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Systematic Computer-Aided Analysis of Big Data Concerning Global Experience in Infected Wound Healing

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ABSTRACT

The present study offers a systematic review of 43,386 research articles investigating wound infection, which were analyzed using data analysis approaches developed by the Yu.I. Zhuravlev and K.V. Rudakov's scientific school. The cluster-based terminology applied to the publications identified in the study suggests (1) diverse inflammatory mechanisms, (2) a range of bacterial and viral pathogens that contribute to impaired wound healing, and (3) a variety of antibiotics and other pharmacological agents, the effects of which are investigated in the scientific publications. The generated map of the most informative terms provides a comprehensive description of the wound infection pathophysiology and identifies promising areas of research focused on wound pharmacotherapy, including approaches to biofilm eradication; use of nanofibers, hydrogels, and nanoparticles; and pharmacological control of wound inflammation. The pharmacological treatment of infected wounds extends beyond the scope of conventional antiseptics and antibiotics to include the use of phytoextracts (and their components, including antioxidant derivatives), pharmaconutraceuticals, essential elements (primarily copper, zinc, and silver), biguanides (for wound treatment in patients with carbohydrate metabolism disorders), hyaluronic acid (for wound dressings), and probiotic bacteria that facilitate the eradication of pathogenic biofilms. This study is supported by a review of pertinent evidence-based studies, highlighting the most promising research trends, including biofilm control, surgical debridement, and pharmaconutraceuticals.

Keywords: wound infection; biofilms; antibiotics; phytoextracts; vitamins; placental peptides; zinc.

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Систематический компьютерный анализ публикаций больших данных, отражающих мировой опыт исследований ранозаживления инфицированных ран

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АННОТАЦИЯ

В работе представлены результаты систематизации массива из 43 386 статей по инфицированию ран, проведенной методами анализа данных научной школы академиков Ю.И. Журавлева и К.В. Рудакова. Выявленная в исследовании кластерная терминологическая структура публикаций указывает (1) на многообразие соответствующих механизмов воспаления, (2) многообразие бактериальных и вирусных патогенов, затрудняющих заживление ран, (3) многообразие антибиотиков и прочих фармакологических средств, эффекты которых исследуются в научной литературе. Полученная карта наиболее информативных терминов не только детально характеризует патофизиологию инфицирования ран, но и указывает на перспективные направления исследований в фармакотерапии ран: подходы к решению проблемы биопленок; использование нановолокон, гидрогелей и наночастиц; фармакотерапия раневого воспаления. В фармакологии ранозаживления инфицированных ран активно исследуются не только антисептики и антибиотики, но и фитоэкстракты (и их компоненты, в том числе антиоксидантные), фармаконутрицевтики, определенные микроэлементы (прежде всего, медь, цинк и серебро), бигуаниды (для лечения ран у пациентов с нарушениями углеводного обмена), гиалуроновая кислота (для перевязок), бактерии-пробиотики, способствующие разрушению патогенных биопленок. Приведены примеры доказательных исследований, указывающие на наиболее перспективные исследовательские тренды: борьба с биопленками; особенности проведения хирургических вмешательств, связанные с инфицированием ран; применение фармаконутрицевтиков.

Ключевые слова: раневая инфекция; биопленки; антибиотики; фитоэкстракты; витамины; пептиды плаценты; цинк.

Как цитировать

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INTRODUCTION

Standard wound management protocols, particularly in combat-related injuries, include hemostasis (with vessel ligation if necessary), wound irrigation with antiseptic solutions (such as hydrogen peroxide, chlorhexidine, etc.), wound closure (to restore tissue integrity), antibacterial therapy (in the presence of or at high risk for infection), and tetanus vaccination (in the case of wound contamination). Minor injuries may heal within 7–10 days, whereas deeper or, more importantly, infected wounds may require several weeks or even months of treatment. Therefore, maximizing the effectiveness and safety of wound healing interventions is of critical importance.

In particular, wound infection significantly complicates healing and increases mortality risk. Before new and more effective treatment protocols can be developed, it is essential to summarize the existing scientific and clinical knowledge about the pathophysiology of wound infections and their management.

CLUSTER-BASED TERMINOLOGICAL STRUCTURE OF PUBLICATIONS

In the present work, a PubMed database analysis was conducted to characterize the structure of publications on this topic. As of September 2024, a total of 217,826 articles were identified under the search term "wound healing." At the same time, the search yielded only 2,887 publications addressing wound healing in soldiers, using the broad query "wound healing AND (military OR soldiers)." This is approximately 1% of all wound healing publications, with the actual volume of research on this topic being even lower.

Thus, according to PubMed-indexed publications, the research topic "wound healing in combat-related injuries" constitutes a very narrow niche within the overall body of wound healing studies. The majority of the remaining studies focus on wound healing in patients with various chronic conditions (primarily diabetes mellitus). Given this imbalance in the scientific publication landscape, it is critical to consider an individual patient's chronic comorbidities (e.g., common liver and/or pancreatic disorders, gastrointestinal dysbiosis, early stages of atherosclerosis, etc.) when developing therapeutic approaches aimed at improving wound healing quality and treatment outcomes in these patients.

Wound infection prevention and treatment is a broader and more extensively studied research area: the search term "wound healing AND (bacterial OR microbiome OR viral OR virus OR infection)" yielded 43,386 publications, accounting for 20% of all wound healing publications. Effective prevention of wound infections and timely, adequate therapeutic care when an infection occurs are critical for improving patient survival and health status.

To enable comprehensive systematization of this body of research, we created a control sample of publications based on the most frequently encountered keywords *unrelated* to infection or wounding. The search query used was: "(Humans [MeSH Terms] OR Animals [MeSH Terms]) AND (Treatment Outcome [MeSH Terms] OR Retrospective Studies [MeSH Terms] OR Follow-Up Studies [MeSH Terms] OR Prospective Studies [MeSH Terms]) NOT wound healing NOT bacterial NOT microbiome NOT viral NOT virus NOT infection." The control sample included 43,386 publications randomly selected from a total of 2,570,468 articles retrieved using this query.

The sample dataset on "infection and wound healing" was compared with the control sample using topological [1, 2], combinatorial [3], and metric [4, 5] data analysis methods developed by the scientific school of Zhuravlev and Rudakov. As a result, a metric diagram of the most informative terms distinguishing the publications in the topic-specific text sample from those in the control text sample was constructed (Fig. 1). Applying metric data analysis methods [4] to this diagram revealed three distinct clusters of terms: "Molecular mechanisms of inflammation" (Cluster 1), "Pathogens" (Cluster 2), and "Antibiotics" (Cluster 3). The majority of the remaining highly informative out-of-cluster terms were, as will be shown below, associated with chronic conditions affecting wound healing in some way.

Each of the terms in Fig. 1 corresponds to 10 to 1,500 publications. The cluster-based terminological structure of publications on infected wound healing characterizes the following:

1) The diversity of inflammatory mechanisms involved (both hyperinflammation and insufficient inflammation due to immune dysfunction can significantly hinder wound healing and patient recovery);

2) The variety of bacterial and viral pathogens that impede wound healing;

3) The wide range of antibiotics and other pharmacological agents whose effects are investigated in scientific publications.

Cluster 1 "Molecular mechanisms of inflammation" included terms characterizing prostaglandin–leukotriene pathways closely associated with the arachidonic acid cascade and cyclooxygenase-2 activity (GO:0004961 Thromboxane A2 receptor activity; GO:1901751 Leukotriene A4 metabolic process; GO:2001306 Lipoxin B4 biosynthetic process; GO:0061737 Leukotriene signaling pathway); cytokine and chemokine mechanisms (GO:0044546 NLRP3 inflammasome complex assembly; GO:0032640 Tumor necrosis factor production; GO:0035926 Regulation of chemokine (C-X-C motif) ligand 2 production; GO:0048020 CCR chemokine receptor binding; GO:0050701 IL-1 production; GO:0090195 Chemokine production); interferon pathways (GO:0004905 Type I interferon receptor activity; GO:0032607 Interferon-alpha production; GO:0032608

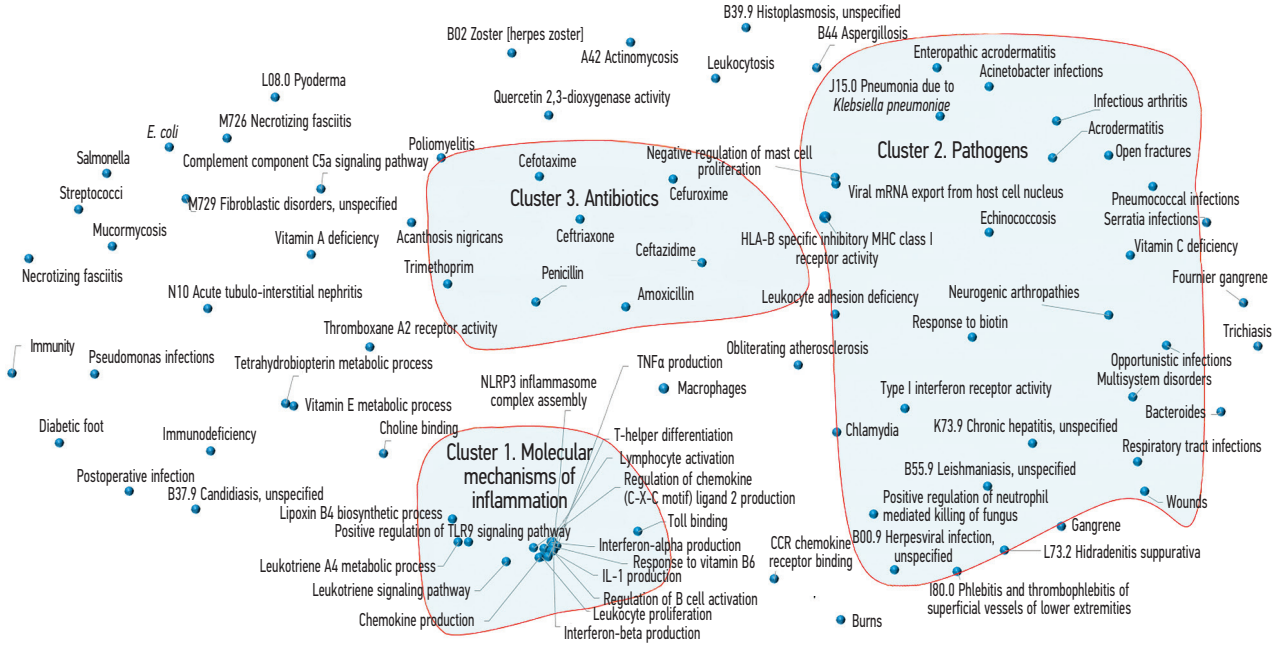

Fig. 1. Metrics chart for the most informative terms representative of the full array of 43,386 publications on wound infection. Each term is represented by a single point on the graph. The strength of the term interaction, or the co-occurrence, is directly proportional to the proximity of the two points. The graph is generated by projecting a multidimensional metric space (pairwise distance matrix between two terms) on the image plane.

Рис. 1. Метрическая диаграмма наиболее информативных терминов, характерных для всего массива из 43 386 публикаций по инфицированию ран. Каждому термину соответствует одна точка на диаграмме. Чем ближе две точки, чем сильнее «взаимодействие» терминов (более высокая совместная встречаемость). Диаграмма получена проецированием многомерного пространства метрической конфигурации (матрица парных расстояний между терминами) на плоскость рисунка.

Interferon-beta production); innate immune responses to bacterial lipopolysaccharides (LPS, GO:0005121 Toll binding; GO:0034165 Positive regulation of TLR9 signaling pathway); histamine-related mechanisms (GO:0070667 Negative regulation of mast cell proliferation); and various leukocyte-related mechanisms (GO:0070965 Positive regulation of neutrophil mediated killing of fungus; GO:0046649 Lymphocyte activation).

Given the diversity of inflammatory mechanisms involved in wound infection, as reflected in Cluster 1, it becomes evident that (a) pharmacological agents targeting only a single inflammatory pathway, such as nonsteroidal anti-inflammatory drugs, which inhibit cyclooxygenase-2 in the prostaglandin-mediated pathway, may be insufficient, and (b) there is a need for agents that modulate other mechanisms, including NF-κB/inflammasome inhibitors, kinase inhibitors, antihistamines, and others. Importantly, an individual patient may have, for example, excessive cytokine-mediated inflammation in the presence of suppressed interferon immunity, low lymphocyte counts, and so on.

Cluster 2 “Pathogens” includes various bacterial and viral pathogens associated with wound infections arising from postoperative and/or opportunistic infections. In addition to the well-known pneumococcal, Pseudomonas, and streptococcal infections, impaired wound healing is also linked to a wide range of other bacterial pathogens (A42 Actinomycosis, B44 Aspergillosis, B67 Echinococcosis, Acinetobacter infections, *Escherichia coli*, mucormycosis, Salmonella, Bacteroides, *Serratia*, trichiasis, acanthosis nigricans, Chlamydia), viral pathogens (B00.9 Herpesviral infection, unspecified, B02 Zoster [*herpes zoster*]), fungal infections, and other infectious agents (B37.9 Candidiasis, unspecified; B39.9 Histoplasmosis, unspecified; B55.9 Leishmaniasis, unspecified).

The high diversity of bacterial and other pathogens involved in wound infection underscores the need for the use of antiseptics and antibiotics with the broadest possible spectrum of activity, as well as agents targeting other types of pathogens. The presence of fungal pathogens in wound cultures obtained from individual patients necessitates the use of antifungal agents. Combating viral pathogens requires strengthening the immune system against specific molecular and biological types of viruses (primarily single-stranded RNA viruses); a systematic analysis of this issue is presented in monograph [6].

Cluster 3 “Antibiotics” includes antibiotics whose effects are most frequently studied in the treatment of wound infections (in descending order of informativeness: amoxicillin, ceftazidime, cefuroxime, penicillin, ceftriaxone, trimethoprim, cefotaxime, etc.; a more complete list is provided below in the analysis of the pharmacological subset of publications on infected wound healing).

The majority of the remaining out-of-cluster terms shown in the diagram (see Fig. 1) are associated with chronic conditions and immune mechanisms in some way. These terms include:

Factors of chronic multisystem disorders that complicate the treatment of patients with wound infections (diabetic foot, obliterating atherosclerosis, N10 Acute tubulo-interstitial nephritis, I80.0 Phlebitis and thrombophlebitis of superficial vessels of lower extremities, J15.0 Pneumonia due to *Klebsiella pneumoniae*, K73.9 Chronic hepatitis, unspecified, L08.0 Pyoderma, L73.2 Hidradenitis suppurativa, M72.6 Necrotizing fasciitis, M72.9 Fibroblastic disorders, unspecified, acrodermatitis, including enteropathic);

Other traumatic injuries and their consequences (burns, open fractures, gangrene, necrotizing fasciitis);

Molecular mechanisms of immunity and its impairments that hinder recovery (immunodeficiency, leukocyte adhesion deficiency, macrophages, GO:0030109 HLA-B specific inhibitory MHC class I receptor activity, GO:0046784 Viral mRNA export from host cell nucleus, GO:0050864 Regulation of B cell activation, GO:0070661 Leukocyte proliferation, GO:2000321 Positive regulation of T-helper 17 cell differentiation, GO:0038178 Complement component C5a signaling pathway);

References to micronutrients and pharmaconutraceuticals that support the treatment of infected wounds (GO:0008127 Quercetin 2,3-dioxygenase activity, GO:0033265 Choline binding, GO:0034516 Response to vitamin B_6, GO:0042360 Vitamin E metabolic process, GO:0046146 Tetrahydrobiopterin metabolic process, GO:0070781 Response to biotin, vitamin A deficiency, vitamin C deficiency).

It should be emphasized that the terminological map in Fig. 1 includes the most informative terms (those whose minimal number makes it possible to distinguish publications on the prevention, treatment, and fundamental research of infected wounds from the control group). In the analysis of the pharmacological subset of publications on infected wound healing [query: "wound healing AND (bacterial OR microbiome OR viral OR virus OR infection) AND (Wound Healing/drug effects [MeSH Terms] OR Anti-Bacterial Agents/therapeutic use [MeSH Terms])", approximately 8,000 articles, with the same control group of texts], the set of points in Cluster 2 "Antibiotics" expands significantly and allows for a number of conclusions regarding promising areas of research on infected wound pharmacotherapy.

This expanded Cluster 2 includes terms associated with studies on:

- Bacterial biofilms, which significantly enhance the survival of pathogenic bacteria and thus aggravate wound infections;
- Nanofibers and hydrogels (used in the development of advanced wound dressings);
- Nanoparticles (employed to improve the delivery of antibacterial agents, such as moxifloxacin, vancomycin, ciprofloxacin, and clindamycin, as well as silver, zinc, zinc oxide, and copper nanoparticles; the effectiveness depends critically on the optimal nanoparticle size);
- Pharmacotherapy of inflammation (NF-κB inhibitors, glucocorticoids, and others);
- Regulators of nitric oxide (NO) metabolism (produced by various types of leukocytes to combat bacterial and viral pathogens);
- Active substances derived from natural extracts (antioxidants, tannins, curcumin, and others).

Notably, current pharmacological research on infected wound healing focuses not only on antiseptics (such as povidone-iodine, chlorhexidine, triclosan, trimethoprim, and colloidal nanosilver-based antiseptics) and broad-spectrum antibiotics from a wide range of pharmacological classes (in descending order of relevance for the treatment and prevention of bacterial wound infections: sulfadiazine, ciprofloxacin, gentamicin, doxycycline, mupirocin, tetracycline, clindamycin, rifampicin, ampicillin, cefazolin, tobramycin, fluoroquinolones, amikacin, sulfadiazine, ofloxacin, cefuroxime, clarithromycin, clavulanate, daptomycin, linezolid, sulfamethoxazole, amoxicillin, azithromycin, cephalexin, metronidazole, imidazoles, penicillin, piperacillin, vancomycin, ceftriaxone, cephalosporins, gatifloxacin, sulbactam, framycetin, Dermazin, Flammazine, and oxytetracycline).

The following promising therapies are also being actively explored:

- Natural antibiotics (such as bacitracin and cathelicidin; the latter is synthesized in the body when vitamin D3 levels are adequate);
- Biguanides (used in the treatment of infected wounds complicated by patient-specific carbohydrate metabolism disorders);
- Hyaluronic acid and citric acid (applied in wound dressing formulations to enhance healing of the connective tissue matrix at the site of injury);
- Phytoextracts (aloe, turmeric, cinnamon) and their individual components (triterpenes, saponins, tannins, including tannic acid);
- Natural pharmaconutraceuticals collectively referred to as antioxidants (e.g., curcumin, bioflavonoids);
- Copper and zinc, which are particularly important for wound healing when applied either topically or systemically, and are used as immunostimulants (in the form of organic salts) and/or antiseptics (as colloidal suspensions of elements or oxides);
- Lactobacilli and other probiotics, which contribute to the breakdown of pathogenic biofilms.

Examples of evidence-based studies illustrating specific findings from the computational scientific data analysis are presented below. The analysis made it possible

to identify three of the most promising research trends aimed at improving treatment outcomes and/or prevention of wound infections, which deserve further consideration:

- Biofilm management strategies;
- Surgical procedure characteristics related to wound infection;
- Pharmaconutraceuticals and natural extracts in the management of wound infections.

BIOFILM MANAGEMENT STRATEGIES

In antibiotic therapy, one important characteristic of bacteria is often overlooked: the formation of so-called biofilms, which are bacterial colonies with enhanced survivability. Pathogenic bacterial biofilms, which are highly resistant to antibiotics, are particularly sensitive to changes in environmental pH and specific modulatory substances that influence biofilm formation.

Biofilms are commonly found in poorly healing "chronic" wounds. For example, in a meta-analysis of 9 studies in patients with chronic wounds (*n*=185), the prevalence of biofilms was 78.2% (95% confidence interval [CI]: 61.6–89, *p* <0.002) [7]. A meta-analysis of 8 clinical trials found insufficient evidence to support the claimed antibiofilm efficacy of conventional topical antiseptics. When assessing wounds using visual methods, including autofluorescence imaging, clinical expertise and physicians' skills play a key role in biofilm removal and improved wound healing outcomes [8].

Biofilm management strategies in wound care are diverse and include the use of specific biofilm-disrupting molecules, standardized colloidal nanosilver solutions, and natural extracts (see below). In terms of micronutrients, topical application of ascorbic acid (vitamin C) promotes the destruction of bacterial biofilms through various molecular mechanisms, such as restoring pH to physiological levels, which also creates optimal conditions for the survival of beneficial lactobacilli biofilms [9]. One approach to reducing biofilm colonization in wounds is the use of silver nanoparticles. Some physicians still perceive silver nanoparticle-based products as part of folk medicine, and even the "nano-" prefix fails to dispel this misconception. However, a series of meta-analyses of clinical studies on nanosilver has confirmed the promise of this approach in wound therapy.

A meta-analysis by Jiang et al. [10] demonstrated that standardized colloidal nanosilver solutions significantly reduce wound healing time compared to iodine-based dressings (–0.95 conventional units, 95% CI: –1.62 to –0.28, I2=92%, *p*=0.005). Moreover, they help reduce exudate volume and may partially alleviate pain symptoms (an effect observed in 3 out of 7 studies included in the meta-analysis), indicating greater antibacterial efficacy of silver compared to povidone-iodine. A meta-analysis by Luo et al. [11], which included seven studies (*n* = 650), confirmed the efficacy of silver nanoparticle dressings in the treatment of diabetic foot ulcers: a significant increase in healing rate and time to complete wound closure was observed, as well as a shorter hospital stay and faster infection resolution. In a meta-analysis of 11 studies, 1% silver sulfadiazine was shown to be effective in promoting tissue healing in burn patients compared to other treatment methods, with a reduction in the mean time to complete wound healing by 4.26 days (95% CI: –5.96 to –2.56, *p* <0.00001) [12].

SURGICAL PROCEDURE CHARACTERISTICS RELATED TO WOUND INFECTION

Topical application of antibiotics is not always effective in preventing or treating wound infections. A meta-analysis by Lin et al. [13] demonstrated that topical antibiotics do not significantly reduce the risk of postoperative wound infections (relative risk [RR] 0.83, 95% CI: 0.61–1.16, *p* >0.1). Subgroup analysis showed no reduction in wound infection rates with the use of topical antibiotics for incisions in spinal (RR0.75, 95% CI: 0.40–1.38), orthopedic (RR0.69, 95% CI: 0.37–1.29), dermatologic (RR0.77, 95% CI: 0.39–1.55), or cardiothoracic surgeries (RR1.31, 95% CI: 0.83–2.06).

At the same time, a meta-analysis of 12 randomized controlled trials (*n*=1,781) conducted by Wang et al. [14] confirmed the effectiveness of topical gentamicin (a broad-spectrum aminoglycoside antibiotic) in the prevention and treatment of wound infections. Compared to the control group without gentamicin, topical application of gentamicin demonstrated significantly higher clinical efficacy (odds ratio [OR] 3.57, 95% CI: 2.52–5.07). Regarding wound healing duration, the gentamicin group showed a shorter healing time than the non-gentamicin group (–4.94 days, 95% CI: –8.37 to –1.51).

A meta-analysis of 10 randomized clinical trials (*n*=1,006,587) revealed that laminar airflow ventilation systems in orthopedic operating rooms do not reduce the risk of wound infections. Moreover, it was shown that these systems may even increase the risk of infection (RR1.27, 95% CI: 1.02–1.59, *p* <0.05) [15].

A meta-analysis of 22 randomized clinical trials (*n*=4,492) conducted by Li et al. [16] confirmed the clinical efficacy of wound edge protectors in reducing surgical site infections following abdominal surgery. The use of protectors significantly reduced the overall infection rate (RR0.66, 95% CI: 0.53–0.83, *p*=0.0003), including superficial infections (RR0.59, 95% CI: 0.38–0.91, *p*=0.02) and the risk of infection in clean-contaminated wounds (RR0.61, 95% CI: 0.40–0.93, *p*=0.02) and contaminated wounds (RR0.47, 95% CI: 0.33–0.67, *p* <0.0001).

A meta-analysis of 22 clinical studies (*n*=5,487), which assessed the effects of nine types of surgical dressings, showed that three types of dressings demonstrated a significant effect in reducing the risk of wound infection. These were dressings containing mupirocin (OR1.076, 95% CI: 1.014–1.142, *p*=0.015), dressings containing dialkylcarbamoyl chloride (OR1.047, 95% CI: 1.012–1.083, *p*=0.008), and dressings containing a vitamin E–silicone compound (OR1.129, 95% CI: 1.016–1.255, *p*=0.025). The vitamin E-silicone dressing was the most effective (SUCRA score 0.37), followed by the mupirocin-containing dressing (SUCRA score 0.31) [17].

Falagas et al. [18] conducted a meta-analysis of 22 studies (*n*=2,467), which demonstrated the effectiveness of vacuum-assisted closure (VAC) therapy in patients with wound infections. Patients who received VAC therapy had significantly lower mortality rates than those treated without VAC (RR0.40, 95% CI: 0.28–0.57). Moreover, VAC therapy was associated with a decreased recurrence rate (RR0.34, 95% CI: 0.19–0.59).

The effectiveness of negative pressure therapy for wounds that have progressed to the chronic stage was demonstrated in a meta-analysis of 15 studies (*n*=3,599) conducted by Burhan et al. [19]. Creating an artificially reduced air pressure in the wound area (by lowering atmospheric pressure to 80–125 mm Hg using a vacuum pump; normal atmospheric pressure being 740–760 mm Hg) significantly improved microcirculation and accelerated healing. To ensure favorable outcomes, the procedure must be performed by qualified medical personnel who properly carry out all stages of the procedure and regularly monitor each patient's condition throughout treatment.

In addition to the aforementioned medical interventions, it is important to emphasize the urgent need for disciplinary measures, primarily the complete cessation of unhealthy habits such as smoking, especially during the wound healing period. A meta-analysis of 11 studies (*n*=218,567; 176,670 individuals were non-smokers or had quit smoking, whereas 41,897 were smokers) showed that patients who had quit smoking or were non-smokers experienced significantly fewer postoperative wound healing complications (OR0.59, 95% CI: 0.43–0.82, *p* <0.001). Moreover, postoperative patients who did not smoke had a significantly lower risk of wound infections compared to those who did (OR0.74, 95% CI: 0.63–0.87, *p* <0.001) [20].

PHARMACONUTRACEUTICALS AND NATURAL EXTRACTS IN THE MANAGEMENT OF WOUND INFECTIONS

An analysis of out-of-cluster high-informative terms (see Fig. 1) identified specific micronutrients and pharmaconutraceuticals that may facilitate the treatment of infected wounds (quercetin, choline, vitamins B_6, B_9, biotin, C, E, A, and D3).

A meta-analysis of 44 randomized trials in older and middle-aged patients (*n*=716; mean age 67 years, 95% CI: 35–87 years) confirmed the effectiveness of vitamin-mineral premix supplementation (typically containing the majority of B vitamins, vitamins A, D3, C, and E, zinc, copper, magnesium, and potassium) in reducing wound healing complications. The average intake of supplementary micronutrients was 588 kcal/day (95% CI: 125–1,750; protein 22 g/day, 95% CI: 0–54); patients followed the diet for an average of 74 days (95% CI: 5–365 days). In the majority of studies included in the meta-analysis (77%), the incidence of wound healing complications was lower than in the control group. The micronutrient-enriched diet reduced wound healing-related complications (infections, pressure ulcers, fracture healing) by an average of 32% (OR0.68, 95% CI: 0.59–0.79, *p* <0.001), both in inpatient care settings (OR0.72, 95% CI: 0.59–0.87, *p*=0.001) and in patients who followed the diet outside the facility (OR0.65, 95% CI: 0.52–0.80, *p* <0.001). A significant reduction in complications, including wound infections, was observed only with high adherence to the micronutrient-enriched diet (OR0.63, 95% CI: 0.48–0.83, *p*=0.001) [21].

A meta-analysis conducted by Tao et al. [22], which included 22 studies (*n*=2,170), confirmed that glutamine supplementation in burn patients reduced the length of hospital stay (–7.95 days, 95% CI: –10.53 to –5.36), improved wound healing quality (9.15 conventional units, 95% CI: 6.30–12.01), and shortened healing time (–5.84 days, 95% CI: –7.42 to –4.27). Moreover, glutamine supplementation lowered the risk of wound infection (RR0.38, 95% CI: 0.21–0.69).

A meta-analysis by Yammine et al. [23], which included 10 studies (*n*=1,644; 817 patients with diabetic foot ulcers and 827 patients with diabetes but no foot complications), showed that severe vitamin D_3 deficiency ($25OHD_3$ <20 ng/mL) was associated with a 3.6-fold increased risk of chronic non-healing foot wounds (95% CI: 2.94–4.42, *p* <0.0001).

The "tissue therapy" approach proposed by Filatov is still applied in wound healing. For example, a meta-analysis of studies in patients after skin grafting (*n*=219) confirmed that amniotic membranes may be beneficial for accelerating wound healing. Compared to other methods, the mean difference in healing time was –3.87 days (95% CI: –4.39 to –3.35, *p* <0.00001) [24]. Notably, Filatov's works paved the way for more systematic research and clinical application of human placenta hydrolysates (HPHs). Studies of the peptide composition of HPHs using modern proteomic techniques have made it possible to propose a set of molecular mechanisms by which HPHs act under various conditions. The effects of HPHs have been demonstrated in the treatment of liver diseases,

atopic dermatitis, viral infections (herpes, COVID-19, viral hepatitis), iron overload disorders, and chronic fatigue syndrome. HPHs stimulate the body's regenerative potential, which is vital not only for accelerating and improving wound healing, but also for treating joint diseases [25].

A meta-analysis of six animal studies demonstrated the effectiveness of probiotics as pharmaconutraceuticals in cutaneous wound models. Wound area percentage at the end of the first week after initial injury was used to assess efficacy. Based on the calculated Hedges' *g* value, the use of probiotics was associated with an accelerated reduction in wound size (*g*=–2.55, 95% CI: –3.59 to –1.50, *p* <0.0001). A meta-regression analysis showed that sterile kefir extract (*g* = –5.6983, *p*=0.0442) and bacterial probiotic therapy (70% kefir gel, *Lactobacillus brevis*, *L. fermentum*, *L. plantarum*, *L. reuteri*; *g*=–2.3814, *p*=0.0003) had a significant, dose-dependent effect [26].

A meta-analysis of nine randomized trials confirmed that standardized aloe vera phytoextracts significantly reduced the average wound healing time in patients with second-degree burns compared to other topical wound treatments (–3.76 days, 95% CI: –5.69 to –1.84), with no significant differences in pain reduction (–0.76 points, 95% CI: –1.53 to 0.01) or risk of wound infection (RR 1.10, 95% CI: 0.34–3.59) [27].

CONCLUSION

The diversity of inflammatory mechanisms, bacterial and viral pathogens, and antibiotics and other pharmacological agents whose effects are explored in scientific publications, makes the development of "magical" treatment protocols for wound infections, based on the principle of "let's try another antibiotic we haven't used yet," problematic. Even with the very limited set of fundamental and evidence-based data presented above, there is a clear need for more comprehensive, integrative, holistic, and multifaceted approaches to the treatment and prevention of wound infections, particularly those sustained in combat settings. It is equally important to consider biofilm management strategies, surgical intervention characteristics, and the use of pharmaconutraceuticals and natural extracts.

The presented data clearly illustrate that medical researchers are actively exploring not only a wide range of antiseptics and antibiotics from various classes, but also the pharmacological effects of natural antibiotics, biguanides (for the treatment of infected wounds complicated by patient-specific carbohydrate metabolism disorders), hyaluronic acid and citric acid (for wound dressing formulations), phytoextracts (aloe, turmeric, cinnamon) and their components collectively referred to as "antioxidants" (curcumin, bioflavonoids), as well as micronutrients such as copper and zinc, lactobacilli, and other probiotics that contribute to the breakdown of pathogenic biofilms.

In addition to the above research areas derived from scientific data analysis, the present review highlights the urgent need to form a cohort of patients with wounds in order to identify, using modern data mining techniques, the factors influencing mortality and wound healing rate and quality.

ADDITIONAL INFO

Authors' contribution. I.Yu. Torshin, O.A. Gromova: analysis of the obtained data, literature review, final editing; concept and design of the study, collection and processing of materials, attraction of funding. The authors have approved the version for publication and have also agreed to be responsible for all aspects of the work, ensuring that issues relating to the accuracy and integrity of any part of it are properly considered and addressed.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. И.Ю. Торшин, О.А. Громова — анализ полученных данных, обзор литературы, внесение окончательной правки, концепция и дизайн исследования, сбор и обработка материалов, привлечение финансирования. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

Источники финансирования. Отсутствуют.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

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