



Beyond Antibiotics: Bacteriophage Therapy, Antimicrobial Peptides, and CRISPR-Based Strategies Against Resistant Bacteria

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ما بعد المضادات الحيوية: العلاج بالعاثيات (البكتريوفاج)، والببتيدات المضادة للميكروبات، والاستراتيجيات القائمة على تقنية "كريسبر" (CRISPR) لمواجهة البكتيريا المقاومة

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Abstract:

Antimicrobial resistance (AMR) is among the leading threats to global health. Bacterial AMR was associated with an estimated 4.71 million deaths in 2021, and forecasts suggest the toll will rise substantially by 2050. At the same time, the pipeline of new antibiotic classes remains thin, and most recent approvals are modifications of existing scaffolds. This review summarizes the principal mechanisms by which bacteria resist antibiotics and then examines three non-conventional approaches that have moved from concept toward clinical translation: bacteriophage therapy (including phage-derived endolysins), antimicrobial peptides (AMPs), and CRISPR-Cas-based antimicrobials. For each approach we discuss mode of action, the strongest available clinical or preclinical evidence, and the main barriers, including bacterial counter-resistance, delivery, stability, safety, and regulation. We also briefly consider artificial intelligence-guided discovery as a complementary route. We conclude that these strategies are unlikely to replace antibiotics outright, but may serve as adjuncts or salvage options for infections with few remaining treatment choices, provided that standardized trials, manufacturing pathways, and stewardship frameworks mature in parallel.

Keywords: Antimicrobial Resistance; Multidrug-Resistant Bacteria; Bacteriophage Therapy; Endolysins; Antimicrobial Peptides; CRISPR-Cas; Alternatives To Antibiotics; ESKAPE Pathogens.

المخلص

تُعد مقاومة مضادات الميكروبات (AMR) واحدة من أكبر التهديدات التي تواجه الصحة العالمية. فقد ارتبطت مقاومة البكتيريا للمضادات الحيوية بنحو 4.71 مليون حالة وفاة في عام 2021، وتشير التوقعات إلى أن هذه الحصيلة سترتفع بشكل ملحوظ بحلول عام 2050. وفي الوقت ذاته، لا تزال قائمة المضادات الحيوية الجديدة قيد التطوير محدودة للغاية، ومعظم الأدوية التي حصلت على الموافقة مؤخراً ليست سوى تعديلات على هياكل كيميائية موجودة بالفعل. تستعرض هذه الورقة الآليات الرئيسية التي تكتسب بها البكتيريا مقاومةً ضد المضادات الحيوية، وتناقش ثلاثة نهج غير تقليدية انتقلت من مرحلة المفهوم النظري نحو التطبيق السريري، وهي: العلاج بالعاثيات (بما في ذلك الإندوليسينات المشتقة من العاثيات)، والببتيدات المضادة للميكروبات (AMPs)، والمضادات المعتمدة على تقنية "كريسبر-كاس" (CRISPR-Cas). وبالنسبة لكل نهج،

نناقش آلية العمل، وأقوى الأدلة السريرية أو ما قبل السريرية المتاحة، والعقبات الرئيسية التي تواجهه - مثل تطوير البكتيريا لمقاومة مضادة، وتحديات التوصيل، والاستقرار، والسلامة، والأطر التنظيمية. كما نتطرق بإيجاز إلى دور الذكاء الاصطناعي في تسريع اكتشاف علاجات جديدة كمسار مكمل. ونخلص إلى أن هذه الاستراتيجيات قد لا تحل محل المضادات الحيوية تماماً، لكنها يمكن أن تعمل كعلاجات مساعدة أو خيارات إنقاذ في حالات العدوى التي لم يتبق لها سوى القليل من خيارات العلاج، شريطة أن تتطور بالتوازي مع ذلك التجارب السريرية الموحدة، وآليات التصنيع، وأطر العمل الخاصة بالاستخدام الرشيد للمضادات الحيوية.

الكلمات المفتاحية: مقاومة مضادات الميكروبات؛ البكتيريا متعددة المقاومة للأدوية؛ العلاج بالعائيات؛ الإندوليسينات؛ الببتيدات المضادة للميكروبات؛ كريسبر-كاس (CRISPR-Cas)؛ بدائل المضادات الحيوية؛ مسببات الأمراض من مجموعة "إسكاب" (ESKAPE).

1. Introduction

The introduction of antibiotics in the twentieth century transformed medicine, making routine surgery, cancer chemotherapy, organ transplantation, and neonatal care far safer. That progress is now eroding. A systematic analysis estimated that bacterial AMR was directly responsible for about 1.27 million deaths and associated with 4.95 million deaths worldwide in 2019 [1]. A later analysis covering 1990 to 2021 estimated 1.14 million attributable and 4.71 million associated deaths in 2021, and projected 1.91 million attributable and 8.22 million associated deaths annually by 2050 [2]. An earlier, widely cited commissioned report projected up to 10 million deaths per year by 2050, a figure that is more speculative than the formal burden estimates but that helped place AMR on the global policy agenda [3].

Resistance is not a purely modern phenomenon. Resistance determinants are ancient and widespread in environmental bacteria, and metagenomic work has recovered resistance genes from 30,000-year-old permafrost sediments [4,5]. What has changed is the selective pressure imposed by human, veterinary, and agricultural antibiotic use, which has enriched these genes in pathogens and mobilized them on plasmids, transposons, and integrons. Meanwhile, antibiotic discovery has slowed markedly: the golden age of natural-product discovery ended in the 1960s, and screening of large synthetic libraries largely failed to yield new classes with Gram-negative activity [6].

The World Health Organization (WHO) maintains a Bacterial Priority Pathogens List to guide research and development. The 2024 update places carbapenem-resistant *Acinetobacter baumannii*, third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales, and rifampicin-resistant *Mycobacterium tuberculosis* in the critical group [7]; the original 2017 list was developed with a similar goal [8]. The acronym ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) captures the pathogens that most often "escape" the effects of antibiotics in hospitals [9].

In this context, interest has grown in strategies that act through mechanisms distinct from those of classical antibiotics. This review focuses on three of them: bacteriophage therapy, AMPs, and CRISPR-based antimicrobials. We first outline the resistance mechanisms these strategies must overcome, then evaluate each approach, compare them, and discuss open challenges.

2. Mechanisms of Bacterial Antibiotic Resistance

Bacterial resistance arises through intrinsic properties, mutation of existing genes, and acquisition of foreign genes by horizontal gene transfer (HGT) [10,11]. The main biochemical mechanisms fall into four groups.

Limiting drug uptake. Gram-negative bacteria are protected by an outer membrane that restricts entry of many hydrophilic and large molecules. Loss or modification of porins (for example, OmpK35/36 in *K. pneumoniae* or OprD in *P. aeruginosa*) further reduces influx of beta-lactams and carbapenems [10,11].

Active efflux. Multidrug efflux pumps, such as the RND-family AcrAB-TolC in *Escherichia coli* and MexAB-OprM in *P. aeruginosa*, expel diverse antibiotics and contribute to both intrinsic and acquired resistance [10].

Modification of the target. Point mutations or enzymatic alterations of drug targets reduce binding. Examples include altered penicillin-binding proteins (PBP2a encoded by *mecA* in methicillin-resistant *S. aureus*, MRSA), ribosomal methylation by Erm and Cfr enzymes, and modification of lipid A with phosphoethanolamine through MCR enzymes, which confers colistin resistance [10,11].

Enzymatic inactivation. Beta-lactamases, including extended-spectrum beta-lactamases (ESBLs) and carbapenemases such as KPC, NDM, and OXA-48-like enzymes, hydrolyze the drug before it reaches its target. Aminoglycoside-modifying enzymes act similarly through acetylation, phosphorylation, or adenylation [11].

Beyond these molecular mechanisms, population-level phenomena matter clinically. Biofilms, structured communities embedded in an extracellular matrix, can tolerate antibiotic concentrations far above those that kill planktonic cells, owing to limited penetration, altered metabolism, and the presence of persister subpopulations [12]. Heteroresistance and tolerance can likewise cause treatment failure despite apparent susceptibility in routine tests. Importantly, sub-inhibitory antibiotic concentrations in patients and in the environment can select for resistance and promote mutation and HGT [13].

To allow consistent reporting, an international expert group proposed definitions of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria based on non-susceptibility to antimicrobial categories [14]. The full set of resistance genes in a given community, termed the resistome, links clinical and environmental reservoirs and underpins the One Health perspective on AMR [15].

3. Bacteriophage Therapy

3.1 Principles

Bacteriophages (phages) are viruses that infect bacteria. Lytic (virulent) phages adsorb to specific receptors, replicate within the host, and lyse the cell, releasing progeny that can infect neighboring cells. Because their activity depends on receptor recognition rather than on inhibiting a conserved cellular target, phages are generally active against antibiotic-resistant strains and typically spare commensal bacteria, offering narrow-spectrum, self-amplifying killing [16,17]. Therapeutic phages are generally selected to be strictly lytic, lacking genes for toxins, antibiotic resistance, or lysogeny [16,18]. Phage therapy predates antibiotics, having been used in the early 1900s in Eastern Europe, and remains in routine use in Georgia and Poland, but rigorous controlled evidence has been limited [16].

3.2 Clinical Evidence

The modern revival has been driven largely by compassionate-use cases. In a well-known 2017 report, a personalized phage cocktail combined with antibiotics was used to treat a patient with a disseminated, multidrug-resistant *A. baumannii* infection, and the patient recovered from coma [19]. In 2019, a genetically engineered three-phage cocktail was used to treat a disseminated drug-resistant *Mycobacterium abscessus* infection in an adolescent lung-transplant recipient, with clinical improvement [20]. A later series of 20 patients with drug-resistant mycobacterial disease reported a favorable clinical or microbiological response in a majority of them (11 of 20) [21]. A multinational retrospective analysis of 100 consecutive personalized phage therapy cases reported clinical improvement in roughly three-quarters of cases and bacterial eradication in about 60%, with few adverse events considered related to the phages; the study also found that antibiotic co-administration was associated with better outcomes, and that neutralizing antibodies against phages and phage resistance were seen in a subset of patients [24].

Controlled trials have been more sobering. The PhagoBurn trial, a phase 1/2 randomized trial in burn wounds infected with *P. aeruginosa*, found that a phage cocktail was well tolerated but reduced bacterial load more slowly than standard of care, a result attributed in part to the low titer of active phage in the applied product, which reflected stability and manufacturing problems [22]. A randomized, placebo-controlled trial of intravesical phages in patients undergoing transurethral resection of the prostate found the phage preparation safe but not superior to placebo or to antibiotic treatment [23]. These results illustrate that dose, formulation, phage-host matching, and trial design are decisive, and that anecdotal success does not guarantee efficacy in standardized settings.

3.3 Phage Resistance, Evolutionary Trade-offs, and Cocktails

Bacteria can resist phages through receptor modification or loss, restriction-modification systems, abortive infection, and CRISPR-Cas adaptive immunity. Resistance emerged in a notable fraction of patients in published case series [25]. Cocktails of phages that use different receptors, and sequential or personalized phage selection, are therefore standard strategies to delay resistance. Interestingly, phage resistance can impose evolutionary costs. In one study, selection with a phage that targeted an efflux-pump component in MDR *P. aeruginosa* led to mutants with restored sensitivity to several antibiotics, supporting the concept of "phage steering" and phage-antibiotic combinations [26].

3.4 Limitations

Key limitations include narrow host range, which requires diagnostics and often phage banks or personalized matching; the need for rigorous purification to remove endotoxin; pharmacokinetic uncertainty, including rapid clearance by the immune system and difficulty reaching intracellular or biofilm-embedded bacteria; and an unsettled regulatory framework, since phage products are biological, evolving, and do not fit neatly into traditional drug-approval models [16,27]. The narrow spectrum that makes phages attractive for microbiome preservation also complicates empirical use.

3.5 Phage-Derived Endolysins

Endolysins are peptidoglycan hydrolases used by phages to release progeny at the end of the lytic cycle. When applied externally, they can degrade the cell wall of Gram-positive bacteria, which lack an outer membrane, causing rapid lysis, and resistance has been difficult to select in the laboratory [28]. Engineering strategies, such as fusion to outer-membrane-permeabilizing peptides, aim to extend activity to Gram-negative bacteria. The lysin exebacase showed promising activity in a phase 2 trial in *S. aureus* bacteremia, including endocarditis, as an adjunct to standard antibiotics [29], although later phase 3 development was discontinued after an interim analysis, reflecting the difficulty of translating early signals.

4. Antimicrobial Peptides

4.1 Overview and Mode of Action

AMPs are short, typically cationic and amphipathic peptides produced by nearly all forms of life as part of innate immunity [30]. Many act by electrostatic attraction to the negatively charged bacterial membrane followed by insertion and disruption, through models such as barrel-stave, toroidal pore, and carpet mechanisms, whereas others penetrate cells and inhibit processes including cell-wall synthesis, protein synthesis, and nucleic-acid synthesis [31,32]. Because they target the membrane, a structure that is difficult to alter without a fitness cost, and often act rapidly, AMPs have been considered less prone to resistance than conventional antibiotics. Many also have immunomodulatory activities, including chemokine induction, anti-endotoxin effects, and promotion of wound healing, which broaden their therapeutic potential [32,33]. The human cathelicidin LL-37 is a well-studied example that combines direct antimicrobial and immune-modulating functions [34].

4.2 Clinical Translation and Challenges

Despite thousands of described AMPs, few have reached the market, and those that have are mostly used topically or are lipopeptide antibiotics of microbial origin, such as polymyxins and daptomycin. The revival of the polymyxin colistin as a last-resort drug for carbapenem-resistant Gram-negative infections shows both the value of membrane-active agents and their liabilities, notably nephrotoxicity and neurotoxicity [35]. A review of the clinical pipeline concluded that AMPs face recurring obstacles: susceptibility to proteolytic degradation, short half-life, toxicity or hemolysis at therapeutic doses, loss of activity in physiological salt and serum conditions, and high production cost [33].

Bacteria are also not defenseless against AMPs. Documented resistance strategies include modification of surface charge (for example, lysyl-phosphatidylglycerol synthesis and D-alanylation of teichoic acids in *S. aureus*), proteolytic degradation, efflux, and capsule or biofilm production [36]. A particular concern is cross-resistance: colistin resistance via *mcr* genes or PhoPQ/PmrAB regulation can reduce susceptibility to host defense peptides, with potential implications for host-pathogen interaction [36].

4.3 Engineering Strategies

Current efforts focus on improving stability and selectivity through D-amino acids, cyclization, peptidomimetics, and stapling; on nanoparticle, hydrogel, or liposomal delivery; and on combination with conventional antibiotics for synergy [33]. Computational and machine-learning approaches are increasingly used to design peptide sequences optimized for activity and low toxicity [33]. Clinical use is likely to remain mostly topical, local, or adjunctive in the near term, with systemic use requiring further advances in pharmacology and safety.

5. CRISPR-Cas-Based Antimicrobials

5.1 Concept

CRISPR-Cas systems are adaptive immune systems of bacteria and archaea that use RNA guides to direct Cas nucleases to complementary nucleic-acid sequences [37,38]. By programming a guide RNA to target a gene unique to a pathogen or to a resistance determinant, the nuclease can be repurposed as a sequence-specific antimicrobial. With Cas9, cleavage of the chromosome is typically lethal to bacteria that lack efficient repair of double-strand breaks, whereas targeting a plasmid can eliminate the plasmid and thereby resensitize cells to antibiotics [39,40]. This allows two distinct goals: selective killing of defined bacterial species or strains, and removal of resistance or virulence genes from a population.

5.2 Proof of Concept

Two 2014 studies established the approach. One delivered Cas9 using phagemids to kill virulent *S. aureus* while sparing avirulent strains within mixed populations, and demonstrated efficacy in a mouse skin colonization model [39]. The other used phagemid delivery of RNA-guided nucleases targeting resistance and virulence genes in *E. coli*, including beta-lactamase genes, and reported selective killing of resistant cells and reduced virulence in an

insect infection model [40]. Later work developed Cas13a-based antimicrobials that target RNA and kill bacteria in a sequence-specific manner when delivered with phage capsids, with activity against *E. coli* and *S. aureus* including resistant strains [41]. Alternative delivery vehicles include bacterial conjugation, in which engineered donor strains transfer a CRISPR nuclease-encoding plasmid to recipients, an approach tested in the gut [42], and phage-delivered Cas9 for strain-specific depletion within the mouse gut microbiome [43].

5.3 Challenges

Delivery is the central barrier: phage vectors have a narrow host range and limited cargo, conjugation efficiency is variable, and nonviral nanoparticle systems for bacteria remain immature. Other obstacles include emergence of escape mutants with target-site mutations or inactive Cas/guide systems, potential immunogenicity of Cas proteins, off-target activity, and uncertainty about environmental release of genetically modified delivery vectors, which raises biosafety and regulatory questions. Most data come from laboratory and animal models, and no CRISPR-based antibacterial has yet completed pivotal clinical testing, so the approach should be viewed as an emerging platform rather than a ready therapy. Combining CRISPR payloads with phages, an area of active development, may help to overcome some of these limitations by merging efficient delivery with sequence-specific resensitization.

6. Complementary Strategies: AI-Guided and Natural-Product Discovery

Machine-learning models trained on growth-inhibition data have identified structurally novel antibacterial compounds, such as halicin, which showed broad activity including against carbapenem-resistant Enterobacterales in vitro and in mice [44]. More recently, explainable deep-learning methods identified a structural class of antibiotics active against MRSA and vancomycin-resistant enterococci, with in vivo efficacy in mouse models [45]. Culturing previously uncultivable soil bacteria through in situ growth devices led to the discovery of teixobactin, which binds lipid II and lipid III precursors and for which no resistant mutants were obtained in laboratory selection [46]. These approaches expand the chemical space of conventional antibiotics and may complement the non-traditional strategies discussed above; broader reviews of alternatives to antibiotics provide further context [47].

7. Comparative Assessment

Table 1. Comparison of three non-conventional strategies against resistant bacteria.

Feature	Bacteriophage therapy	Antimicrobial peptides	CRISPR-Cas antimicrobials
Primary mode of action	Receptor-specific infection and lysis	Membrane disruption; intracellular targets; immunomodulation	Sequence-specific DNA/RNA cleavage
Spectrum	Narrow (strain or species level)	Broad to moderate	Programmable (gene, strain, species)
Strongest evidence	Compassionate-use series; limited RCTs	Topical products and lipopeptides; many preclinical	Animal and <i>in vitro</i> models
Main bacterial counter-measures	Receptor mutation, CRISPR-Cas, restriction-modification	Charge modification, proteases, efflux	Target mutation, loss of Cas or guide expression
Key barriers	Host range, titer and stability, immune clearance, regulation	Stability, toxicity, cost, systemic delivery	Delivery, biosafety, regulation
Likely near-term role	Personalized salvage therapy; adjunct to antibiotics	Topical, local, and adjunct use	Research tool; future decolonization or resensitization

The three approaches differ in maturity. Phage therapy has the most human data, although largely uncontrolled; AMPs have a longer pharmaceutical history but have been limited by pharmacology; and CRISPR antimicrobials are the most programmable but least clinically advanced. Importantly, they are not mutually exclusive: phages can serve as vehicles for CRISPR payloads, engineered lysins can incorporate peptide domains, and phage-antibiotic or peptide-antibiotic combinations may exploit synergy and evolutionary trade-offs [26,33].

8. Challenges and Future Perspectives

Several themes cut across all three strategies. First, **diagnostics**: narrow-spectrum agents require rapid identification of the pathogen and, ideally, of its susceptibility to the candidate phage or compound. Second, **trial design**: randomized, adequately powered trials with standardized preparations are needed, and adaptive or platform designs may be better suited to personalized products than conventional phase 3 programs. Third, **manufacturing and regulation**: phage banks, quality control for biologics, and frameworks that allow evolving products require regulatory innovation and international coordination. Fourth, **economics**: narrow-spectrum, short-course therapies have limited market value under current reimbursement models, which strengthens the case for pull incentives and public funding [3]. Fifth, **stewardship and prevention**: no new therapy removes the need to reduce unnecessary antibiotic use, improve infection control, vaccines, and sanitation, and apply a One Health approach across human, animal, and environmental sectors, since resistance will otherwise erode any new agent [3,13].

Future research should prioritize head-to-head and combination trials, better pharmacokinetic and pharmacodynamic models for phages and peptides, characterization of resistance trajectories before clinical deployment, safer and more efficient delivery systems for CRISPR payloads, and integration of AI-based design with experimental validation.

9. Conclusion

AMR is a growing global threat, and incremental modification of existing antibiotics alone is unlikely to be sufficient. Bacteriophage therapy, antimicrobial peptides, and CRISPR-based antimicrobials each offer mechanisms that differ from those of conventional drugs and each has distinct strengths and weaknesses. The evidence supports cautious optimism: phages have shown clinical promise in difficult cases but need controlled trials; AMPs need better stability and safety; and CRISPR antimicrobials need effective delivery. Their most realistic role in the coming decade is as adjuncts or salvage options within a broader strategy that couples innovation with stewardship, diagnostics, and prevention.

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