REVIEW ARTICLE

Gram-Negative Bacterial Resistance

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SUMMARY

The rapid worldwide spread of antimicrobial resistance among gram-negative bacteria is driven by a complex interplay of human, environmental, and health care–associated factors and accelerated by mobile genetic elements that facilitate the dissemination of resistance genes. Resistance in gram-negative bacteria arises primarily through reduced drug entry, active drug efflux, modification of antibiotic targets, and enzymatic drug inactivation, most notably through β-lactamase production. Clinically important resistant pathogens include extended-spectrum β-lactamase–producing Enterobacterales, carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* with difficult-to-treat resistance, and carbapenem-resistant *Acinetobacter baumannii*. Limited access to effective antibiotics and the continued emergence of resistance to available agents pose substantial challenges to the management of these infections. Appropriate management requires timely and accurate diagnostics, targeted use of newer β-lactam agents, effective source control, and judicious selection of treatment durations.

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Antimicrobial resistance represents an increasingly urgent international health threat. In 2019, antimicrobial-resistant infections — driven largely by gram-negative bacterial species — were estimated to cause 1.27 million deaths worldwide,[1,2] and projections suggest that attributable mortality may increase more than 70% by 2050 — approaching current global cancer mortality.[1] The burden of gram-negative antimicrobial resistance is disproportionately concentrated within health care environments, with the greatest effect observed in intensive care units and skilled nursing facilities owing to prolonged patient stays, frequent antibiotic exposure, and an increased colonization burden, all of which facilitate transmission.[3,4] Without effective control, the continued spread of gram-negative antimicrobial resistance threatens to undermine modern medicine and increase risks associated with routine medical and surgical care.

After a prolonged decline in antibiotic development, several agents targeting gram-negative antimicrobial resistance have emerged over the past decade.[5] However, access remains limited — particularly in low- and middle-income countries, which contribute disproportionately to antimicrobial resistance–associated mortality, and in rural regions of high-income nations.[6] Even where newer antibiotic agents are available, resistance might have already developed, in part because many antibiotics — including recent additions — share overlapping bacterial targets; consequently, a single resistance mechanism can compromise multiple agents.[7,8]

This review summarizes the drivers of gram-negative antimicrobial resistance, major mechanisms of gram-negative resistance, and the current and emerging therapeutic landscape with a focus on extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* exhibiting difficult-to-treat resistance, and carbapenem-resistant *Acinetobacter baumannii*

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complex infections. Although antimicrobial resistance is an international challenge, given the substantial regional variability in dominant resistance mechanisms and therapeutic availability, a United States–focused perspective is provided to enable a more targeted review.

DEFINING GRAM-NEGATIVE ANTIMICROBIAL RESISTANCE

No consensus definition of gram-negative antimicrobial resistance exists, for several reasons. First, a mechanism-based definition is problematic because antimicrobial resistance determinants vary according to species — ESBLs, for instance, are relatively commonly produced by *Escherichia coli* but rarely by *P. aeruginosa*. Second, intrinsic activity of antibiotic compounds varies by species, which makes it challenging to apply resistance to a single agent as a standard marker (e.g., wild-type *E. coli* is predictably susceptible to ceftriaxone, whereas *P. aeruginosa* is not). This species-specific variability is further reflected in antibiotic-specific susceptibility criteria, because antibiotic breakpoints frequently differ across organisms (e.g., the meropenem breakpoint for *E. coli* is ≤1 μg per milliliter, whereas the breakpoint for *P. aeruginosa* is ≤2 μg per milliliter).[9] Finally, attempts to classify antimicrobial resistance as multidrug resistance also fall short.[10,11] Some organisms remain susceptible to narrower-spectrum agents despite being resistant to broader-spectrum ones. *P. aeruginosa* is a classic example, with roughly half of isolates that show resistance to meropenem remaining susceptible to cefepime or piperacillin–tazobactam.[12]

To better identify bacterial-resistance phenotypes that are associated with the most substantial therapeutic challenges, the concept of "difficult-to-treat resistance" has gained traction, particularly for *P. aeruginosa*, given its propensity for unpredictable resistance patterns. Difficult-to-treat resistance signifies gram-negative pathogens that are resistant to all traditional β-lactams (including carbapenems) and fluoroquinolones,[13] effectively restricting reliable treatment options to the newest available antibiotics.

DRIVERS OF DISSEMINATION

The rapid acceleration and widespread dissemination of gram-negative antimicrobial resistance stem from a combination of human, environmental, and microbiologic factors. Key drivers include the international movement of people, animals, and goods; overuse and misuse of antibiotics in human medicine, agriculture, and veterinary practice; and contamination of environmental reservoirs — such as sink drains, wastewater, and soil — with drug-resistant bacteria.[14-16] Lapses in infection-control practices, including inconsistent hand hygiene, inadequate cleaning and disinfection of shared equipment, and suboptimal isolation of patients who are colonized or infected with resistant bacteria, further facilitate transmission.[17]

Together, these human and environmental drivers establish conditions under which resistance can emerge and spread — a process further amplified by the remarkable capacity of gram-negative bacteria to exchange resistance determinants. Mobile genetic elements (e.g., plasmids) that can harbor multiple resistance genes can readily transfer between bacteria, enabling susceptible organisms to acquire multidrug resistance in a single step. Over time, some of these transferable genetic elements have adapted to bacterial host defenses — for example, by modifying DNA sequences normally recognized and cleaved by bacterial restriction enzymes.[18,19] Larger plasmids often encode antirestriction systems that expand their host range; over 60% colonize multiple species, facilitating the spread of antimicrobial resistance genes across gram-negative pathogens.[20]

MECHANISMS OF RESISTANCE

Mechanisms span from relatively simple to highly complex. One comparatively straightforward example in *E. coli* is the horizontal acquisition of the *mcr* gene, which confers resistance to the antibiotic colistin.[21] In contrast, resistance in *P. aeruginosa* is often multifactorial, involving combinations of overexpressed efflux pumps that extrude various antibiotics (e.g., MexAB–OprM), porin loss that reduces antibiotic entry (e.g., OprD alteration), and both chromosomally encoded (e.g., pseudomonas-derived cephalosporinases) and acquired (e.g., OXA-10) β-lactamase enzymes that hydrolyze a broad range of β-lactam antibiotics,[22] complicating therapeutic decision making. Resistance in gram-negative organisms arises through four primary pathways: reduced membrane permeability, active antibiotic efflux, target-site modification, and

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enzymatic modification of the antibiotic molecule (Fig. 1).

In addition, gram-negative bacteria have developed increasingly sophisticated adaptive responses to survive antibiotic pressure. These responses include up-regulation of global stress pathways,[23] metabolic reprogramming that reduces antibiotic uptake,[24] induction of persister-like states in which bacteria temporarily reduce their metabolic activity and tolerate otherwise lethal antibiotic concentrations,[25] and promotion of biofilm formation, which creates microenvironments that reduce antibiotic efficacy.[26]

REDUCED MEMBRANE PERMEABILITY

Porins — outer-membrane channels that enable the diffusion of important bacterial nutrients — are necessary for antibiotic entry.[27] Distinct gram-negative species express distinct porins; mutations can lead to partial or complete loss of function and may affect several classes of antibiotics or a single class. For example, disruption of OmpK36 in *Klebsiella pneumoniae* reduces permeability to several cephalosporins, carbapenems, and β-lactam–β-lactamase inhibitor combinations,[28] whereas OprD alterations in *P. aeruginosa* specifically restrict carbapenem uptake.[29] A notable exception to porin-dependent entry is the siderophore-based cephalosporin antibiotic cefiderocol, which hijacks bacterial iron-transport pathways to access the periplasm, bypassing traditional porin channels.[30] Even this strategy is vulnerable to bacterial adaptation: mutations or disruptions in iron-transport components, such as TonB-dependent receptors, can markedly reduce cefiderocol entry.[31]

ACTIVE ANTIBIOTIC EFFLUX

Efflux pumps are membrane-embedded transport proteins that extrude toxic compounds — including antibiotics — from the periplasmic space or cytoplasm, thereby reducing intracellular drug concentrations and contributing to resistance.[32] Expression of efflux pumps can be constitutive or upregulated in response to antibiotic exposure, and, like porins, efflux pumps are species-specific in both structure and substrate range. Many efflux pumps have broad substrate profiles, enabling resistance to multiple antibiotic classes simultaneously. For example, upregulation of the AcrAB–TolC complex in *E. coli* exports β-lactams, fluoroquinolones, tetracyclines, and numerous other compounds.[33]

TARGET-SITE MODIFICATION

Even when antibiotics reach their intracellular targets, structural modifications to those targets can render the antibiotic agents ineffective. For instance, point mutations in the genes encoding DNA gyrase (e.g., *gyrA*) or topoisomerase IV (e.g., *parC*) reduce fluoroquinolone binding affinity, conferring resistance despite inhibitory drug concentrations within the bacterial cell.[33] Although traditionally associated with gram-positive organisms, β-lactam resistance owing to alterations in penicillin-binding proteins is increasingly recognized in gram-negative pathogens.[34] In vitro data suggest that this resistance mechanism may be partially overcome through the use of dual β-lactam regimens that lead to complementary inhibition of multiple penicillin-binding proteins.[35,36]

ENZYMATIC DRUG MODIFICATION

Among gram-negative pathogens, enzymatic modification is one of the most rapidly evolving mechanisms of antibiotic resistance.[37,38] Examples of enzymatic modification are shown in Table 1; however, the most clinically consequential enzymes are β-lactamases,[38] which have the potential to inactivate multiple β-lactam antibiotics and currently comprise more than 12,000 characterized variants.[37]

CLINICALLY IMPORTANT β-LACTAMASE FAMILIES

An expanding body of comparative-effectiveness studies shows that effective management of infections caused by β-lactamase–producing organisms relies on identification of the specific β-lactamase enzyme involved, underscoring the importance of a mechanism-based approach to guiding treatment decisions (Fig. 2).[5] Increasingly, clinical microbiology laboratories use rapid molecular diagnostics capable of detecting key β-lactamase families.[39] These include the CTX-M family, which comprises over 95% of ESBL enzymes, in addition to several carbapenemase families, as outlined below. β-Lactamase testing is most commonly performed on blood culture, with results typically available within 1 hour after organism growth; however, commercially available assays can identify β-lactamases in other sample types (e.g., urine, respiratory samples, and intraabdominal fluid).[40,41] Major

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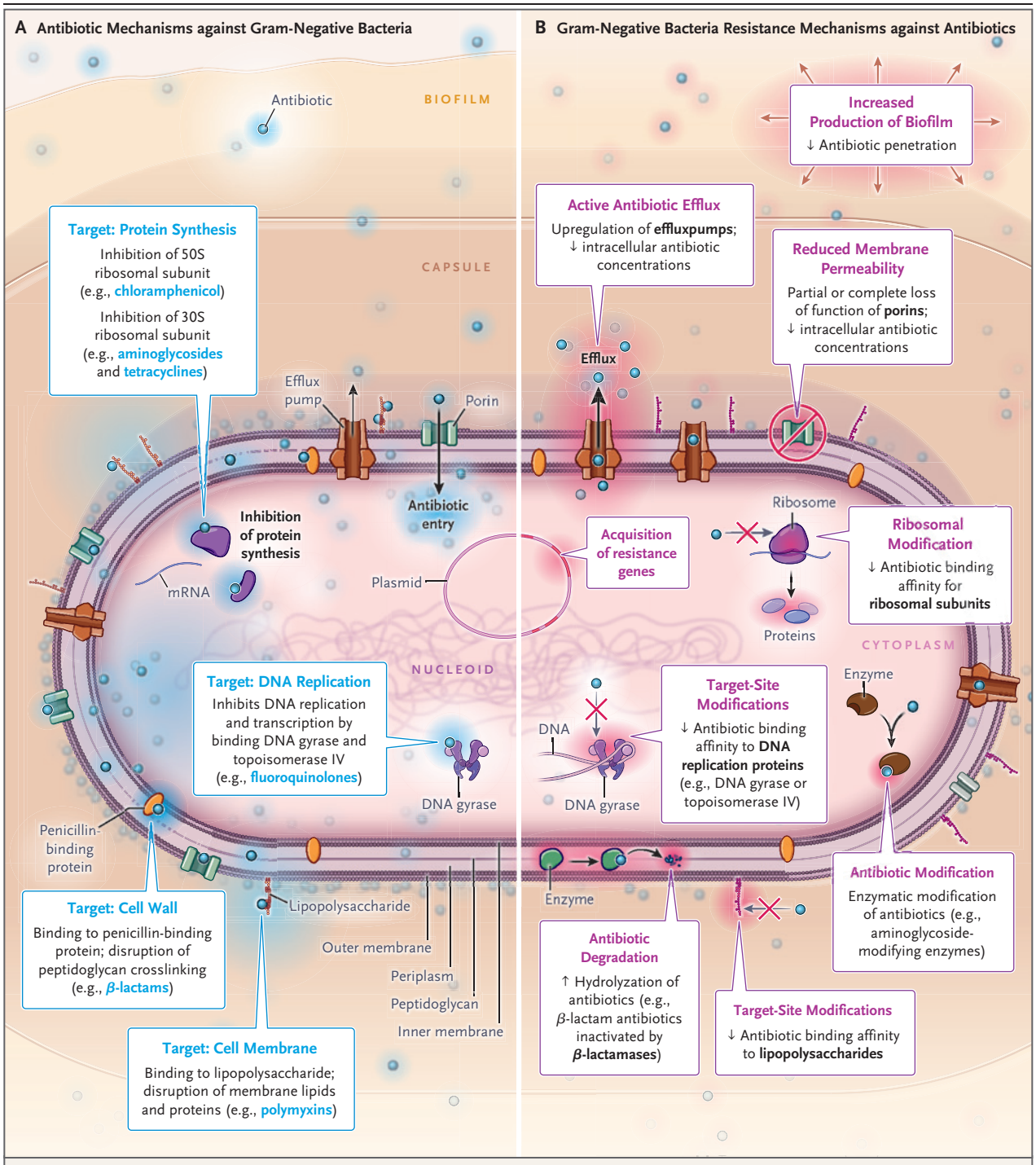

Figure 1. Gram-Negative Bacterium.

Shown is a representative gram-negative bacterial cell and the principal mechanisms of antibiotic activity and resistance. Antibiotics reach their cellular targets through distinct pathways, including passage across the outer membrane through porin channels. Once they reach their targets, antibiotics disrupt essential bacterial processes. For example, β-lactam antibiotics bind to penicillin-binding proteins, inhibiting peptidoglycan cross-linking and ultimately leading to bacterial cell death (Panel A). Gram-negative bacteria use several mechanisms to evade antibiotic activity, including reduced expression or loss of outer-membrane porins, which restricts antibiotic entry; increased expression of efflux pumps, which expel antibiotics from the periplasm or cytoplasm and reduce drug accumulation; production of enzymes that modify or inactivate antibiotics; and alterations in antibiotic targets that diminish drug binding (Panel B).

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Table 1. Common Mechanisms of Antimicrobial Resistance to Antibiotics Frequently Used for the Treatment of Gram-Negative Infections.*

General Categories and Examples	Bacterial Species Typically Involved	Antibiotics Typically Affected
Reduced membrane permeability		
Reduced production of OmpK35, OmpK36, and Ompk37	*Klebsiella pneumoniae*	Cephalosporins, carbapenems, ceftazidime–avibactam, and meropenem–vaborbactam
Reduced production of OmpC and OmpF	*Escherichia coli*	Penicillins, cephalosporins, aztreonam, carbapenems, and meropenem–vaborbactam
Reduced production of OprD porin	*Pseudomonas aeruginosa*	Carbapenems (imipenem more affected than meropenem)
Reduced production of CarO	*Acinetobacter baumannii* complex	Carbapenems (imipenem more affected than meropenem)
Mutations in the TonB-dependent transporter system (e.g., TonB, ExbB, ExbD, CirA, and FecA)	Enterobacterales, *P. aeruginosa*, *A. baumannii* complex	Cefiderocol
Active antibiotic efflux		
Increased expression of AcrAB–TolC efflux pump	*E. coli*	Ampicillin, cefazolin, fluoroquinolones, and tetracyclines
Increased expression of MexAB–OprM efflux pump	*P. aeruginosa*	Piperacillin–tazobactam, cefepime, meropenem, and fluoroquinolones
Increased expression of AdeABC efflux pump	*A. baumannii* complex	Aminoglycosides, fluoroquinolones, and tetracyclines
Increased expression of the major facilitator superfamily (e.g., TetA, TetB, TetC, and TetD)	Enterobacterales, *A. baumannii* complex	Tetracyclines
Target-site modification		
Modification of dihydrofolate reductase for trimethoprim (e.g., *dfrA*) and dihydropteroate synthase for sulfamethoxazole (e.g., *sul*)	Enterobacterales	TMP-SMX
Modifications of DNA gyrase (e.g., *gyrA*) and topoisomerase IV (e.g., *parC*)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Fluoroquinolones
Modification of the lipid A component of lipopolysaccharide (e.g., *mcr*)	Enterobacterales	Polymyxins
Modification of PBP3 target	Enterobacterales and *P. aeruginosa*	Ceftazidime, cefepime, aztreonam, cefiderocol, aztreonam–avibactam, ceftazidime–avibactam, and ceftolozane–tazobactam
Modifications in the outer membrane (e.g., PhoPQ and PmrAB)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Polymyxins
Enzymatic drug modification		
ESBL (e.g., CTX-M and SHV variants)	Enterobacterales	Ceftriaxone, ceftazidime, and aztreonam
Increased production of AmpC β-lactamases (e.g., AmpC, CMY, DHA, and FOX)	Enterobacterales	Ampicillin, cefazolin, ceftriaxone, ceftazidime, aztreonam, and piperacillin–tazobactam
Increased production of pseudomonas-derived cephalosporinases	*P. aeruginosa*	Piperacillin–tazobactam, ceftazidime, and aztreonam
Increased production of acinetobacter-derived cephalosporinases	*A. baumannii* complex	Ceftriaxone and aztreonam
Carbapenemases (e.g., KPC, NDM, VIM, IMP, OXA-48–like, and OXA-23)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Penicillins, cephalosporins, and carbapenems
Aminoglycoside-modifying enzymes (e.g., AAC, ANT, and APH)	Enterobacterales, *P. aeruginosa*, and *A. baumannii* complex	Aminoglycosides

* ESBL denotes extended-spectrum β-lactamase, IMP imipenemase, KPC *Klebsiella pneumoniae* carbapenemase, NDM New Delhi metallo-β-lactamase, TMP-SMX trimethoprim–sulfamethoxazole, and VIM Verona integron-encoded metallo-β-lactamase.

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β-lactamase families encountered in the United States are reviewed below.

EXTENDED-SPECTRUM β-LACTAMASES

ESBLs are produced by several gram-negative pathogens, most notably *E. coli* and *K. pneumoniae*, together accounting for more than 90% of ESBL-producing isolates.[42] ESBLs hydrolyze most β-lactam antibiotics — excluding carbapenems — and are generally carried on plasmids that also harbor determinants of resistance to other antibiotic families, such as fluoroquinolones, trimethoprim–sulfamethoxazole (TMP-SMX), tetracyclines, and aminoglycosides, further limiting therapeutic options.[43] In the United States, ESBL production is identified in approximately 20% of *E. coli* urinary tract infections (UTIs), with prevalence in some regions exceeding 40%,[44,45] frequently leading to hospitalization owing to limited oral treatment options. By contrast, CRE, although increasing in incidence, still accounts for less than 2% of all Enterobacterales infections in the United States.[46,47] The percentage of pathogens that produce ESBL is notably higher in many other countries; for example, ESBL production is reported in 77% of isolates of *E. coli* in Egypt, 64% of those in China, 62% of those in Russia, and 58% of those in Mexico.[48]

The prevalence of ESBL-producing Enterobacterales is largely driven by community spread and most commonly by a single lineage of *E. coli* (i.e., sequence type [ST]131).[43] In the United States, the incidence of ESBL-producing Enterobacterales increased by 53% between 2012 and 2017.[49] Beyond previously noted drivers of antimicrobial resistance dissemination, international travel to regions where antimicrobial resistance is endemic plays a distinct role in the

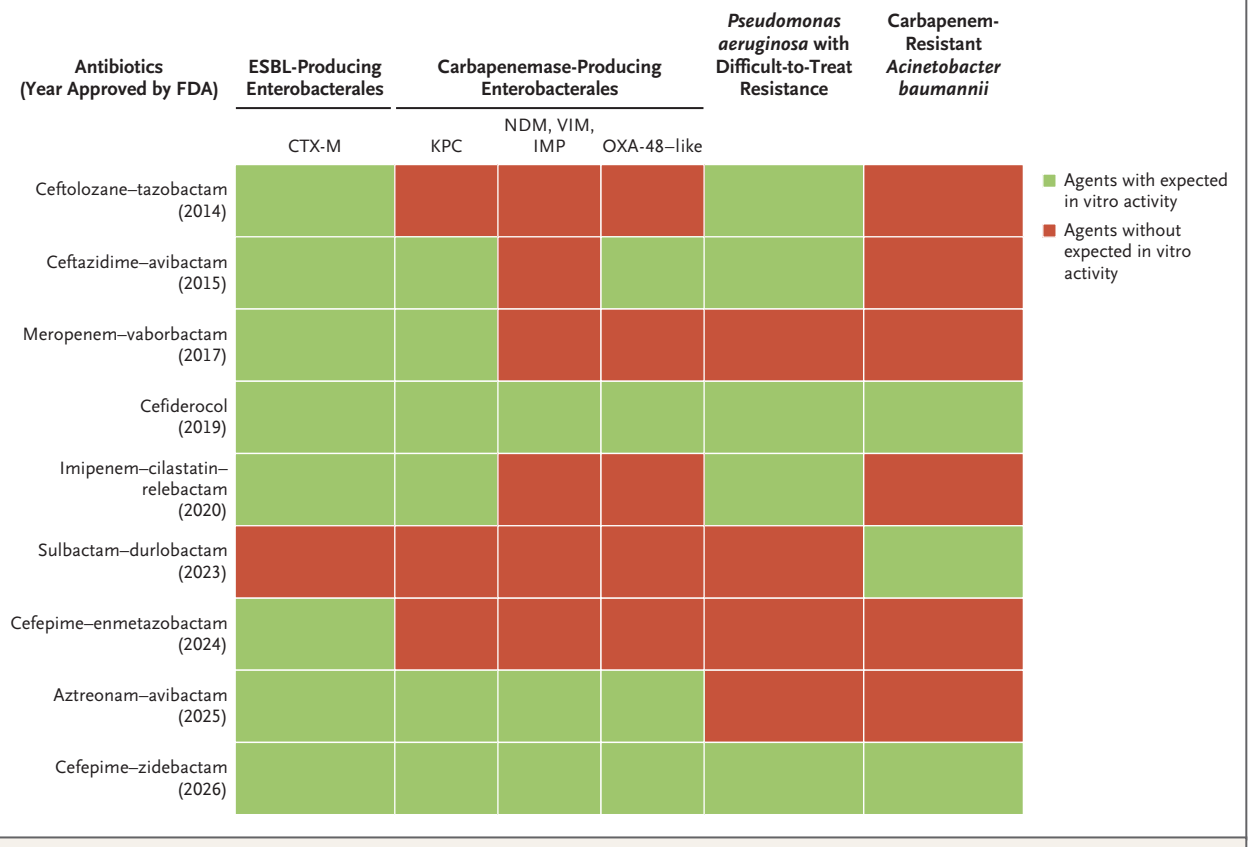

Figure 2. Approved Intravenous β-Lactam Agents Available in the United States with Activity against Selected Gram-Negative Antimicrobial-Resistant Infections.

ESBL denotes extended-spectrum β-lactamase, FDA Food and Drug Administration, IMP imipenemase, KPC *Klebsiella pneumoniae* carbapenemase, NDM New Delhi metallo-β-lactamase, and VIM Verona integron-encoded metallo-β-lactamase.

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transmission of ESBL-producing Enterobacterales. An estimated 20 to 35% of travelers returning from such regions acquire intestinal colonization of ESBL-producing Enterobacterales, with the highest rates — up to 70% — seen among persons who have traveled to South Asia.[50-52] Although colonization typically resolves over time, approximately 10% of travelers continue to have intestinal colonization 12 months after their return.[50,53] Of particular concern, ESBL-producing *Salmonella enterica* serovar Typhi has emerged in South Asia and is increasingly identified among travelers returning with typhoid fever.[54]

K. PNEUMONIAE CARBAPENEMASES

First identified in 1996 in a *K. pneumoniae* isolate from a patient in North Carolina, *K. pneumoniae* carbapenemase (KPC)–producing organisms were subsequently reported in Israel, Europe, and Latin America and have since disseminated among diverse Enterobacterales species and, less commonly, *P. aeruginosa*.[55,56] This rapid worldwide spread was driven by both the clonal expansion of successful global lineages (e.g., ST258) and the horizontal transfer of bla_{KPC}-bearing plasmids, which allowed KPC to become the dominant carbapenem-resistance mechanism worldwide.[56] In the United States, KPC account for approximately 80% of carbapenemase-producing Enterobacterales[57]; this percentage has been declining as other carbapenemases increase in prevalence.[58-60] KPC enzymes also remain highly prevalent throughout much of South America, China, and the Mediterranean region.[55,56,59,60]

NEW DELHI METALLO-β-LACTAMASES

The bla_{NDM} gene was first recognized in 2008 in *E. coli* and *K. pneumoniae* isolates from a Swedish patient who had received medical care in New Delhi, India.[61] Although New Delhi metallo-β-lactamase (NDM)–producing Enterobacterales remain relatively uncommon in the United States, the incidence of these bacteria increased by approximately 461% between 2019 and 2023, with *K. pneumoniae* emerging as the species most frequently associated with NDM production.[58] Internationally, prevalence varies markedly: NDM is endemic across South Asia and the Balkan region, where widespread environmental contamination has been documented — including detection in municipal water supplies.[62,63] Production of NDM remains extremely rare in nonfermenting bacteria in the United States but is more prevalent in bacteria in other regions; in carbapenem-resistant *A. baumannii*, the prevalence is 42%, 36%, and 18% in the Middle East, North Africa, and Southeast Asia, respectively.[64]

As compared with KPC-producing organisms, those that produce NDM show broader geographic distribution and greater sequence-type diversity, reflecting efficient horizontal gene transfer rather than expansion of a single clone.[65] NDM is a zinc-dependent enzyme. It is alarming that NDM variants with improved stability under the zinc-limited conditions typical of human infection are being increasingly reported.[66]

VERONA INTEGRON-ENCODED METALLO-β-LACTAMASES

Over the past decade, Verona integron-encoded metallo-β-lactamase (VIM) enzymes have spread among internationally disseminated *P. aeruginosa* lineages, with associated infections contributing to mortality exceeding 30%.[67,68] The increase in *P. aeruginosa*–produced VIM is particularly striking in southern and eastern Europe and Latin America.[69,70] In Greece, for example, the proportion of carbapenem-resistant *P. aeruginosa* isolates producing VIM increased from approximately 14% in 2011 to over 50% by 2020.[69-71] Although still rare in the United States,[72] bacteria that produce VIM nevertheless remain clinically significant when identified. A 2022–2023 outbreak linked to contaminated artificial tears resulted in 81 infections across 18 states in the United States, 22% of which resulted in enucleation and 7% of which resulted in death.[73]

IMIPENEMASES

Infections caused by imipenemase (IMP)–producing organisms are generally associated with lower mortality than infections caused by other metallo-carbapenemase enzymes (i.e., NDM and VIM).[74] Several factors contribute to this difference: IMP producers more frequently retain susceptibility to traditional gram-negative agents, which increases the likelihood of effective treatment options; IMP variants have not developed survival advantages under zinc-limited conditions; and high expression levels are required for IMPs to confer carbapenem resistance, which introduces a fitness cost that limits bacterial competitiveness.[74,75]

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OXACILLINASES

Oxacillinases (OXA enzymes) are broadly divided into those typically produced by Enterobacterales (e.g., OXA-48–like enzymes) and those associated with *A. baumannii* complex (e.g., OXA-23, OXA-24/40). In the United States, organisms that produce OXA-48–like enzymes account for approximately 5% of CRE isolates, although their prevalence is gradually rising.[57,58] By contrast, OXA-48–like enzymes represent the dominant carbapenemase class across parts of Europe, North Africa, and the Middle East.[76] The global spread of OXA enzymes reflects both efficient horizontal plasmid transfer and the clonal expansion of high-risk *K. pneumoniae* and *E. coli* lineages. In comparison, more than 90% of carbapenem-resistant *A. baumannii* isolates produce OXA-type enzymes, a pattern observed both in the United States and most regions of the world.[77]

TREATMENT FOR GRAM-NEGATIVE ANTIMICROBIAL-RESISTANT INFECTIONS

Before reviewing specific antibiotic options, it is essential to highlight treatment strategies that minimize the progression of antimicrobial resistance. Judicious prescribing of antibiotics remains critical: unnecessary initiation of therapy, prolonged treatment courses, and use of broad-spectrum agents without microbiologic justification all increase selective pressure.[78] When antibiotic therapy is warranted, refining dosing and infusion strategies helps prevent subtherapeutic concentrations that enable bacterial persistence and promote selection of resistant subpopulations.[79] Prioritizing source control — such as abscess drainage or removal of infected devices — and shortening treatment to the minimum effective duration further reduce both the need for antibiotics and the total duration of antibiotic exposure.[80] Antimicrobial resistance alone does not warrant longer treatment durations; the duration of active therapy should be the same regardless of the susceptibility phenotype.[81]

THE CURRENT ANTIBIOTIC LANDSCAPE

Preferred and alternative treatment options for the most commonly encountered antimicrobial-resistant gram-negative infections in adults and children in the United States are summarized in Table 2. Suggested antibiotic dosing regimens for adults are shown in Table 2; pediatric dosing regimens are available elsewhere.[5,82]

TREATMENT FOR ESBL-PRODUCING ENTEROBACTERALES INFECTION

ESBL-producing Enterobacterales most commonly cause UTIs but are also important pathogens in intraabdominal infections, bloodstream infections, and a variety of health care–associated infections.[43] Treatment differs substantially between uncomplicated UTIs — characterized by local bladder signs and symptoms (e.g., dysuria) without evidence of infection beyond the bladder (e.g., fever) — and complicated UTIs, which involve systemic illness or anatomic or functional abnormalities of the urinary tract.[83] This distinction informs treatment selection.

For uncomplicated UTIs caused by ESBL-producing Enterobacterales, nitrofurantoin and TMP-SMX are the preferred agents.[83,84] In contrast, the management of complicated UTIs is more nuanced; initial empiric therapy typically aligns more closely with approaches used for bloodstream infections. A randomized clinical trial comparing piperacillin–tazobactam with meropenem for bloodstream infections caused by ESBL-producing Enterobacterales was terminated early owing to increased mortality in the piperacillin–tazobactam group, establishing carbapenems as the preferred initial therapy for invasive disease caused by ESBL-producing Enterobacterales.[85] However, once clinical stability is achieved, alternative non–β-lactam agents — such as fluoroquinolones or TMP-SMX — may be considered, with susceptibility results, site of infection, and drug-specific adverse events taken into account.[5]

TREATMENT FOR CRE INFECTION

CRE, defined by resistance to at least one carbapenem agent,[5] causes many of the same infections seen with ESBL-producing Enterobacterales. In cases in which carbapenemase genes have not been identified, therapy is guided primarily by susceptibility results, with preferred agents including newer β-lactam–β-lactamase inhibitor combinations such as ceftazidime–avibactam and meropenem–vaborbactam. These agents have displaced older options like polymyxins, owing

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Table 2. Preferred and Alternative Antibiotic Agents for the Treatment of Gram-Negative Antimicrobial-Resistant Infections.*

Organism or Resistance Mechanism	Preferred Treatment	Alternative Treatment
ESBL-producing Enterobacterales	Uncomplicated UTI: Amikacin 15 mg/kg of body weight IV, 1 dose Gentamicin 5 mg/kg/dose IV, 1 dose Gepotidacin 1.5 g orally every 12 hr for 5 days Nitrofurantoin 100 mg orally every 12 hr for 5 days Pivmecillinam 370 mg orally every 8 hr for 3 days Sulopenem–etzadroxil (500 mg)–probenecid (500 mg) orally every 12 hr for 5 days Tobramycin 5 mg/kg/dose IV, 1 dose TMP-SMX 160 mg (trimethoprim component) IV or orally every 12 hr for 3 days Complicated UTI (7 days): Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr) Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Ertapenem 1 g IV every 24 hr Imipenem–cilastatin 500 mg IV every 6 hr or 1000 mg IV every 8 hr† Levofloxacin 750 mg IV or orally every 24 hr Meropenem 1 g IV every 8 hr† TMP-SMX 8–15 mg per kg of body weight per day (trimethoprim component) IV or orally, divided every 8 to 12 hr Invasive infection (≥7 days): Imipenem–cilastatin 500 mg IV every 6 hr or 1000 mg IV every 8 hr Meropenem 1 g IV every 8 hr	Uncomplicated UTI: Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr)† Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Ertapenem 1 g IV every 24 hr† Fosfomycin 3 g orally, 1 dose Levofloxacin 750 mg IV or orally every 24 hr Tebipenem 600 mg orally every 6 hr for 5 days† Complicated UTI (7 days): Fosfomycin 6 g IV every 8 hr Piperacillin–tazobactam 4.5 g IV every 6 hr (infused over ≥3 hr) Invasive infection (≥7 days): Cefepime–enmetazobactam: cefepime 2 g IV plus enmetazobactam 0.5 g IV every 8 hr (infused over 2 hr) Ciprofloxacin 400 mg IV every 8 hr or 750 mg orally every 12 hr Levofloxacin 750 mg IV or orally every 24 hr TMP-SMX 8–15 mg/kg/day (trimethoprim component) IV or orally, divided dose every 8 to 12 hr
KPC-producing Enterobacterales	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV every 8 hr (infused over 3 hr) Meropenem–vaborbactam: meropenem 2 g IV plus vaborbactam 2 g IV every 8 hr (infused over 3 hr)	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr) Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hours (infused over 3 hr)† Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr
NDM-producing Enterobacterales	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr)‡: Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hr (infused over 3 hr)	Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr

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OXA-48-like–producing Enterobacterales	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV (infused over 3 hr)	Aztreonam–avibactam: aztreonam 2 g IV plus avibactam 0.67 g IV loading dose (infused over 3 hr), then aztreonam 1.5 g IV plus avibactam 0.5 g IV every 6 hr (infused over 3 hr) Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)† Cefiderocol 2 g IV every 8 hr (infused over 3 hr)† Eravacycline 1 mg/kg per dose IV every 12 hr Tigecycline 200 mg IV as a single dose, then 100 mg IV every 12 hr
P. aeruginosa with difficult-to-treat resistance	Ceftazidime–avibactam: ceftazidime 2 g IV plus avibactam 0.5 g IV every 8 hr (infused over 3 hr) Ceftolozane–tazobactam: ceftolozane 2 g IV plus tazobactam 1 g IV every 8 hr (infused over 1 hr)	Cefepime–zidebactam 3 g IV every 8 hr (infused over 1 hr)†§ Cefiderocol 2 g IV every 8 hr (infused over 3 hr)§
Carbapenem-resistant *A. baumannii* complex	Sulbactam–durlobactam: sulbactam 1 g plus durlobactam 1 g IV (2 g total) every 6 hr (infused over 3 hr) plus either imipenem or meropenem (infused over 3 hr)	High-dose ampicillin–sulbactam: 9 g of ampicillin–sulbactam (6 g ampicillin plus 3 g sulbactam) IV every 8 hr (infused over 4 hr) or 27 g of ampicillin–sulbactam (18 g ampicillin plus 9 g sulbactam) IV as a continuous infusion over 24 hr Plus at least one of the following: Minocycline 200 mg IV or orally every 12 hr Polymyxin B loading dose of 2.0–2.5 mg/kg (20,000–25,000 IU/kg) (infused over 1 hr) followed by 1.25–1.5 mg/kg (12,500–15,000 IU/kg) every 12 hr (infused over 1 hr) Tigecycline 200 mg IV as a single dose, followed by 100 mg IV every 12 hr Cefiderocol 2 g IV every 8 hr (infused over 3 hr)

* Suggested doses assume normal renal function; derived from the Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections 2026. IV denotes intravenous, and UTI urinary tract infection.

† Although this antibiotic is expected to be active, its use should be reserved for situations in which side effects or resistance precludes the use of other preferred agents, thereby helping preserve its activity.

‡ If aztreonam–avibactam is not available, administer ceftazidime–avibactam (ceftazidime 2 g IV plus avibactam 0.5 g IV) every 8 hr (infused over 3 hr) plus aztreonam administered simultaneously at a dose of 2 g IV every 8 hr (infused over 3 hr).

§ Cefepime–zidebactam and cefiderocol are the only antibiotic agents with activity against VIM-producing *P. aeruginosa*.

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to inferior clinical outcomes and considerable toxic effects with the latter.[86,87] Cefiderocol and cefepime–zidebactam are uniquely effective among β-lactam antibiotics against the spectrum of carbapenemase-producing and non–carbapenemase-producing CRE and *P. aeruginosa* that have difficult-to-treat resistance.[88] Accordingly, to preserve the activity of these agents, their use is generally reserved for situations in which resistance or toxic effects preclude the use of other β-lactams. If a carbapenemase enzyme is identified, treatment selection is enzyme-specific, as summarized in Table 2. Several β-lactamase inhibitors that are currently under development, when paired with existing β-lactam agents, hold promise for restoring the activity of the β-lactam agent.[89]

Non–β-lactam agents remain therapeutic considerations for treating patients with CRE infections, as well. For example, tetracycline derivatives such as tigecycline and eravacycline retain activity against CRE regardless of carbapenemase production. Their usefulness, however, is diminished by extensive tissue distribution, resulting in poor serum and urinary drug concentrations, rendering these agents less suitable for the treatment of bacteremia and UTIs.[90] Likewise, although many CRE pathogens harbor additional resistance determinants that affect TMP-SMX, fluoroquinolones, and aminoglycosides, these agents may be used when susceptibility is confirmed, with infection site and severity of illness taken into account.

TREATMENT FOR *P. AERUGINOSA* INFECTION WITH DIFFICULT-TO-TREAT RESISTANCE

P. aeruginosa with difficult-to-treat resistance remains a major cause of health care–associated infections worldwide.[91] Treatment selection is guided by susceptibility results, with available options including cefepime–zidebactam, ceftazidime–avibactam, ceftolozane–tazobactam, and cefiderocol.[5] Among these agents, cefepime–zidebactam and cefiderocol are unique in retaining activity against VIM-producing *P. aeruginosa*; however, given the rarity of VIM enzymes in the United States, targeted coverage is generally unnecessary unless VIM production is confirmed or strongly suspected. Comparative effectiveness data indicate that β-lactams lead to favorable outcomes as monotherapy, whereas combination regimens (e.g., fluoroquinolones, aminoglycosides, and polymyxins) and adjunctive inhaled antibiotics for ventilator-associated pneumonia have not shown a survival benefit.[5,92]

A notable challenge in the management of *P. aeruginosa* with difficult-to-treat resistance is the emergence of resistance during therapy, particularly with ceftolozane–tazobactam and ceftazidime–avibactam, with reports of resistance during therapy in at least 20% of cases.[93] This incidence underscores the importance of susceptibility testing for the index *P. aeruginosa* isolate with difficult-to-treat resistance — and any subsequent isolates — given the potential for evolving, unpredictable resistance patterns.

TREATMENT OF CARBAPENEM-RESISTANT *A. BAUMANNII* INFECTION

Carbapenem-resistant *A. baumannii* is one of the most challenging pathogens in health care settings, with death due to ventilator-associated pneumonia and bacteremia exceeding 40% in the setting of intensive care units.[94] Sulbactam-based therapy forms the backbone of treatment for carbapenem-resistant *A. baumannii* infection. The antibiotic sulbactam–durlobactam in combination with a carbapenem is preferred, having shown improved outcomes relative to older options.[36,95] When sulbactam–durlobactam is unavailable or cannot be obtained promptly, high-dose ampicillin–sulbactam (at a dose of at least 9 grams per day of the sulbactam component) is suggested as an alternative,[5] often in combination with at least one other active agent, until sulbactam–durlobactam becomes available (Table 2).

CHALLENGES IN ANTIBIOTIC DEVELOPMENT

The struggle to control gram-negative antimicrobial resistance is intensified by structural obstacles in antibiotic development. Unpredictable market returns have prompted many pharmaceutical companies to withdraw from the space, eroded investor confidence, and reduced the drug-development workforce.[96,97] These pressures are compounded by a broader contraction in public health infrastructure and fragmented funding options. Although antimicrobial resis-

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KEY POINTS

GRAM-NEGATIVE BACTERIAL RESISTANCE

- The rapid worldwide spread of gram-negative antimicrobial resistance is driven by human, environmental, and health care–associated factors and accelerated by mobile genetic elements that facilitate the spread of resistance genes.
- Although several antibiotics are available to treat resistant gram-negative infections, limited access to these agents and the continued emergence of resistance constrain their clinical usefulness; nonantibiotic treatment strategies are under investigation.
- Resistance in gram-negative bacteria arises primarily through reduced drug entry, active drug efflux, modification of antibiotic targets, and enzymatic drug inactivation, most notably through β-lactamase production.
- Clinically important resistant pathogens include extended-spectrum β-lactamase–producing Enterobacterales, carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* with difficult-to-treat resistance, and carbapenem-resistant *Acinetobacter baumannii*, with outcomes maximized when pathogen- and mechanism-informed treatment approaches are used.
- Appropriate management of resistant gram-negative infections requires timely and accurate diagnostics, targeted use of newer β-lactam agents, effective source control, and judicious selection of treatment durations.
- Sustained progress will depend on the revitalization of antibiotic development and implementation of economic models that support innovation while ensuring equitable global access.

tance is an escalating threat, its clinical burden in high-income settings is concentrated primarily among persons with frequent health care exposure. Antibiotics are typically prescribed for short durations; as a result, companies often prioritize agents for chronic diseases, which offer larger and more predictable markets.

Scientific ingenuity alone will not sustain the antibiotic pipeline. Reversing the decline requires intentional rebuilding of research and manufacturing capacity, robust international trial networks capable of rapidly evaluating new agents, and economic frameworks that decouple revenue from volume — such as subscription models, pull incentives, or pooled procurement agreements — that reward innovation while safeguarding stewardship and ensuring equitable access.[98,99] Without such reforms, the gap between rising resistance and therapeutic capability will widen; with them, antibiotic development can again become viable, strengthening preparedness in the global response to gram-negative antimicrobial resistance.

ADVANCEMENTS IN ANTIBIOTIC ALTERNATIVES

In response to the growing crisis of antimicrobial resistance, there has been a renewed interest in nonantibiotic therapeutic strategies — with arguably the most progress occurring with phage therapy.[100] Phages are species-specific viruses that infect, replicate within, and lyse bacterial cells and are naturally eliminated from human hosts once their target bacteria are no longer present.[100,101] An advantage of phage therapy is that the same phage is typically active against both pan-susceptible and highly-resistant isolates of the same species. Published reports of clinical experiences suggest a reassuring safety profile.[102] Several clinical trials aimed at investigating the efficacy of phage therapy against antimicrobial-resistant infections are underway.[103]

Other nonantibiotic options being explored include monoclonal antibodies targeting bacterial surface components (e.g., endotoxins and capsular polysaccharides), antivirulence agents that disarm rather than kill pathogens, engineered phage-derived lysins capable of rapid bacterial killing by combining peptidoglycan hydrolase activity with outer-membrane–permeabilizing capabilities, manipulation of the microbiome, and immune-modulating therapies that enhance host defenses.[103-109] Although nonantibiotic therapies remain investigational, they hold promise as adjunctive or stand-alone options for the treatment of antimicrobial-resistant infections.

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CONCLUSIONS

The rise of gram-negative antimicrobial resistance threatens to erode the foundations of modern medicine, yet its trajectory is not predetermined. Recent innovations in diagnostics and therapeutics show that scientific solutions exist; what remains is constructing governance, financing, and research networks capable of deploying them where they are most needed. Because antimicrobial resistance is inherently global, its solutions must be collective — treating antibiotics as shared public goods and aligning incentives with stewardship and access. The salient question is whether the international community can act with sufficient urgency; if so, resistance may be contained well enough to preserve the gains of modern medicine.

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REFERENCES

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399:629-55.
2. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. Lancet 2024;404:1199-226.
3. Fridkin SK. Increasing prevalence of antimicrobial resistance in intensive care units. Crit Care Med 2001;29:Suppl:N64-N68.
4. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012-2017. N Engl J Med 2020;382:1309-19.
5. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2026 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clin Infect Dis 2026 August 8 (Epub ahead of print).
6. Lewnard JA, Charani E, Gleason A, et al. Burden of bacterial antimicrobial resistance in low-income and middle-income countries avertible by existing interventions: an evidence review and modelling analysis. Lancet 2024;403:2439-54.
7. Theuretzbacher U, Bush K, Harbarth S, et al. Critical analysis of antibacterial agents in clinical development. Nat Rev Microbiol 2020;18:286-98.
8. Rodriguez de Evgrafov MC, Faza M, Asimakopoulos K, Sommer MOA. Systematic investigation of resistance evolution to common antibiotics reveals conserved collateral responses across common human pathogens. Antimicrob Agents Chemother 2020;65(1):e01273-20.
9. Performance standards for antimicrobial susceptibility testing. 36th ed. CLSI M100. Wayne, PA: Clinical and Laboratory Standards Institute, 2026.
10. Magiorakos A-P, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
11. Cosentino F, Viale P, Giannella M. MDR/XDR/PDR or DTR? Which definition best fits the resistance profile of Pseudomonas aeruginosa? Curr Opin Infect Dis 2023;36:564-71.
12. Gill CM, Aktaþ E, Alfouzan W, et al. Multicenter, prospective validation of a phenotypic algorithm to guide carbapenemase testing in carbapenem-resistant *Pseudomonas aeruginosa* using the ERACE-PA global surveillance program. Open Forum Infect Dis 2021;9:ofab617.
13. Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. Clin Infect Dis 2018;67:1803-14.
14. Larsson DGJ, Flach C-F. Antibiotic resistance in the environment. Nat Rev Microbiol 2022;20:257-69.
15. Vikesland P, Garner E, Gupta S, Kang S, Maile-Moskowitz A, Zhu N. Differential drivers of antimicrobial resistance across the world. Acc Chem Res 2019;52:916-24.
16. Hernando-Amado S, Coque TM, Baquero F, Martínez JL. Defining and combating antibiotic resistance from One Health and Global Health perspectives. Nat Microbiol 2019;4:1432-42.
17. Lee MH, Lee GA, Lee SH, Park Y-H. A systematic review on the causes of the transmission and control measures of outbreaks in long-term care facilities: back to basics of infection control. PLoS One 2020;15(3):e0229911.
18. Shaw LP, Rocha EPC, MacLean RC. Restriction-modification systems have shaped the evolution and distribution of plasmids across bacteria. Nucleic Acids Res 2023;51:6806-18.
19. Chen H, Tao S, Li N, et al. Functional comparison of anti-restriction and anti-methylation activities of ArdA, KlcA, and $KlcA_{HS}$ from *Klebsiella pneumoniae*. Front Cell Infect Microbiol 2022;12:916547.
20. Redondo-Salvo S, Fernández-López R, Ruiz R, et al. Pathways for horizontal gene transfer in bacteria revealed by a global map of their plasmids. Nat Commun 2020;11:3602.
21. Liu Y-Y, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16:161-8.
22. Botelho J, Grosso F, Peixe L. Antibiotic resistance in *Pseudomonas aeruginosa* — mechanisms, epidemiology and evolution. Drug Resist Updat 2019;44:100640.
23. Crane JK, Alvarado CL, Sutton MD. Role of the SOS response in the generation of antibiotic resistance *in vivo*. Antimicrob Agents Chemother 2021;65(7):e0001321.
24. Acierno C, Barletta F, Nevola R, et al. Metabolic rewiring of bacterial pathogens in response to antibiotic pressure — a molecular perspective. Int J Mol Sci 2025;26:5574.
25. Harms A, Maisonneuve E, Gerdes K. Mechanisms of bacterial persistence during stress and antibiotic exposure. Science 2016;354:aaf4268.
26. Liu HY, Prentice EL, Webber MA. Mechanisms of antimicrobial resistance in biofilms. NPJ Antimicrob Resist 2024;2:27.
27. Vergalli J, Bodrenko IV, Masi M, et al. Porins and small-molecule translocation across the outer membrane of Gram-negative bacteria. Nat Rev Microbiol 2020;18:164-76.
28. Tsai Y-K, Fung C-P, Lin J-C, et al. *Klebsiella pneumoniae* outer membrane porins OmpK35 and OmpK36 play roles in both antimicrobial resistance and virulence.

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Antimicrob Agents Chemother 2011;55:1485-93.
29. Shen J, Pan Y, Fang Y. Role of the outer membrane protein OprD2 in carbapenem-resistance mechanisms of *Pseudomonas aeruginosa*. PLoS One 2015;10(10):e0139995.
30. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and in vivo profiles of a novel siderophore cephalosporin. Clin Infect Dis 2019;69:Suppl 7:S538-S543.
31. Egge SL, Rizvi SA, Simar SR, et al. Cefiderocol heteroresistance associated with mutations in TonB-dependent receptor genes in *Pseudomonas aeruginosa* of clinical origin. Antimicrob Agents Chemother 2024;68(8):e0012724.
32. Li X-Z, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clin Microbiol Rev 2015;28:337-418.
33. Elkins CA, Mullis LB. Substrate competition studies using whole-cell accumulation assays with the major tripartite multidrug efflux pumps of *Escherichia coli*. Antimicrob Agents Chemother 2007;51:923-9.
34. Bellini D, Koekemoer L, Newman H, Dowson CG. Novel and improved crystal structures of *H. influenzae*, *E. coli* and *P. aeruginosa* penicillin-binding protein 3 (PBP3) and *N. gonorrhoeae* PBP2: toward a better understanding of β-lactam target-mediated resistance. J Mol Biol 2019;431:3501-19.
35. Rahme C, Butterfield JM, Nicasio AM, Lodise TP. Dual beta-lactam therapy for serious Gram-negative infections: is it time to revisit? Diagn Microbiol Infect Dis 2014;80:239-59.
36. Veeraraghavan B, Shin E, Bakthavatchalam YD, et al. A microbiological and structural analysis of the interplay between sulbactam/durlobactam and imipenem against penicillin-binding proteins (PBPs) of *Acinetobacter* spp. Antimicrob Agents Chemother 2025;69(4):e0162724.
37. Warecki BA, Moreno DM, Bonomo RA, Vila AJ. Let's dance: how protein dynamics drive β-lactamase evolution and antibiotic resistance? Biochemistry 2025;64:4498-512.
38. Bush K, Bradford PA. Epidemiology of β-lactamase-producing pathogens. Clin Microbiol Rev 2020;33(2):e00047-19.
39. De Angelis G, Grossi A, Menchinelli G, Boccia S, Sanguinetti M, Posteraro B. Rapid molecular tests for detection of antimicrobial resistance determinants in Gram-negative organisms from positive blood cultures: a systematic review and meta-analysis. Clin Microbiol Infect 2020;26:271-80.
40. Decousser J-W, Poirel L, Nordmann P. Recent advances in biochemical and molecular diagnostics for the rapid detection of antibiotic-resistant Enterobacteriaceae: a focus on β-lactam resistance. Expert Rev Mol Diagn 2017;17:327-50.
41. Zhuang Q, Guo H, Peng T, et al. Advances in the detection of β-lactamase: a review. Int J Biol Macromol 2023;251:126159.
42. Hareza DA, Bergman Y, Jacobs E, et al. Molecular epidemiology of β-lactamases in ceftriaxone-resistant Enterobacterales bloodstream infections in the mid-Atlantic United States. Antimicrob Agents Chemother 2025;69(3):e0125824.
43. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. JAC Antimicrob Resist 2021;3:dlab092.
44. Critchley IA, Cotroneo N, Pucci MJ, Mendes R. The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. PLoS One 2019;14(12):e0220265.
45. Talan DA, Takhar SS, Krishnadasan A, et al. Emergence of extended-spectrum β-lactamase urinary tract infections among hospitalized emergency department patients in the United States. Ann Emerg Med 2021;77:32-43.
46. Wolford H, McCarthy NL, Baggs J, et al. Antimicrobial-resistant infections in hospitalized patients. JAMA Netw Open 2025;8(3):e2462059.
47. Sader HS, Mendes RE, Carvalhaes CG, Kimbrough JH, Castanheira M. Changing epidemiology of carbapenemases among carbapenem-resistant Enterobacterales from United States hospitals and the activity of aztreonam-avibactam against contemporary Enterobacterales (2019-2021). Open Forum Infect Dis 2023;10:ofad046.
48. ResistanceMap. Washington DC: One Health Trust, 2026 (https://resistancemap.onehealthtrust.org/AntibioticResistance.php).
49. Duffy N, Karlsson M, Reses HE, et al. Epidemiology of extended-spectrum β-lactamase-producing Enterobacterales in five US sites participating in the Emerging Infections Program, 2017. Infect Control Hosp Epidemiol 2022;43:1586-94.
50. Arcilla MS, van Hattem JM, Haverkate MR, et al. Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. Lancet Infect Dis 2017;17:78-85.
51. Kantele A, Lääveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Clin Infect Dis 2015;60:837-46.
52. Tängdén T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. Antimicrob Agents Chemother 2010;54:3564-8.
53. ÖstholmBalkhed Å, Tärnberg M, Nilsson M, et al. Duration of travel-associated faecal colonisation with ESBL-producing Enterobacteriaceae — a one year follow-up study. PLoS One 2018;13(10):e0205504.
54. Chatham-Stephens K, Medalla F, Hughes M, et al. Emergence of extensively drug-resistant *Salmonella Typhi* infections among travelers to or from Pakistan — United States, 2016–2018. MMWR Morb Mortal Wkly Rep 2019;68:11-3.
55. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis 2013;13:785-96.
56. Rojas LJ, Weinstock GM, De La Cadena E, et al. An analysis of the epidemic of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: convergence of two evolutionary mechanisms creates the "perfect storm." J Infect Dis 2017;217:82-92.
57. Sabour S, Huang JY, Bhatnagar A, et al. Detection and characterization of targeted carbapenem-resistant health care-associated threats: findings from the Antibiotic Resistance Laboratory Network, 2017 to 2019. Antimicrob Agents Chemother 2021;65(12):e0110521.
58. Rankin DA, Stahl A, Sabour S, et al. Changes in carbapenemase-producing carbapenem-resistant Enterobacterales, 2019 to 2023. Ann Intern Med 2025;178:1818-21.
59. Hu F, Guo Y, Yang Y, et al. Resistance reported from China antimicrobial surveillance network (CHINET) in 2018. Eur J Clin Microbiol Infect Dis 2019;38:2275-81.
60. Zhang Y, Wang Q, Yin Y, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae infections: report from the China CRE Network. Antimicrob Agents Chemother 2018;62:e01882-17.
61. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrob Agents Chemother 2009;53:5046-54.
62. Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance. J Med Microbiol 2013;62:499-513.
63. Nordmann P, Poirel L, Walsh TR, Livermore DM. The emerging NDM carbapenemases. Trends Microbiol 2011;19:588-95.
64. Karakonstantis S, Tziolos RN, Paneta M, et al. Global and regional prevalence of metallo-β-lactamases in carbapenem-resistant *Acinetobacter baumannii*: a systematic review and meta-analysis. J Antimicrob Chemother 2026;81:dkag037.

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65. Zhang Y, Liu M, Zhang J, et al. Large-scale comparative analysis reveals phylogenomic preference of bla_{NDM-1} and bla_{KPC-2} transmission among Klebsiella pneumoniae. Int J Antimicrob Agents 2024;64:107225.
66. Bahr G, Vitor-Horen L, Bethel CR, Bonomo RA, González LJ, Vila AJ. Clinical Evolution of New Delhi Metallo-β-Lactamase (NDM) Optimizes Resistance under Zn(II) Deprivation. Antimicrob Agents Chemother 2017;62(1):e01849-17.
67. Del Barrio-Tofiño E, López-Causapé C, Oliver A. *Pseudomonas aeruginosa* epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents 2020;56:106196.
68. Oliver A, Rojo-Molinero E, Arca-Suarez J, et al. *Pseudomonas aeruginosa* antimicrobial susceptibility profiles, resistance mechanisms and international clonal lineages: update from ESGARS-ESCMID/ISARPAE Group. Clin Microbiol Infect 2024;30:469-80.
69. Pérez A, Gato E, Pérez-Llarena J, et al. High incidence of MDR and XDR *Pseudomonas aeruginosa* isolates obtained from patients with ventilator-associated pneumonia in Greece, Italy and Spain as part of the MagicBullet clinical trial. J Antimicrob Chemother 2019;74:1244-52.
70. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF. Longitudinal analysis of ESBL and carbapenemase carriage among Enterobacterales and *Pseudomonas aeruginosa* isolates collected in Europe as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance programme, 2013-17. J Antimicrob Chemother 2020;75:1165-73.
71. Karampatakis T, Antachopoulos C, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant *Pseudomonas aeruginosa* in an endemic area: comparison with global data. Eur J Clin Microbiol Infect Dis 2018;37:1211-20.
72. Reyes J, Komarow L, Chen L, et al. Global epidemiology and clinical outcomes of carbapenem-resistant *Pseudomonas aeruginosa* and associated carbapenemases (POP): a prospective cohort study. Lancet Microbe 2023;4(3):e159-e170.
73. Grossman MK, Rankin DA, Maloney M, et al. Extensively drug-resistant *Pseudomonas aeruginosa* outbreak associated with artificial tears. Clin Infect Dis 2024;79:6-14.
74. Suzuki D, Sakurai A, Wakuda M, Suzuki M, Doi Y. Clinical and genomic characteristics of IMP-producing *Enterobacter cloacae* complex and *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2024;68(5):e0167223.
75. Cheung CHP, Alorabi M, Hamilton F, et al. Trade-offs between antibacterial resistance and fitness cost in the production of metallo-β-lactamases by enteric bacteria manifest as sporadic emergence of carbapenem resistance in a clinical setting. Antimicrob Agents Chemother 2021;65(8):e0241220.
76. Pitout JDD, Peirano G, Kock MM, Strydom K-A, Matsumura Y. The global ascendency of OXA-48-type carbapenemases. Clin Microbiol Rev 2019;33(1):e00102-19.
77. Wang M, Ge L, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant *Acinetobacter baumannii* among patients from different global regions. Clin Infect Dis 2024;78:248-58.
78. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62(10):e51-e77.
79. Monogue ML, Kuti JL, Nicolau DP. Optimizing antibiotic dosing strategies for the treatment of gram-negative infections in the era of resistance. Expert Rev Clin Pharmacol 2016;9:459-76.
80. Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. Eur J Intern Med 2022;99:7-12.
81. Soto CL, Hsu AJ, Lee JH, et al. Identifying effective durations of antibiotic therapy for the treatment of carbapenem-resistant enterobacterales bloodstream infections: a multicenter observational study. Clin Infect Dis 2024;78:27-30.
82. Lockowitz CR, Hsu AJ, Chiotos K, et al. Suggested dosing of select beta-lactam agents for the treatment of antimicrobial-resistant gram-negative infections in children. J Pediatric Infect Dis Soc 2025;14(2):piaf004.
83. Infectious Diseases Society of America. IDSA 2025 guideline update on complicated urinary tract infections (cUTI). July 17, 2025 (https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/).
84. Zeng L, Hamasaki T, Ge L, He Y, Evans SR. Benefit-risk assessments during a clinical trial using desirability of outcome ranking (DOOR) methodology: a prediction approach. In: Chen DG, ed. Biostatistics in biopharmaceutical research and development: 80-years of contributions and dedications from the Deming Conference. Cham, Switzerland: Springer, 2024:161-80,
85. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA 2018;320:984-94.
86. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment options for carbapenem-resistant Enterobacteriaceae infections. Open Forum Infect Dis 2015;2:ofv050.
87. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017;17:726-34.
88. McCreary EK, Heil EL, Tamma PD. New perspectives on antimicrobial agents: cefiderocol. Antimicrob Agents Chemother 2021;65(8):e0217120.
89. Katsarou A, Stathopoulos P, Tzvetanova ID, Asimotou C-M, Falagas ME. β-Lactam/β-lactamase inhibitor combination antibiotics under development. Pathogens 2025;14:168.
90. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. Curr Drug Metab 2009;10:13-21.
91. Serra-Burriel M, Keys M, Campillo-Artero C, et al. Impact of multi-drug resistant bacteria on economic and clinical outcomes of healthcare-associated infections in adults: systematic review and meta-analysis. PLoS One 2020;15(1):e0227139.
92. Horcajada JP, Gales AC, Isler B, et al. Current and future options for the treatment of serious infections due to carbapenem-resistant *Pseudomonas aeruginosa*. Clin Microbiol Rev 2025;38(4):e0023324.
93. Hareza DA, Cosgrove SE, Bonomo RA, et al. Clinical outcomes and emergence of resistance of *Pseudomonas aeruginosa* infections treated with ceftolozane-tazobactam versus ceftazidime-avibactam. Antimicrob Agents Chemother 2024;68(10):e0090724.
94. Shields RK, Paterson DL, Tamma PD. Navigating available treatment options for carbapenem-resistant *Acinetobacter baumannii*-calcoaceticus complex infections. Clin Infect Dis 2023;76:Suppl 2:S179-S193.
95. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis 2023;23:1072-84.
96. Piddock LJV, Paccaud J-P, O'Brien S, Childs M, Malpani R, Balasegaram M. A nonprofit drug development model is part of the antimicrobial resistance (AMR) solution. Clin Infect Dis 2022;74:1866-71.

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97. Piddock LJV, Alimi Y, Anderson J, et al. Advancing global antibiotic research, development and access. Nat Med 2024; 30:2432-43.
98. Monnier AA, Schouten J, Tebano G, et al. Ensuring antibiotic development, equitable availability, and responsible use of effective antibiotics: recommendations for multisectoral action. Clin Infect Dis 2019;68:1952-9.
99. Vogler S, Habimana K, Haasis MA, Fischer S. Pricing, procurement and reimbursement policies for incentivizing market entry of novel antibiotics and diagnostics: learnings from 10 countries globally. Appl Health Econ Health Policy 2024;22:629-52.
100. Suh GA, Lodise TP, Tamma PD, et al. Considerations for the use of phage therapy in clinical practice. Antimicrob Agents Chemother 2022;66(3):e0207121.
101. Kim MK, Suh GA, Cullen GD, et al. Bacteriophage therapy for multidrug-resistant infections: current technologies and therapeutic approaches. J Clin Invest 2025;135(5):e187996.
102. Liu D, Van Belleghem JD, de Vries CR, et al. The safety and toxicity of phage therapy: a review of animal and clinical studies. Viruses 2021;13:1268.
103. Uchechukwu CF, Shonekan A. Current status of clinical trials for phage therapy. J Med Microbiol 2024;73:001895.
104. Wang C-H, Hsieh Y-H, Powers ZM, Kao C-Y. Defeating antibiotic-resistant bacteria: exploring alternative therapies for a post-antibiotic era. Int J Mol Sci 2020;21: 1061.
105. Zumla A, Rao M, Wallis RS, et al. Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. Lancet Infect Dis 2016; 16(4):e47-e63.
106. Ding W, Cheng Y, Liu X, et al. Harnessing the human gut microbiota: an emerging frontier in combatting multidrug-resistant bacteria. Front Immunol 2025;16:1563450.
107. Heselpoth RD, Euler CW, Schuch R, Fischetti VA. Lysocins: bioengineered antimicrobials that deliver lysins across the outer membrane of gram-negative bacteria. Antimicrob Agents Chemother 2019; 63(6):e00342-19.
108. Theuretzbacher U, Piddock LJV. Non-traditional antibacterial therapeutic options and challenges. Cell Host Microbe 2019;26:61-72.
109. La Guidara C, Adamo R, Sala C, Micoli F. Vaccines and monoclonal antibodies as alternative strategies to antibiotics to fight antimicrobial resistance. Int J Mol Sci 2024;25:5487.

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