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Narrative Review of β-lactam Resistance in Key Bacterial Pathogens: Efficacy and Innovations in Combination Therapies

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ABSTRACT

Background: β-Lactam antibiotics (BLIs) are essential for treating bacterial infections, but resistance is increasing due to β-lactamases, altered penicillin-binding proteins (PBPs), and reduced permeability in pathogens, such as *Escherichia coli*, *Klebsiella pneumonia Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii*, *Neisseria gonorrhoeae*, and vancomycin-resistant *Enterococcus faecium* (VRE). BLIs aim to restore the effectiveness of these antibiotics, but non-enzymatic resistance remains a challenge.

Materials and Methods: This narrative review searched databases including PubMed, Scopus, Web of Science, and Google Scholar for articles published between 2020 and 2025. Key search terms included "beta-lactam resistance" and "clustered regularly interspaced short palindromic repeats (CRISPR)-mediated antimicrobial resistance." Out of approximately 1,200 articles, 88 peer-reviewed studies were selected, focusing on resistance mechanisms, prevalence, and innovative therapies for selected pathogens.

Results: *E. coli* and *K. pneumoniae* exhibit high prevalence rates of extended-spectrum β-lactamases, (ESBL) with cefotaximasemunich (CTX-M) found in 72.5% of cases and carbapenemase bla_{KPC-2} in 66% of *K. pneumoniae*. Methicillin-resistant *S. aureus* (MRSA) relies on the *mecA* gene (30% prevalence in burn infections), while *A. baumannii* shows a prevalence of bla_{OXA-23} at 68.9%, and *N. gonorrhoeae* has blaTEM-1 in 86.88% of cases. The combination of ceftazidime and avibactam reduces mortality in carbapenem-resistant *K. pneumoniae* (CRKP) infections by 52%, with additional synergy observed when combined with aztreonam (89% effectiveness). Phage therapy and CRISPR/Cas9 have shown effectiveness in targeting multidrug-resistant (MDR) strains and restoring susceptibility.

Conclusion: Managing β-lactam resistance effectively requires a deep understanding of pathogen-specific mechanisms. While β-lactamase inhibitors (BLIs), such as ceftazidime/avibactam, are useful,

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their effectiveness is limited by efflux pumps and modifications to penicillin-binding proteins (PBPs). Bacteriophage therapy has proven highly effective in significantly reducing MDR *A. baumannii* in vivo, and CRISPR/Cas9 can precisely target resistance genes such as bla_{KPC} to restore antibiotic sensitivity. Additionally, nanocarrier systems improve drug delivery by overcoming challenges like efflux and biofilm formation. This review synthesizes advancements made since 2020, highlighting innovative strategies involving phage therapy, CRISPR, and nanocarriers, while addressing critical research gaps in understudied pathogens, paving the way for precision antimicrobial therapies.

Introduction

β-lactam antimicrobials, encompassing penicillins, cephalosporins, and carbapenems, constitute a foundational pillar in managing bacterial infections [1, 2]. These agents represent one of the most heterogeneous and extensively utilized categories of antibacterial therapeutics. β-lactam antibiotics, introduced with the clinical use of penicillin in the early 1940s, revolutionized the treatment of bacterial infections and dramatically reduced mortality from common diseases, such as pneumoniae, sepsis, and wound infections. Over the next three decades, the development of semi-synthetic penicillins and cephalosporins further expanded their spectrum and established β-lactams as the cornerstone of antibacterial therapy worldwide [2]. Despite their pivotal role, the pervasive application and occasional inappropriate deployment of β-lactam compounds in clinical practice and veterinary settings have precipitated a marked escalation in resistance among nosocomial and community-acquired bacterial isolates [2]. Such resistance threatens global health security by constraining therapeutic alternatives for infectious diseases [3]. The predominant resistance modalities against β-lactams comprise β-lactamase elaboration, modifications in penicillin-binding proteins (PBPs), and diminished outer membrane permeability [4]. These adaptive strategies are ubiquitous across salient pathogens, including *Escherichia coli*, *Klebsiella pneumoniae Pseudomonas aeruginosa*, Methicillin-resistant *Staphylococcus aureus* (MRSA), and *Acinetobacter baumannii* [5, 6].

The presence of distinct β-lactamase-encoding genes, such as bla_{OXA} and bla_{TEM} in *K. pneumoniae*, has been demonstrated to impart elevated resistance to a spectrum of antibiotics [7]. The World Health Organization (WHO) anticipates that antimicrobial resistance will result in 10 million fatalities annually by 2050 [8]. Genomic investigations have identified several dominant β-lactamase determinants. In Iranian cohorts, bla_{TEM} emerged as the most frequent *AmpC*-type β-lactamase gene, detected in 48% of the samples [7]. In Argentina, the incidence of bla_{SHV} increased from 24% to 72% following the COVID-19 pandemic, concurrent with the advent of the $bla_{CTX\text{-}M\text{-}2}$ cluster, which was identified in 43% of isolates during the latter study phase [9].

A salient therapeutic paradigm entails the co-administration of β-lactam antibiotics with β-lactamase inhibitors (BLIs). These synergistic formulations aim to restore β-lactam potency by shielding the core molecule from hydrolytic inactivation [10]. Pharmacokinetically refined dosing protocols for β-lactam/BLI pairings can eradicate high-density populations of extended-spectrum β-lactamase (ESBL)-harboring strains, yielding a concentration-proportional decrement in β-lactam minimum inhibitory concentrations (MICs) [11]. Notwithstanding the utility of these regimens, microbial evolution can lead to resistance to β-lactam/BLI combinations through diverse mechanisms [10].

Most of the antecedent overviews on β-lactam resistance antedate 2020 and predominantly emphasize canonical resistance pathways and orthodox interventions, while underrepresenting nascent modalities for instance, bacteriophage therapeutics, clustered regularly interspaced short palindromic repeats (CRISPR)-mediated resistance abrogation, and nanomaterial-facilitated drug conveyance. This comprehensive review synthesizes contemporary insights into β-lactam resistance across principal bacterial taxa, evaluates the performance of entrenched and innovative combinatorial strategies, especially β-lactam/β-lactamase inhibitor adducts and adjuvant non-antibiotics, and delineates investigative lacunae in lesser-explored organisms, such as vancomycin-resistant *Enterococcus faecium* (VRE) and *Neisseria gonorrhoeae*.

Materials and Methods

This narrative review was conducted to synthesize current knowledge on beta-lactam resistance mechanisms in key bacterial pathogens and evaluate the efficacy of established and emerging combination therapies. A com-

prehensive literature search was performed using electronic databases including PubMed, Web of Science, and Google Scholar. The search spanned from 2020 to 2025 to prioritize recent advancements, while including foundational studies for historical context where necessary.

Key search terms and phrases included "beta-lactam resistance," "ESBL-producing bacteria," "carbapenem-resistant Enterobacterales," "MRSA resistance mechanisms," "*Acinetobacter baumannii* carbapenemases," "*Pseudomonas aeruginosa* efflux pumps," "*Neisseria gonorrhoeae* cephalosporin resistance," "*Enterococcus faecium* VRE," "beta-lactam/beta-lactamase inhibitor combinations," "phage therapy for multidrug-resistant (MDR) bacteria," "CRISPR-Cas9 antimicrobial resistance," and "nanomaterial-based antibiotic delivery." Boolean operators (AND, OR, NOT) were used to refine queries. Inclusion criteria encompassed peer-reviewed articles, systematic reviews, meta-analyses, clinical trials, epidemiological studies, and in vitro/in vivo experimental reports published in English that addressed resistance mechanisms, prevalence data, or therapeutic innovations in the selected pathogens.

Initial searches yielded approximately 1,200 articles. Titles and abstracts were screened manually for relevance, resulting in 350 full-text articles for detailed review. Of these, 88 were selected based on their contribution to the narrative, with a focus on high-impact studies. Data extraction emphasized resistance genes/enzymes, prevalence rates, mechanisms, and outcomes of combination therapies.

Results

Mechanisms of beta-lactam resistance in relevant bacteria

E. coli, K. pneumoniae, P. aeruginosa

E. coli, a gram-negative, facultative anaerobic rod-shaped bacterium [12], poses a significant healthcare challenge because of the emergence of antimicrobial-resistant strains, primarily driven by β-lactamase production [13]. ESBLs, plasmid-encoded enzymes that hydrolyze cephalosporins and monobactams [14], are clinically crucial, with cefotaximasemunich (CTX-M), sulfhydryl variable (SHV), and Temoniera (TEM) variants being the most prevalent [15]. TEM-type ESBLs evolved from TEM-1, with TEM-2 (carrying a Gln-39Lys substitution) serving as a progenitor of over 240 *TEM* variants [16]. CTX-M β-lactamases (Ambler class A, group 2be) confer resistance by hydrolyzing third-generation cephalosporins [17]. SHV-type ESBLs also diversify, with substitutions, such as E240K and E240R, potentially conferring latent resistance to BLI [18]. Epidemiological data show a rising trend: In 2021, 21% of uropathogenic *E. coli* isolates were ESBL producers, carrying CTX−M and TEM genes in 21% and 20% of cases, respectively [19]. This trend is expected to increase significantly by 2025, with CTX−M and TEM identified in 72.5% and 58% of clinical isolates, respectively, underscoring the dominance of CTX−M [20]. *K. pneumoniae* is a gram-negative encapsulated bacillus [21]. Carbapenem-resistant *K. pneumoniae* (CRKP) is driven by carbapenemase production: class A enzymes, such as KPC (encoded by bla_{KPC}), class B metallo-β-lactamases (MBLs), such as NDM (encoded by bla_{NDM}), and class D OXA-48-like variants (OXA_{-181}, $OXA_{-23}2$, OXA_{-163}) [22, 23]. A study conducted from 2016 to 2023 found that bla_{KPC-2} and sequence type 11 (ST11) were predominant in CRKP, with 66% of isolates exhibiting a hypervirulent phenotype, highlighting the convergence of resistance and pathogenicity [24]. The hypervirulent phenotype, most classically described in certain *K. pneumoniae* clones (e.g. CG23, K1/K2), is defined by the ability to cause severe, community-acquired, metastatic infections in healthy individuals due to enhanced capsule production and siderophore-mediated iron acquisition; alarmingly, many such strains have now acquired carbapenem-resistance and other β-lactamase genes, creating highly virulent MDR pathogens [25]. *P. aeruginosa*, classified as a critical priority pathogen [26], exhibits multidrug resistance primarily through conserved MDR efflux pumps [27]. These tripartite systems, consisting of a periplasmic membrane fusion protein (*MexA*), an RND transporter (*MexB*), and an outer membrane factor (*OprM*), span the bacterial envelope and extrude substrates [28]. Efflux pump expression is tightly regulated by repressors, such as *mexR* and *nalC*, and mutations in these regulators can enhance resistance [29]. Targeted efflux pump inhibitors are a promising strategy to restore antibiotic efficacy by blocking extrusion and enhancing intracellular drug accumulation [30]. Clinical evidence indicates that *mexB* overexpression significantly contributes to the MDR phenotype. In one Iranian study, 29.26% of MDR strains exhibited more than a three-fold increase in *mexB* expression, which correlated with elevated MICs of ciprofloxacin and reduced antibiotic efficacy [31].

S. aureus

S. aureus, a gram-positive bacterium, is a leading etiological agent of skin and soft tissue infections (SSTIs) [32]. The rise of community-acquired methicillin-resis-

Table 1. Comparison of β-lactam resistance mechanisms across selected pathogens

Pathogen	Resistance Mechanism	Genes/Enzymes	Prevalence (%)	Ref.
E. coli	ESBL production (hydrolysis of cephalosporins/ monobactams)	CTX-M, SHV, TEM (e.g. TEM-1, TEM-2, >240 variants)	72.5% (CTX-M), 58% (TEM) in 2025	[16, 20]
K. pneumoniae	Carbapenemase production, porin loss	bla_{KPC} (KPC), bla_{NDM} (NDM), bla_{OXA-48}-like (OXA$_{-181}$, OXA-232, OXA$_{-163}$), *OmpK35/36* loss	66% bla_{KPC-2}, hypervirulent ST11	[24]
P. aeruginosa	MDR efflux pumps (*MexAB-OprM*), *AmpC* β-lactamases	*mexB, MexA, OprM* (regulated by *mexR, nalC*)	29.26% *mexB* overexpression in MDR strains	[31]
S. aureus (MRSA)	PBP2a production, biofilm formation	*mecA* (on SCC*mec*), biofilm genes	30% (burn isolates), 24% (wound isolates)	[41]
A. baumannii	CHDLs, efflux pumps	bla_{OXA-23}, *blaOXA-24,* bla_{OXA-51}, *blaOXA-58,* ISAba1, ISAba3, bla_{KPC} (61.9%), bla_{IMP} (59.5%), bla_{VIM} (45.2%)	68.9% (bla_{OXA-23}), 83.3% (bla_{OXA-40}), 18.9% (ISAba-bla_{OXA-51}), 54.8% MDR	[52, 53]
N. gonorrhoeae	Penicillinase production, cephalosporin resistance via *penA* mutations	bla_{TEM-1} (86.88%), $bla_{TEM-135}$ (4.37%), *penA, porB1b*	86.88% (bla_{TEM-1}) in recent isolates	[44]
E. faecium (VRE)	Low-affinity PBPs, β-lactamase production, vancomycin resistance (D-Ala-D-Lactate)	PBP5, *vanA* (Tn1546), *vanB* (Tn1549/Tn5382), *vanC*	50.8% VRE, 53.2% *vanA/vanB*	[56]

Abbreviations: PBPs: Penicillin-binding proteins; ESBL: Extended-spectrum β-lactamases; MDR: Multidrug-resistant; SHV: Sulfhydryl variable; TEM: Temoniera; SCC: Staphylococcal cassette chromosome; AMPs: Antimicrobial peptides; CTX-M: Cefotaximasemunich.

tant *S. aureus* (CA-MRSA), which is genetically and epidemiologically distinct from its hospital-acquired counterpart (HA-MRSA), has intensified the reliance on anti-staphylococcal antibiotics, thereby amplifying resistance [33, 34]. β-Lactam antibiotics, constituting nearly two-thirds of antimicrobial prescriptions [35], target the robust peptidoglycan layer of gram-positive bacteria comprising repeating N-acetylglucosamine and N-acetylmuramic acid disaccharides by inhibiting PBPs [36]. However, resistance to methicillin in *S. aureus* is conferred by an alternative transpeptidase, PBP2a, encoded by the *mecA* gene harbored within mobile genetic elements known as staphylococcal cassette chromosome mec (SCC*mec*) [37]. While conventional PBPs (PBP1–PBP4) are vulnerable to β-lactams, which emulate the D-Ala-D-Ala substrate to obstruct transpeptidation [38], PBP2a exhibits a low affinity for these agents, thereby sustaining cell wall synthesis [39]. The SCC*mec* element integrates the *mec* gene complex (encompassing *mecA*) and the *ccr* gene complex (encoding recombinases *ccrA*, *ccrB*, and *ccrC*), which orchestrates excision and chromosomal integration [40]. Molecular epidemiology underscores the global dissemination of *mecA* in *S. aureus*. A 2022–2023 Iraqi study reported *mecA* prevalence in 30% of burn isolates and 24% of wound isolates, with all tested strains harboring the gene [41]. Additionally, a 2021–2022 survey in Shanxi Province identified 38 MRSA strains among 212 *S. aureus* isolates, exhibiting pronounced resistance to penicillin (98.11%), erythromycin (64.62%), and clindamycin (59.91%). Biofilm-associated genes were active in 13.16% of these MRSA isolates, with the dominant clone, ST59-SCC*mec*IV-t437, being linked to robust resistance and biofilm formation, whereas ST59-SCC*mec*V-t437 was associated with elevated Panton-Valentine leukocidin positivity and heightened pathogenicity [42].

Emerging therapeutic strategies, including CRISPR-Cas systems, monoclonal antibodies (mAbs), and bacteriophage-based interventions, offer promising avenues for counteracting resistant *S. aureus* [43]. These innovations target resistance determinants or virulence factors, potentially circumventing conventional resistance mechanisms and restoring susceptibility to β-lactams. A comprehensive understanding of PBP2a functionality, SCC*mec* diversity, and clonal epidemiology is critical for devising precision therapeutics and mitigating the escalating burden of MRSA infections.

N. gonorrhoeae

N. gonorrhoeae, a gram-negative diplococcus, poses a significant global health challenge owing to its escalating resistance to β-lactam antibiotics, including penicillins and cephalosporins. According to Qin et al. dynamic shifts in plasmid profiles have been observed, with the prevalence of $bla_{TEM-135}$ (linked to cephalosporin resistance) decreased from 52.63% to 4.37%, while bla_{TEM-1} surged from 47.37% to 86.88%, and novel bla_{TEM} variants also emerged [44].

Beyond plasmid-mediated resistance, the cephalosporin resistance, notably that of ceftriaxone, is frequently driven by mutations in the *penA* gene, which encodes PBP2. Palace et al. highlight that although *penA* muta-

tions altering the target site are the primary mechanism of ceftriaxone resistance, certain resistant isolates lack these alterations. Notably, mutations in RNA polymerase across multiple lineages have been identified as contributors to ceftriaxone resistance, emphasizing the importance of surveillance for non-penA-mediated mechanisms, especially as extended-spectrum cephalosporins remain critical therapeutic options [45]. These findings highlight the need for ongoing genomic surveillance and exploration of novel therapeutic strategies to address the evolving resistance landscape of this pathogen.

A. baumannii

A. baumannii, a gram-negative opportunistic pathogen, has emerged as a formidable MDR challenge, driven by widespread antibiotic overuse [46]. Carbapenem-resistant *A. baumannii* is a leading cause of nosocomial infections, rendering β-lactam antibiotics, key inhibitors of bacterial cell wall synthesis, largely ineffective owing to multifaceted resistance mechanisms [47]. The cornerstone of carbapenem resistance lies in the production of carbapenem-hydrolyzing class D β-lactamases (CHDLs), notably OXA-type enzymes [48]. The predominant OXA genes include bla_{OXA-23} (the most globally prevalent), bla_{OXA-24}, bla_{OXA-51}, and bla_{OXA-58}, which are frequently plasmid-encoded, facilitating their dissemination via horizontal gene transfer (HGT) [49].

In addition to β-lactamase production, *A. baumannii* employs tripartite efflux pump systems comprising an inner membrane transporter, a periplasmic adaptor, and an outer membrane channel to expel antibiotics, thereby reducing intracellular drug concentrations. These pumps often synergize with β-lactamases to enhance resistance [50]. *A. baumannii* requires innovative therapeutic approaches, such as antimicrobial peptides (AMPs), which disrupt bacterial membranes and are increasingly being explored in combination with conventional antibiotics to restore efficacy [51]. Recent epidemiological data underscore the severity of this resistance. A 2024 study analyzing 150 clinical isolates reported that 29.4% were *A. baumannii*, with all isolates resistant to meropenem and 88.1% resistant to cefiderocol. Gentamicin exhibited the highest susceptibility (7.1%); however, 54.8% of the isolates were MDR. Among the 42 tested isolates, 39 harbored at least one carbapenemase gene, with bla_{KPC} (61.9%), bla_{IMP} (59.5%), and bla_{VIM} (45.2%) being prevalent [52]. A separate study from Poland, conducted in 2024, examined 90 clinical isolates and found that 52.2% were resistant to all tested antibiotic classes. Key carbapenem resistance determinants included bla_{OXA-23} (68.9%), bla_{OXA-40} (83.3%), and ISAba1-bla_{OXA-51} (18.9%), with 68.8% of isolates exhibiting biofilm production, further complicating treatment [53].

Enterococcus spp.

Enterococcus spp. particularly *E. faecium*, have emerged as hospital-acquired pathogens [54]. Resistance to β-lactams in *E. faecium* is driven by intrinsically low-affinity PBPs and β-lactamase production [55]. Epidemiological data highlight the increasing burden of VRE. The 2023 Australian Enterococcus Sepsis Outcome Programme reported 1,599 enterococcal bacteremia cases, with *E. faecium* accounting for 41.1% of these cases. VRE prevalence increased from 46.9% in 2022 to 50.8% in 2023, with 53.2% of isolates carrying *vanA* and/or *vanB* and a 30-day mortality rate of 26.3% [56]. In Guangzhou, China, the prevalence of VRE among *E. faecium* isolates rose from 13.3% in 2022 to 26.4% in 2023, driven by intensified antibiotic use and lapses in infection control [57]. Species-specific resistance profiles further revealed additional disparities. A 2020–2021 Egyptian study identified 52 Enterococcus isolates (57.7% E. faecalis and 42.3% *E. faecium*), with 38.4% classified as VRE. Common virulence genes included *asa1* (84.6%), *esp* (80.7%), and *gelE* (73%), with higher VRE prevalence in *E. faecalis* harboring *gelE* and *asa1* [58]. Conversely, a 2022–2023 study of 120 urinary tract infection isolates in Shanghai found that *E. faecium* exhibited near-universal resistance to ampicillin (100%) compared to *E. faecalis* (6.2%), with elevated resistance to fosfomycin (17.5% vs 3.8%) and nitrofurantoin (62.5% vs 2.5%). Notably, all isolates remained susceptible to vancomycin and teicoplanin [59].

Combinations of β-lactams with daptomycin demonstrate synergistic effects, re-sensitizing the resistant strains. Additional synergy is observed when daptomycin is combined with gentamicin or fosfomycin, enhancing bactericidal activity [60]. To elucidate the diversity and convergence of β-lactam resistance mechanisms across the studied pathogens, Table 1 summarizes the primary mechanisms, associated genes/enzymes, and prevalence data from recent studies (2020–2025). In summary, despite widespread β-lactam resistance in *Enterococcus* spp., synergistic combinations of β-lactams or daptomycin with aminoglycosides or fosfomycin restore bactericidal activity and represent a critical treatment option for VRE infections.

Efficacy of combination therapies

The combination of meropenem and vaborbactam effectively neutralizes class A carbapenemases, such as

KPC, thereby preserving the efficacy of meropenem by preventing enzymatic hydrolysis [61]. Ceftazidime/avibactam (CAZ/AVI) demonstrates superior outcomes, reducing 30-day mortality by 52% and achieving clinical cure rates of up to 82.4% in ICU patients with CRKP infections [62]. CAZ/AVI exhibits synergistic effects when combined with aztreonam, restoring susceptibility in 89% of MBL-producing bacterial isolates [63]. Additionally, combining CAZ/AVI with aminoglycosides amplifies their efficacy [62].

Torres et al. investigated β-lactamase-producing pathogens within a modified microbiological intent-to-treat group, excluding MBL. Ceftazidime–avibactam (CZA) achieved a clinical cure rate of 88.1% (334/379), matching the comparator group's rate (88.1%, 364/413), but showed a higher microbiological eradication rate (76.5%, 290/379 vs 68.8%, 284/413) [64]. In a rabbit model of *E. coli* OXA-48/ESBL osteomyelitis, CZA, whether used alone or with gentamicin, colistin, or fosfomycin, significantly decreased bone bacterial loads compared to colistin alone or the control [65]. Similarly, Mataraci Kara et al. found that CZA combined with colistin, gentamicin, and levofloxacin had synergistic effects against *P. aeruginosa*, with no antagonistic interactions, making CZA with colistin or gentamicin a viable option for colistin-resistant strains [66]. *P. aeruginosa* resistance is predominantly driven by overexpressed RND efflux pumps (e.g. *MexAB-OprM, MexXY*) due to regulatory mutations [28], with *MexXY* contributing to aminoglycoside resistance [67].

MRSA poses significant therapeutic challenges and forms robust biofilms [68]. The combination of daptomycin (DAP), a cyclic lipopeptide, with β-lactams (DAP+BLs) reduces treatment failure by 20%, persistent infections by 35%, and shortens the infection duration by 1.2 days [69]. This combination helps prevent the simultaneous development of daptomycin nonsusceptibility and resistance to host cationic AMPs [70]. Combining DAP or rifampin with β-lactams enhances antimicrobial activity against biofilm-producing *S. aureus*, which is crucial for managing biofilm-associated infections [71]. Additionally, bacteriophage therapy combined with daptomycin significantly boosts the antimicrobial efficacy within biofilms, offering a promising adjunctive approach [72].

A. baumannii, a gram-negative bacterium, shows significant resistance to last-resort antibiotics, such as carbapenems due to β-lactamases (e.g. OXA-23, OXA-40), efflux pumps, and modified membrane proteins [73]. Recent extensive clinical trials have indicated that colistin combination therapy does not outperform monotherapy in lowering 28-day mortality rates in severe infections caused by MDR pathogens, including *A. baumannii* [74]. Phage therapy holds considerable promise for treating MDR *A. baumannii* infections. A lytic bacteriophage successfully reduced the survival of an MDR clinical isolate in both ex vivo and in vivo models [75]. Grygorcewicz et al. identified bacteriophage vB_AbaP_AGC01, sourced from fish farm water, which infected approximately 50% of the *A. baumannii* isolates tested [76]. Wang et al. explored vB_AbaM_IME285 and its depolymerase Dp49, derived from hospital wastewater, and showed high survival rates and notable decreases in bacterial load in the lungs and spleen of BALB/c mice challenged intraperitoneally with *A. baumannii* [77]. Moreover, LysSS, a novel phage-derived endolysin, exhibits strong antimicrobial activity against MDR *A. baumannii* by degrading peptidoglycan, resulting in cell lysis [78].

ESBLs continue to be a key factor in β-lactam resistance, with a 2020 U.S. study indicating their prevalence in *E. coli* at 60% and 40% [79]. A 2024 global surveillance study found 34.7% ESBL positivity among clinical isolates, with CTX-M-15 being the most common (47.6%) [80].

Complementary strategies involve combining antibiotics with inhibitors, such as β-lactamase inhibitor-loaded nanocarriers, which improve therapeutic outcomes beyond those of monotherapy [81]. By exploiting their distinct physicochemical properties, nanomedicines effectively combat multiple resistance mechanisms, including decreased drug uptake, efflux pump activity, and biofilm formation, while enhancing antimicrobial effectiveness and reducing toxicity [82].

Phage therapy and CRISPR-based innovations

Lytic bacteriophage therapy, enhanced by genome-editing tools such as CRISPR/Cas9, presents a promising alternative to traditional antibiotics for combating AMR. Phages possess unique benefits, such as their high specificity to bacteria and their capability to infiltrate biofilms, which help overcome challenges such as limited host range and phage resistance [83, 84]. Advances in genetic engineering, particularly with the CRISPR/Cas9 system from Streptococcus thermophilus, combined with phage-encoded recombinases (as observed in the CRISPY-BRED and CRISPY-BRIP platforms), have notably increased the therapeutic potential of phages. These systems allow precise, marker-free editing of phage genomes across various bacterial hosts,

improving their adaptability and effectiveness [84, 85]. A crucial approach to counteract AMR involves using CRISPR/Cas9-mediated genome editing to directly target resistance determinants spread through HGT, such as resistance genes and plasmids [86]. Resistance genes, including *mecA*, *ermB* (erythromycin), *ramR* (tigecycline), *tetA* (tetracycline), *mqrB* (colistin), and bla_{KPC}, have been successfully targeted using the *S. pyogenes* CRISPR/Cas9 system, thereby restoring antibiotic susceptibility [87]. For example, engineering a prokaryotic CRISPR/Cas9 plasmid to cleave the bla_{KPC-2} gene achieved efficient plasmid clearance and significantly restored imipenem sensitivity in resistant strains [88].

Conclusion

Effective countermeasures against β-lactam resistance depend on elucidating pathogen-specific resistance mechanisms. While BLIs, such as CZA, exhibit robust efficacy against enzyme-producing pathogens, such as *K. pneumoniae*; however, their utility is constrained by non-enzymatic resistance mechanisms, including efflux pumps and target-site modifications. To address these challenges, a new wave of non-antibiotic interventions, led by bacteriophage therapy and CRISPR/Cas9 technology, has gained prominence.

Phage therapy, particularly effective against MDR pathogens, offers distinct advantages by significantly reducing bacterial burden and, in some cases, restoring susceptibility to legacy antibiotics, often through mechanisms such as capsular disruption. The future of combating AMR lies in the synergistic integration of advanced technologies. CRISPR/Cas9 systems, capable of precisely targeting resistance determinants such as bla_{KPC}, when combined with bacteriophages and nanocarrier-based delivery systems, hold transformative potential to overcome the limitations of conventional therapies, enhancing both specificity and efficacy in addressing complex resistance profiles.

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Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

The authors declared no conflict of interest.

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