UDC 615.468 https://doi.org/10.15407/biotech15.02.007

CHARACTERISTICS OF WOUND INFECTIONS AND METHODS OF THEIR TREATMENT USING PREPARATIONS OF BIOLOGICAL ORIGIN

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Received 04.02.2022
Revised 09.04.2022
Accepted 29.04.2022

Surgical wound infections are the most common patients' complications in the postoperative period. In the modern clinic, they worsen the disease prognosis and remain the most important and acute health problem in all countries of the world.

The *aim* of the work was to analyze current scientific data on the peculiarities of the pathogenesis of wound infections and types of their pathogens, as well as drugs of biological origin in the treatment of wound infections.

The paper discusses in detail the problem of infection of wound injuries during surgery and domestic injuries of various kinds. The main pathogens of wound infections are considered. Specific pathogenicity factors for bacteria of the genera *Staphylococcus*, *Pseudomonas*, *Enterobacteriaceae* were analyzed. Based on the analysis of literature sources, a list of drugs of biotechnological origin that can be effectively used in combination therapy for the treatment and prevention of wound infections was determined.

Conclusions. The result is the identification of those mechanisms of pathogenesis of wound infections that determine the effectiveness of the use of drugs of biological origin in this pathology treatment.

Key words: wound infections, contaminations by microorganisms, *Staphylococcus, Pseudomonas, Enterobacteriaceae,* antibiotics, immunomodulatory.

The doctrine of the wound and the wound process is one of the current problems. The tendency to increase the number of patients in surgery and as a consequence, numerous surgical interventions increasing the complexity and duration of operations, as well as progressive antibiotic resistance of pathogenic microflora complicate the problem of prevention and treatment of wounds.

The increase in the number of purulent diseases and complications after surgery, the growth in cases of infection generalization and the existence of various toxic-allergic reactions, cause negative results in the treatment of patients with this type of pathology, which indicates the urgency of purulent infection in surgery.

According to the World Health Organization (WHO), 1.7% to 44.8% of patients in the European region have been diagnosed with nosocomial infections (NIS) in the last 25 years. Home and foreign studies have found that this type of infection is the most common form of complications of surgical treatment of acute surgical disease in the postoperative period. About 17–35% of the operated patients' cases was diagnosed. The frequency of surgical wound infections directly depends on the type and nature of surgical intervention: for clean wounds it is 1.5–6.9%, conditionally clean – 7.8–11.7%, contaminated – 12.9–17%, when the same for "dirty" it is 10–40%.

Although the type of infection in patients in different countries around the world may be

influenced by different factors, it is generally accepted that every tenth patient who seeks medical attention is affected by NIS.

It was also found that in surgical hospitals in Ukraine an average of 13.4–38.8% of STIs are found among patients during the postoperative period, which correlates with those of other countries.

Surgical wound infections (SWI) are the most common complications in patients at the postoperative period. In the modern clinic, they worsen the prognosis of the disease, remain the most important and acute health problem in all countries of the world due to high prevalence, morbidity and mortality, as well as socio-economic damage [1–2].

Peculiarities of the pathogenesis of wound infections and types of their patients

Wound infection is a disease that causes pathogenic microorganisms to enter the human body through the wound and thus leads to the development of purulent and inflammatory processes.

Infection in the wound or infectious process develops when the balance between the microorganisms that contaminate the wound and the protective forces of the macroorganism, which is displayed as clinical symptoms of inflammation.

The mechanism of the wound process development is very complex and is still the subject of close attention and study by morphologists, microbiologists, immunologists, and clinicians. Its first period, defined as the melting of necrotic tissues and the cleansing of the wound defect from them, can be represented in the most general terms as follows. When natural external barriers (skin or mucous membrane) are damaged and microorganisms penetrate into the wound, the protective mechanisms of cellular (T-cells, polymorphonuclear leukocytes, macrophages) and humoral (B-cells) immunity come into action. At the same time, cellular immunity factors phagocytize microbial bodies and necrotic tissues, cleaning the wound. At this time, a granulation shaft is formed in the region of the edges of the wound, which prevents the spread of infection to the surrounding tissues. If the insufficiency of the body's defenses does not allow to reliably delimiting the wound, this can lead to a generalization of the infection [3–6]. Developing infectious complications are manifested in the form of near-wound abscesses, near-wound phlegmon, purulent streaks, fistulas, thrombophlebitis, lymphangitis and lymphadenitis. With generalization of infection, sepsis may develop [7].

During the infectious process in a wound, the pathogens spread through the blood and lymphatic system throughout the human body. After that, the acute phase of the inflammatory process begins, which occurs not only in areas of tissue damage, but also covers the whole body.

In the development of pathological processes, microorganisms are usually divided into saprophytes, opportunistic and pathogenic. One of the main criteria for the pathogenicity of microorganisms is invasiveness – the ability of microorganisms to multiply in the body, overcoming its defense mechanisms. Therefore, in the framework of this problem, it is believed that conditionally pathogenic bacteria, which are not characterized by an active form of invasiveness, can cause infections in wounds, in those clinical cases where anti-infective resistance is suppressed [8–9].

The generally accepted classification of wounds is their division into surgical and accidental. The first, in turn, are divided into "pure" and purulent. Accordingly, a certain pathogenic microflora is isolated in each type of wound [10–12].

"Clean" wounds occur during surgery in asepsis, where there is minimal exposure to bacterial microflora. The most common bacterial species detected were *Staphylococcus aureus* (37%), *Pseudomonas aeruginosa* (17%), *Proteus mirabilis* (10%), *Escherichia coli* (6%), and *Corynebacterium spp.* (5%). Polymicrobial infection was detected in 59 samples (27.1%) and was mainly of two types [13].

Staphylococci have a variety of antigens that are localized mainly in the cell wall: peptidoglycan and protein A, which is localized on its surface. It is *S. aureus* that has this protein, which is capable of non-specific association with Fc–fragments of IgG, which indicates the ability to agglutination with human serum and to a positive reaction when interacting with heterologous drugs [14–16].

Staphylococci induce large numbers of immunocytes, leading to inflammation and abscesses. Capsule polysaccharides inhibit the activity of phagocytes. Protein A, contained in the cell wall of *S. aureus*, has antiphagocytic properties. Pathogenic factors in bacteria of

the genus *Staphylococcus* are microcapsules, teichoic acid, protein A, as well as enzymes catalase, β-lactamase, lipase, hyaluronidase [10, 11, 17].

Purulent surgical wounds are most often infected with gram-negative microflora, mainly blue purulent bacillus (*Pseudomonas aeruginosa*) [18–19].

For a long time, *Pseudomonas aeruginosa* was considered an conditionally pathogenic microorganism, but due to the widespread use of antibiotics, the number of cases of various purulent-inflammatory processes caused by *P. aeruginosa* has increased significantly.

Pseudomonas aeruginosa is a gram-negative, rod-shaped bacterium that quickly adapts to different environmental conditions. As an obligate aerobic, it can also use anaerobic respiration using nitrates as electron acceptors [20].

O- and H-antigens are characteristic for *P. aeruginosa*. Pathogenic factors for this type of microorganism are exotoxin A, membrane toxins, lecocidin [21, 22].

The virulence of *Pseudomonas aeruginosa* is provided by saws, capsule shell, surface membrane proteins and cell wall, which are involved in adhesion processes. This microorganism produces a number of enzymes and toxins. The capsule-like glycoprotein is easily separated from the bacterial cell, provides protection against phagocytosis, and is toxic to host cells.

Diseases caused by this microorganism are primarily associated with purulent-inflammatory processes, which occur mainly in associations with staphylococcus. They are observed in the infection of surgical wounds and burns. Therefore, it is considered one of the main pathogens of NIS [10–12, 23].

Accidental wounds. This group of wounds includes traumatic wounds of various origins — domestic, industrial, gunshot wounds, etc. Such wounds are accompanied by significant damage and deep penetration into the body tissues of various foreign substances and particles. Accidental wounds are always primarily bacterially contaminated,

The main representative of the microflora of random infections are bacteria of the genus *Enterobacteriaceae — Escherichia coli* [24, 25].

This type of microorganism has a complex structure of antigens, which consists of somatic O-antigen, capsular K-actigen and flagellar — H-antigen.

In many cases, *E. coli* is the causative agent of exogenous purulent infections in various localizations of the body. It causes purulent processes together with bacteria of the *Staphylococcus* and *Pseudomonas* genus. Severe immunodeficiency can cause sepsis [17–22, 26].

Drugs of biological origin in the treatment of wound infections

Followed by the analysis of literature sources, it was found that in practice the fight against various types of wound infections is carried out comprehensively. The main drugs in the fight against pathogenic microflora are drugs of biotechnological origin, namely antibiotics, antiseptics for bandages and immunomodulators [1–2, 10, 27].

All strains of microorganisms that were removed from postoperative wounds showed polyresistance to most traditional antibiotics. According to official statistics, more than 30% of hospitalized patients receive antibiotics, of which almost half are patients for prophylactic purposes. Rational tactics of antibiotic therapy used for surgical type of wounds is pre-anesthetic administration of the first dose of antibiotic. Prophylactic antibiotics have been shown to reduce the incidence of postoperative complications from 40% to 2% in most cases.

Penicillin, aminoglycoside, fluoroquinolone, and cephalosporin antibiotics are the most commonly prescribed [28, 29].

The use of antibiotics is aimed at suppressing the microflora of the wound through the use of drugs with selective antimicrobial action. Topical administration of antibiotics and systemic antibacterial therapy, both in isolation and in combination with other agents, can effectively help to heal wound infection. However, the prerequisite for the choice of therapy is the selection of the dose and routes of administration [30, 31].

With a wide selection of antibiotics, the range of drugs for topical use is limited. After all, the use of local forms of antibiotics may be accompanied by an increase in the pathogen resistance. Also, the risk of developing resistance is significantly reduced if the drug for topical use is not used systematically. From this point of view, mucirocin and bacitracin are the most suitable drugs, because when using them there is no risk of selection of cross-resistance to other antimicrobial drugs.

Thus, antibiotics that are available in the form of ointments and powders for the local treatment of infected and purulent wounds include neomycin, bacitracin, fusidic acid, mupirocin, metronidazole, ofloxacin and others.

Examples of the above combinations that have shown high microbiological and clinical efficacy are Baneocin, a mixture of neomycin and bacitracin, and Neosporin, a mixture of bacitracin, neomycin and polymyxin B [29, 32–34].

However, the efficiency of application of existing antibiotics for the local treatment of wound infections is gradually declining, so the vectors of modern treatments are aimed at finding alternative ways to influence the wound process, one of which is the use of immunostimulatory drugs, including immunomodulators. different directions on the immune system depending on its initial state. They recover the normal functioning of the immune system in the required therapeutic doses, that is, they restore effective immune protection

For example, the use of recombinant IL-2, a means of local treatment of purulent wounds, mainly in combination with traditional treatments, causes an increase in lymphocytes and macrophages in the wound, thereby accelerating changes in the stages of the wound process, increasing the activity of phagocytic cells in the wound [35, 36].

Also promising is the use of a drug of local action — superlymph, which is a composite of a number of antimicrobial peptides and heterologous cytokines in their natural ratio in the fight against inflammatory diseases of different localization.

The study of the bacterial polysaccharides effect on neutrophilic granulocytes, which took place *in vitro* made it possible to establish their ability to affect not only the synthesis of cytokines but activate the main effector reactions of these cells as well, such as phagocytosis, chemotaxis, adhesion and inhibition of apoptosis. The ability of these immunomodulators to affect other cell populations, in particular monocytes and macrophages, has also been studied experimentally [37].

Due to the change in a body reactivity in the event of wound infections, new approaches are needed to diagnose disorders and their appropriate correction. Modern methods of immunodiagnostics enable to study even T- and B-systems of immunity, and this, in turn, made it possible to develop clinical and immunological criteria for assessing immune disorders in patients with wound infections, especially purulent, and monitoring the effectiveness of immunotherapy [35, 38–41].

Immunotherapy as one of the components of complex treatment of wound infections also gives positive results, especially the use of antistaphylococcal gamma globulin and hyperimmune antistaphylococcal plasma. The use of immunomodulators, especially thymic drugs, for this method of treatment is very promising [42–44].

As immunomodulators for wound healing in wound surgical infections, supernatants of adhesion-activated neutrophils are used, which are applied to the wound in 3–4 days after surgery, five times with an interval of 24 hours in 0.5–1.0 ml of diluted supernatant 3.0 ml of saline solution, and after 12 h apply bandages with antiseptics.

The use of supernatants can increase the intensity of therapy by stimulating local immunity. As a result: the local inflammatory reaction is decreased, the level of bacterial contamination of the wound is reduced and the rate of wound defect reduction is increased [45].

The principle of these immunomodulators use is the local application of autologous secretory products that are activated by neutrophil adhesion in addition to complex therapy for the treatment of purulent-inflammatory soft tissue diseases. An example of such a drug is Polyoxidonium – a drug with immunomodulatory action. It increases the body's resistance to various infectious diseases. The main mechanism of action is a direct effect on natural killers and phagocytic cells, as well as stimulation of appropriate antibodies formation. It is also characterized by detoxifying action, increases the resistance of cell membranes to cytotoxic substances, helps to restore immune responses in purulent-inflammatory processes and burns. It is used mainly in combination therapy [46, 47].

Interferons can be used as drugs with immunomodulatory action in the complex treatment of wound infections. For example, Interferon alfa 2b has an immunomodulatory, antiproliferative effect [48]. It contains recombinant human interferon that is completely identical to Interferon alpha 2b, which is synthesized by leukocytes of donor blood in response to interferon virus. It is non-toxic and harmless, especially effective in purulent-inflammatory processes that

accompany wound processes, is intravenous and endolymphatic administration of the drug [36, 49–53].

Conclusions

Thus, wound infections can be of different origins and are caused by different types of pathogens, among which the most common are microorganisms of the genus *Staphylococcus, Pseudomonas* and *Enterobacteriaceae*.

For the treatment of wound infections, regardless of its origin, in most cases a comprehensive therapy is used based on drugs of biotechnological origin, namely different types of antibiotics. Effective antibiotics are selected according to the type of pathogen and the damage degree to the body in order to determine the optimal course and dose of drugs.

Since the treatment of wound infections involves a comprehensive approach, the use of antibiotics, antiseptics for dressings and some immunomodulatory drugs is recommended.

After all, the latter are able to accelerate the healing process of wounds, by increasing the body's ability to carry out immune defense responses and by enhancing the effect of the main therapy.

Due to the fact that the use of immunomodulatory drugs in the treatment of this type of infection is still poorly understood and due to the high resistance of pathogens to existing traditional antibiotics, there is a large number of clinical studies in this area. The vector of their research is mainly aimed at finding individual drugs and complex therapies that will promote rapid wound healing, elimination of infectious contamination by possible pathogens and the use of a single therapy against polymicrobial type of wound infections.

This study did not receive any financial support from a government, community or commercial organization. The authors state that they have no conflict of interest.

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ХАРАКТЕРИСТИКА РАНОВИХ ІНФЕКЦІЙ ТА СПОСОБІВ ЇХ ЛІКУВАННЯ ІЗ ВИКОРИСТАННЯМ ПРЕПАРАТІВ БІОЛОГІЧНОГО ПОХОДЖЕННЯ

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Хірургічні ранові інфекції є найбільш частими ускладненнями у пацієнтів у післяопераційний період. У сучасній клініці вони погіршують прогноз хвороби, залишаються найбільш важливою і гострою проблемою охорони здоров'я в усіх країнах світу.

Метою роботи був аналіз сучасних наукових даних щодо особливостей патогенезу ранових інфекцій та типів їх збудників, а також препаратів біологічного походження у лікуванні ранових інфекцій.

У роботі детально обговорюється проблема інфікування ранових ушкоджень за оперативного втручання та побутових травмах різного характеру. Розглянуто основні збудники ранових інфекцій. Проаналізовано специфічні фактори патогенності для бактерій родів *Staphylococcus, Pseudomonas, Enterobacteriaceae*. На підставі аналізу джерел літератури, було визначено перелік препаратів біотехнологічного походження, що можуть ефективно використовуватися в комплексній терапії для лікування і профілактики ранових інфекцій.

Результатом роботи є виявлення тих механізмів патогенезу ранові інфекції, які обумовлюють ефективність використання препаратів біологічного походження у лікуванні даної патології.

Ключові слова: ранова інфекція, контамінація мікроорганізмами, *Staphylococcus, Pseudomonas, Enterobacteriaceae,* антибіотики, імуномодулятори.