), which covers the whole family, are also highly recommended reads [1].

## Discussion

Most *Enterobacteriaceae* isolates are found in the bloodstream, spinal fluid, synovial fluid, bone, meninges, peritoneal cavity, respiratory system, genital tract, urinary tract, biliary system, and abscess, as well as various locations in the abdominal cavity [4,6]. Certain *Enterobacter* species are found in the microflora of vertebrate GIT, whereas others are found in exposed human skin, water, specific food products, sediments, and sewage waste [10,11]. Patients with diabetes or alcohol abuse are at high risk for oropharyngeal colonization with members of this family. Also, the enterobacterial species can rapidly colonize the oropharynx of hospitalized patients regardless of antibiotic use [4].

### *Enterobacteriaceae* in the rectovaginal region

The natural vaginal habitat is an essential host defense mechanism against external urogenital pathogens. However, several conditions, including sexual intercourse, antibiotic use, and douching, cause a deficiency of $H_2O_2$-producing lactobacilli, increasing the likelihood of *Escherichia coli* vaginal colonization, which is a crucial stage for urinary tract infections (UTI). Gupta., *et al*. (2000) found that women who

used diaphragms or spermicidal medicines for contraception and postmenopausal women had higher rates of vaginal colonization with *E. coli* and other near relatives [12].

Furthermore, hormonally-driven alterations in vaginal flora associated with menopause are likely to play a role in UTI etiology. After menopause, the vaginal pH rises, lactobacilli decreases, and *Enterobacteriaceae* invasion occurs [13]. Liu., *et al*. (2019) investigated antimicrobial susceptibility and neonatal birth complications due to the colonization of pathogenic *E. coli* in pregnant women. About 35.8% of asymptomatic pregnant women had colonization of *E. coli* in the rectovaginal area.

These women neonates had high hospitalization rates, hyperbilirubinemia, and GIT concerns. Vaginal *E. coli* infection in pregnant women is associated with premature membrane rupture, chorioamnionitis, and preterm delivery. *E. coli* colonization can often be attributed to exposure to livestock and medication use throughout pregnancy [14].

## Beta-lactamase

Beta-lactams are commonly recommended antibiotics for bacterial infections. They inhibit bacterial growth by blocking penicillin-binding proteins, which are required for cell wall cross-linking [15,16]. Also, gram-positive and gram-negative bacteria produce β-lactamases, disrupting or breaking the β-lactam ring, inactivating β-lactams. These enzymes are found on chromosomes and mobile genetic material, such as plasmids [17].

These enzymes were discovered in strains of *Staphylococcus aureus* in the late 1940s before penicillin was introduced as a therapeutic option [18]. Pollock coined the term β-lactamase in 1960. The first plasmid-mediated β-*lactamases* were called TEM (named after the first patient, Temoniera) [16].

Beta-lactamases are commonly classified using the Ambler molecular classification system or the Bush-Jacoby-Medeiros classification system (Figure 2) [19]. The Ambler classification is based on the molecular structural identity. It categorizes serine β-lactamases into classes A, C, and D (based on enzyme protein homology) and metallo-β-lactamases (MBLs) into Class B.

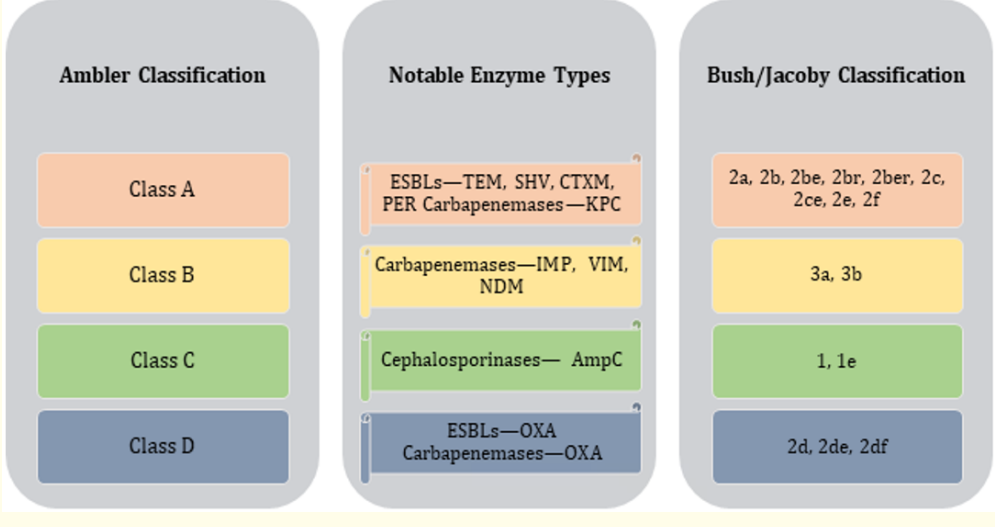


***Figure 2:*** *Classification schema of β-lactamase genes. Abbreviations: ESBL, extended-spectrum β-lactamase; IMP, active on imipenem metallo-β-lactamase; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase [19,20].*

The Bush-Jacoby-Medeiros strategy is based on the functional properties of enzymes and their ability to hydrolyze certain β-lactam families from groups 1 (Class C [i.e., cephalosporinases]) and 2 (Classes A [i.e., extended-spectrum-β-lactamases] and D [i.e., OXA-β-lactamases]) to their substrates via a serine active site [20,21].

In contrast, MBLs structurally differ from other β-lactamases requiring a zinc ion at the active site. MBLs have a low affinity or hydrolytic capacity for monobactams. The IMP, VIM, and NDM are the most frequently occurring MBL families [21].

## Extended-spectrum β-lactamase (ESBL)

Bacterial strains producing extended-spectrum β-lactamase (ESBL) were first identified in Western Europe in the mid-1980s and then in the United States in the late 1980s [22]. These enzymes degrade extended-spectrum β-lactam antibiotics, such as third-generation cephalosporins, penicillin, and aztreonam [23]. Most clinically relevant ESBLs are encoded by plasmids, which can also contain genes that encode enzymes that confer resistance to other drug classes, such as aminoglycosides [24]. Figure 3 details how ESBL differs from normal β-lactamases [16,25-30].

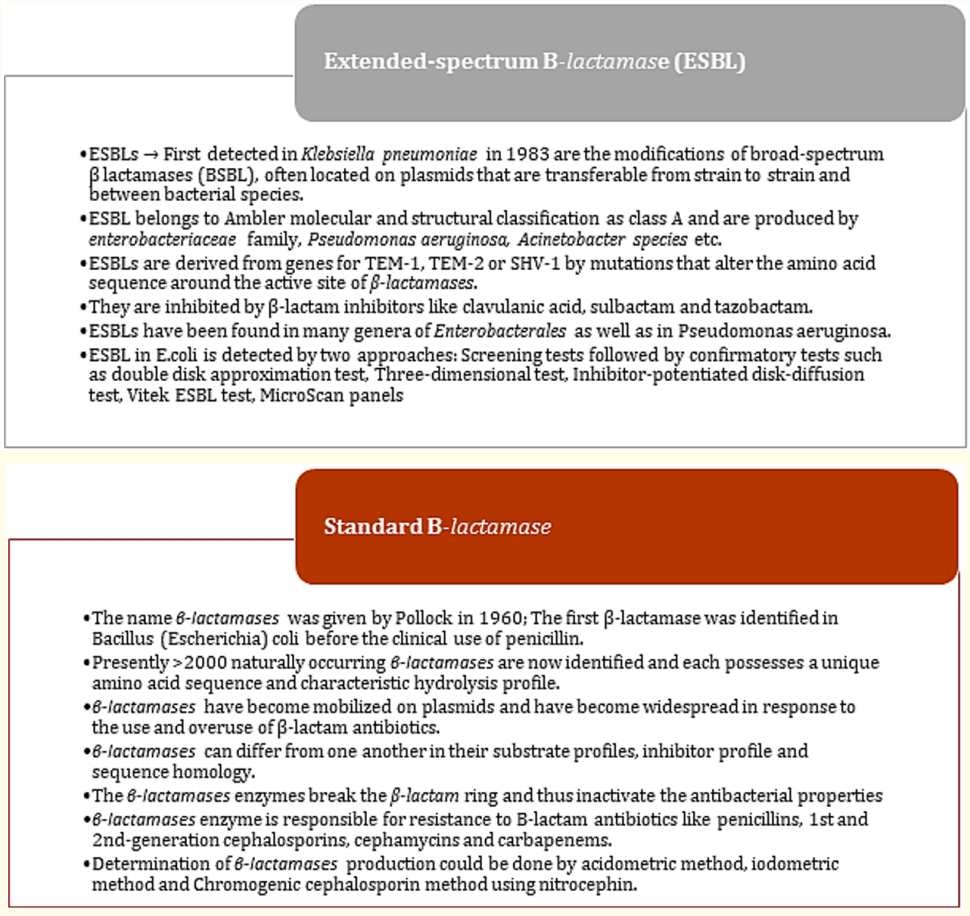


***Figure 3:*** *Differences between extended-spectrum β-lactamases (ESBLs) and standard β-lactamases.*

ESBL-producing organisms present new difficulties for hospital biochemists, physicians, infectious disease specialists, and antimicrobial agent researchers [29] because they do not hydrolyze cephamycin. However, β-*lactamase* inhibitors such as clavulanate are effective against these bacteria [31]. Over time, these bacteria have spread worldwide and are commonly isolated from patients with hospital-associated and community-acquired diseases [28].

Resistance induced by ESBL to extended-spectrum cephalosporins is increasing. ESBLs have been discovered in *E. coli* and *Klebsiella* spp., as well as other members of the *Enterobacteriaceae* family, such as *Providencia* spp., *Proteus* spp., *Serratia* spp., *Morganella* spp., *Salmonella* spp., *Citrobacter* spp., and *Enterobacter* spp. [32].

More than 300 varieties of ESBL have been identified in the *Enterobacteriaceae* family and other non-enteric species; the genotypes TEM, SHV, and CTX-M are the most frequent [32]. The TEM and SHV enzymes result from mutations in ubiquitous plasmid-encoded penicillinases in *E. coli and Klebsiella*. In contrast, CTX-M enzymes are due to plasmid acquisition of β-lactamase genes ordinarily located on the chromosome in *Kluyvera* spp. [33].

ESBL resistance is caused by the efflux pump, decreased penetrability, modified transpeptidases, and β-lactamase inhibition. Horizontal gene transfer (HGT) is the most common method associated with the transmission of antimicrobial resistance among harmful microbial pathogens, such as carbapenemase-producing *Enterobacteriacea*e [34].

ESBL-producing bacteria are frequently identified in hospitalized patients admitted to critical or intensive care units (ICUs). However, they can also cause infections in other hospital sections, long-term care institutions, and care facilities [30,35]. Risk factors for ESBL-producing bacteria infections are detailed in Figure 4 [36]. In India, ESBL-E colonization rates in high-risk ICU patients may range from 2.3% to 49% [37].

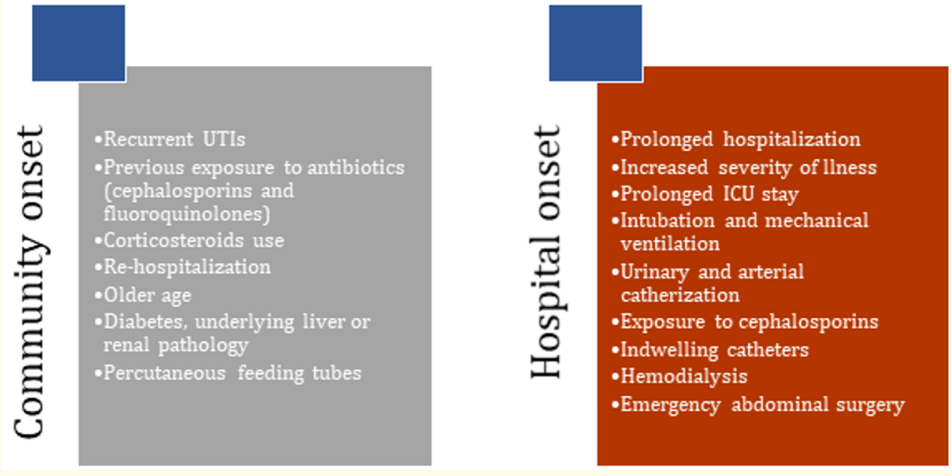


***Figure 4:*** *Risk factors for ESBL-producing infections [36].*

According to recent research based on the global surveillance data set of the Tigecycline Evaluation and Surveillance Trial (TEST), the rate of ESBL production in *K. pneumoniae* isolates was highest in South America (44%), followed by the Asia-Pacific region (22.4%), the

European Union (13.3%) and North America (7.5%). However, ESBL production in *E. coli* isolates was somewhat low when ranked in the same order across geographical locations (13.6%, 12.1%, 7.5%, and 2.2%, respectively) [38].

ESBL-E causes several nosocomial and community-acquired infections. Figure 5 lists some of the human infections that may be caused by ESBL-E [10,11,33].

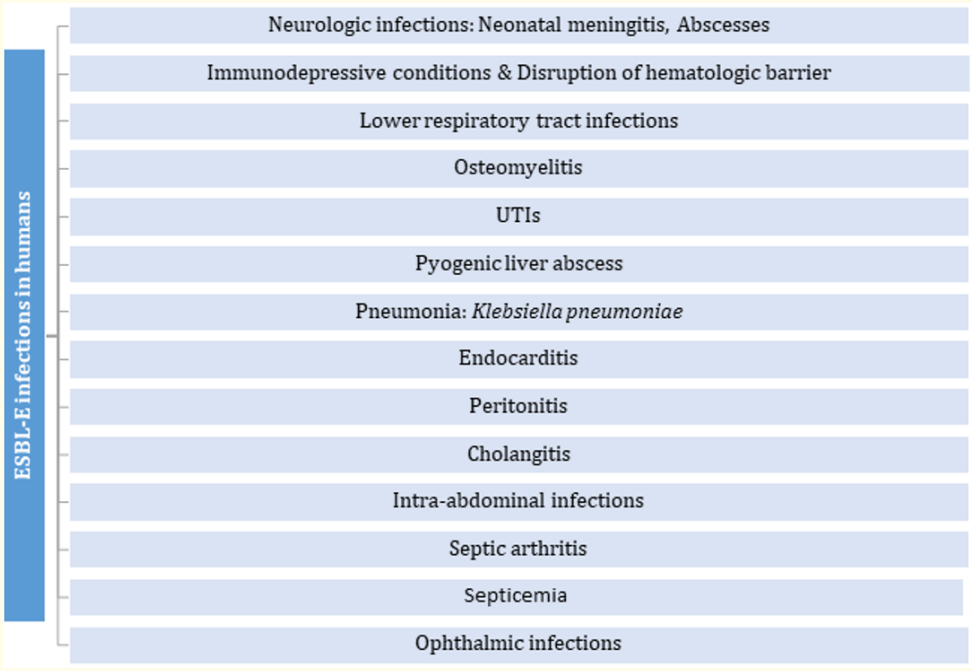


***Figure 5:*** *Nosocomial and community-acquired infections caused by ESBL-E.*

## Treatments for ESBL-E infection

### Classic β-lactam/β-lactamase inhibitor

Beta-lactam inhibitors suppress ESBLs, and classic β-lactam/β-lactamase inhibitors (BLBLIs) such as piperacillin-tazobactam, amoxiclav, ticarcillin-sulbactam, ampicillin-sulbactam, and cefoperazone-sulbactam are effective against ESBL producers in the absence of additional resistant strains [39].

Seo., *et al*. (2017) conducted an open-label randomized controlled study in 3 hospitals to compare the therapeutic efficacies of piperacillin with tazobactam versus ertapenem in patients with UTI due to ESBL-E. Patients with urinary tract blockage or prostatitis were excluded from the study. The patients received piperacillin (n = 33), tazobactam, or ertapenem (n = 33).

In the treatment arms, 27% and 21% had bacteremia, and 24% and 33% experienced septic shock.

The clinical efficacy, microbiological efficacy, and fatality rates with piperacillin-tazobactam were 94%, 97%, and 6%, respectively, while the values with ertapenem were 97%, 97%, and 6%, respectively [40].

### Fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole

In CTX-M-producing *Enterobacteriacea*e, fluoroquinolone tolerance has reached epidemic proportions, with a prevalence of susceptibility varying from 55% to 100% in different areas of the world. Therefore, fluoroquinolones play a minor role in treating infections caused by ESBL-E [30].

Tumbarello., *et al*. (2007) discovered that 8 of the 16 patients with bloodstream infection (BSI) caused by ESBL-E and treated with ciprofloxacin died. Minimum inhibitory concentrations (MIC) of ciprofloxacin in these patients ranged from 0.5 to 1 mg/L [41]. In a small-cohort study, Endimiani., *et al*. (2004) reported that ciprofloxacin had poorer outcomes than imipenem in patients with BSIs caused by TEM-52-producing *K. pneumoniae*. They found that ciprofloxacin MICs were typically > 0.25 mg/L [42].

Most factors associated with fluoroquinolones and ESBL are similar to aminoglycosides [29]. The recent appearance of CTX-M-15-producing *E. coli* in the community has worsened resistance to aminoglycosides. Of the many aminoglycosides used in clinical practice, amikacin susceptibility is highest among ESBL producers [30].

Trimethoprim-sulfamethoxazole can be effective against a limited percentage of ESBL-E isolates. Unfortunately, clinical trials explicitly testing the efficacy of this drug are absent. However, the findings may be similar to those of non-ESBL producers, demonstrating its potential as a viable alternative for complicated urinary tract infections (cUTIs) [39].

### Cephamycins

Cephamycins—such as cefotetan, cefmetazole, moxalactam, and cefoxitin—are effective against ESBL producers in the absence of other resistant strains because ESBLs cannot hydrolyze these drugs. However, clinical data on the use of cephamycins for treating severe infections caused by ESBL producers are lacking. Resistance to cephamycin may be attributed to the generation of porin-deficient mutants [29,39].

### Oxyiminocephalosporins (Cefotaxime, Ceftriaxone, Ceftazidime, and Cefepime)

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI), certain ESBL-E are sensitive to cephalosporins. Cefotaxime is more effective against TEM and SHV ESBL producers than CTX-M producers, whereas the inverse is true for cefepime and ceftazidime. These findings can be attributed to the variable capacity of ESBL subtypes to solubilize different cephalosporins. The fraction of AmpC producers susceptible to cephalosporins (excluding cefepime) is less [39].

*Enterobacteriaceae* with a MIC for cephalosporin < 8 mg/L were previously considered susceptible. Patients with BSIs caused by ESBL-E managed with cephalosporins had poorer outcomes than predicted, although the isolates had MICs within the susceptibility spectrum, indicating the development of resistance [43].

### Fosfomycin

Developed in the 1960s, fosfomycin is still effective against several strains of ESBL- and AmpC-producing *E. coli* and *K. pneumoniae*, as well as certain multidrug-resistant (MDR) *Enterobacteriacea*e. Oral fosfomycin trometamol is available in certain countries and is success-

fully used to treat uncomplicated UTIs. The drug is also highly effective in treating cystitis caused by ESBL-producing bacteria [39]. In an observational study, fosfomycin trometamol was compared with ertapenem as a step-down regimen in patients with invasive infections caused by ESBL-E. The results demonstrated that the readmission rates were comparable (14.6% and 13.5%, respectively) [44].

### Carbapenems (Imipenem, Meropenem, and Doripenem)

Carbapenems have historically been considered a treatment option for infections caused by ESBL-E because they are unaffected by resistant strains. In addition, they have reduced failure rates compared to other drugs, particularly fluoroquinolones and cephalosporins [39]. A meta-analysis included 21 controlled studies involving patients with bacteremia caused by ESBL-E. Treatment with carbapenems was associated with lower mortality rates than treatment with cephalosporins, fluoroquinolones, or aminoglycosides. Furthermore, the differences were insignificant for the BLBLI combination [45].

Similarly, an international investigation of individuals with *K. pneumoniae* bacteremia found that carbapenem alone had an all-cause 14-day mortality rate of 3.7% (1 of 27) compared to 36.3% and 44.4% for monotherapy with quinolone and non-carbapenem, respectively. Fourteen-day mortality rates for patients with ESBL-producing *K. pneumoniae* were 4.8% (2 of 42) in those who received carbapenem monotherapy or combination therapy and 27.6% (8 of 29) in those who received noncarbapenem antibiotics [46].

### Tamoxicillin

Tamoxicillin is effective against *Enterobacteriaceae* and is resistant to enzyme hydrolysis by ESBL and AMPC β-lactamases; however, it demonstrates weak activity against *Pseudomonas* spp. Documented experience with tamoxicillin for these diseases is lacking, although it is currently the only intravenous drug available in a few countries [39]. Balakrishna., *et al*. (2011) examined temocillin for *Enterobacteriaceae* infection in 92 patients; of the isolates, 53 were ESBL or derepressed AMPC producers. The study showed that the clinical cure rate was 86%, and the microbiological cure rate was 84% [47].

### Newer BLBLIs (Ceftolozane-Tazobactam, Ceftazidime-Avibactam, and Cefoperazone-Sulbactam)

Ceftolozane-tazobactam combines a novel cephalosporin (ceftolozane) with improved antipseudomonal efficacy and tazobactam, a traditional β-lactamase inhibitor. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have authorized this drug to treat complicated intra-abdominal infections (cIAIs); in conjunction with metronidazole) and cUTI, especially pyelonephritis. *In vitro*, this chemical was shown to be active against > 90% of ESBL-producing *E. coli* and 42% - 98% of ESBL-producing *E. coli*, *K. pneumoniae,* and isolates of *Pneumococcus pneumoniae* [48].

Popejoy., *et al*. (2017) analyzed the results of 150 patients with ESBL-E infection in breakthrough trials of ceftolozane-tazobactam against cUTI (against levofloxacin) and cIAI (against meropenem). The clinical cure and microbiological eradication rates with ceftolozane-tazobactam were greater (82.6%) than those with levofloxacin (47.8%) against cUTIs; 82% of strains were sensitive to ceftolozane-tazobactam, whereas only 25% were sensitive to levofloxacin. However, the efficacy of ceftolozane-tazobactam and meropenem against cIAI was comparable (clinical cure rates were 95.8% and 88.5%; similar rates were found for microbiological eradication) [49].

Ceftazidime-avibactam combines third-generation cephalosporin and a novel β-lactamase inhibitor (non-β-lactam). The EMA and the FDA have recently approved this combination to treat cUTI and cIAI (with metronidazole). The EMA has also included indications for hospital-acquired pneumonia (HAP) and other gram-negative bacterial infections with limited treatment approaches. Avibactam is a new non-BLBLI that inhibits Class A Ambler (GEM, SHV, CTX-M, and KPC), Class C (AmpC), and specific Class D (OXA-48) β-lactamases, but not MBLs [48,50].

Ceftazidime action against different *Enterobacteriaceae* and *P. aeruginosa* is restored when avibactam is added, extending the activity range of ceftazidime to gram-negative bacteria of MDR [50]. Ceftazidime-avibactam and doripenem were evaluated in a vital study against cUTI. The clinical cure rate was 89.3% with ceftazidime-avibactam and 89.3% with doripenem in patients with ceftazidime-resistant isolates (mainly because of ESBL generation) [51].

According to recent data from the SENTRY antibacterial monitoring program, cefoperazone-sulbactam is active against 91.6% of Enterobacterales *in vitro*, making it one of the most active drugs. The susceptibility rate in Western Europe is 94.4%, while the same in Eastern Europe is 82.0% [52].

Su., *et al*. (2018) compared cefoperazone-sulbactam with tigecycline for BSIs caused by carbapenem-resistant *Acinetobacter baumannii*. The researchers illustrated that tigecycline was associated with a substantially higher 28-day mortality rate [53].

Other antibiotics with potent *in vitro* efficacy against UTIs include pivmecillinam, trimethoprim, and nitrofurantoin. However, clinical evidence on using these medications against diseases caused by ESBL-E is lacking [29].

### Considerations for further research and potential antibiotics in development

Re-evaluating older antimicrobial drugs with minimal clinical use for possible antibacterial activity and clinical usefulness against today's resistant microbes may provide an interim solution to the growing concern about bacterial antibiotic resistance. Additionally, combining existing cephalosporins with β-lactamase antagonists can improve the efficacy of these drugs against ESBL-E [54].

Combining an authorized carbapenem and a new β-lactamase inhibitor, such as imipenem/cilastatin and relebactam, can be a potential therapeutic option for ESBL-E infections. Relebactam, similar to avibactam, has a diazabicyclooctane core that attaches Class A and C β-lactamases covalently and reversibly *in vitro*, with an inhibiting mechanism comparable to avibactam [50].

Cefepime-zidebactam, a combination of second-generation BLI zidebactam and broad-spectrum cephalosporin cefepime, could be a future antibiotic for ESBL-E infections. Zidebactam is more effective against Class C β-lactamases *in vitro* than avibactam or relebactam [55]. Nacubactam is another diazabicyclooctane BLI. It has shown *in vivo* efficacy against carbapenem-resistant *K. pneumoniae*, *E. coli*, and AmpC-depressed *P. aeruginosa* when combined with meropenem [56].

Cefepime-enmetazobactam is a possible therapy for Enterobacterales expressing ESBL. Enmetazobactam has been proven to be more beneficial than tazobactam in restoring the effectiveness of cefepime and piperacillin toward specific ESBL-producing bacteria. *In vitro*, cefepime/enmetazobactam was as effective against the same ESBL-producing bacteria as meropenem and imipenem [57].

## Conclusion

Pathogens from the *Enterobacteriaceae* family are significant sources of infections. Many family members are becoming increasingly resistant to the antibiotics currently available. ESBLs are examples of the increasing number and variety of compounds that inactivate the β-lactam type of antibacterials. Drug resistance and the ability of these microbes to adapt to their environment are demonstrated by the coupling of these enzymes with other resistance features. A multifaceted approach is recommended to effectively treat infections caused by these bacteria, including continued research and innovation of novel antibacterial classes, more prudent use of established agents, and greater dependence on impactful preventive measures.

## Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

## References

1. Vazquez C. The *Enterobacteriaceae*: general characteristics (2022). https://uomustansiriyah.edu.iq/media/lectures/4/4_2021_09_21!10_11_23_PM.pdf

2. Janda JM and Abbott SL. "The changing face of the family *Enterobacteriaceae* (order: "Enterobacterales"): New members, taxonomic issues, geographic expansion, and new diseases and disease syndromes". *Clinical Microbiology Reviews* 34.2 (2021). https://pubmed.ncbi.nlm.nih.gov/33627443/

3. Rahn O. "New Principles for the Classification of Bacteria". Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene. Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene Abteilung II 96 (1937): 273-286. https://scirp.org/reference/ReferencesPapers.aspx?ReferenceID=1710753

4. Donnenberg MS. "*Enterobacteriaceae*". In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier (2015): 2503-2517.e5. https://en.wikipedia.org/wiki/*Enterobacteriaceae*

5. Octavia S and Lan R. "The Family *Enterobacteriaceae*". In: The Prokaryotes. Springer Berlin Heidelberg (2014): 225-286. https://link.springer.com/referenceworkentry/10.1007/978-3-642-38922-1_167

6. Enteric gram-negative rods (*Enterobacteriaceae*) (2022). https://link.springer.com/10.1007/978-3-642-38922-1_167

7. Rock C and Donnenberg MS. "Human Pathogenic *Enterobacteriaceae*". In: Reference Module in Biomedical Sciences. Elsevier (2014): 1-8. https://www.researchgate.net/publication/290907123_Human_Pathogenic_*Enterobacteriaceae*

8. Micro: Gram neg rods. Heart pathology (2022). https://www.iheartpathology.net/micro-gramnegrods

9. Groman RP. "Gram-Negative Infections". In: Small Animal Critical Care Medicine. Elsevier (2009): 469-473.

10. Ramirez D and Giron M. "Enterobacter Infections". In: Stat Pearls. Stat Pearls Publishing (2021). https://pubmed.ncbi.nlm.nih.gov/32644722/

11. Paterson DL. "Resistance in gram-negative bacteria: *Enterobacteriaceae*". *The American Journal of Medicine* 119.6-1 (2006): S20-28. https://www.sciencedirect.com/science/article/abs/pii/S0196655306008534

12. Gupta K., *et al*. "Effects of contraceptive method on the vaginal microbial flora: a prospective evaluation". *The Journal of Infectious Diseases* 181.2 (2000): 595-601. https://www.sciencedirect.com/science/article/abs/pii/S0196655306008534

13. Raz R and Stamm WE. "A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections". *The New England Journal of Medicine* 329.11 (1993): 753-756. https://pubmed.ncbi.nlm.nih.gov/8350884/

14. Liu TH., *et al*. "Rectovaginal colonization with pathogenic Escherichia coli during pregnancy and neonatal outcomes". *Infection and Drug Resistance* 12 (2019): 3103-3112. https://pubmed.ncbi.nlm.nih.gov/31686871/

15. Sieber SA. Comprehensive Natural Products II || Small Molecules as Versatile Tools for Activity-Based Protein Profiling Experiments (2010): 629-674. https://www.researchgate.net/publication/287459075_Small_Molecules_as_Versatile_Tools_for_Activity-Based_Protein_Profiling_Experiments

16. Basak S and Rajurkar MN. "Newer β-lactamases and E. coli-a cause of concern". *Trends in Infectious Diseases* 3 (2014): 47-72. https://www.intechopen.com/chapters/46203

17. B-Lactams. MSD Manual Professional Edition (2022). https://www.msdmanuals.com/en-in/professional

18. Fahd K., *et al*. Molecular analysis of β-lactamase structure and function 292 (2002): 137. https://www.nature.com/articles/srep05270

19. Lukac PJ., *et al*. "Extended-spectrum β-lactamase-producing *Enterobacteriaceae* in children: old foe, emerging threat". *Clinical Infectious Diseases* 60.9 (2015): 1389-1397. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4415054/

20. Bush K and Jacoby GA. "Updated functional classification of β-lactamases". *Antimicrobial Agents and Chemotherapy* 54.3 (2010): 969-976. https://pubmed.ncbi.nlm.nih.gov/19995920/

21. Sartelli M., *et al*. "Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA)". *World Journal of Emergency Surgery* 11.1 (2016). https://wjes.biomedcentral.com/articles/10.1186/s13017-016-0089-y

22. Chaudhary U and Aggarwal R. "Extended-spectrum β-lactamases (ESBL)-An emerging threat to clinical therapeutics". *Indian Journal of Medical Microbiology* 22 (2004): 75-80. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1265908/

23. Brolund A. "Overview of ESBL-producing *Enterobacteriaceae* from a Nordic perspective". *Infection Ecology and Epidemiology* 4.1 (2014): 24555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4185132/

24. Rawat D and Nair D. "Extended-spectrum ß-lactamases in gram-negative bacteria". *Journal of Global Infectious Diseases* 2.3 (2010): 263-274. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2946684/

25. Extended-spectrum agent | pharmacology. In: Encyclopedia Britannica (2022). https://www.britannica.com/science/extended-spectrum-agent

26. Bonomo RA. "B-lactamases: A focus on current challenges". Cold Spring Harbor Perspectives in Medicine 7.1 (2017): a025239. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204326/

27. Saxena SK. "Trends in Infectious Diseases || Newer Î2-Lactamases and *E. coli* Â: A Cause of Concern". Chapter (2014).

28. Castanheira M., *et al*. "Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection". *JAC-Antimicrobial Resistance* 3.3 (2021): dlab092. https://pubmed.ncbi.nlm.nih.gov/34286272/

29. Rupp ME and Fey PD. "Extended-spectrum lactamase (ESBL)-producing *Enterobacteriaceae*: Considerations for diagnosis, prevention and drug treatment". *Drugs* 63.4 (2003): 353-365. https://pubmed.ncbi.nlm.nih.gov/12558458/

30. Pitout JDD. "Infections with extended-spectrum β-lactamase-producing *Enterobacteriaceae*: changing epidemiology and drug treatment choices: Changing epidemiology and drug treatment choices". *Drugs* 70.3 (2010): 313-333. https://pubmed.ncbi.nlm.nih.gov/20166768/

31. Retamar P., *et al*. "AMS in an era of multidrug-resistant bacteria". In: Antimicrobial Stewardship. Elsevier (2017): 219-231. https://www.sciencedirect.com/science/article/pii/B9780128104774000180

32. Parajuli NP., *et al*. "Emerging perils of extended-spectrum β-lactamase producing *Enterobacteriaceae* clinical isolates in a teaching hospital of Nepal". *BioMed Research International* (2016): 1782835. https://www.hindawi.com/journals/bmri/2016/1782835/

33. Jenkins C., *et al*. "*Enterobacteriaceae*". In: Infectious Diseases. Elsevier (2017): 1565-1578.e2. https://en.wikipedia.org/wiki/*Enterobacteriaceae*

34. Sawa T., *et al*. "Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance". *Journal of Intensive Care Medicine* 8.1 (2020): 13. https://jintensivecare.biomedcentral.com/articles/10.1186/s40560-020-0429-6

35. Pitout JDD., *et al*. "Emergence of *Enterobacteriaceae* producing extended-spectrum β-lactamases (ESBLs) in the community". *Journal of Antimicrobial Chemotherapy* 56.1 (2005): 52-59. https://pubmed.ncbi.nlm.nih.gov/15917288/

36. Singleton A and Cluck D. The pharmacist's role in treating extended-spectrum β-lactamase infections (2022). https://dc.etsu.edu/etsu-works/9987/

37. Pana ZD and Zaoutis T. "Treatment of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBLs) infections: what have we learned until now?" *F1000Research* 7 (2018): 1347. https://pubmed.ncbi.nlm.nih.gov/30228863/

38. Reinert RR., *et al*. "Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe, and Latin and North America collected as part of TEST and the in vitro activity of tigecycline". *Journal of Antimicrobial Chemotherapy* 60.5 (2007): 1018-1029. https://pubmed.ncbi.nlm.nih.gov/17855724/

39. Rodríguez-Baño J., *et al*. "Treatment of infections caused by extended-spectrum-β-lactamase-, AmpC-, and carbapenemase-producing *Enterobacteriaceae*". *Clinical Microbiology Reviews* 31.2 (2018). https://pubmed.ncbi.nlm.nih.gov/29444952/

40. Seo YB., *et al*. "Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum β-lactamase-producing Escherichia coli". *BMC Infectious Diseases* 17.1 (2017). https://pubmed.ncbi.nlm.nih.gov/28592240/

41. Tumbarello M., *et al*. "Predictors of mortality in patients with Bloodstream infections caused by extended-spectrum-β-lactamase-producing *Enterobacteriaceae*: Importance of inadequate initial antimicrobial treatment". *Antimicrobial Agents and Chemotherapy* 51.6 (2007): 1987-1994. https://pubmed.ncbi.nlm.nih.gov/17387156/

42. Endimiani A., *et al*. "Bacteremia due to Klebsiella pneumonia isolates producing the TEM-52 extended-spectrum β-lactamase: Treatment outcome of patients receiving imipenem or ciprofloxacin". *Clinical Infectious Diseases* 38.2 (2004): 243-251. https://pubmed.ncbi.nlm.nih.gov/14699457/

43. Paterson DL., *et al*. "Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: Implications for the clinical microbiology laboratory". *Journal of Clinical Microbiology* 39.6 (2001): 2206-2212. https://pubmed.ncbi.nlm.nih.gov/11376058/

44. Veve MP., *et al*. "Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum β-lactamase urinary tract infections". *International Journal of Antimicrobial Agents* 48.1 (2016): 56-60. https://pubmed.ncbi.nlm.nih.gov/27234673/

45. Vardakas KZ., *et al*. "Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to *Enterobacteriaceae* producing extended-spectrum -lactamases: a systematic review and meta-analysis". *Journal of Antimicrobial Chemotherapy* 67.12 (2012): 2793-2803. https://www.valueinhealthjournal.com/article/S1098-3015(16)31718-1/fulltext

46. Paterson DL., *et al*. "Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended-spectrum β-lactamases". *Clinical Infectious Diseases* 39 (2004): 31-37. https://pubmed.ncbi.nlm.nih.gov/15206050/

47. Balakrishnan I., *et al*. "Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum or derepressed AmpC β-lactamase-producing *Enterobacteriaceae*". *Journal of Antimicrobial Chemotherapy* 66.11 (2011): 2628-2631. https://academic.oup.com/jac/article/66/11/2628/746201

48. Van Duin D and Bonomo RA. "Ceftazidime/avibactam and ceftolozane/tazobactam: Second-generation β-lactam/β-lactamase inhibitor combinations". *Clinical Infectious Diseases* 63.2 (2016): 234-241. https://pubmed.ncbi.nlm.nih.gov/27098166/

49. Popejoy MW., *et al*. "Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae: a pooled analysis of Phase 3 clinical trials". *Journal of Antimicrobial Chemotherapy* 72.1 (2017): 268-272. https://academic.oup.com/jac/article/72/1/268/2643153

50. Sheu CC., *et al*. "Infections caused by carbapenem-resistant *Enterobacteriaceae*: An update on therapeutic options". *Frontiers in Microbiology* 10 (2019): 80. https://pubmed.ncbi.nlm.nih.gov/30761114/

51. Wagenlehner FM., *et al*. "Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program". *Clinical Infectious Diseases* 63.6 (2016): 754-762. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4996135/

52. Niu T., *et al*. "Comparison of Tigecycline or Cefoperazone/Sulbactam therapy for bloodstream infection due to Carbapenem-resistant Acinetobacter baumannii". *Antimicrobial Resistance and Infection Control* 8.1 (2019): 52. https://aricjournal.biomedcentral.com/articles/10.1186/s13756-019-0502-x

53. Su J., *et al*. "Comparison of empirical therapy with cefoperazone/sulbactam or a carbapenem for bloodstream infections due to ESBL-producing *Enterobacteriaceae*". *Journal of Antimicrobial Chemotherapy* 73.11 (2018): 3176-3180. https://www.sciencedirect.com/science/article/pii/S1198743X19301557

54. Falagas ME and Karageorgopoulos DE. "Extended-spectrum β-lactamase-producing organisms". *Journal of Hospital Infection* 73.4 (2009): 345-354. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3768795/

55. Papp-Wallace KM., *et al*. "Strategic approaches to overcome resistance against Gram-negative pathogens using β-lactamase inhibitors and β-lactam enhancers: Activity of three novel diazabicyclooctanes WCK 5153, zidebactam (WCK 5107), and WCK 4234". *Journal of Medicinal Chemistry* 61.9 (2018): 4067-4086. https://pubmed.ncbi.nlm.nih.gov/29627985/

56. Barnes MD., *et al*. "Nacubactam enhances meropenem activity against carbapenem-resistant Klebsiella pneumoniae producing KPC". *Antimicrobial Agents and Chemotherapy* 63.8 (2019). https://pubmed.ncbi.nlm.nih.gov/31182530/

57. Papp-Wallace KM., *et al*. "Beyond piperacillin-tazobactam: Cefepime and AAI101 as a potent β-lactam-β-lactamase inhibitor combination". *Antimicrobial Agents and Chemotherapy* 63.5 (2019). https://pubmed.ncbi.nlm.nih.gov/30858223/

**Volume 11 Issue 12 December 2022**