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NEW APPROACHES FOR COMBATING POLYRESISTANT ESKAPE PATHOGENS

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СОВРЕМЕННЫЕ ПОДХОДЫ К БОРЬБЕ С ПОЛИРЕЗИСТЕНТНЫМИ ПАТОГЕНАМИ ГРУППЫ ESKAPE

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Abstract

Antibiotic resistance of microorganisms is the most pressing global health problem due to the ever-increasing number of deaths caused by ineffective antibiotic therapy. The COVID-19 pandemic has only exacerbated pre-existing issue of increasing resistance of bacterial strains worldwide. Lack of public awareness about proper use of antibiotics directly impacts on uncontrolled antibiotic administration associated with weak antibiotic dispensing controls as well as limited access to health facilities in low- and middle-income countries. It is reported that 68.9% of COVID-19 patients used antibiotics for prophylaxis against bacterial complications or to treat coronavirus infection (mainly azithromycin and ceftriaxone) before hospitalization, with a self-medication rate of 33.0%. The most antibiotic-resistant and dangerous to global public health group of microorganisms is known as ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species*. The proportion of resistant strains among these microorganisms can reach 95%. In light of the rapid increase in the number of infections caused by antibiotic-resistant strains, a need to create new antibacterial drugs is the most urgent task.

The development of new antibiotics is a high-cost goal and it's often ineffective. Therefore, more and more often their developers resort to the use of antibiotics combinations or using them together with adjuvants of different mechanisms of action. In recent years, special devices and coatings with nanoparticles of various metals deposited on their surface have become increasingly widespread. Some successes achieved in the use of antimicrobial peptides have been leveled by the loss of activity in the human body and their high production cost. In this regard, the use of bacteriophages, especially in combination with antibiotics, has been becoming a promising approach. The observed synergism both in vitro and in vivo experiments allow to hope for certain successes in the fight against ESKAPE group multidrug-resistant pathogens.

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Keywords: antibiotic resistance, multidrug resistance, gram-negative bacteria, gram-positive bacteria, phage-antibiotic synergy, ESKAPE pathogens.

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Резюме

Антибиотикорезистентность микроорганизмов — наиболее актуальная проблема мирового здравоохранения, обусловленная все более возрастающим количеством смертей по причине неэффективной антибактериальной терапии. Пандемия COVID-19 лишь усугубила и без того существующую проблему нарастания резистентности штаммов бактерий во всем мире. Отсутствие осведомленности населения об адекватном применении антибиотиков оказало прямое влияние на их бесконтрольное применение, связанное со слабыми мерами контроля отпуска антибиотиков, а также ограниченным доступом к медицинским учреждениям в странах с низким и средним уровнем доходов. Сообщается, что 68,9% пациентов с COVID-19 использовали антибиотики в качестве профилактики бактериальных осложнений либо для лечения коронавирусной инфекции (в основном азитромицин и цефтриаксон) до госпитализации, при этом уровень самолечения составил 33,0%. Наиболее устойчивая к антибиотикам и опасная для мирового здравоохранения группа микроорганизмов известна как ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* species. При этом доля резистентных штаммов среди этих микроорганизмов может достигать 95%. В свете стремительного роста количества случаев инфекций, вызванных антибиотикорезистентными штаммами, необходимость создания новых антибактериальных препаратов является наиболее актуальной задачей.

Разработка новых антибиотиков высокозатратна и зачастую малоэффективна. Поэтому все чаще их разработчики прибегают к использованию комбинаций антибиотиков или сочетанию их с адъювантами с разным механизмом действия. В последние годы все более широкое распространение получают специальные устройства и покрытия с нанесенными на их поверхность наночастицами различных металлов. Некоторые успехи, достигнутые при использовании антимикробных пептидов, были нивелированы потерей

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активности в организме человека и высокой стоимостью их производства. В связи с этим перспективным направлением становится использование бактериофагов, особенно в сочетании с антибиотиками. Наблюдаемый при этом синергизм как в экспериментах in vitro, так и in vivo, позволяет надеяться на определенные успехи в борьбе с полирезистентными патогенами группы ESKAPE.

Ключевые слова: антибиотикорезистентность, множественная лекарственная устойчивость, грамположительные бактерии, грамотрицательные бактерии, бактерии группы ESKAPE**,** синергизм фагов с антибиотиками.

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1 Introduction

In recent decades, the overuse and misuse of antibiotics, as well as social and economic factors, have accelerated the spread of antibiotic-resistant bacteria, making the etiologic therapy of infectious processes with antibacterial drugs ineffective. In 2024, in light of growing antibiotic resistance, the World Health Organization (WHO) published a list of pathogens designated by the acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and members of the genus *Enterobacter*). It is these microorganisms that pose the greatest threat to global health [110]. Understanding the resistance mechanisms of these bacteria is a key step in the development of new antimicrobial agents to combat antibiotic-resistant bacteria [63].

Currently, at least 700,000 people worldwide die each year from bacterial infections due to antimicrobial resistance. WHO predicts that without new and more effective treatments, this number could rise to 10 million by 2050 [74]. The global problem of antibiotic resistance was greatly exacerbated during the COVID-19 pandemic. Despite the fact that antibiotics are not effective against viruses, including the causative agent of COVID-19, antibiotic use increased throughout the pandemic along with the number of new COVID-19 infections.

Of concern is the dramatic increase in resistance of ESKAPE strains to carbapenems, which has become a major public health problem due to the lack of effective alternative antibacterial agents, as well as significant difficulties in developing new antibiotics. In 2021, only six of the thirty-two antibiotics in clinical development had some efficacy against ESKAPE group bacteria and were categorized as novel. This situation prompted the search for alternative treatments for bacterial infections to avoid the emergence or spread of resistance in microorganisms [20].

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Alternative modern therapies currently in practice or undergoing trials include the use of antibiotics in combination with adjuvants, bacteriophage therapy, the use of antimicrobial peptides and antibodies, phytochemicals, and nanoparticles as antibacterial agents [64].

Main part

1. Background.

Researchers all over the world note that microorganisms of the ESKAPE group are the main cause of nosocomial infections [24]. Carbapenem-resistant *A. baumannii* and representatives of the *Enterobacteriaceae* family (*K. pneumoniae, K. aerogenes, Enterobacter cloacae*, etc.) resistant to 3rd generation cephalosporins and carbapenems are included by WHO in the list of pathogens with critical priority, while vancomycin-resistant *E. faecium* and methicillin-resistant *E. faecium* and methicillin-resistant *S. aureus* (MRSA) and carbopenem-resistant *P. aeruginosa* are listed as a high priority group [110].

One of the critical microorganisms is *A. baumannii*. It is defined as multidrug resistant when the pathogen is resistant to at least 3 classes of antibiotics (penicillins and cephalosporins including their combinations, fluoroquinolones and aminoglycosides) and as extensively drug resistant when it is resistant to more than 3 classes of antibiotics and to carbapenems. A strain resistant to all the above antibiotics as well as to polymyxin and tigecycline is referred to as panresistant [62]. The ability of *A. baumannii* to persist on surfaces and resist disinfectants helps the survival of the bacteria in healthcare settings [65].

A. baumannii poses a major challenge to clinicians due to the presence of a number of resistance determinants: efflux pumps, internal ADC cephalosporinase, OXA-51 β-lactamase, and acquired carbapenemases such as OXA (Figure 1: Global carbapenem resistance of *A. baumanii* strains) [9].

P. aeruginosa is an opportunistic microorganism with intrinsic resistance mechanisms including impaired cell wall permeability to drugs, efflux pumps for drug efflux from the cell, and cephalosporinase [55]. In addition, *P. aeruginosa* expresses many virulence factors [46]. The resistance of *P. aeruginosa* clinical isolates worldwide is increasingly complemented by acquired resistance determinants, including extended-spectrum beta-lactamases and carbapenemases (Figure 2: Global carbapenem resistance of *Ps. aeruginosa* strains) [5].

β-lactam antibiotics are the therapy of choice for infections caused by methicillin-sensitive *Staphylococcus aureus* (MSSA). Meanwhile, methicillin-resistant *Staphylococcus aureus* (MRSA) shows resistance to most β-lactams (Figure 3. Global antibiotic resistance of MRSA (methicillin-resistant *Staphylococcus aureus*) strains.

Therefore, vancomycin remains the antibiotic of choice in the therapy of staphylococcal infections. Toxicity and increasing resistance to vancomycin require a reassessment of the treatment strategy for such infections. However, clinical data on the use of alternative agents do not provide reliable evidence for the complete replacement of vancomycin as the working antibiotic for MRSA infections [67].

Enterococci are commensals of the human gastrointestinal tract. Most *E. faecalis* isolates retain sensitivity to ampicillin with low resistance to vancomycin (5-10%) [68]. At the same time, hospital-acquired *E. faecalis* strains are resistant to ampicillin in most cases, and 0.3-3% of strains are resistant to vancomycin in Eastern Europe, 30-60% of strains in South America, and 20-50% of strains in the United States (Figure 4: Global vancomycin resistance of *E. faecalis* strains) [3].

Several members of the ESKAPE group belong to the *Enterobacteriaceae* family, including *K. pneumoniae, Klebsiella aerogenes*, and *Enterobacter cloacae* [97]. *Escherichia coli* is also a serious threat [80]. These microorganisms often manifest in urinary tract infections (UTIs), pneumonia, and bacteremia [79], and possess a

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genome complemented with conjugative plasmids carrying resistance genes: extended-spectrum β-lactamases and carbapenemases (e.g., KPC and OXA-48-like serine carbapenemases; NDM, VIM, and IMP metallo-β-lactamases) (Fig. 5: Carbapenem-resistant strains of the *Enterobacteriaceae* family) [86].

Thus, today there is an urgent need to develop new strategies for the therapy of bacterial infections, as existing drugs are increasingly ineffective. The search for new antibiotics seems to be the surest way out, as alternative therapies for bacterial infections have gained insufficient evidence and clinical trial base. But there are factors holding back the search for new antibiotics [20]:

1. High requirements for new antibiotics. Drugs including antibiotics undergo many tests and clinical trials to ensure their safety and efficacy. New antibiotics must meet strict criteria that are set by regulatory organizations. Recently approved antibiotics are delafloxacin, varobactam + meropenem (Vabomere), plazomicin, eravacycline, omadacycline, relabactam + imipenem (Recarbrio), lefamulin, pretomanid, lascufloxacin, cefiderocol, levonadifloxacin [36]. Of the 11 new antibiotics approved since 2017, including three newly approved antibiotics from 2019, only two, varobactam + meropenem and lefamulin, represent new classes. Resistance has already been detected to these antibiotics [13], as bacteria are forming resistance much faster than new antibacterial drugs entering the market. Other recently approved antibiotics are derivatives of existing classes whose clinical utility is limited and for which resistance mechanisms already exist.

2. High research costs, which are not always recouped due to the fact that most antibiotics are used for short courses of treatment, which may not be profitable for drug manufacturers in the long term. Because of this, many pharmaceutical companies are not interested in developing new antibiotics [36].

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That is why our review emphasizes the need to develop modern alternative therapies for bacterial infections that will provide an opportunity to avoid the spread of global microbial resistance [109].

Alternative therapies currently in practice or undergoing clinical and preclinical trials include the use of antibiotics in combination or with adjuvants, phage therapy, the use of antimicrobial peptides, antibacterial antibodies, phytochemicals, and nanoparticles as antibacterial agents [64].

2. Phage therapy.

With the increasing resistance of bacteria to antibiotics, bacteriophages have attracted the attention of researchers. The use of bacteriophage preparations has a significant advantage: phages have strict specificity without increasing the risk of opportunistic infections; the need for low doses to achieve a therapeutic effect; rapid proliferation within host bacteria and achievement of the necessary therapeutic concentrations [28]. In contrast to antibiotics, phages also have the advantage of being able to evolve and mutate with their host, circumventing emerging resistance [78]. Phages can become both therapeutic alternatives and adjuvants to traditional antibiotics [33].

A considerable amount of preclinical data and a growing body of clinical data indicate the enormous therapeutic potential of bacteriophages in a wide range of infectious diseases [58]. However, the use of phage therapy can be complicated by the development of resistance to bacteriophages and the need to tailor phage cocktails for the specific bacterial strain causing the infection, which confronts clinicians with strict public health legislation [99].

One of the limitations of using phages as stand-alone antimicrobials is that bacteria develop resistance to phages as well with high frequency [39]. The use of a combination of phages can limit resistance, but like antibiotics, combinations need to be carefully selected [41].

Various methods of administration of bacteriophages have been investigated and data from clinical studies have been reported, including topical, inhalation, oral, and injectable methods of administration (intravenous, intramuscular, subcutaneous, and directly into the lesion). When phages are administered orally, recombination between phage genomes in the intestine is possible [10], but intravenous delivery is effective in almost all known cases [23,98] (Table 1. Studies on the in vivo use of bacteriophages).

Phage-antibiotic combinations are a promising therapeutic alternative, especially when limited antibiotic options are available. Combination therapy has achieved success in the treatment of infectious diseases such as endocarditis, bacteremia, osteomyelitis and peritonitis [25]. Reports [94] describing the effects of phage-antibiotic combinations often demonstrate enhanced phage activity in the presence of sub-inhibitory concentrations of antibiotics. This phenomenon was named [21] phage-antibiotic synergy (PAS), which is characterized by an increase in the number of phages released after phage cell lysis in the presence of sublethal doses of β-lactam antibiotics.

The effectiveness of combinations of antibiotics and lytic bacteriophages was first shown in 1941 by the example of the combined use of bacteriophages with sulfonamide drugs against *S. aureus* and *Escherichia coli* [49]. Later, the positive effects of joint exposure were demonstrated in animal models [25]. Similar results were obtained with penicillin [42]. The term “synergism” (“synergistic effect”) was introduced in 2007. An increase in the size of lysis zones of E. coli culture under the action of bacteriophage in the presence of subinhibitory concentrations of antibiotics (aztreonam, cefotaxime, ticarcillin, piperacillin, ampicillin, nalidixic acid, mitomycin C) was described [21]. Over time, the term “synergism” acquired a broader meaning. It began to be understood as cases when the efficacy of the phage and antibiotic combination as a whole significantly exceeds the sum of individual effects [90, 26]. In one of the studies, positive effects are subdivided into additive

effect, synergism and facilitation, where under additive effect the authors understand the result when the combined use of two agents leads to cell growth suppression equal to the sum of the effects of each component separately, under synergism - exceeding the additive effect, and under facilitation - the effect when the combined action gives a more significant suppression of bacterial growth than the most effective agent when administered separately, but less in comparison with additive effect [90].

3. Combination therapy.

Combination therapy is the use of several antibiotics in combination to target different mechanisms of bacterial resistance simultaneously. Combination therapy can be effective in the treatment of bacterial infections because it targets several aspects of the pathogen's infectious potential simultaneously. Combination antimicrobial therapy has become an option for the treatment of infections caused by multidrug-resistant bacteria due to its broader coverage of susceptible microorganisms and synergistic effect [11]. However, with such therapy, there is a risk of increased toxicity and development of multidrug resistance [70].

Combination of antibiotics has been tested as a treatment method by a number of researchers because the probability of pathogen resistance development to a combination of two drugs is much less than to a single drug. The combination of drugs also extends the spectrum of action [100] in severe infections caused by multidrug-resistant pathogens [1]. Gram-positive members of ESKAPE, *E. faecium* and *S. aureus*, have been tested against a combination of fosfomycin and daptomycin, which successfully eliminated the infection [92,22]. Most combinations tested against *S. aureus* in vitro include daptomycin or vancomycin with other antibiotics, including ceftaroline, an antibiotic recently approved for use. The effects of these and other similar combinations have also been tested in various mouse models that eliminated staphylococcal infection with minimal toxicity [60]. The efficacy of combination therapy has also been demonstrated with combinations with

colistin. Colistin (polymyxin E) is an antibiotic of last resort prescribed against Gram-negative bacteria. In recent years, studies on the treatment of infections caused by *K. pneumoniae* and *A. baumannii* using the combination of colistin or tigecycline with other antibiotics in vitro and in cohort studies have been conducted and promising results have been shown [4,108].

The original β-lactam-β-lactamase β-lactamase inhibitor (BL-BLI) combinations (i.e., amoxicillin-clavulanic acid, ampicillin-sulbactam, cefoperazone-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanic acid) were highly active against class A serine β-lactamases [29, 75]. *K. pneumoniae* resistance to them evolved with the emergence of four structurally and functionally different groups of β-lactamases: class B metallo-β-lactamases (MBL), class C serine β-lactamases AmpC, oxacillinases (OXA)-class D serine β-lactamases, and novel class A carbapenemases (KPC) [29,75].

As a result, BL-BLIs with activity against all clinically important β-lactamases (e.g., KPC-2, OXA-23, OXA-24/40, AmpC, and New Delhi MBL-1 [NDM-1]) have become less effective, but new combinations such as cefepime-taniborbactam and cefepime-zidebactam are being developed that cover a broad spectrum of these enzymes and may fulfill this need [75,106].

Diazabicyclooctanes (DBOs) are non-β-lactam synthetic inhibitors of β-lactamases [29]. Most studies show that DBOs inhibit class A and C β-lactamases, while minor activity against class D β-lactamases has also been observed [75]. In February 2015, avibactam became the first DBO drug approved by the FDA, the Food and Drug Administration, which is responsible for protecting and promoting public health through the control and supervision of food, drugs, and cosmetics. The activity of avibactam depends on the partner (e.g., ceftazidime, ceftaroline, aztreonam, cefepime, or imipenem), β-lactam-avibactam combinations are potentially highly effective against many ESKAPE pathogens, including *Enterobacteriales* and *P. aeruginosa* [72]. Replacing the β-lactam partner antibiotic with a clinically available

β-lactamase inhibitor is another approach to treat infections caused by strains carrying multiple classes of β-lactamases, such as combining tazobactam with the novel cephalosporin ceftolozane [107, 104].

Nevertheless, the increasing resistance of microorganisms every year requires testing more and more new combinations of antibiotics, which leads to an endless search. Therefore, antibiotic combinations are a temporary solution to preserve the use of existing drugs while alternative strategies are being developed and tested.

4. Nanoparticles

Nanomedicine is one of the emerging areas for the elimination of antibiotic-resistant pathogens. Various nanomaterials with intrinsic antibacterial properties are being developed: metal-based nanoparticles (NPs) (e.g. silver, gold, copper and zinc oxide). They are widely used not only to enhance the efficacy of already existing antibiotics but also to reduce bacterial drug resistance [34,61]. At the nanoscale, the physical and chemical properties of metals change dramatically compared to bulk material due to size and shape effects and the high surface area to volume ratio of nanomaterials [95]. That is, several properties must be considered at once: ion release, hardness, plasmon and superparamagnetism [19].

Nanoparticles affect the cell in several ways at once. Physical contact of bacteria with nanoparticles leads to membrane damage due to their adsorption and penetration into the cell [96]. Adsorption of nanoparticles causes depolarization of the cell wall, changing its negative charge and making it more permeable. As a result, the cell wall is destroyed and reactive oxygen species are formed [81] causing DNA denaturation [91]. The antibacterial activity of nanoparticles can also be due to leaching of ions. These ions can diffuse inside the cell and interact with the cell membrane and wall, as well as with cell macromolecules such as proteins and nucleic acids [16,52] High concentrations of reactive oxygen species produced inside or outside the cell due to nanoparticles, damage the cell membrane [83], put

243 bacterial cells into oxidative stress, carry out lipid peroxidation, and destroy the cell
244 wall by disrupting the structure of peptidoglycan [43,44], degrade proteins and
245 nucleic acids [32], leading to cell death.

246 One of the most common applications of nanoparticles in modern medicine is
247 implantable devices. Implants must have biocompatibility, corrosion resistance, and
248 antibacterial properties that nanoparticles can provide [56]. Nanoparticles are used
249 to treat catheters, dental implants, and are used as antibacterial additives in dressings
250 to treat skin wounds and burns. Both Gram-positive and Gram-negative pathogenic
251 bacteria can cause chronic infections associated with skin wounds. For example,
252 silver nanoparticles significantly inhibit bacterial growth and increase the rate of
253 wound healing when used in combination with polyvinyl alcohol and chitosan
254 [18,35,57].

255 In the field of new antibacterial agents, nanoparticles represent a promising
256 alternative to antibiotics. Due to the combination of different effects on the bacterial
257 cell, they have a wide range of antibacterial activity, affecting also drug-resistant
258 microorganisms [40]. Nevertheless, toxicity to eukaryotic cells at high dosages of
259 nanoparticles, as well as acceleration of horizontal transfer of resistance genes at low
260 dosages, sublethal for bacteria, requires further study of this area and refinement of
261 existing methods of nanoparticle application [93].

262 5. Antibiotic adjuvants

263 Antibiotic adjuvants are compounds that are used in combination with antibiotics to
264 enhance their action against bacterial infections. Some molecules are combined with
265 antibiotics to make an ineffective drug effective. These molecules, called
266 “adjuvants” or “resistance disruptors”, have little or no intrinsic antimicrobial
267 activity [38], but can inhibit mechanisms that confer resistance, making pathogens
268 susceptible to the action of antibiotics [7]. Adjuvants can effectively enhance the
269 action of existing antibiotics by reducing the minimum inhibitory concentration of

antibiotic required to kill bacteria, allowing the use of existing therapies that may have been ineffective for a particular patient [66].

Several classes of adjuvants are known such as efflux pump inhibitors, β-lactamase inhibitors, quorum sensing inhibitors and adjuvants that disrupt bacterial cell wall synthesis and membrane permeability [73]. Also, depending on the intended purpose and the tasks performed, adjuvants can be categorized into 2 classes: class I antibiotic adjuvants act directly on the resistance mechanisms of bacterial cells to help antibiotics regain their efficacy, while class II adjuvants enhance the activity of the antibiotic in the host [105]. Class I includes active resistance inhibitors (β-lactamase inhibitors) [38], passive resistance inhibitors (efflux pump inhibitors [88], quorum sensing inhibitors [37, 47], biofilm inhibitors [37] and cell membrane permeability enhancers [82]. Class II includes antibiotic action enhancers (antimicrobial peptides that stimulate immunity) [2].

The strategy of using antibiotic adjuvants also has certain limitations, such as the labor-intensive and expensive identification of compounds and substances with the required physicochemical properties that can be used as adjuvants and administered together with antibiotics. In addition, it is necessary to evaluate the possibility of side effects when using certain adjuvants in each patient [17].

6. Antimicrobial peptides

Antimicrobial peptides are short, positively charged defense oligopeptides produced by all living organisms including protozoa, bacteria, archaea, fungi, plants and animals [103]. They show a broad spectrum of activity against a large number of bacterial pathogens. The ability of antimicrobial peptides to interact with the bacterial cell membrane and thereby induce cell lysis makes them a potential alternative for combating multidrug-resistant pathogens [6]. In addition, unlike antibiotics, antimicrobial peptides physically damage the bacterial cell through

electrostatic interactions, thereby making it difficult for bacteria to develop resistance to them [77].

Histatin 5 is a natural cationic peptide of human saliva that is rich in histidine. This peptide shows strong antibiofilm and bactericidal activity against ESKAPE in vitro [30]. The cationic peptide WLBU-2 and the natural antimicrobial peptide LL-37 demonstrated 90% biofilm inhibition compared to tobramycin, ciprofloxacin, ceftazidime and vancomycin [54].

Similar to the positive in vitro results, antimicrobial peptides also show promising in vivo activity against ESKAPE group bacteria. For example, the peptide HLR1r, a structural derivative of the human milk protein, lactoferrin, at a very low concentration (5 mg/kg) was found to exhibit antimicrobial activity against an MRSA-infected rat wound excision model, as well as anti-inflammatory and anti-cytotoxic effects in vitro, suggesting the use of HLR1r in topical application formulations for the treatment of skin infections [8].

However, the paucity of antimicrobial peptides seeking clinical approval makes them an underpowered alternative to antibiotics for widespread use in healthcare settings. Despite their high in vitro and in vivo activity, antimicrobial peptides have yet to be clinically tested. Also, cytotoxicity for mammalian cells, tendency to degradation by tissue proteases, loss of activity at low salt concentrations or in the presence of plasma proteins, and higher production costs compared to other antimicrobial agents make it difficult to implement this type of therapy [59,85].

7. Conclusion.

Economic incentives for pharmaceutical companies and private and public sector collaboration can help filling the gap in antimicrobial drug development. Continuous epidemiologic surveillance and monitoring of antibiotic prescribing and consumption can delay the spread of antibiotic-resistant microorganisms. In

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addition, other potential ways to reduce the incidence of resistance are the use of antibiotic combinations or the development of alternative therapies [102].

However, despite the large number of studies conducted on the efficacy of alternative therapies for bacterial infections, each of them has been found to have drawbacks that hinder their adoption into routine use by clinicians. When combinations of antibiotics are used, the phenomenon of antagonism may occur [15]. The toxicity of such a drug increases [31,70]. The use of adjuvants is complicated by labor costs in the search for new representatives and insufficient base of clinical use [101]. When phage therapy is used, resistance is also formed due to alteration of phage receptors of the host cell, and patient side effects are also possible [70]. Antibacterial peptides lose their activity at low salt concentrations or in the presence of plasma proteins and also have cytotoxicity [85, 60]. Nanoparticles are not used in routine clinical practice due to the lack of research base to verify toxicity, immunomodulatory response and pharmacokinetics conducted in vivo, [69].

Therefore, document No. 2045-r (dated September 25, 2017) “Strategy for the Prevention of the Spread of Antimicrobial Resistance” was adopted at the state level, according to which one of the main directions of public health will be to study the mechanisms of antibiotic resistance, create alternative drugs for treatment, and inform the population about the rational use of antibiotics.

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ТАБЛИЦЫ

Table 1. Studies on the use of bacteriophages in vivo.

Target microorganism	Study model	Agent, doses	Effectiveness
P. aeruginosa	Clinical case, man, 76 years old, chronic aortic graft infection	1×10^8 PFU of personalized phage cocktail + ceftazidime intravenously 2 times daily for 21 days [14].	Elimination of infection
P. aeruginosa	Clinical case, man, 26 years old, cystic fibrosis, bacterial lung infection.	4×10^9 PFU of personalized phage cocktail intravenously every 8 hours daily for 8 weeks [51].	Elimination of infection
P. aeruginosa	Clinical case, man, 67 years old, bacterial infection of urinary tract.	2×10^7 PFU of personalized phage cocktail + colistin and meropenem into the bladder every 12 hours daily for 10 days [45].	Elimination of infection
K. pneumoniae	Clinical case, man, 62 years old, knee prothesis infection.	$6{,}3 \times 10^{10}$ PFU of monovalent bacteriophage intravenously daily for 40 days [12].	Elimination of infection
A. baumanii	Clinical case, man, 77 years old,	$8{,}5 \times 10^7$ PFU of monovalent	Elimination of infection

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	hospital-acquired bacterial infection after craniectomy.	bacteriophage suspended in Ringer solution with lactate through the central catheter every 2 hours 98 times [50].	
S. aureus	Clinical case, woman, 35 years old, trophic leg ulcer.	3.2×10^{10} PFU of the phage cocktail topically on the wound surface daily for 7 days [48, 84].	Treatment failure, purulent inflammation of the wound
K. pneumoniae	Clinical case, woman, 40 years old, cystic fibrosis, bacterial lung infection.	2-phage cocktail with 2×10^8 PFU by inhalation and 1.8×10^9 PFU daily via nasogastric tube for 4 days [87].	Elimination of the pathogen in bronchoalveolar lavage but presence in feces
E. faecalis	Clinical case, 3 men, 52, 61 and 68 years old, chronic bacterial prostatitis.	2×10^9 PFU of personalized phage cocktail rectally 2 times a day for 1 month [53].	Elimination of infection
E. coli	Clinical case, man, 66 years, chronic bacterial prostatitis.	Intesti and Ses phage cocktails orally and rectally daily for 30 days [45].	Elimination of infection

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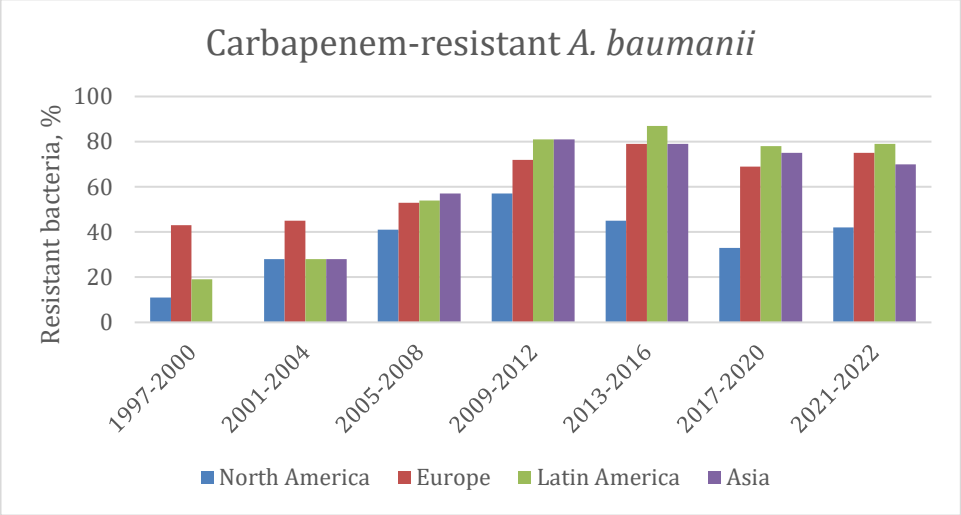
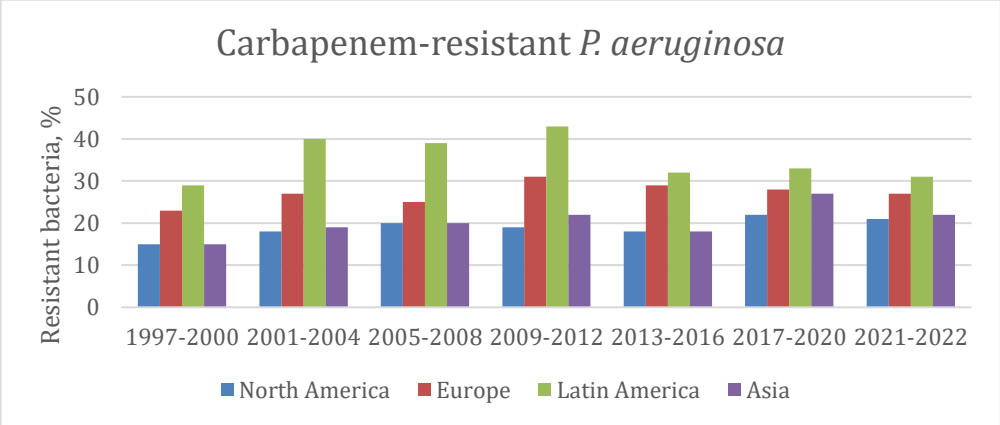
РИСУНКИ

Figure 1. Global carbapenem resistance of *A. baumanii*.



Notes: Percentage of carbapenem-resistant *A. baumanii* strains from 1997 to 2022 worldwide.

Figure 2. Global carbapenem resistance of *P. aeruginosa*.



Notes: Percentage of carbapenem-resistant *P. aeruginosa* strains from 1997 to 2022 worldwide.

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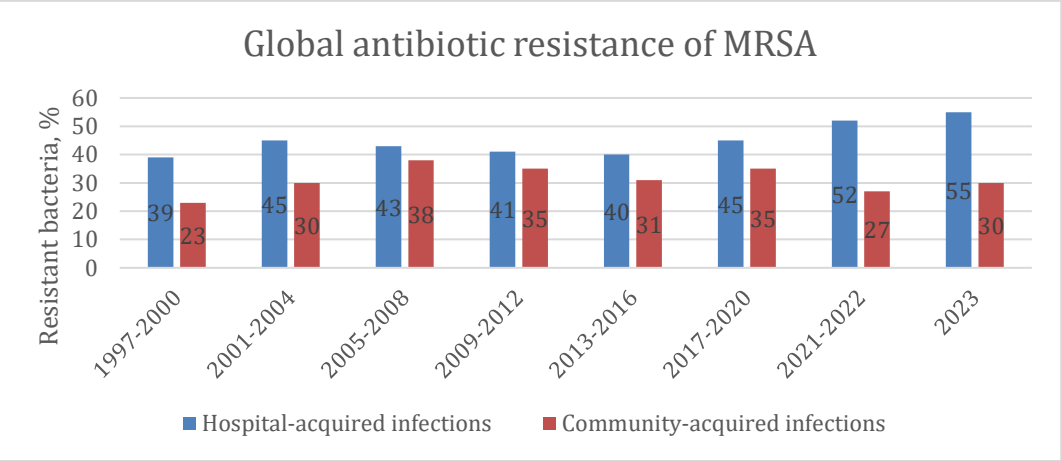
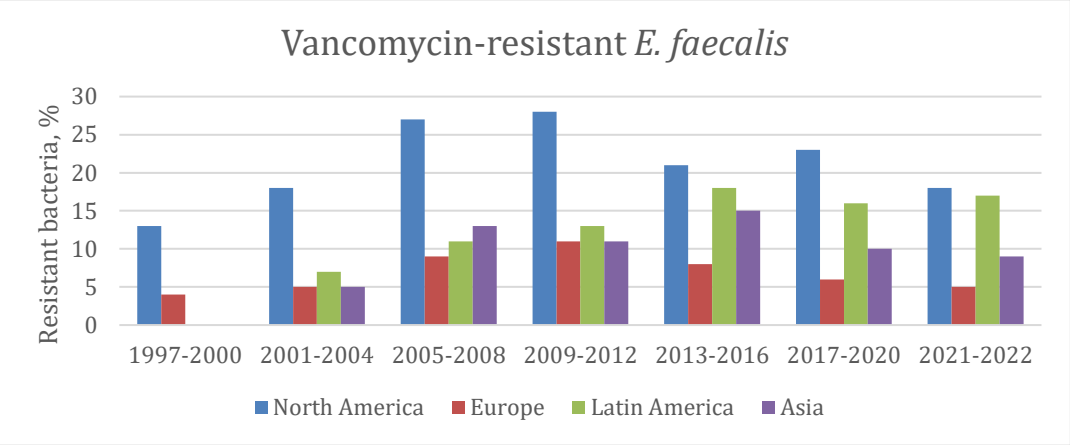
Figure 3. Global antibiotic resistance of MRSA (methicillin-resistant *Staphylococcus aureus*).



Notes: Percentage of antibiotic-resistant *S. aureus* strains from 1997 to 2023 worldwide.

Figure 4. Global vancomycin resistance of *E. faecalis.*



Notes: Percentage of vancomycin resistant *E. faecalis* from 1997 to 2022 worldwide.

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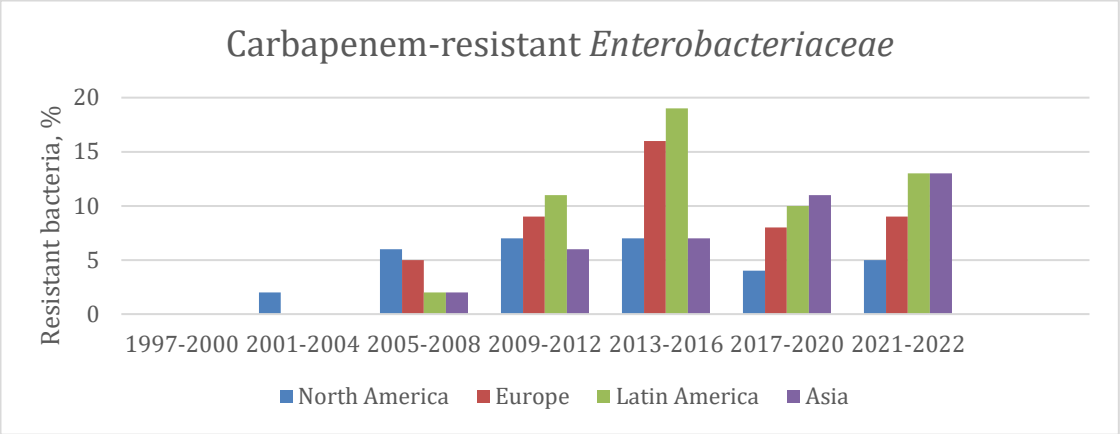
Figure 5. Global carbapenem resistance of *Enterobacteriaceae*.



Notes: Percentage of carbapenem resistant *Enterobacteriaceae* from 1997 to 2022 worldwide.

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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

NEW APPROACHES OF COMBATING POLYRESISTANT ESKAPE PATHOGENS

СОВРЕМЕННЫЕ ПОДХОДЫ К БОРЬБЕ С ПОЛИРЕЗИСТЕНТНЫМИ ПАТОГЕНАМИ ГРУППЫ ESKAPE

Сокращенное название статьи для верхнего колонтитула:

NEW APPROACHES OF COMBATING ESKAPE

БОРЬБА С РЕЗИСТЕНТНЫМИ ESKAPE

Keywords: antibiotic resistance, multidrug resistance, gram-negative bacteria, gram-positive bacteria, phage-antibiotic synergy, ESKAPE pathogens.

Ключевые слова: антибиотикорезистентность, множественная лекарственная устойчивость, грамположительные бактерии, грамотрицательные бактерии, бактерии группы ESKAPE**,** синергизм фагов с антибиотиками.

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