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Review

NOSOCOMIAL INFECTIONS: PATHOGENICITY, RESISTANCE AND NOVEL ANTIMICROBIALS

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Background. The fight against the spread of infectious diseases creates the problem of resistance to pathogens and the most resistant of them – the propagators of nosocomial infections – are formed in hospitals because of a number of reasons. The solution of the problem lies in different areas, but the search of new effective means for the treatment of such diseases remains relevant right today. The shortest way to do this is to find the "pain points" of the pathogens themselves, i.e. the factors of their pathogenicity and resistance to which the action of novel antiseptics should be directed.
Objective. We aimed to analyse and evaluate the main factors of pathogenicity and resistance of pathogens of nosocomial infections to determine modern approaches to the development of novel antimicrobials.
Methods. Search and systematization of new scientific data and results concerning pathogenic factors of microbial pathogens that can be used as targets for the action of drugs.
Results. Over the last 10–20 years, due to the development of new research methods in biology, it has become possible to clarify the features and additional conditions for the detection of pathogenic factors of nosocomial infections. Additional mechanisms of manifestation of resistance, adhesiveness, invasiveness, transmission of signs, secretion of toxins by pathogens are shownthat determines the general increase of their resistance to the action of currently used means. The general idea of creating antiseptics that will not increase the resistance of pathogens can now be implemented by using substances with multidirectional or indirect mechanisms of action that minimally affect the metabolism of the cell and significantly reduce its resistance and pathogenicity.
Conclusions. Factors of pathogenicity of propagators of nosocomial infections and mechanisms of their implementation can be considered as the main targets for the action of novel antiseptics that will inhibit the spread of pathogens without increasing their resistance. The promising substances for such drugs, among other things, are bacteriophages and their modifications, enzybiotics, immunobiotics, autoinducer inhibitors, quorum sensing-system inhibitors, β-lactamase inhibitors and others. Some of these substances in combination with the new generation of antibiotics significantly enhance their effectiveness and together they are able to overcome the resistance of even multidrug-resistant pathogens.

Keywords: microbial pathogens; resistance factors; pathogenic factors; mechanisms of pathogenicity; antibiotic resistance; novel antimicrobial substances.

Introduction

The era of antibiotics, which began with the discovery of penicillin in the XX century, may soon end and humanity will face a challenge to overcome which will have to find new solutions. This challenge is now the "era of antibiotic resistance", caused not only by evolutionary mechanisms of protection of pathogens, but also by many factors of human activity [1–3].

Particular importance are methods of combating infectious agents when they are in treatment centers and a large number of people can both become infected and be a source of their spread. Such infections are nosocomial (hospital-acquired infection) and are defined by World Organization of Health (WHO) as infections that can be infected the patient during care in a hospital or other health care facility [3–5]. The sources of infection in hospitals are not only other patients and staff, but also surfaces, instruments, medical manipulations and operations, which is due to problems in ensuring proper conditions. However, one of the important factors in the treatment of nosocomial infections is their resistance to many antibiotics used in hospitals at the same time, and as a result "superbug" arise, for which there is no effective counteraction [4–6]. WHO defines a list of such relevant "superbugs", and almost half of them are included in the already established acronym ESCAPE – ***E****nterococcus faecium,* ***S****taphylococcus aureus,* ***K****lebsiella pneumoniae,* ***A****cinetobacter baumannii,* ***P****seudomonas aeruginosa* and ***E****nterobacter spp.* [1, 5, 7–9].

It was found that the natural and induced variability of microorganisms that cause inflammatory processes leads to an increase in their resistance due to the acquisition of resistance – the ability to resist the action of previously effective antiseptics. In addition, there was a selection of resistant forms of microbial pathogens, which caused low efficiency of therapy, severe disease, long-term treatment or, in some cases, the inability to overcome the infection at all [4, 9, 10]. The above and many other sources, citing WHO and the Center for Disease Control (CDC, USA), state that the need to develop effective antimicrobials against these and other nosocomial infections is a "need of the hour" [3–5].

Obviously, the solution of the problem of overcoming nosocomial infections has many dimensions, including organizational, educational, medical and so on. But these long-term strategies do not remove the urgent task of finding effective antimicrobials or new combinations to treat these severe, often combined infections, right today. This work currently involves a large number of scientists and practitioners, each of whom chooses his own approach, one of the most effective of which is undoubtedly the identification of the most vulnerable sites of infectious agents and their use as targets for new drugs [11–13]. Such vulnerable points of microbial pathogens mainly determine their resistance and pathogenicity, and therefore these factors can be considered more closely to find the target.

Therefore, it is important to search and systematize new scientific data and results in this regard, and *the aim of our work* is to analyze and evaluate the main factors of pathogenicity and resistance of nosocomial infections to determine modern approaches to the development of novel antimicrobials.

Factors and mechanisms of pathogenicity

Pathogens cause pathogenicity to the host mainly through four steps, including adhesion, colonization, invasion and toxin production, among which adhesin play essential roles in binding to host epithelial and endothelial cells, interactions with host mucosal layers and components of the extracellular matrix (ECM) that surround host cells, and in biofilm formation [14–16]. It can not only be an inherent component of a pathogen that causes damage to host cells and/or tissues (e.g., exotoxins), but also a molecule or structure (e.g., capsule, biofilm) that enables the pathogen to evade or modulate host defense systems to its replicative advantage. Moreover, it enhances the ability of a pathogen to resist host fluid flow, attach to specific target cells, and potentially invade those target cells.

Bacteria have evolved an abundance of mechanisms to engage with host cells and manipulate their cellular signaling programs to facilitate colonization [17].

Adhesion of bacteria to host surfaces is a crucial aspect of host ***colonization*** as it prevents the mechanical clearing of pathogens and confers a selective advantage towards bacteria of the endogenous flora. Bacteria have evolved a very large arsenal of molecular strategies allowing them to target and adhere to host cells. Depending on the biochemical identity of the adhesive structure, its role during colonization may vary: it may be to enable initial, weak, and nonspecific adhesion, by establishing hydrophobic interactions with the host surface, thereby overcoming the electrostatic repulsion between bacterial and host surface. Other adhesins engage in highly specific interactions with host surface receptors, giving rise to high-affinity, stable interactions.

Pili, which are polymeric hair-like organelles protruding from the surface of bacteria, represent a first class of structures involved in the binding of bacteria to host cells [14]. The base of these structures, initially discovered in gram-negative bacteria, is anchored to the bacterial outer membrane, whereas the tip is usually an adherence factor conferring the binding specificity of these structures. The most important pili kinds are Type I pili and Type IV pili. Type I pili at the surface of gram-negative bacteria, which have binding specificity to d-mannosylated receptors, such as the uroplakins of the bladder [18]. Type IV pili constitute another class of polymeric adhesive surface structure expressed by different gram-positive bacteria [19]. Type IV pili can retract through the bacterial cell wall, while the pilus tip remains attached to its target surface, allowing the so-called "twitching motility", a flagella-independent mode of motility important for efficient colonization of host surfaces [20].

In the last decade, pili structures have also been observed in gram-positive bacteria. Two types of pili have been described so far in these species. The first class consists in "sortase-assembled pili", in which successive pilin subunits are linked by isopeptide bonds after translocation across the bacterial membrane. This linkage is catalyzed by bacterial transpeptidases called "sortases" allowing the formation of completely covalent polymers that are eventually linked to the pentapeptide crossbridge found within the lipid II component of the

peptidoglycan layer [21–23]. The second class consists in "type IV-like pili", which are like type IV pili of Gram-negative bacteria, even though the lack of outer membranes and the thick peptidoglycan structures of Gram-positive bacteria imply differences in the assembly mechanisms of these filaments [19].

In addition to pili, a wide range of bacterial surface factors with adhesive properties have been described. These adhesins recognize various classes of host molecules including transmembrane proteins such as integrins or cadherins, or components of the extracellular matrix such as collagen, fibronectin, laminin or elastin [14, 24, 25]. Some of these adhesins, after allowing the binding of bacteria to host cell surfaces, are also triggering the internalization of bacteria inside host cells.

In parallel to these canonical mechanisms of bacterial adhesion, the EPEC (Entero-Pathogenic *E. coli*) and EHEC (Entero-Hemorragic *E. coli*) pathogens, which are responsible respectively for diarrheal disease in children, and severe foodborne infections, use a very particular mechanism to create an intimate contact with host cells: they inject an effector, called Tir, that inserts into the host cell plasma membrane and serves as an "exogenous" receptor for the bacterial surface protein intimin [26].

Over time, we can discover more adhesion factors and mechanisms. Adhesion represents a crucial step for extracellular bacteria that facilitates their persistence in the host. We will learn more about intracellular bacteria, which is first essential step that precedes their internalization within host cells.

Professional phagocytes, such as macrophages or M-cells of the intestinal Peyer's patches, represent a frontline defense against pathogens. Although these cells are playing a key role in coordinating the innate and adaptative immune response to limit the colonization of pathogens in the host, they also constitute entry portals for pathogens. Many bacteria can also induce their internalization into non-professional phagocytes. Translocation through non phagocytic cells of the intestinal epithelium is another key mechanism used by pathogens to reach the lamina propria and to cause infections. Two main mechanisms of entry are involved in this case, namely the zipper and the trigger mechanisms [27].

In the case of their ***internalization mechanism***, engagement of bacterial proteins with host membrane proteins normally involved in cellular adhesion such as cadherins or integrins, leads to the recruitment of various host factors involved in the strengthening of cell–cell or cell–matrix contacts. These proteases can not only degrade the immune molecule's action and destroy tissue structure to facilitate the spread of bacteria but also exert more invasive effects by activating or inhibiting proteases in the human body to activate receptors [28]. For example, the alkaline protease of *P. aeruginosa* can hydrolyze complement components C1q and C3, as well as a variety of cytokines and chemokines, blocking the effects of immune factors on bacteria.

A significant factor of the virulence and pathogenicity of pathogens of nosocomial infections is their ability to secrete toxins. Typical exotoxins are *S. aureus* hemolysins, endogenous toxic compounds are synthesized by *Shigella dysenteriae*, and *Clostridium botulinum* pathogenic clostridia are capable of synthesizing neurotoxins that are partially bound to the cell. Both cellular proteins and nucleic acids can be targets for bacterial toxins. Some of them, such as lethal distending toxins (CDTs), like DNAse I, can cleave DNA during its replication, inhibiting cell division.

Genetic determinism of toxin synthesis has been shown in *P. aeruginosa*, as well as the expression of genes responsible for their oversynthesis (genes toxA, lasB and exoS) has also been established [29]. It is obvious that the very process of gene expression may be a target for the action of new antimicrobials, which has been noted in the study of metabolism of *S. aureus* [30].

Resistance development and mechanisms

The selection pressure caused using of tons of antibiotics over the past 75 years since antibiotics were introduced has made almost all disease-causing bacteria resistant to antibiotics commonly used to treat them. Nearly 1000 resistance-related β-lactamases that inactivate these antibiotics have been identified, a ten times increase since before 1990 [31]. The distribution of resistance genes, such as *Enterobacteriaceae*-producing extended-spectrum ***β-lactamase*** (ESBL), New Delhi ***metallo-β-lactamase 1*** (NDM-1), and *K. pneumoniae* ***carbapenemase*** (KPC), indicates the ease with which resistance can spread. Findings of a study done in New Delhi showed NDM-1-producing bacteria (including *Shigella boydii* and *Vibrio cholera*) in two (4%) of 50 drinking water samples and 51 (30%) of 171 seepage samples suggesting the possibility of acquiring resistance outside health-care facilities [32].

Quinolone antibiotics are synthetic and so do not arise in nature, yet 30 years after their wide-

spread introduction resistance is epidemic [33]. More specifically, whole genome studies suggest that quinolone resistance was a crucial factor in the evolution of hospital methicillin-resistant *S. aureus* (MRSA) [34], which indicates it is a long way to understand present epidemics of resistant health-care-associated infections [35].

In health-care settings, the spread of a resistant clone can be rapid and have severe consequences for vulnerable hosts. The proportion of *Enterobacteriaceae* that were resistant to carbapenems increased from 0% in 2001 to 1.4% in 2010, with most of the increase recorded in *Klebsiella* sp. [36]. Healthcare associated infections are also increasingly recognized in low- and middle-income countries. Findings of a recent review showed that pooled prevalence of healthcare-associated infections in resource-limited settings (15.5 per 100 patients) was twice the average prevalence in Europe (7.1 per 100 patients) [37]. Incidence of infections acquired in intensive care units in developing countries (pooled density 47.9 per 1000 patient-days) was three times the rate in the USA (13.6 per 1000 patient-days).

Increasing rates of resistance to ***colistin*** and ***polymyxin B*** in Gram-negative organisms are being reported from countries around the world, including South Korea [38], Italy [39], Greece [40], and Saudi Arabia [41]. Moreover, there is some evidence of cross-resistance to colistin and host antimicrobial peptides that are part of the body's immune response [42].

Antibiotics are a subset of antimicrobials that inhibit essential functions in bacteria. Antibiotics are natural products or derivatives of natural products and are used widely to treat and prevent bacterial infections in humans and other animals. Most antibiotic-resistant infections are thought to occur in hospitals, where they increase the risks associated with medical treatments and undermine the ability of hospitals to provide safe places to heal [43, 44]. Bacterial ***antibiotic resistance*** (AR) is already making routine surgeries and hospital visits increasingly risky. The epidemic is particularly problematic in long-term acute care facilities, where over 25% of healthcare-associated infections are caused by antibiotic-resistant bacteria. Resistant bacterial populations spread when antibiotics exert selective pressures that favor resistance. Antibiotics can also eliminate susceptible microbial populations, reducing competition and expanding the resources available to resistant bacteria [45, 46]. Additionally, AR is spreading rapidly because once a resistance gene evolves in one bacterium, it can spread to other cells and other bacterial species [47–49]. To tackle the rising problem of AR, we must understand how bacteria acquire and ***transmit resistant genes*** in clinical settings.

Mechanisms for the manifestation of virulence and pathogenicity of pathogens include their genetic evolutionary natural changes, as well as caused by artificial factors. However, in any case, such signs of resilience are passed on as survival benefits [50–53]. It should also be noted that such artificial factors of increasing resistance include not only medical practice, but also the widespread use of antibiotics in various fields – primarily in food and agriculture [54, 55]. Another factor in the rapid transfer of acquired antibiotic resistance is the coexistence of pathogens of different species in one association (in the wound, in the hospital in general), which is carried out by ***horizontal or lateral gene transfer*** (HGT) [56, 57].

Plasmids, bacteriophages, and extracellular DNA are the three primary drivers of HGT through the processes of conjugation, transduction, and natural transformation, respectively. The capacity for natural transformation is more sporadically distributed, yet it predates diversification of the bacterial Gram-positive and Gram-negative clades [58]. Gene transfer by each of the three mechanisms is favored between closely related organisms, but can occur between phylogenetically distant organisms [59]. Reservoirs of antibiotic-resistant organisms in hospitals have been well documented [60, 61], as have transmission routes between these reservoirs [62, 63], but the rates of horizontal transfer in clinical environments and the impacts of HGT on disease frequency remain unknown or speculative.

The development of drug resistance, which is based on mutations in chromosomal genes or the acquisition of drug resistance plasmids, is another component of pathogen resistance [64, 65]. Known families of microorganisms are naturally resistant to certain antibiotics: in their genome there are genes that control this characteristic. The highest level of mutations is observed in the genes mutS, mutL, mutH, mutT, mutY, mutM and uvrD, which are included in the MMR system [66–69]. The consequence of such mutations is an increase in genetic recombination and an overall increase in various mechanisms of resistance. For the genus *Acinetobacter*, for example, resistance to penicillin is a taxonomic trait. Polyresistant to antibiotics and representatives of pseudomonads, non-clostridial anaerobes and some other microorganisms. Such bacteria are essentially natural repositories of drug resistance genes.

Adaptive resistance can be the result of numerous environmental factors and lead to the invention of effective defense mechanisms by pathogens [69–71]. Perhaps the most effective of them – the formation of biofilms. And the possibility of such existence of pathogens both on wound surfaces, and on catheters, endoscopes, etc. makes them important factors of their pathogenicity and targets for fight against causative agents of nosocomial infections. Increased resistance of pathogens in the form of biofilms to antibiotics is due to the following reasons [72–74]:

– inactivation of antibiotics by extracellular polymers or enzymes;

– slowing down the metabolism and, accordingly, reducing the growth rate of microorganisms in the conditions of limiting nutrients in the biofilm, due to which the antibacterial drug diffuses from the biofilm faster than it has time to act on it;

– expression of possible genes for antibiotic resistance;

– appearance of persister microorganisms in the biofilm under the action of antibiotics.

The most well-known mechanism of protection of pathogens from antimicrobial substances is ***enzymatic inactivation*** of antibiotics, which is realized through their synthesis of hydrolytic and redox enzymes, as well as transferases [75–77]. One such well-known enzyme is β-lactamase, which provides resistance of microorganisms to β-lactam antibiotics due to direct cleavage of the beta-lactam ring of these drugs. Other enzymes are able not to break down but to modify the active part of the antibiotic molecule, as is the case with enzymatic inactivation of aminoglycosides and chloramphenicol. Changing the permeability of the cell wall for an antibiotic or inhibiting its transport into bacterial cells, for example, underlies resistance to tetracycline. Structural changes in bacterial ribosomes are accompanied by increased resistance to aminoglycosides and macrolides, and changes in the structure of RNA synthetases – to rifampicin [78–82].

Antimicrobials for the "superbugs"

The traditional way to solve the problem of nosocomial infections is to search for new antimicrobial substances and create complex drugs that combine several antimicrobial substances with different mechanisms of action. Among the new classes of antiseptics developed by pharmaceutical companies, ***new peptides*** are attracting special attention; drugs that block fatty acid synthesis or early stages of protein synthesis in the microbial cell, as well as ***β-lactamase inhibitors*** that do not have their own antibacterial activity [83]. Thus, a new synthetic low molecular weight boron-containing drug (AN3365) blocks protein synthesis in gram-negative bacteria by inhibiting the synthesis of aminoacyl-t-RNA.

Another promising direction in the search for ***new antibiotic compounds*** is the selection of microbial producers from exotic and non-studied ecotopes. One of them is new antibiotics hexalactin and hexamycin, related to ansamycins, which include the currently used rifampicin [84–86]. The OSMAC (one strain many compounds) approach led to the discovery of three new *S. leeuwenhoekii* compounds of the rare class of 22-membered macrolactone polyketides, hexalactins A-C. Similarly, *S. leeuwenhoekii* was found to produce four new ansamycin-type compounds called hexamycins, which inhibit the development of *S. aureus* ATCC 25923 (minimum inhibitory concentration 0.05–0.13 μg/ml) and inhibit a number of methicillin-resistant isolates [86].

Isolated from marine sediments in California strain *Streptomyces* sp. CNH365 showed significant activity against the anthrax pathogen *B. anthracis* and methicillin-resistant staphylococcus, and the resulting antibiotic – polyketide antibiotic with a 14-membered macrolide ring, enolized β-diketone and lactone was named anthramycin [87, 88]. Polyketide 13 was obtained and structurally characterized polycarbonic compound of endophytic actinomycete *S. sundarbansensis* isolated from *Algerian algae Fucus* sp., shows selective activity against gram-positive microorganisms resistant to methicillin [89, 90].

In addition to finding new compounds among microbial producers, ***screening sensitivity-based techniques*** are proposed: when the intracellular level of the target affected by the desired antibiotic is reduced by the action of the corresponding antisense-RNA, test strains become more sensitive to this antibiotic. Thus, it is possible to detect compounds that under normal conditions do not inhibit the growth of test strains. This method has identified a new class of antibiotics, which includes platensimycin, which is produced by *S. platensis* [91].

Such approaches to the development of new antiseptics to combat nosocomial infections are one way to solve the problem. However, more promising is the development of antiseptics aimed at the selected target in pathogen cells, which is potentially the least associated with the possibility of developing resistance. Therefore, the choice of such targets is a fundamental and decisive factor in the development of new antiseptics.

The development of drugs aimed at ***inhibiting the quorum sensing*** (QS) systems of pathogens as the main target, avoids the rapid development of resistance, as such substances do not have bactericidal or bacteriostatic action on pathogenic bacteria. Such drugs lead to the suppression of pathogenicity and are called "poisons of pathogenicity" [92, 93]. Inhibition of QS systems can be achieved in several ways. One of the strategies is to inhibit the synthesis of precursor molecules of autoinducers or autoinducers themselves (acylhomoserine lactones (AGL), peptides, amino acids and similar amine compounds). Second, drugs may be targeted by inhibiting the binding of autoinducers to the corresponding receptor proteins. Considerable attention is paid to such natural QS antagonists as furane derivatives, the role of which has already been proven in the suppression of QS in *P. aeruginosa* and *E. coli* [94].

Among other promising compounds that can solve the problem of fighting nosocomial infections – ***enzybiotics***, which now include substances with a specific mechanism of action (bacteriocins, cathelicins, lysines, bacteriophages, immunobiotics) [95–98] The authors identify the benefits and broad prospects of such drugs, which significantly increase the effectiveness of antimicrobial action without causing the emergence of resistant forms of pathogens. Part of the development focuses on the ***destruction of the biofilm*** of pathogens as an important factor in their stability. It is shown that the combination of antimicrobial enzyme and fluoroquinolone antibiotic causes a synergistic effect against *S. aureus*, which is based on the breakdown of the biofilm layer by the enzyme and the subsequent bactericidal action of the antibiotic [99]. A similar mechanism is used in the development of a new drug "Dispersin" that acts on biofilms by destroying the cementitious substance of the biofilm matrix – poly-N-acetyl-glucosamine [100].

In the study of the combinative action of antibiotics and lytic enzymes, the effectiveness of their joint use in the treatment of superficial wounds of various etiologies and internal infections has been shown [101]. Therefore, the synergistic effect of enzymes and antibiotics will significantly reduce the effective dose of the latter, and consequently – reduce the cost of the drug and the development of pathogen resistance [102].

The experience of using bacteriophages as a basis for antimicrobial drugs already has a history but continues to be a promising way to combat resistant microbial pathogens [103]. Preparations of bacteriophages as antimicrobial agents have advantages because they do not affect the normal human microflora, do not cause resistance to pathogens, but their activity depends on the effectiveness of their replication. The development of this direction is the use of bacteriophage enzymes as an antimicrobial substance [104]. This solution provides high selectivity of the antimicrobial effect, while the enzymes (unlike the bacteriophages themselves) have no effect on the environment and the transfer of genetic information to microorganisms. An example of modern antibacterial and antifungal drugs is the development of a preparate of this profile, which differs from analogues in the content of bacteriophages with impaired replication function. Such drugs do not have these defects of live bacteriophage preparations and their enzymes.

Conclusions

Microbial pathogens have developed a variety of mechanisms to counteract antimicrobial agents and are constantly developing them, increasing their resistance and pathogenicity. It is on these mechanisms that the action of the novel antiseptics should be directed, which at the same time should not contribute to the emergence of additional resistance to pathogens. Analysis of numerical research results shows that antimicrobial agents that inhibit autoinducers, quorum sensing-systems of pathogens, biofilms, as well as the synthesis of enzymes that destroy antibiotics will be promising. It is important to develop multicomponent drugs with different mechanisms of action that will enhance the overall effect by destroying the protection of pathogens at different points in the process. It is interesting to use bacteriophages and antibiotics in such agents, as well as to search for substances with highly specific action on critical points of signal transmission of protective reactions of microorganisms. In concern of this, it is important to study new aspects of pathogenicity and resistance of pathogens of nosocomial infections, their analysis and consideration in the development of novel antiseptics.

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НОЗОКОМІАЛЬНІ ІНФЕКЦІЇ: ПАТОГЕННІСТЬ, СТІЙКІСТЬ І НОВІТНІ АНТИСЕПТИКИ

Проблематика. Боротьба з поширенням інфекційних захворювань породжує проблему резистентності патогенів, а найбільш стійкі з них – збудники нозокоміальних інфекцій – формуються в лікарнях унаслідок низки причин. Проблема вирішується в різних площинах, але актуальним лишається пошук нових ефективних засобів для лікування таких захворювань уже сьогодні. Найкоротший шлях до цього – знайти "больові точки" самих збудників, тобто фактори їх патогенності та резистентності, на які й має бути спрямована дія новітніх антисептиків.
Мета. Аналіз та оцінка основних факторів патогенності та стійкості збудників нозокоміальних інфекцій для визначення сучасних підходів до розробки новітніх антимікробних засобів.
Методика реалізації. Пошук і систематизація нових наукових даних і результатів щодо факторів патогенності мікробних збудників, що можуть бути використані як цілі для дії лікувальних препаратів.
Результати. Упродовж останніх 10–20 років унаслідок появи нових методів досліджень у біології стало можливим з'ясування особливостей і додаткових умов вияву факторів патогенності збудників нозокоміальних інфекцій. Показані додаткові механізми вияву стійкості, адгезивності, інвазивності, трансмісії ознак, секреції токсинів патогенами, що визначає загальне підвищення їх резистентності до дії використовуваних нині засобів. Загальна ідея створення антисептиків, які не сприятимуть підвищенню стійкості патогенів, наразі може бути реалізована з використанням субстанцій із різноспрямованими або опосередкованими механізмами дії, що мінімально впливають на метаболізм самої клітини та суттєво знижують її стійкість і патогенність.
Висновки. Фактори патогенності збудників нозокоміальних інфекцій та механізми їх реалізації можуть розглядатися як основні мішені для дії новітніх антисептиків, що будуть гальмувати поширення патогенів, не підвищуючи їх резистентність. Серед перспективних субстанцій для таких засобів – бактеріофаги та їх модифікації, ензибіотики, імунобіотики, інгібітори аутоіндукторів, інгібітори quorum sensing-системи, інгібітори β-лактамаз та інші. Частина з цих речовин у комбінації з антибіотиками нового покоління значно підсилює їх ефективність, і разом вони здатні долати опір навіть полірезистентних патогенів.

Ключові слова: мікробні збудники; фактори стійкості; патогенні фактори; механізми патогенності; антибіотикорезистентність; новітні антимікробні речовини.

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НОЗОКОМИАЛЬНЫЕ ИНФЕКЦИИ: ПАТОГЕННОСТЬ, СТОЙКОСТЬ И НОВЕЙШИЕ АНТИСЕПТИКИ

Проблематика. Борьба с распространением инфекционных заболеваний порождает проблему резистентности патогенов, а наиболее стойкие из них – возбудители нозокомиальных инфекций – формируются в больницах в результате ряда причин. Решение проблемы находится в разных плоскостях, но актуальным остается поиск новых эффективных средств для лечения таких заболеваний уже сегодня. Наиболее короткий путь к этому – найти "болевые точки" самих возбудителей, то есть факторы их патогенности и резистентности, на которые и должно быть направлено действие новейших антисептиков.
Цель. Анализ и оценка основных факторов патогенности и стойкости возбудителей нозокомиальных инфекций для определения современных подходов к разработке новейших антимикробных средств.
Методика реализации. Поиск и систематизация новых научных данных и результатов относительно факторов патогенности микробных возбудителей, которые могут быть использованы как цели для действия лекарственных препаратов.
Результаты. В течение последних 10–20 лет в результате появления новых методов исследований в биологии стало возможным выяснение особенностей и дополнительных условий проявления факторов патогенности возбудителей нозокомиальных инфекций. Показаны дополнительные механизмы проявления устойчивости, адгезивности, инвазивности, трансмиссии признаков, секреции токсинов патогенами, определяющие общее повышение их резистентности к действию используемых ныне средств. Общая идея создания антисептиков, которые не будут способствовать повышению устойчивости патогенов, сейчас может быть реализована с использованием субстанций с разнонаправленными или опосредованными механизмами действия, минимально влияющими на метаболизм самой клетки и существенно снижающими ее стойкость и патогенность.

Выводы. Факторы патогенности возбудителей нозокомиальных инфекций и механизмы их реализации могут рассматриваться как основные мишени для действия новейших антисептиков, которые будут приостанавливать распространение патогенов, не повышая их резистентность. Среди перспективных субстанций для таких средств – бактериофаги и их модификации, энзибиотики, иммунобиотики, ингибиторы аутоиндукторов, ингибиторы quorum sensing-системы, ингибиторы β-лактамаз и другие. Часть из этих веществ в комбинации с антибиотиками нового поколения значительно усиливает их эффективность, и вместе они способны преодолевать сопротивление даже полирезистентных патогенов.

Ключевые слова: микробные возбудители; факторы стойкости; механизмы патогенности; антибиотикорезистентность; новейшие антимикробные вещества.

Peer Reviewing Features

One of the co-authors of the article belongs to the editorial board of this journal. Therefore, the peer-review process was a little bit different from the standard one.

The peer review process was handled by the Editor-in-Chief and Managing Editor without the involvement of editorial members of the Biotechnology and Bioengineering Section. So, only external referees evaluated the article (the double-blind peer-review was applied). Referees' feedbacks contained no significant remarks, and only minor edits were needed. The team of authors took into account all the referees' comments, as well as few remarks of the Editor-in-Chief, and corrected the article.