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Review of Alternative Antimicrobial Therapies

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ABSTRACT

Antimicrobial resistance is a most challenging global public health problem. Today, the number of antibiotic-resistant bacterial strains has been increasing to the point of economic and social disaster. Thus, it is necessary to find alternative effective approaches to antimicrobial therapy and prevention. The most promising alternative antimicrobial therapies include antibodies; bacteriophages and bacteriophage-derived enzymes; antivirulence agents; probiotics and microbiome-modulating agents; immunostimulants; host-protective antimicrobial peptides; nanoparticles and liposomes, etc. A comprehensive approach to treating infections without exacerbating the antimicrobial resistance problem provides for combining these alternative treatments with strategies to maintain the efficacy of existing antimicrobial agents.

The review is aimed to summarize data on the causes and mechanisms underlying the development of resistance; limitations of standard treatments; alternative resistance-inhibiting treatments, their advantages and disadvantages; and future challenges. The paper presents summary of alternative antimicrobial agents at different stages of pharmaceutical development.

Keywords: alternative anti-resistance agents; monoclonal antibodies; bacteriophages; antivirulence agents; antimicrobial peptides and proteins; probiotics and microbiome-modulating substances; antibiotic resistance.

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Обзор альтернативных средств антимикробной терапии

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АННОТАЦИЯ

Резистентность к противомикробным препаратам — одна из самых сложных проблем мирового здравоохранения. В настоящее время наблюдается рост числа антибиотикорезистентных штаммов бактерий на грани экономической и социальной катастрофы, в связи с чем необходим поиск альтернативных эффективных подходов к антимикробной терапии и профилактике. Наиболее перспективными альтернативными средствами антимикробной терапии являются антитела; бактериофаги и ферменты, полученные из бактериофагов; антивирулентные агенты; пробиотики и микробиом-модулирующие вещества; иммуностимуляторы; антимикробные пептиды, защищающие хозяина; наночастицы и липосомы и т. д. Комплексный подход к лечению инфекций без усугубления проблемы устойчивости к противомикробным препаратам предполагает сочетание этих альтернативных методов лечения со стратегиями сохранения эффективности существующих противомикробных средств.

Цель обзора — обобщить информацию о причинах и механизмах, лежащих в основе развития резистентности; ограничениях стандартных методов лечения; альтернативных методах лечения, способных бороться с развитием резистентности, их преимуществах и недостатках; а также о будущих задачах. Приведены сводные данные по альтернативным средствам антимикробной терапии, находящимся на разных этапах фармацевтической разработки.

Ключевые слова: альтернативные средства борьбы с бактериальной устойчивостью; моноклональные антитела; бактериофаги; антивирулентные агенты; антимикробные пептиды и белки; пробиотики и микробиом-модулирующие вещества; антибиотикорезистентность.

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INTRODUCTION

Antimicrobial resistance is one of the most challenging global health problems. Approximately 700,000 people worldwide die each year from infections caused by microorganisms resistant to antibacterial agents. By 2050, annual deaths from antibiotic-resistant bacterial infections may reach 1.91 million.[1]

The prevalence of antibiotic-resistant bacterial strains is increasing. The World Health Organization has published the updated 2024 Bacterial Priority Pathogens List, which includes 15 families of antibiotic-resistant bacteria, categorized into critical, high, and medium priority groups [1, 2]. Notably, this list highlights Gram-negative bacteria resistant to last-resort antibiotics, drug-resistant *Mycobacterium tuberculosis*, and other high-burden resistant pathogens such as *Salmonella*, *Shigella*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The inclusion of these pathogens in the list underscores their global impact in terms of burden on healthcare systems, as well as highlighting issues related to treatment and prevention.[2,3]

Currently, promising alternative antimicrobial therapies include antibodies, probiotics, immunostimulants, photosensitizers, bacteriophages, phage lysins, antimicrobial peptides, antibiofilm agents, efflux pump inhibitors, immunosuppressants, vaccines, and liposomal toxin traps [3]. Meanwhile, the search for new ways to overcome resistance continues.

METHODOLOGY OF SOURCE SEARCH

A traditional review method was applied to Russian and international publications from 2010 to 2024, based on current data on antibiotic resistance and alternative approaches to overcoming it.

Sources were searched in the eLIBRARY.RU, PubMed, Scopus, and Web of Science databases using the following keywords: *альтернативные средства борьбы с бактериальной устойчивостью (alternative agents for bacterial resistance), моноклональные антитела (monoclonal antibodies), бактериофаги (bacteriophages), антивирулентные агенты (antivirulence agents), антимикробные пептиды и белки (antimicrobial peptides and proteins), пробиотики и микробиом-модулирующие вещества (probiotics and microbiome-modulating agents), and антибиотикорезистентность (antibiotic resistance).*

ALTERNATIVE ANTIMICROBIAL THERAPIES

The growing number of resistant bacterial strains has created the need to develop new antimicrobial agents for the treatment of infections [4]. Epidemics and pandemics in recent years have demonstrated that infectious diseases pose a global public health threat, further emphasizing the urgency of developing modern and effective antimicrobial agents [5].

Currently, the development of new antibacterial agents is hindered by several factors. Most antibiotics target only three key prokaryotic processes: 1) protein biosynthesis, 2) deoxyribonucleic acid (DNA) replication, and 3) bacterial cell wall biosynthesis [6]. The main mechanisms targeting these processes were identified in prior years. Moreover, spontaneous bacterial mutations can rapidly nullify the results of years of investigation, significantly increasing the risks and costs of development. An additional challenge lies in the fact that discovering a single new antibiotic requires screening of approximately one million actinomycete strains [7], which greatly increases the cost of the process.

Development of new therapeutic approaches is urgently needed in the context of growing antibiotic resistance. As traditional antibiotics cannot handle growing microbial threats, researchers are developing a range of approaches: from phage therapy and antimicrobial peptides to immunotherapy and microbiome modulation [8]. These alternatives offer promising opportunities to address the pressing global health challenge of antibiotic resistance and bring hope in the fight against infectious diseases.[4]

Supplement 1 presents alternative antimicrobial therapies at various stages of pharmaceutical development.

MONOCLONAL ANTIBODIES AND THEIR COMBINATIONS

Monoclonal antibodies represent a modern therapeutic strategy for managing various diseases, including infectious diseases. Their potential use is based on properties such as homogeneity, selectivity, and a lower potential for cross-reactivity.[5]

[1] Antimicrobial resistance. In: World Health Organization [Internet]. 2020. Available at: https://www.who.int/ru/news-room/fact-sheets/detail/antimicrobial-resistance Accessed on January 24, 2025.

[2] WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. In: World Health Organization [Internet]. 2024. Available at: https://www.who.int/publications/i/item/9789240093461 Accessed on January 31, 2025.

[3] The era of antibiotics: is there hope for continuation? In: Meditsinskiy Vestnik. Information Portal for Healthcare Professionals of Belarus. Available at: https://medvestnik.by/news/era-antibiotikov-est-li-nadezhda-na-prodolzhenie Accessed on January 31, 2025.

[4] 10 new alternatives to antibiotics: alternative therapeutic strategies to treat antibiotic-resistant pathogens. In: Yahoo.finance [Internet]. 2024. Available at: https://finance.yahoo.com/news/10-alternatives-antibiotics-alternative-therapeutic-150657089.html Accessed on January 24, 2025.

[5] Antibacterial agents in clinical and preclinical development: an overview and analysis. In: World Health Organization [Internet]. 2023. Available at: https://www.who.int/publications/i/item/9789240094000. Accessed on January 24, 2025.

The high specificity of monoclonal antibodies, especially when targeting highly variable antigens such as capsules and O-antigens, narrows their spectrum of application [9]. However, advances in diagnostics that enable precise identification of the pathogen causing the infection have facilitated the use of monoclonal antibodies as novel therapeutic agents. Monoclonal antibodies exhibit exceptional diversity (up to 10^{12} different molecules), which significantly increases the likelihood of identifying effective antibacterial agents among potential candidates [10, 11].

However, the complexity of the mechanism of action and the production process of antibacterial monoclonal antibodies limits the number that reach clinical trials, and to date, only three have been approved by the US Food and Drug Administration: raxibacumab[6] and obiltoxaximab[6] for the treatment of inhalational anthrax [12], and bezlotoxumab for the prevention of recurrent *Clostridium difficile* infection [9].

According to Appendix 1, ten antibody-based agents and their combinations are currently in clinical development. Eight of these agents are narrow-spectrum, targeting specific pathogens. Three promising agents are being developed against *S. aureus*: tosatoxumab[6] (AR-301), suvratoxumab[6] (AR-320), and 9MW1411; two against *P. aeruginosa*: Resp-X and panobacumab[6] (AR-101); one against *Campylobacter jejuni* and *Escherichia coli* (LMN-101); one against *Acinetobacter baumannii* (AR-401); one against *Clostridioides difficile* (IM-01); and two antibodies (CMTX-101 and TRL1068) targeting biofilms composed of various Gram-positive and Gram-negative bacteria.

Several candidates developed by Aridis (USA) show significant promise: tosatoxumab[6] (AR-301), suvratoxumab[6] (AR-320), and panobacumab[6] (AR-101).

AR-301 protects host cells from alpha-toxin–mediated damage, preserving human immune cells. The mechanism of action of AR-301 is independent of the antibiotic resistance profile of *S. aureus*; it is active against infections caused by both methicillin-resistant *S. aureus* (methicillin-resistant *Staphylococcus aureus*, MRSA) and methicillin-sensitive *S. aureus*. Significant data have been obtained from two phases of a clinical trial evaluating the safety, pharmacokinetics, and efficacy of a single dose of AR-301 as adjunctive therapy to standard antibiotics in patients (n = 174) diagnosed with ventilator-associated pneumonia caused by *S. aureus*. AR-301 demonstrated good tolerability in the overall population of the full analysis set. In the microbiologically confirmed full analysis set population (n = 120), a clinically relevant trend toward cure was observed on day 21 at a level of 11.3% (p = 0.23) [12].

Similar to AR-301, AR-320 also targets the pore-forming α-toxin of *S. aureus*. The primary indication is the prevention of hospital-acquired pneumonia [13].

AR-101 is effective against multidrug-resistant clinical isolates of *P. aeruginosa*. It is intended as an adjunct first-line therapy for intensive care unit patients with severe *P. aeruginosa* pneumonia. In the phase 2 clinical trial, AR-101 demonstrated positive outcomes in patients with hospital-acquired pneumonia and ventilator-associated pneumonia.[7]

Several reports have described insufficient efficacy of candidate antibodies despite promising phase 1 safety data: neither gremubamab[6] (MEDI3902) nor AR-105 met the primary endpoint in phase 2 clinical trials involving patients with *P. aeruginosa*-associated pneumonia (NCT02696902) or NCT03027609[8] [14, 15].

The development of drugs capable of conjugating with antibodies has become a novel approach in targeted therapy. Given the high specificity of antibodies, antibody–antimicrobial conjugates (AACs) can selectively target bacteria with high precision [12]. Antibody conjugates exhibit lower toxicity. Currently, several systematic reviews exist regarding the design strategies, implementation effects, and future prospects of AACs [16, 17–19].

The pharmaceutical company Roche (Switzerland) is developing the drug DSTA4637A, which consists of a monoclonal antibody against human immunoglobulin (IgG1) that specifically binds to the teichoic acids of *S. aureus*; a novel antibiotic, 4-dimethylamino piperidino-hydroxybenzoxazinorifamycin (dmDNA31); a rifamycin-class antibiotic with an *in vitro* minimum inhibitory concentration of <10 nM against MRSA; and a protease-cleavable valine-citrulline linker that enables antibiotic release within the phagosome. The proposed mechanism of action involves the binding of the AAC to a surface antigen of *S. aureus*, leading to bacterial opsonization, linker cleavage, and release of the antibiotic in its active form. The prolonged presence of the AAC, due to the long circulation time of such molecules, immediately "tags" these bacteria for elimination. Safety evaluation of DSTA4637A is currently underway in a phase 1 clinical trial [17–21].

BACTERIOPHAGES

The antibacterial activity of bacteriophages is mediated by the injection of their genetic material into a bacterial cell, followed by replication and lysis of the host cell. The phage particles released after lysis subsequently infect and lyse other bacterial cells, continuing the cycle of infection

[6] Hereinafter: the drug is not registered in the Russian Federation.

[7] AR-101 (AERUMAB). In: Aridis Pharmaceuticals [Internet]. 2025. Available at: https://www.aridispharma.com/ar-101/ . Accessed on January 27, 2025.

[8] Adjunctive therapeutic treatment with human monoclonal antibody AR-105 (Aerucin®) in P. aeruginosa pneumonia. In: National Library of Medicine [Internet]. Available at: https://clinicaltrials.gov/study/NCT03027609. Accessed on January 27, 2025.

and destruction until the pathogen is fully eliminated from the site of inflammation [22].

The pharmaceutical company Armata Pharmaceuticals (USA) is currently developing three innovative bacteriophage-based agents.

AP-PA02 is a formulation composed of natural *P. aeruginosa* phages derived from different families and subfamilies, targeting multiple classes of bacterial receptors. The selected phage combination acts against pathogen *P. aeruginosa* and is intended for the treatment of severe respiratory infections, with a focus on patients with cystic fibrosis and non–cystic fibrosis bronchiectasis.[9] AP-PA02 was well tolerated and showed an adverse event profile comparable to that of placebo. In a phase 2 clinical trial, AP-PA02 demonstrated a favorable safety and tolerability profile.[10]

AP-SA02 is a novel biologic drug composed of natural lytic phages targeting *S. aureus*. It demonstrates potent antimicrobial activity against approximately 95% of tested *S. aureus* isolates, including drug-resistant strains (MRSA and vancomycin-resistant *S. aureus*), and exhibits a unique mechanism of action that can provide independent or synergistic effects in combination with standard antibiotic therapy.[11] A clinical trial evaluating the use of AP-SA02 in adults with *S. aureus* bacteremia has been completed.[12] In August 2022, the US Food and Drug Administration approved an application for a second indication—prosthetic joint infections.[13]

BX004 is currently undergoing clinical trials to evaluate its efficacy and safety in patients with *P. aeruginosa* respiratory infections in cystic fibrosis and in patients with bronchiectasis. In phase 1b/2a clinical trials, BX004 has demonstrated therapeutic efficacy in treating chronic pulmonary infections in patients with cystic fibrosis. Preclinical trials are also underway to assess the use of BX004 in bronchiectasis. *In vitro* experimental data confirmed the activity of BX004 against antibiotic-resistant *P. aeruginosa* strains, including its ability to penetrate biofilms and achieve the necessary effectiveness with pathogen elimination.[14]

In 2023, a phase 1/2a clinical trial of VRELysin® was initiated, marking another significant milestone toward the development of a safe and effective phage therapy for treating multidrug-resistant bacterial infections, such as those caused by vancomycin-resistant enterococci.[15]

Currently, a phase 1/2a clinical trial of the bacteriophage-based drug EcoActive® is underway to evaluate the safety and efficacy of its oral administration against adherent invasive Escherichia coli in patients with inactive Crohn disease.[16]

LBP-EC01 is an innovative agent based on six genetically modified bacteriophages developed by Locus Biosciences (USA) for the treatment of urinary tract infections caused by *E. coli*, regardless of antibiotic resistance [23].

Two products developed by the Russian company Microgen—a purified polyvalent bacteriophage targeting *Enterobacter* species, including *Enterobacter aerogenes*, *Enterobacter cloacae*, and *Enterobacter agglomerans*, and an *Acinetobacter baumannii* bacteriophage—have received approval for clinical trials to assess safety and efficacy in surgical infections in patients. No data on the results of these studies have been found, and the State Register of Medicinal Products contains no information on the completion of these clinical trials.[17,18]

Russian researchers have also identified two new types of bacteriophages: antimicrobial agents of natural origin that represent particular interest as potential therapeutic agents against enterococcal infections: bacteriophage SSsP-1,

[9] Positive topline results announced for multiphage therapeutic in cystic fibrosis. In: RareDiseaseAdvisor [Internet]. 2023. Available at: https://www.rarediseaseadvisor.com/news/positive-topline-results-announced-multi-phage-therapeutic-cf/. Accessed on February 5, 2025.

[10] Ph 1/2 study evaluating safety and tolerability of inhaled AP-PA02 in subjects with chronic pseudomonas aeruginosa lung infections and cystic fibrosis (SWARM-Pa). In: ICH GCP [Internet]. Available at: https://ichgcp.net/clinical-trials-registry/NCT04596319?ysclid=m2sztpqm2d856860765. Accessed on February 5, 2025.

[11] AP-SA02. In: Armata Pharmaceuticals [Internet]. Available at: https://www.armatapharma.com/pipeline/ap-sa02/. Accessed on March 19, 2025.

[12] Armata pharmaceuticals announces first patient dosed in phase 1b/2a 'diSArm' Study of AP-SA02 in adults with bacteremia due to Staphylococcus aureus. In: BioSpace [Internet]. 2022. Available at: https://www.biospace.com/armata-pharmaceuticals-announces-first-patient-dosed-in-phase-1b-2a-disarm-study-of-ap-sa02-in-adults-with-bacteremia-due-to-staphylococcus-aureus. Accessed on March 19, 2025.

[13] Armata Pharma gets FDA IND clearance for AP-SA02 in prosthetic joint infection. In: Nasdaq [Internet]. 2022. Available at: https://www.nasdaq.com/articles/armata-pharma-gets-fda-ind-clearance-for-ap-sa02-in-prosthetic-joint-infection. Accessed on March 21, 2025.

[14] BiomX reports second quarter 2022 financial results and provides business update. In: BiomX [Internet]. 2022. Available at: https://ir.biomx.com/news-events/press-releases/detail/76/biomx-reports-second-quarter-2022-financial-results-and. Accessed on March 21, 2025.

[15] Intralytix launches phase 1/2a phage therapy trial of Its VRELysin™ phage preparation, to assess safety and efficacy in healthy and VRE-colonized subjects. In: Intralytix [Internet]. 2023. Available at: https://www.intralytix.com/article/115. Accessed on March 21, 2025.

[16] Safety and efficacy of EcoActive against adherent invasive Escherichia coli in patients with inactive Crohn disease. In: ICH GCP [Internet]. 2023. Available at: https://ichgcp.net/ru/clinical-trials-registry/NCT03808103?ysclid=m2t1xcswm5913619320. Accessed on March 26, 2025.

[17] RCT No. 460 (October 23, 2012). In: State Register of Medicinal Products [Internet]. Available at: https://grls.minzdrav.gov.ru/ClPermissionMini.aspx?ClStatementGUID=30f98233-5594-4823-aab4-fb177a6f302a&ClPermGUID=6fc30ee2-d810-48d0-82f8-7a17b18f35a4. Accessed on March 31, 2025.

[18] RCT No. 326 (June 16, 2017) In: State Register of Medicinal Products [Internet]. Available at: https://grls.minzdrav.gov.ru/ClPermissionMini.aspx?ClStatementGUID=24bdc6f6-0122-4ca2-a4ea-d6c2b3477823&ClPermGUID=bfc5d1e0-ab9c-45cb-b02f-b3db1dc97125. Accessed on March 31, 2025.

belonging to the *Saphexavirus* genus of the *Siphoviridae* family (viruses infecting prokaryotes), and bacteriophage GVEsP-1 (*Schiekvirus* genus) of the *Herelleviridae* family (viruses infecting bacteria). Experiments on laboratory mice demonstrated that these novel phage agents exhibit pronounced activity against systemic enterococcal infections. The genomic analysis revealed the presence of specific sequences within the bacteriophage genomes encoding proteins that inhibit the bacterial CRISPR-Cas system, which enhances their virulence and effective colonization of host bacteria. The obtained results confirm the high clinical potential of the investigated bacteriophages.[19]

ANTIVIRULENCE AGENTS

antivirulence agents are compounds that inhibit the activity of bacterial virulence factors or the expression of virulence-associated bacterial phenotypes. Targets for bacterial suppression include virulence factors that play key roles in both acute and chronic infectious processes: adhesins, toxins, bacterial communication systems, and secretion systems [24]. Antivirulence agents may be effective as part of combination therapy or for prophylaxis in the treatment of nosocomial, complicated, and chronic infections [25].

ALS-4 possesses antivirulence properties by inhibiting a key enzyme in the biosynthesis of staphyloxanthin in major MRSA strains, as well as in *S. aureus* strains with intermediate susceptibility to vancomycin and methicillin-sensitive *S. aureus.*[20] A double-blind, placebo-controlled clinical trial assessing dose escalation to evaluate the safety, tolerability, and pharmacokinetics of single and multiple ascending doses in healthy volunteers has been successfully completed.[21]

The evolutionary adaptation of uropathogenic Escherichia coli strains has led to the development of specialized virulence factors that ensure adhesion to uroepithelial cells, survival outside the intestinal environment, modification of cell surface hydrophobicity, and induction of cytopathic effects [26].

The most characteristic bacterial adhesin is FimH, produced by uropathogenic *E. coli* strains [27]. Free D-mannose in urine can saturate *E. coli* FimH structures and subsequently block adhesion of *E. coli* to uroepithelial cells. This so-called competitive inhibition is regarded as one of the potential mechanisms for preventing urinary tract infections [28].

GSK3882347, developed by the pharmaceutical company GlaxoSmithKline (United Kingdom), is a type 1 fimbrial D-mannose–specific adhesin inhibitor and demonstrates its antivirulence properties through FimH inhibition. GSK3882347 is active against *E. coli* and was evaluated in a phase 1 clinical trial for the treatment of uncomplicated urinary tract infections.[22]

At the Gamaleya National Research Center for Epidemiology and Microbiology, the antivirulence agent fluorothiazinon was developed and authorized. It has demonstrated *in vitro* and *in vivo* activity against a broad range of resistant pathogens, including *Chlamydia* spp., *Salmonella enterica*, *P. aeruginosa*, *A. baumannii*, *Klebsiella pneumoniae*, and *E. coli* [29–32]. The drug is an original compound of the thiadiazinone class—4-(3-ethoxy-4-hydroxybenzyl)-5-oxo-5,6-dihydro-4H-[1,3,4]-thiadiazine-2-(2,4-difluorophenyl)-carboxamide—with unique antibacterial activity. The pharmacologic action of fluorothiazinon is based on the inhibition of adenosine triphosphatase of the type III secretion system, a key virulence factor of Gram-negative bacteria, as well as the flagellar apparatus.[23]

ANTIMICROBIAL PEPTIDES AND PROTEINS

Antimicrobial peptides and proteins (AMPs) are natural compounds with direct activity against a broad spectrum of pathogens, including bacteria, fungi, and viruses. AMPs can function as chemoattractants for immune-competent cells (neutrophils, monocytes, T lymphocytes, and dendritic cells) at the site of inflammation. They also influence antigen-presenting cells, modulating adaptive T-cell immune responses [33, 34]. AMPs exert their antimicrobial activity primarily through two distinct mechanisms: membrane targeting (barrel-stave, toroidal pore models, and carpet model), which leads to membrane disruption, and intracellular action via interactions on nucleic acids, proteins, organelles, or the cell wall. Another mechanism involves non-membrane targets [35]. AMPs exhibit diverse mechanisms of action and are indicated for various conditions; selected representatives of this class are listed in Supplement 1.

[19] Russian scientists have found an alternative to antibiotics for treating enterococcal infections. In: Ministry of Science and Higher Education of the Russian Federation [Internet]. 2022. Available at: https://minobrnauki.gov.ru/press-center/news/nauka/52412/. Accessed on March 31, 2025.

[20] Aptorum Group announces submission of clinical trial application for ALS-4, an orally administered small molecule agent for the treatment of Staphylococcus aureus infections, including methicillin-resistant Staphylococcus aureus (MRSA). In: Interfax [Internet]. 2020. Available at: https://www.interfax.ru/pressreleases/742317?ysclid=m9l1urbfzq584569503. Accessed on February 21, 2025.

[21] Clinical trial NCT05274802. In: ICH GCP [Internet]. 2022. Available at: https://ichgcp.net/ru/clinical-trials-registry/NCT05274802. Accessed on February 21, 2025.

[22] Clinical trial NCT05138822. In: ICH GCP [Internet]. 2025. Available at: https://ichgcp.net/ru/clinical-trials-registry/nct05138822?ysclid=m2yrmvh3gd956668168. Accessed on February 21, 2025.

[23] Fluorothiazinon. In: Medgamal [Internet]. Available at: https://medgamal.ru/products/ftortiazinon/?ysclid=m2bk9hwdyb445479017. Accessed on March 10, 2025.

Exeporfinium chloride[6] (XF-73) is a synthetic derivative of dicationic porphyrin with rapid onset of action, potent bactericidal effects, and a low propensity for inducing bacterial resistance. The drug is intended for the prevention of postoperative staphylococcal nasal infections. XF-73 is equally unaffected by inhibitors of cell wall synthesis (β-lactams, carbapenems, glycopeptides, and cephalosporins), protein synthesis inhibitors (oxazolidinones, macrolides, and tetracyclines), DNA synthesis inhibitors (fluoroquinolones), and folic acid synthesis inhibitors [36]. A phase 2 clinical trial has been completed [37].

Omiganan[6] (CLS001, MX-226) is a synthetic indolicidin (a cathelicidin originally isolated from bovine neutrophils). The compound acts by depolarizing the cytoplasmic membrane, leading to cell disruption and bacterial death. It has demonstrated antibacterial and antifungal activity in several preclinical and clinical works, with a favorable safety profile [38].

Ramoplanin[6] (NTI-851) is a glycolipodepsipeptide antibiotic produced by *Actinomycetes* spp. Its pharmacological action involves selective binding to lipid II, a key precursor in bacterial cell wall peptidoglycan. NTI-851 exhibits bactericidal activity against *C. difficile* and other Gram-positive bacteria. The pharmacokinetic properties of the drug (oral administration, lack of systemic absorption, and rapid inactivation in the bloodstream) support its use in the treatment of intestinal infections. The drug is currently in phase 3 clinical trials for the oral treatment of vancomycin-resistant enterococcal infections and in phase 2 trials for the treatment of *C. difficile* infection [39].

Melittin[6], a membrane-active peptide fusion derivative of melittin/protamine from honeybee venom, is currently undergoing preclinical evaluation [40]. The developed agent exhibits strong antibiofilm activity by inhibiting biofilm formation and, in combination with antibiotics, induces death of biofilm-producing bacteria such as *A. baumannii* and *P. aeruginosa* [41]. The compound shows potential for use in combination with colistimethate sodium and imipenem against multidrug-resistant *A. baumannii* isolates [42].

The synthetic peptide containing three tryptophan residues at the *C*-terminus of a 17-amino acid endogenous sequence of human kininogen protein—DPK 060 (GKH17-WWW) exerts antimicrobial effects by disrupting bacterial membranes. It is active against *E. coli*, *P. aeruginosa*, *S. aureus*, and *A. baumannii* in acute external otitis and infections associated with atopic dermatitis [43].

Brilacidin[6] (PMX-30063) is a synthetic arylamide foldamer structurally mimicking a cationic tripeptide and reproducing the amphiphilic properties of natural defensins. The drug demonstrates a broad antimicrobial spectrum, including the activity against *S. aureus*, *P. aeruginosa*, *Haemophilus influenzae*, and *Serratia marcescens* [44]. Potential indications include acute bacterial skin and soft tissue infections, as well as oral mucositis (NCT02324335, NCT01211470) [45].

AP138L-arg26 exhibits multiple bactericidal mechanisms, including membrane disruption and metabolic imbalance. The drug causes damage to the cell membrane or wall by integrating into lipid bilayers, altering membrane fluidity, and disrupting normal homeostasis, which leads to leakage of cellular components and bacterial death. The presence of multiple mechanisms reduces the likelihood of resistance development to the agent. AP138L-arg26 can penetrate mammalian cells and eliminate intracellular bacterial pathogens such as *S. aureus* CVCC 546 in RAW264 mouse macrophages. Antimicrobial activity of AP138L-arg26 was maintained across a wide range of salt concentrations, pH values, temperatures, and in the presence of pepsin [46]. Preclinical studies conducted by the developer show promising results [47].

A promising strategy for treating MRSA infections is the use of ribosomally synthesized and posttranslationally modified peptide antibiotics called lantibiotics. Mutacin[6] 1140 (Mu1140) is a peptide belonging to the lantibiotic class of antibiotics and is naturally produced by the common oral cavity bacterium *Streptococcus mutans* JH1140. The antibiotic is ribosomally synthesized and undergoes enzymatic posttranslational modifications, resulting in the formation of four lanthionine rings. The mechanism of action of Mu1140 is twofold: it binds to the cell wall precursor lipid II, inhibiting cell wall synthesis, and also forms a homogeneous complex around the bacterial target that disrupts the bacterial membrane [48, 49].

Plectasin[6] NZ2114, developed by the biotechnology company Novozymes A/S (Denmark), is undergoing preclinical studies and demonstrates potent bactericidal activity against Gram-positive pathogens. The compound showed the activity comparable to penicillin and vancomycin against *Streptococcus pneumoniae*, exerting bactericidal effects in the experimental models of pneumococcal peritonitis and pneumonia.[24]

PROBIOTICS AND MICROBIOME-MODULATING AGENTS

One of the most promising areas in probiotic research is their potential use in preventing the development and spread of antibiotic resistance. Recent findings have revealed numerous therapeutic effects of probiotics, including direct pathogen suppression and modulation of the immune response. Probiotic strains produce a variety of antimicrobial compounds (bacteriocins, organic acids, biosurfactants, hydrogen peroxide) that are effective against resistant Gram-positive and Gram-negative bacteria [50].

[24] Plectasin NZ2114—Novel Microbial Agent. In: ClinicalTrials Arena [Internet]. Available at: https://www.clinicaltrialsarena.com/projects/plectasin/?cf-view. Accessed on February 7, 2025.

Appendix 1 lists microbiome-modulating agents, three of which are live biotherapeutic products (one also functions as an antibiotic inactivator).

SER-155 is a fermented microbiome drug composed of a community of commensal bacteria designed to reduce the risk of gastrointestinal infections, bacteremia, and graft-versus-host reaction in immunocompromised patients, including those who have undergone allogeneic hematopoietic stem cell transplantation.[25]

VE303 is also a bacterial consortium composed of eight well-characterized, nonpathogenic, nontoxigenic commensal Clostridia strains (5 strains from cluster *Clostridia* XIVa, 2 from cluster IV, and 1 from cluster XVII), isolated from healthy human stool samples and produced using clonal cell banks. In a phase 1a/b trial in healthy volunteers, VE303 was found to be safe and well tolerated at all tested doses [51].

A high dose of VE303 prevented recurrence compared with placebo in a phase 2 clinical trial in adults with laboratory-confirmed *C. difficile* infection. A larger clinical trial is planned to confirm these results.[26]

MET-2 is a live biotherapeutic product composed of 40 live nonpathogenic, nontoxigenic commensal bacterial strains. It offers an innovative therapeutic approach developed as an alternative to fecal microbiota transplantation for the treatment of recurrent infections, caused by *C. difficile*. MET-2 contains 40 live bacterial strains commonly found in the gastrointestinal tract of healthy individuals [52]. In 2020, a phase 1 clinical trial (NCT02865616) of MET-2 for the treatment of recurrent *C. difficile* infection was completed, demonstrating a positive efficacy and safety profile; further trial phases are planned [53].

The company Theriva Biologics (USA) developed SYN-004, ribaxamase (an oral beta-lactamase enzyme) intended for co-administration with intravenous beta-lactam antibiotics to degrade excess drugs in the upper gastrointestinal tract. SYN-004 protects the gut microbiota from disruption by reducing the harmful effects of recurrent *C. difficile* infection, limiting colonization by opportunistic microorganisms, and decreasing the development of antibiotic resistance within the gut microbiome. In 2016, a phase 2 clinical trial (NCT02563106) was completed. It evaluated SYN-004 for the prevention of recurrent *C. difficile* infection in patients with lower respiratory tract infections [54]. Currently, a phase 1 clinical trial (NCT04692181) is underway to assess the safety and tolerability profile of the oral formulation of SYN-004 [55].

HOST-DIRECTED THERAPY

Alternative therapeutic strategies to conventional antibiotics include approaches aimed at modulating the host immune response and other defense mechanisms [56].

Counteracting pathogen-induced immune modulation through host-directed therapy is a promising adjunctive strategy, as it targets both drug-resistant and drug-sensitive bacteria, as well as potentially dormant mycobacteria [57].

In most clinical trials, host-directed agents are administered alongside standard antibiotics targeting *M. tuberculosis*, regardless of whether the infection is rifampin-sensitive or rifampin-resistant.

The most studied agent is dovramilast[6] (CC-11050, AMR-634), which, when used in combination with the antibiotic isoniazid in mice and rabbits, improved lung pathology and reduced *M. tuberculosis* bacterial load in the lungs more effectively than isoniazid alone [58]. A study of CC-11050 in patients with rifampin-resistant tuberculosis is currently underway [59].

Dovramilast[6] is a selective inhibitor of the PDE4 enzyme that suppresses the production of tumor necrosis factor-alpha and interleukin-10 in macrophages, thereby reducing excessive immune activation induced by *M. tuberculosis*. The agent has been studied in a phase 2a clinical trial for tuberculosis (NCT02968927) and a phase 1 two-part trial for nontuberculous mycobacteria (NTM).[5]

Russian researchers at the Gamaleya National Research Center for Epidemiology and Microbiology (Moscow) are developing a recombinant anti-tuberculosis vaccine as an immunomodulatory agent. The vaccine consists of two fusion proteins of mycobacterial antigens (Ag85A and ESAT6-CFP10), fused to a dextran-binding domain and anchored to dextran. The adjuvant formulation includes diethylaminoethyl (DEAE)-dextran and CpG oligonucleotides (a TLR9 receptor agonist) [60]. Experimental investigations using two infection models (aerosol and intravenous) demonstrated the vaccine's protective efficacy against *M. tuberculosis* H37Rv. The most pronounced effect was observed when the vaccine was used as a booster following primary immunization with a tuberculosis vaccine prepared from an attenuated live bacillus (*Mycobacterium bovis*) strain [61]. Phase 3 clinical trials were approved in 2022.[27]

NANOPARTICLES AND LIPOSOMES

Nanomaterial-based therapy represents a promising strategy for combating bacterial infections that are difficult to treat, offering the ability to bypass existing mechanisms

[25] Seres Therapeutics announces FDA Clearance of IND for SER-155, an investigational microbiome therapeutic for the prevention of antibiotic-resistant bacterial infections and graft-versus-host disease (GvHD). In: Seres Therapeutics [Internet]. 2021. Available at: https://ir.serestherapeutics.com/news-releases/news-release-details/seres-therapeutics-announces-fda-clearance-ind-ser-155. Accessed on February 7, 2025.

[26] VE303 for prevention of recurrent clostridioides difficile infection (RESTORATiVE303). In: National Library of Medicine [Internet]. Available at: https://www.clinicaltrials.gov/study/NCT06237452?term=NCT06237452&rank=1. Accessed on February 7, 2025.

[27] Clinical trial NCT04975737. In: ICH GCP [Internet]. Available at: https://ichgcp.net/ru/clinical-trials-registry/NCT04975737. Accessed on March 11, 2025.

associated with acquired drug resistance. The unique size and physical properties of nanomaterials enable them to affect biofilms and overcome persistent infections [62].

The properties and size of nanoparticles may allow them to easily penetrate bacterial membranes and target specific biosynthetic and enzymatic pathways. Nanoparticles can act against pathogens through various mechanisms, either exhibiting intrinsic antibacterial activity or serving as carriers for antibiotics, which may be attached to or encapsulated within them. In such cases, they are referred to as nanobiotics or nanoantibiotics. Metal-based nanoparticles can exert toxic effects on microorganisms, as they are capable of generating reactive oxygen species under certain conditions, such as exposure to ultraviolet radiation [63].

The studies conducted by McShan et al. demonstrated that tetracycline–Ag-NPs (silver nanoparticles) and neomycin–Ag-NPs exert a synergistic effect in inhibiting the growth of *Salmonella typhimurium* when used in combination. The minimum inhibitory concentrations required to inhibit 50% of microbial growth were 0.07 μg/mL for tetracycline–Ag-NPs and 0.43 μg/mL for neomycin–Ag-NPs [64]. In a work by Abo-Shama et al., the antibiotics azithromycin, cefotaxime, cefuroxime, fosfomycin, and chloramphenicol were combined with Ag-NPs. The authors demonstrated that the synergistic effect against *E. coli* was significantly stronger than with antibiotics alone. In the presence of Ag-NPs, all antibiotics also showed synergistic activity against *Salmonella* spp. The combined use of oxacillin and neomycin substantially increased the efficacy of Ag-NPs against *S. aureus* compared with the monotherapy [65].

According to Brown et al., ampicillin-functionalized Ag-NPs exhibited synergistic effects against multiple strains of *P. aeruginosa*, *E. aerogenes*, and methicillin-resistant *S. aureus* that were antibiotic resistant [66].

Recent research by Abo-Shama et al. demonstrated that ZnO-NPs (zinc oxide nanoparticles) significantly enhance the efficacy of imipenem against *K. pneumoniae* and *E. coli* [65]. A synergistic effect of levofloxacin combined with ZnO-NPs against MRSA was also observed. This effect was dose-dependent [66].

Additionally, Naqvi et al. investigated the antimicrobial activity of copper and copper-based nanoparticles in combination with ciprofloxacin and streptomycin against *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Proteus mirabilis* and *Klebsiella oxytoca* [67]. Faisal et al. showed that combinations of CuNP and copper-based NP with imipenem, meropenem, and ciprofloxacin can increase their antimicrobial activity by 0.5 to 3.0 times [68].

Other nanoparticles such as Fe, Pt, Pd, Ba, and Ti also have potential to significantly enhance the efficacy of commercial antibiotics through synergistic effects [69, 70].

Challenges in nanoparticle application include potential high toxicity, complex synthesis procedures, and unclear antimicrobial mechanisms of action [71, 72].

Lipid-based nanoscale carriers can directly disrupt bacterial cell membranes by lysing them and inhibit bacterial growth via multiple mechanisms. CAL02, a liposomal agent composed of cholesterol and sphingomyelin currently in phase 2 clinical trials, is a promising development for infection control. Taking into account the global rise of antibiotic resistance, antimicrobial lipids delivered by nanocarriers may represent a novel alternative in combating infectious diseases [73].

Virulence factors attach to host cell lipid platforms to target host cells and tissues. CAL02 mimics these platforms in a highly stable manner. Virulence factors bind CAL02 with higher affinity than host cells. Thus, CAL02 acts as a high-affinity trap [74].

CAL02 neutralizes bacterial pore-forming toxins, enzymes, and toxin-effector virulence factors that play critical roles in pathogenesis and severity of infections such as severe pneumonia, bacteremia, and sepsis [75].

CAL02 is a non-antibiotic new antitoxin with a unique mechanism of action. This agent consists of a mixture of liposomes that sequester bacterial toxins known to dysregulate inflammation, cause organ damage, and impair immune defense. Preclinical studies demonstrated that, in combination with antibiotics, CAL02 significantly improves survival in mice with severe community-acquired pneumonia and bacteremia. A randomized, double-blind, multicenter, placebo-controlled phase 2 clinical trial was conducted involving patients with severe pneumococcal community-acquired pneumonia [76].

AR-501 is an inhaled formulation of gallium citrate that acts as an iron analog, depriving bacteria of this essential micronutrient.[28] Its effect on pulmonary bacterial infection in patients with cystic fibrosis is currently under investigation[5].

The mechanism of action of AR-501 differs from that of all antibiotics and is effective against antibiotic-resistant bacteria. Intravenous administration of gallium was found to be safe and effective in a recent phase 2 clinical trial involving patients with cystic fibrosis. Inhaled AR-501 was also well tolerated by healthy adult volunteers ($n = 48$) across five repeated weekly doses and all tested dose levels (6.4, 20, and 40 mg), with no serious adverse events reported.[28]

CONCLUSIONS

The fight against drug-resistant bacteria has entered a new phase due to the growing number of promising advances in non-antibiotic therapies. These approaches hold great potential to address the alarming rise of antibiotic resistance by offering effective alternatives to conventional treatments.

[28] AR-501 (Gallium Citrate): Novel anti-infective for the growing problem of antibiotic resistance. In: Aridis Pharmaceuticals [Internet]. Available at: https://www.aridispharma.com/ar-501/. Accessed on February 14, 2025.

Current alternative agents under development are designed to meet modern challenges and target priority bacterial pathogens aligned with the international strategies and lists of the World Health Organization. It can be estimated that approximately 68% of the total antimicrobial agents currently in development are active against the multidrug-resistant nosocomial pathogens of the ESKAPE group (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* spp.). Among these, 34.6% show activity against *S. aureus*, 23.1% against *P. aeruginosa*, 15.4% against *E. coli*, 7.7% against vancomycin-resistant *Enterobacteriaceae,* and the remaining (19.2%) target multiple pathogens.

Thus, current research findings demonstrate the promise of further development of alternative agents to combat antibiotic resistance, focusing on increasingly potent compounds based on AMPs, monoclonal antibodies, and antivirulence agents.

However, these new therapies have complex mechanisms of action, and extensive clinical trials are necessary to confirm their efficacy and safety. Therefore, their adoption as standard treatment and prevention approaches requires careful evaluation. A coordinated effort by the scientific community and regulatory authorities is needed to coordinate and promote the growth of such developments.

ADDITIONAL INFORMATION

Supplement 1: Alternative antimicrobial agents at various stages of pharmaceutical development.
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REFERENCES | СПИСОК ЛИТЕРАТУРЫ

1. Dzhioev YP, Zlobin VI, Salovarova VP, et al. Analysis of the "superbacteria" issue and contemporary approaches to its solution. Proceedings of Universities. *Applied Chemistry and Biotechnology.* 2019;9(4):665–678. doi: 10.21285/2227-2925-2019-9-4-665-678 EDN: JYFFNC

2. Shafaati M, Salehi M, Zare M. The twin challenges of longevity and climate change in controlling antimicrobial resistance. *J Antibiot (Tokyo).* 2024;77(7):399–402. doi: 10.1038/s41429-024-00730-6 EDN: ZNOYWS

3. Nazarov PA. Alternatives to antibiotics: phage lytic enzymes and phage therapy. *Bulletin of Russian State Medical University.* 2018;(1):5–15. doi: 10.24075/vrgmu.2018.002 EDN: XQWGXR

4. Neubauer D, Jaśkiewicz M, Migoń D, et al. Retro analog concept: comparative study on physico-chemical and biological properties of selected antimicrobial peptides. *Amino Acids.* 2017;49(10):1755–1771. doi: 10.1007/s00726-017-2473-7 EDN: HHWFOV

5. Tsepelev VY, Lazareva IA, Gunov SV. Antimicrobial peptides — a modern alternative to antibiotics. *Modern Problems of Science and Education.* 2023;(3):104. doi: 10.17513/spno.32620 EDN: JDIGZA

6. Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. *Nat Rev Microbiol.* 2010;8(6):423–435. doi: 10.1038/nrmicro2333

7. Lewis K. Platforms for antibiotic discovery. *Nat Rev Drug Discov.* 2013;12(5):371–387. doi: 10.1038/nrd3975 EDN: YDTISH

8. Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics-a pipeline portfolio review. *Lancet Infect Dis.* 2016;16(2):239–251. doi: 10.1016/S1473-3099(15)00466-1

9. 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(10):5487. doi: 10.3390/ijms25105487 EDN: ETJEHY

10. Briney B, Inderbitzin A, Joyce C, Burton DR. Commonality despite exceptional diversity in the baseline human antibody repertoire. *Nature.* 2019;566(7744):393–397. doi: 10.1038/s41586-019-0879-y

11. Lanini S, Milleri S, Andreano E, et al. Safety and serum distribution of anti-SARS-CoV-2 monoclonal antibody MAD0004J08 after intramuscular injection. *Nat Commun.* 2022;13(1):2263. doi: 10.1038/s41467-022-29909-x EDN: ECONNN

12. Zurawski DV, McLendon MK. Monoclonal antibodies as an antibacterial approach against bacterial pathogens. *Antibiotics (Basel).* 2020;9(4):155. doi: 10.3390/antibiotics9040155 EDN: QVMNQX

13. François B, Jafri HS, Chastre J, et al. Efficacy and safety of suvratoxumab for prevention of Staphylococcus aureus ventilator-associated pneumonia (SAATELLITE): a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial. *Lancet Infect Dis.* 2021;21(9):1313–1323. doi: 10.1016/S1473-3099(20)30995-6 EDN: DGTUQR

14. Chastre J, François B, Bourgeois M, et al. Safety, efficacy, and pharmacokinetics of gremubamab (MEDI3902), an anti-Pseudomonas aeruginosa bispecific human monoclonal antibody, in P. aeruginosa-colonised, mechanically ventilated intensive care unit patients: a randomised controlled trial. *Crit Care.* 2022;26(1):355. doi: 10.1186/s13054-022-04204-9 EDN: CAWTEK

15. Ali SO, Yu XQ, Robbie GJ, et al. Phase 1 study of MEDI3902, an investigational anti-Pseudomonas aeruginosa PcrV and Psl bispecific human monoclonal antibody, in healthy adults. *Clin Microbiol Infect.* 2019;25(5):629.e1–629.e6. doi: 10.1016/j.cmi.2018.08.004

16. Yu L, Shang Z, Jin Q, et al. Antibody-antimicrobial conjugates for combating antibiotic resistance. *Adv Healthc Mater.* 2023;12(1):e2202207. doi: 10.1002/adhm.202202207 EDN: BQSOVT

17. Zhou C, Lehar S, Gutierrez J, et al. Pharmacokinetics and pharmacodynamics of DSTA4637A: A novel THIOMAB™ antibody antibiotic conjugate against Staphylococcus aureus in mice. *MAbs.* 2016;8(8):1612–1619. doi: 10.1080/19420862.2016.1229722

18. Deng R, Zhou C, Li D, et al. Preclinical and translational pharmacokinetics of a novel THIOMAB™ antibody-antibiotic conjugate against Staphylococcus aureus. *MAbs.* 2019;11(6):1162–1174. doi: 10.1080/19420862.2019.1627152

19. Cavaco M, Castanho MARB, Neves V. The use of antibody-antibiotic conjugates to fight bacterial infections. *Front Microbiol.* 2022;13:835677. doi: 10.3389/fmicb.2022.835677 EDN: HEKPPG
20. Tvilum A, Johansen MI, Glud LN, et al. Antibody-drug conjugates to treat bacterial biofilms via targeting and extracellular drug release. *Adv Sci (Weinh).* 2023;10(23):e2301340. doi: 10.1002/advs.202301340 EDN: KHUGNH
21. Darbandi A, Abdi M, Dashtbin S, et al. Antibody-antibiotic conjugates: a comprehensive review on their therapeutic potentials against bacterial infections. *J Clin Lab Anal.* 2024;38(10):e25071. doi: 10.1002/jcla.25071 EDN: NXQCIA
22. Łusiak-Szelachowska M, Międzybrodzki R, Drulis-Kawa Z, et al. Bacteriophages and antibiotic interactions in clinical practice: what we have learned so far. *J Biomed Sci.* 2022;29(1):23. doi: 10.1186/s12929-022-00806-1 EDN: WKSOBC
23. Kim P, Sanchez AM, Penke TJR, et al. Safety, pharmacokinetics, and pharmacodynamics of LBP-EC01, a CRISPR-Cas3-enhanced bacteriophage cocktail, in uncomplicated urinary tract infections due to Escherichia coli (ELIMINATE): the randomised, open-label, first part of a two-part phase 2 trial. *Lancet Infect Dis.* 2024;24(12):1319–1332. doi: 10.1016/S1473-3099(24)00424-9 EDN: CXOLCC
24. Abaturov AE, Kryuchko TA. Inhibition of bacterial quorum sensing (general concept). *Zdorov'e rebenka.* 2019;14(1):54–59. doi: 10.22141/2224-0551.14.1.2019.157881 EDN: RQCVHS
25. Savitskii MV, Moskaleva NE, Zigangirova NA. Experimental pharmacokinetics, metabolism and tissue distribution studies fluorothiazinon, a of novel antivirulence drug. *Journal Biomed.* 2023;19(1):73–84. doi: 10.33647/2074-5982-19-1-73-84 EDN: RBEKKA
26. Liu H, Ma J, Yang P, et al. Comparative analysis of biofilm characterization of probiotic Escherichia coli. *Front Microbiol.* 2024;15:1365562. doi: 10.3389/fmicb.2024.1365562 EDN: VVYCPW
27. Sarshar M, Behzadi P, Ambrosi C, et al FimH and anti-adhesive therapeutics: a disarming strategy against uropathogens. *Antibiotics (Basel).* 2020;9(7):397. doi: 10.3390/antibiotics9070397 EDN: MOIMKD
28. Ala-Jaakkola R, Laitila A, Ouwehand AC, Lehtoranta L. Role of D-mannose in urinary tract infections — a narrative review. *Nutr J.* 2022;21(1):18. doi: 10.1186/s12937-022-00769-x EDN: WUSFRF
29. Bondareva NE, Soloveva AV, Sheremet AB, et al. Preventative treatment with Fluorothiazinon suppressed Acinetobacter baumannii-associated septicemia in mice. *J Antibiot (Tokyo).* 2022;75(3):155–163. doi: 10.1038/s41429-022-00504-y EDN: DEMGBU
30. Koroleva EA, Soloveva AV, Morgunova EY, et al. Fluorothiazinon inhibits the virulence factors of uropathogenic Escherichia coli involved in the development of urinary tract infection. *J Antibiot (Tokyo).* 2023;76(5):279–290. doi: 10.1038/s41429-023-00602-5 EDN: WJNICV
31. Tsarenko SV, Zigangirova NA, Soloveva AV, et al. A novel antivirulent compound fluorothiazinone inhibits Klebsiella pneumoniae biofilm in vitro and suppresses model pneumonia. *J Antibiot (Tokyo).* 2023;76(7):397–405. doi: 10.1038/s41429-023-00621-2 EDN: XJRTTK
32. Zigangirova NA, Nesterenko LN, Sheremet AB, et al. Fluorothiazinon, a small-molecular inhibitor of T3SS, suppresses salmonella oral infection in mice. *J Antibiot (Tokyo).* 2021;74(4):244–254. doi: 10.1038/s41429-020-00396-w EDN: AEQAFN
33. Iksanova AM, Arzumanian VG, Konanykhina SY, Samoylikov PV. Antimicrobial peptides and proteins in human biological fluids. *Microbiology Independent Research Journal.* 2022;9(1):37–55. doi: 10.18527/2500-2236-2022-9-1-37-55 EDN: OSJIOH
34. Mishra R, Panda AK, De Mandal S, et al. Natural anti-biofilm agents: strategies to control biofilm-forming pathogens. *Front Microbiol.* 2020;11:566325. doi: 10.3389/fmicb.2020.566325 EDN: BUYYLC
35. Bucataru C, Ciobanasu C. Antimicrobial peptides: Opportunities and challenges in overcoming resistance. *Microbiol Res.* 2024;286:127822. doi: 10.1016/j.micres.2024.127822 EDN: NXIJGX
36. Mangino JE, Firstenberg MS, Milewski RKC, et al. Exeporfinium chloride (XF-73) nasal gel dosed over 24 hours prior to surgery significantly reduced Staphylococcus aureus nasal carriage in cardiac surgery patients: Safety and efficacy results from a randomized placebo-controlled phase 2 study. *Infect Control Hosp Epidemiol.* 2023;44(7):1171–1173. doi: 10.1017/ice.2023.17 EDN: SMGADH
37. Rhys-Williams W, Galvin HM, Love WG. Screening of the novel antimicrobial drug, XF-73, against 2,527 Staphylococcus species clinical isolates. *Front Cell Infect Microbiol.* 2023;13:1264456. doi: 10.3389/fcimb.2023.1264456 EDN: OJFJBM
38. Niemeyer-van der Kolk T, Assil S, Buters TP, et al. Omiganan enhances imiquimod-induced inflammatory responses in skin of healthy volunteers. *Clin Transl Sci.* 2020;13(3):573–579. doi: 10.1111/cts.12741 EDN: YDCWQM
39. Alshrari AS, Hudu SA, Elmigdadi F, Imran M. The urgent threat of Clostridioides difficile infection: a glimpse of the drugs of the future, with related patents and prospects. *Biomedicines.* 2023;11(2):426. doi: 10.3390/biomedicines11020426 EDN: QOXVMO
40. Lima WG, Batista Filho FL, Lima IP, et al. Antibacterial, anti-biofilm, and anti-adhesive activities of melittin, a honeybee venom-derived peptide, against quinolone-resistant uropathogenic Escherichia coli (UPEC). *Nat Prod Res.* 2022;36(24):6381–6388. doi: 10.1080/14786419.2022.2032047 EDN: MWCVOM
41. Yang H, Ma R, Chen J, et al. Discovery of melittin as triple-action agent: broad-spectrum antibacterial, anti-biofilm, and potential anti-quorum sensing activities. *Molecules.* 2024;29(3):558. doi: 10.3390/molecules29030558 EDN: JPTBEQ
42. Mirzaei R, Alikhani MY, Arciola CR, et al. Prevention, inhibition, and degradation effects of melittin alone and in combination with vancomycin and rifampin against strong biofilm producer strains of methicillin-resistant Staphylococcus epidermidis. *Biomed Pharmacother.* 2022;147:112670. doi: 10.1016/j.biopha.2022.112670 EDN: VDKKDM
43. Håkansson J, Ringstad L, Umerska A, et al. Characterization of the in vitro, ex vivo, and in vivo efficacy of the antimicrobial peptide DPK-060 Used for topical treatment. *Front Cell Infect Microbiol.* 2019;9:174. doi: 10.3389/fcimb.2019.00174
44. Kaplan CW, Sim JH, Shah KR, et al. Selective membrane disruption: mode of action of C16G2, a specifically targeted antimicrobial peptide. *Antimicrob Agents Chemother.* 2011;55(7):3446–3452. doi: 10.1128/AAC.00342-11
45. Safronova VN, Bolosov IA, Panteleev PV, et al. Therapeutic potential and application prospects of antimicrobial peptides in the era of global spread of antibiotic resistance. *Bioorganicheskaya khimiya.* 2023;49(3):243–258. doi: 10.31857/S0132342323030181 EDN: PEADRY
46. Zhang K, Yang N, Teng D, et al. Expression and characterization of the new antimicrobial peptide AP138L-arg26 anti Staphylococcus aureus. *Appl Microbiol Biotechnol.* 2024;108(1):111. doi: 10.1007/s00253-023-12947-w EDN: IRZMCX
47. Wu J, Zhou X, Chen Q, et al. Defensins as a promising class of tick antimicrobial peptides: a scoping review. *Infect Dis Poverty.* 2022;11(1):71. doi: 10.1186/s40249-022-00996-8 EDN: LTKQBN
48. Burgin DJ, Liu R, Hsieh RC, et al. Investigational agents for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia: progress in clinical trials. *Expert Opin Investig Drugs.* 2022;31(3):263–279. doi: 10.1080/13543784.2022.2040015 EDN: LXMAUO
49. Ju M, Joseph T, Hansanant N, et al. Evaluation of analogs of mutacin 1140 in systemic and cutaneous methicillin-resistant Staphylococcus aureus infection models in mice. *Front Microbiol.* 2022;13:1067410. doi: 10.3389/fmicb.2022.1067410 EDN: BDBDOS
50. Andreev VA, Stetsiouk OU, Andreeva IV. Probiotics: controversial issues. *Clinical Microbiology and Antimicrobial Chemotherapy.* 2022;24(4):345–360. doi: 10.36488/cmac.2022.4.345-360 EDN: WFLVRE
51. Dsouza M, Menon R, Crossette E, et al. Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe.* 2022;30(4):583–598.e8. doi: 10.1016/j.chom.2022.03.016 EDN: FTLGBK
52. Strum WB, Boland CR. Advances in acute and chronic pancreatitis. *World J Gastroenterol.* 2023;29(7):1194–1201. doi: 10.3748/wjg.v29.i7.1194 EDN: YBECDT
53. Kao D, Wong K, Franz R, et al. The effect of a microbial ecosystem therapeutic (MET-2) on recurrent Clostridioides difficile infection: a phase 1, open-label, single-group trial. *Lancet Gastroenterol Hepatol.* 2021;6(4):282–291. doi: 10.1016/S2468-1253(21)00007-8 EDN: WHTFRL

54. Roberts T, Kokai-Kun JF, Coughlin O, et al. Tolerability and pharmacokinetics of SYN-004, an orally administered β-lactamase for the prevention of clostridium difficile-associated disease and antibiotic-associated diarrhea, in two phase 1 studies. *Clin Drug Investig.* 2016;36(9):725–734. doi: 10.1007/s40261-016-0420-0
55. Kokai-Kun JF, Roberts T, Coughlin O, et al. Use of ribaxamase (SYN-004), a β-lactamase, to prevent Clostridium difficile infection in β-lactam-treated patients: a double-blind, phase 2b, randomised placebo-controlled trial. *Lancet Infect Dis.* 2019;19(5):487–496. doi: 10.1016/S1473-3099(18)30731-X
56. Wallis RS, O'Garra A, Sher A, Wack A. Host-directed immunotherapy of viral and bacterial infections: past, present and future. *Nat Rev Immunol.* 2023;23(2):121–133. doi: 10.1038/s41577-022-00734-z EDN: ALCZEI
57. Strong EJ, Lee S. Targeting autophagy as a strategy for developing new vaccines and host-directed therapeutics against mycobacteria. *Front Microbiol.* 2021;11:614313. doi: 10.3389/fmicb.2020.614313 EDN: CHQWRW
58. Subbian S, Tsenova L, Holloway J, et al. Adjunctive phosphodiesterase-4 inhibitor therapy improves antibiotic response to pulmonary tuberculosis in a rabbit model. *EBioMedicine.* 2016;4:104–114. doi: 10.1016/j.ebiom.2016.01.015
59. Mi J, Wu X, Liang J. The advances in adjuvant therapy for tuberculosis with immunoregulatory compounds. *Front Microbiol.* 2024;15:1380848. doi: 10.3389/fmicb.2024.1380848 EDN: GVRZQF
60. Tkachuk AP, Gushchin VA, Potapov VD, et al. Multi-subunit BCG booster vaccine GamTBvac: Assessment of immunogenicity and protective efficacy in murine and guinea pig TB models. *PLoS One.* 2017;12(4):e0176784. doi: 10.1371/journal.pone.0176784 EDN: XNFCKE
61. Kleymenov DA, Mazunina EP, Lunin VG, et al. Immunological memory formed in response to administration of GamTBvac recombinant tuberculosis vaccine candidate: clinical trials in healthy volunteers. *Bulletin of Russian State Medical University.* 2017;(5):29–37. EDN: ZVZDQJ
62. Wang L, Hu C, Shao L. The antimicrobial activity of nanoparticles: present situation and prospects for the future. *Int J Nanomedicine.* 2017;12:1227–1249. doi: 10.2147/IJN.S121956 EDN: WLABYY
63. Mondal SK, Chakraborty S, Manna S, Mandal SM. Antimicrobial nanoparticles: current landscape and future challenges. *RSC Pharm.* 2024;1:388. doi: 10.1039/d4pm00032c
64. McShan D, Zhang Y, Deng H, et al. Synergistic antibacterial effect of silver nanoparticles combined with ineffective antibiotics on drug resistant salmonella typhimurium DT104. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2015;33(3):369–384. doi: 10.1080/10590501.2015.1055165 EDN: XYOFIF
65. Abo-Shama UH, El-Gendy H, Mousa WS, et al. Synergistic and antagonistic effects of metal nanoparticles in combination with antibiotics against some reference strains of pathogenic microorganisms. *Infect Drug Resist.* 2020;13:351–362. doi: 10.2147/IDR.S234425 EDN: JIPQHG
66. Brown AN, Smith K, Samuels TA, et al. Nanoparticles functionalized with ampicillin destroy multiple-antibiotic-resistant isolates of Pseudomonas aeruginosa and Enterobacter aerogenes and methicillin-resistant Staphylococcus aureus. *Appl Environ Microbiol.* 2012;78(8):2768–2774. doi: 10.1128/aem.06513-11 EDN: PHSIHJ
67. Naqvi SS, Anwer H, Siddiqui A, Zohra RR. Novel synthesis of maltol capped copper nanoparticles and their synergistic antibacterial activity with antibiotics. *Plasmonics.* 2021;16(6):1–14. doi: 10.1007/s11468-021-01452-3 EDN: FLKRHN
68. Faisal S, Al-Radadi NS, Jan H, et al. Curcuma longa Mediated synthesis of copper oxide, nickel oxide and Cu-Ni bimetallic hybrid nanoparticles: Characterization and evaluation for antimicrobial, anti-parasitic and cytotoxic potentials. *Coatings.* 2021;11(7):849. doi: 10.3390/coatings11070849 EDN: FTPGHF
69. Hamid OS, Mahmood SS. The synergistic effect of gold nanoparticle loaded with ceftazidium antibiotic against multidrug ersistance pseudomonas aeruginosa. *Iraqi Journal of Agricultural Sciences.* 2021;52(4):828–835. doi: 10.36103/ijas.v52i4.1391
70. Abdullah, Jamil T, Atif M, et al. Recent advances in the development of metal/metal oxide nanoparticle and antibiotic conjugates (MNP-Antibiotics) to address antibiotic resistance: review and perspective. *Int J Mol Sci.* 2024;25(16):8915. doi: 10.3390/ijms25168915 EDN: ENXFUN
71. Yu R, Chen H, He J, et al. Engineering antimicrobial metal-phenolic network nanoparticles with high biocompatibility for wound healing. *Adv Mater.* 2024;36(6):e2307680. doi: 10.1002/adma.202307680 EDN: DZXMBK
72. Gbian DL, Omri A. Lipid-based drug delivery systems for diseases managements. *Biomedicines.* 2022;10(9):2137. doi: 10.3390/biomedicines10092137 EDN: IBMVEU
73. Zhang Q, Wu W, Zhang J, Xia X. Antimicrobial lipids in nano-carriers for antibacterial delivery. *J Drug Target.* 2020;28(3):271–281. doi: 10.1080/1061186X.2019.1681434
74. Azeredo da Silveira S, Shorr AF. Critical parameters for the development of novel therapies for severe and resistant infections-a case study on CAL02, a non-traditional broad-spectrum anti-virulence drug. *Antibiotics (Basel).* 2020;9(2):94. doi: 10.3390/antibiotics9020094 EDN: OVTRNS
75. Laterre PF, Colin G, Dequin PF, et al. CAL02, a novel antitoxin liposomal agent, in severe pneumococcal pneumonia: a first-in-human, double-blind, placebo-controlled, randomised trial. *Lancet Infect Dis.* 2019;19(6):620–630. doi: 10.1016/S1473-3099(18)30805-3
76. Sellarès-Nadal J, Burgos J, Falcó V, Almirante B. Investigational and experimental drugs for community-acquired pneumonia: the current evidence. *J Exp Pharmacol.* 2020;12:529–538. doi: 10.2147/JEP.S259286 EDN: ULSHOY

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