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K.V. Ksenchyna, O.O. Ksenchyn, O.A. Nazarchuk, D.V. Dmytriiev
Vinnytsya National Pirogov Memorial Medical University, Vinnytsia, Ukraine

The role of microbial wound contamination in chronic pain development in patients with injuries

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Abstract. *Nowadays, with the start of hostilities in Ukraine, the number of people with injuries has increased and continues to grow. Of course, one of the main issues facing by medical professionals is preventing complications and restoring sufficient functional capacity. Pain is one of the protective mechanisms of the human body; its prolonged course is one of the most important causes for reducing the quality of life and limiting a person's work capacity. Acute pain is positioned as the body's main signal for help, usually as a disease symptom, while chronic pain can be an independent nosological unit and mostly appears after primary cause. Secondary chronic pain is one of the injury consequences that can occur and significantly worsen the patient's prognosis and reduce quality of life. Prevention of the secondary chronic pain is possible if all prerequisites are known. Furthermore, the human body interacts with a complex community of bacteria, fungi, and viruses. Several microorganisms create the microbiome of the skin, which ensures its barrier function and plays an important role in the immune response in wounds. These processes are not always predictable, and both positive and negative effects on wound healing can be observed. After all, the duration of wound healing directly depends on the type of microorganisms and their sensitivity to the antibiotic treatment. The long process of wound surface healing can lead more likely to a violation of all physiological processes in this body part. This can be quite an important factor in chronic pain occurrence.*

Keywords: *chronic pain; infected wound; biofilms; healing; postsurgical pain; skin microbiota*

Introduction

Undoubtedly, pain is one of the most common complaints worldwide. The frequency of patient referrals due to pain is 22 % of all consultations at the primary care. According to the analyzed data, patients suffering from chronic pain visit general practitioner twice as often as those who do not experience chronic pain. Also, people with a feeling of chronic pain have a significantly higher level of need for emergency and unplanned medical care [1].

Although pain itself is one of the protective mechanisms of the human body, its prolonged sensation is one of the most important causes for reducing the quality of life and limiting a person's work capacity. Different types of pain are defined depending on their main characteristics: duration, cause, and intensity. There are two types of pain depending on duration, acute and chronic. Acute pain is positioned as the body's main signal for help, that is, it is a symptom of the disease, while chronic pain can be evaluated as an independent nosological unit. Chronic pain, according to the definition of the International Association for the Study of Pain, is a multi-component concept that includes an unpleasant feeling and emotional experience that occurs as a result of actual or potential tissue damage and lasts longer than 12 weeks.

In recent years, the prevalence of such complaints as chronic pain has increased significantly throughout the world. The data from many studies indicate that about 30 % of the entire population suffer from chronic pain, which in turn affects the physical and emotional health components and leads to social maladjustment and disruption of usual life activities. For example, the results of a widely cited study conducted in the US indicated that among 8,781 participants, 55.7 % of adults experienced pain in the past three months, with 32 % having pain every or almost every day, and

Для кореспонденції: Ксенчина Катерина Володимирівна, асистент, кафедра внутрішньої та сімейної медицини, Вінницький національний медичний університет імені М.І. Пирогова, вул. Пирогова, 56, м. Вінниця, 21018, Україна; e-mail: zaluzhna.katia@gmail.com; тел.: +380 (97) 524-45-21
For correspondence: Kateryna Ksenchyna, Assistant, Department of Internal and Family Medicine, Vinnytsya National Pirogov Memorial Medical University, Pirogov st., 56, Vinnytsia, 21018, Ukraine; e-mail: zaluzhna.katia@gmail.com; phone: +380 (97) 524-45-21
Full list of authors' information is available at the end of the article.

11.2 % reporting severe debilitating pain. In Great Britain, according to a systematic review, data were obtained indicating a high overall chronic pain prevalence, which is 43.5 %. Among this group of patients, up to 14 % of people suffer from mild and moderate pain, which as a consequence leads to disability [2].

The total annual cost of health care for individuals with chronic pain (including medical care, lost work days, disability benefits, and legal fees) in the United States is estimated to be between $550 and $625 billion per year [3].

Due to what causes chronic pain formation, it is divided into primary and secondary. The definition of primary chronic pain does not include a clear underlying cause and its manifestations are disproportionate to any apparent injury or disease, while secondary chronic pain occurs as a direct result of injuries, surgeries, or chronic diseases.

Among the civilian population, 11 to 40 % of patients suffer from chronic pain after receiving injuries [4].

We suspect chronic pain in patients with primary tumors and metastases, intervertebral hernias, radiculopathy, and neuritis, conditions after surgical interventions, consequences of craniocerebral injuries, consequences of amputations (phantom pains), and diabetes.

Given that since 2014 hostilities began on the territory of Ukraine as a result of the Russian invasion, the frequency of injuries and wounds has increased significantly. According to research, in the general structure of injuries among the antiterrorist operation participants, limb injuries predominate with 62.5 % [5].

A limb loss as a combat trauma result is one of the leading amputation causes in most countries in the world. For example, according to the US Limb Injury and Amputation Center, 1,718 servicemen had at least one limb amputation (excluding finger amputations) between 2001 and 2017, and in the UK the total number of servicemen with amputations for 2013–2018 was 176, of which 113 were due to a combat injury [6].

Of course, amputation is not a simple decision, which is carried out in the absence of other possibilities to save the patient's life, because irreversible changes in the functional capacity of the human body develop. Post-amputation pain is one of the main consequences of losing a limb or only its part.

However, a limb amputation can lead to both the development of painful sensations and painless conditions. Pain following amputation is classified as phantom sensitivity, phantom limb pain, and residual limb pain (formerly known as stump pain). Phantom pain is the perception of unpleasant sensations in the part of the body that has been lost. Residual pain is pain in the remaining part of the body. According to literature data, about 47–79 % of patients experience phantom pain after amputation, and residual pain occurs in about 32–93 % of cases [7].

The prevalence of residual pain is very high among people with lower limb amputations and is associated with phantom pain. The ability to control phantom pain remains a complex issue in terms of its etiology and diagnosis, although diagnostic criteria (Budapest criteria) and treatment recommendations are available [8].

It is worth noting that despite the significant improvement in providing medical care, the amputation level remains relatively high, about 4 % by the end of 2016 [9].

Therefore, chronic postsurgical or post-traumatic pain is pain that develops after surgery or trauma (any injury, in-

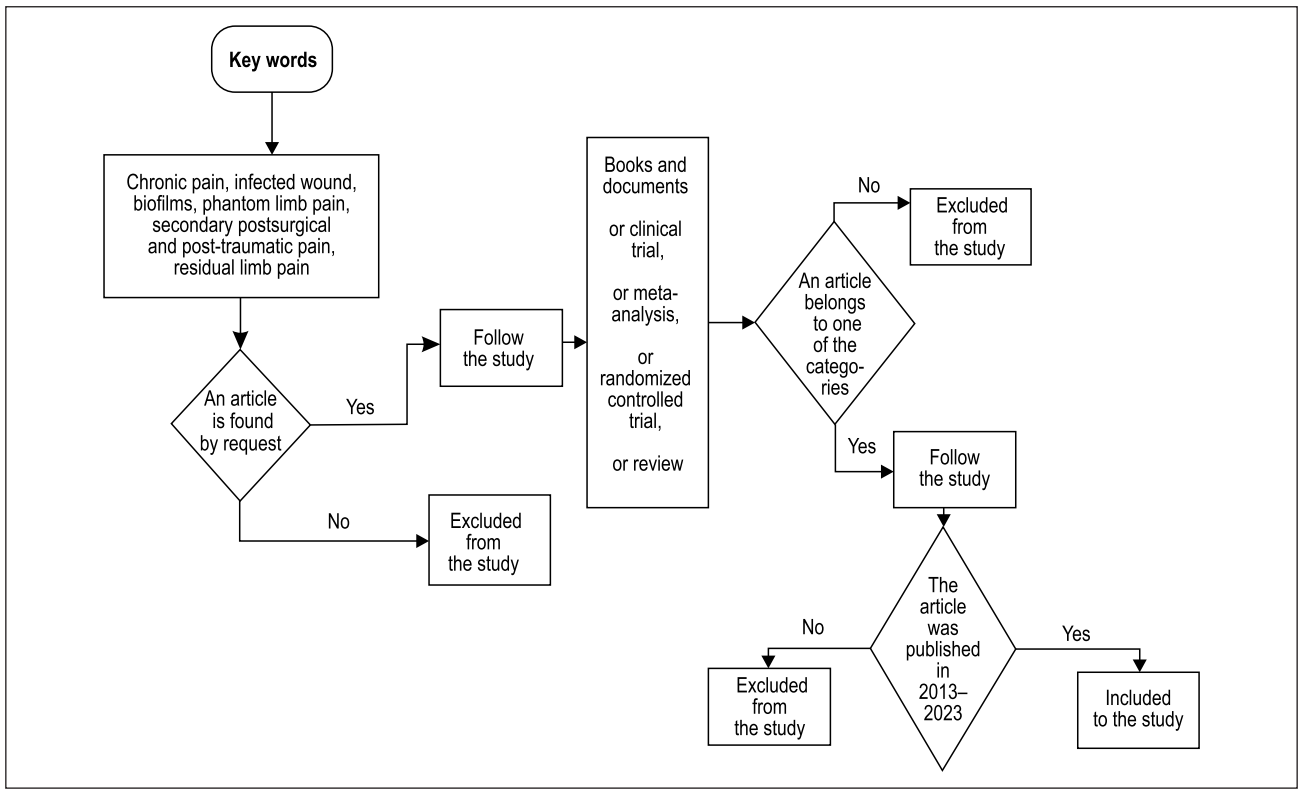

Figure 1. Algorithm of including articles to the study

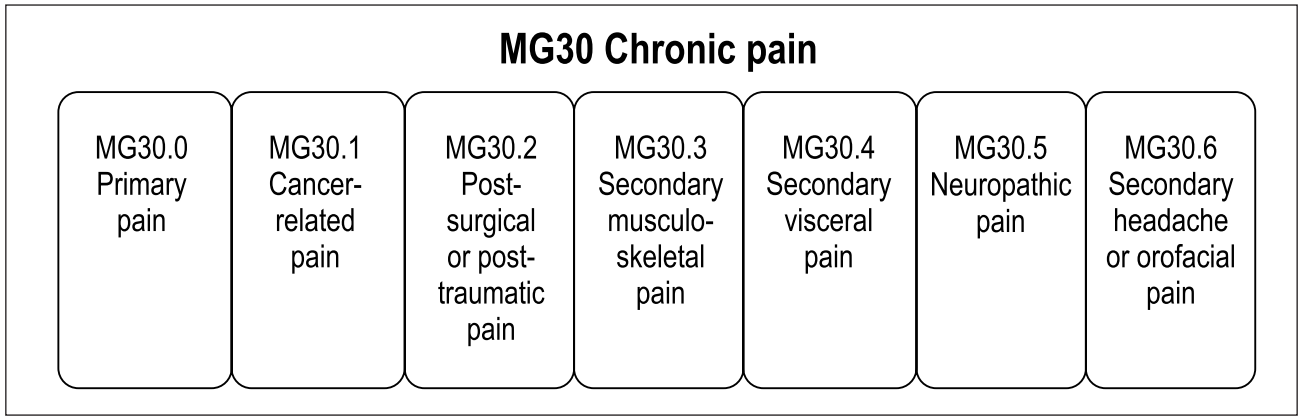

Figure 2. Classification of chronic pain according to the ICD-11

cluding burns) and persists after the wound healing process ends for at least 3 months (International Classification of Diseases, Eleventh Revision (ICD-11), World Health Organization, 2019/2021).

A negative prognostic sign is a pain associated with tissue damage, which indicates deterioration of the wound condition and the healing process as a whole. Wound healing is a complex and highly organized process necessary to restore the physiological skin barrier function, which prevents further damage or infectious complications. The complexity of wound healing lies in the interaction between skin compartments, cells, extracellular matrix, and systemic processes. The main causes for delayed wound healing are infection, a weak immune response, the patient's age, obesity, poor wound oxygen saturation, or other irritating factors such as intolerance to wound dressing materials. The long process of wound healing contributes to chronic pain development, which affects the patient's health and sleep [10, 11].

Overall, postsurgical wound infection (PSWI) is one of the most common forms of healthcare-associated infection and occurs in approximately 1 of 20 surgical patients in hospital, but can develop after hospital discharge. PSWI is an unfavorable factor for wound healing: it increases the length of hospital stay, creates the need for antibiotics use, initiates pain development, and, in extreme cases, can even be the cause of death. That is why preventing PSWI is one of the key tasks of wound care [12].

Methods

For this descriptive review, a 10-year research analysis was performed, i.e. for 2013–2023. All studies were related to the prevalence and study of chronic pain, assessment of the infectious factor as one of the important aspects in its development. The exclusion group consisted of clinical cases, abstracts regardless of the publication year, and studies published before 2013. We searched for systematic reviews in the electronic databases PubMed, Google Scholar, and the Cochrane using the following keywords: "chronic pain", "infected wound", "biofilms", "phantom limb pain", "secondary postsurgical and post-traumatic pain", "residual limb pain" (Fig. 1).

According to the ICD-11, the following types of chronic pain are distinguished: primary, cancer-related, postsurgical or post-traumatic, secondary musculoskeletal, secondary visceral, neuropathic, secondary headache or orofacial pain (Fig. 2).

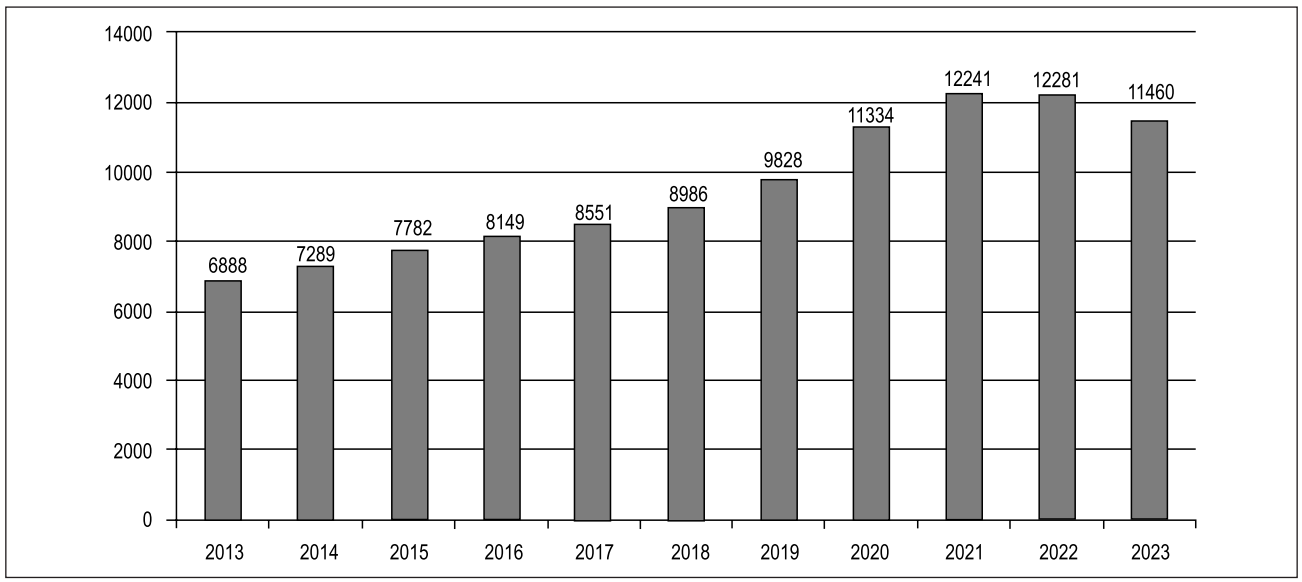

Figure 3. The dynamics of publications in the PubMed database by the keywords "chronic pain" for 2013–2023

However, in reality, the mechanisms of pain are often combined, and this greatly complicates the diagnosis and pain syndrome control [13].

Analysis of the dynamics of article publication in PubMed

The results of the search by the keywords "chronic pain" indicate the importance of this issue. In recent years, there have been more and more attempts to understand the mechanism of chronic pain formation and to find effective means of its control. For example, only in the PubMed National Library of Medicine search system, the total number of publications with a search depth of 10 years is 91,594. The annual dynamics of publications for 2013–2023 was also analyzed (Fig. 3).

An analysis of the number of scientific works using the keywords "chronic pain" was also carried out by the language parameter in the PubMed database, also for a 10-year period (2013–2023). We have chosen for comparison English, Polish, Slovak, Ukrainian, Japanese, Hungarian, and Romanian languages. Our choice was based on a comparison of the state issues in Ukraine, highly developed countries and countries bordering Ukraine (Table 1).

Table 1. Activity of article publication in the PubMed database by the keywords "chronic pain" and the language parameter from 2013 to 2023

Language	Publication number
English	88019
Polish	66
Ukrainian	22
Japanese	191
Hungarian	43
Romanian	0
Slovak	0

According to the results of a search using the keywords "infected wound" in the electronic system PubMed, 38,335 publications were found over the last 10 years. Based on the analysis of the number of publications every year for the same period, it can be stated that interest in the topic of the course and infected wound treatment is growing (Fig. 4).

The analysis on the number of scientific works by the keywords "infected wound" in the PubMed database and by the language parameter was also carried out for the last 10-year period, i.e. 2013–2023. We chose the same languages (English, Polish, Slovak, Ukrainian, Japanese, Hungarian, and Romanian) for comparison using the keywords "infected wound" according to the same principle (Table 2).

Table 2. Distribution of articles in the PubMed database by the keywords "infected wound" and the language parameter from 2013 to 2023

Language	Publication number
English	36542
Polish	21
Ukrainian	8
Japanese	84
Hungarian	8
Romanian	0
Slovak	0

In this way, we managed to illustrate and show the growing importance of studying chronic pain problems and the features of occurrence, course, and treatment of infected wounds over the last 10 years based on the data obtained from the PubMed electronic database. The results of the search show that in Ukraine, the issues of studying chronic pain and infectious wounds are considered in the PubMed database compared to neighboring countries, although they are still insufficiently studied in comparison with more developed countries. This is the impetus for further research in this area.

Biofilm as a factor in the development of a chronic wound

The human body interacts with a complex community of bacteria, fungi, and viruses. Several microorganisms create the microbiome of the skin, which ensures its barrier func-

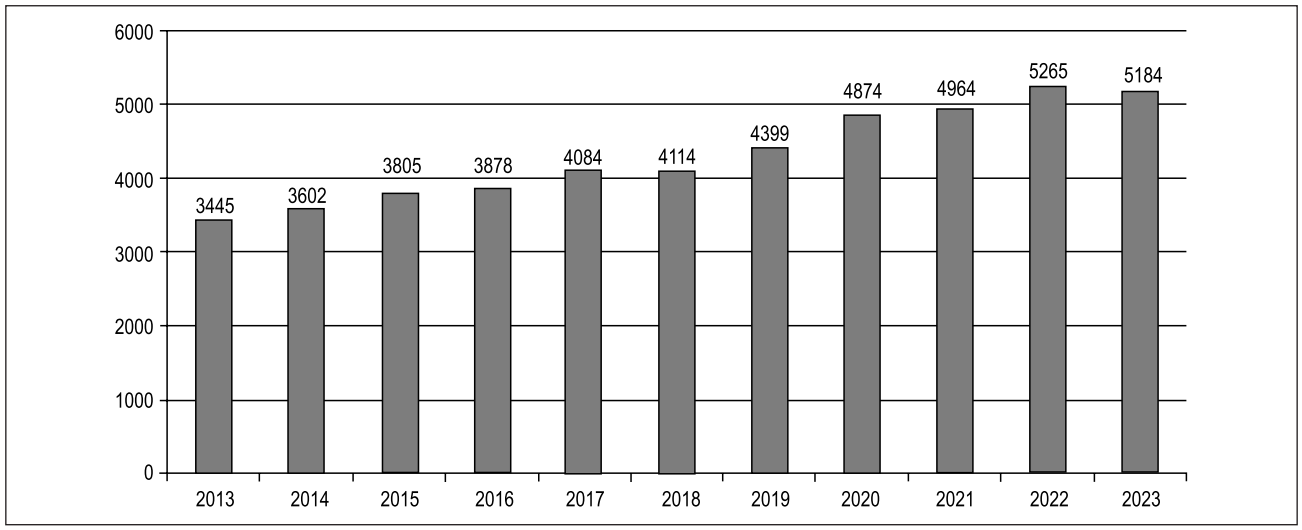

Figure 4. The dynamics of publications in the PubMed database by the keywords "infected wound" for 2013–2023

tion. Skin microbiota is quite diverse and plays an important role in the formation of the immune response in wounds. The surface of the skin under normal physiological conditions is an acidic, high-salt, dry, and aerobic environment, but in the follicular-sebaceous structures, the environment is relatively anaerobic [14].

The processes occurring with the participation of microorganisms are not always predictable, and both positive and negative effects on wound healing can be observed. Mechanisms of wound healing include keratinocyte proliferation, epithelial differentiation, growth of epidermal blood vessels, and cell signaling. All these processes differ depending on the type of bacteria, their number, and the type of interaction between the microorganism and the host.

Active monitoring of the wound colonization phase helps prevent local wound infection. The results of various studies show that the healing process is impaired if the wound contains more than 10^4 CFU/g. Also, this leads to increased resistance to immunological, antimicrobial, and chemical factors [15].

The successive phases of healing process are hemostasis, inflammation, proliferation, and remodeling. These phases target the elimination of invading microorganisms and cleaning wound surface from damaged cells. Additional damage to host tissues occurs due to microbicidal molecules synthesized by neutrophils. Prolonged inflammation provokes the synthesis of pro-inflammatory mediators whose high levels can disrupt the repair process [16].

Neutrophils and basophils are the first responders to injury. In addition, macrophages, mast cells, Langerhans cells, T and B cells are involved in the process. Macrophages are the main effector cells in the tissue repair. The maximum peak of their infiltration occurs after about 7 days. It is known that macrophages are classically divided into two groups: pro-inflammatory, or M (CD86+), macrophages that release cytokines including IL-12, IL-1β, IL-6, TNFα, and induced nitric oxide synthase, and are involved in pathogen elimination, inflammatory cytokines release. Additionally, a phenotypic switch of the M1 macrophages to the M2 "anti-inflammatory" phenotype triggers proliferation stage. Neutrophils amplify inflammation by releasing cytokines and chemokines such as TNFα, IL-1β, IL-6, CXCL8, CXCL2, and MCP-1, which in turn attract more neutrophils, as well as macrophages and T cells. A closed circle of such processes can contribute to a long-term inflammatory process and prevent the transformation of M1 type macrophages into M2 [17] (Fig. 5).

For example, one of the most common commensals, *Staphylococcus epidermidis*, can reduce the severity of the inflammatory process. This is possible due to the ability to increase the regulation of Toll-like receptors and the modulation of TNFα, which, through CD8+ T cells of the skin, accelerates the progression of keratinocyte activity.

It is worth mentioning that commensalism is a type of symbiotic interaction between two living organisms, when one of them, the commensal, receives food elements or other benefits from the other without harming it, but also without providing any advantages.

Another normal commensal among the skin microbiota is *Staphylococcus aureus*, which affects the process of reducing skin inflammation by lowering local production of IL-17 and neutrophil chemotactic factors. However, it can produce superantigens, which are harmful in high systemic concentrations but beneficial in small amounts. Therefore, *S.aureus* can negatively affect wound healing in conditions of a high microbial load because keratinocytes produce a large

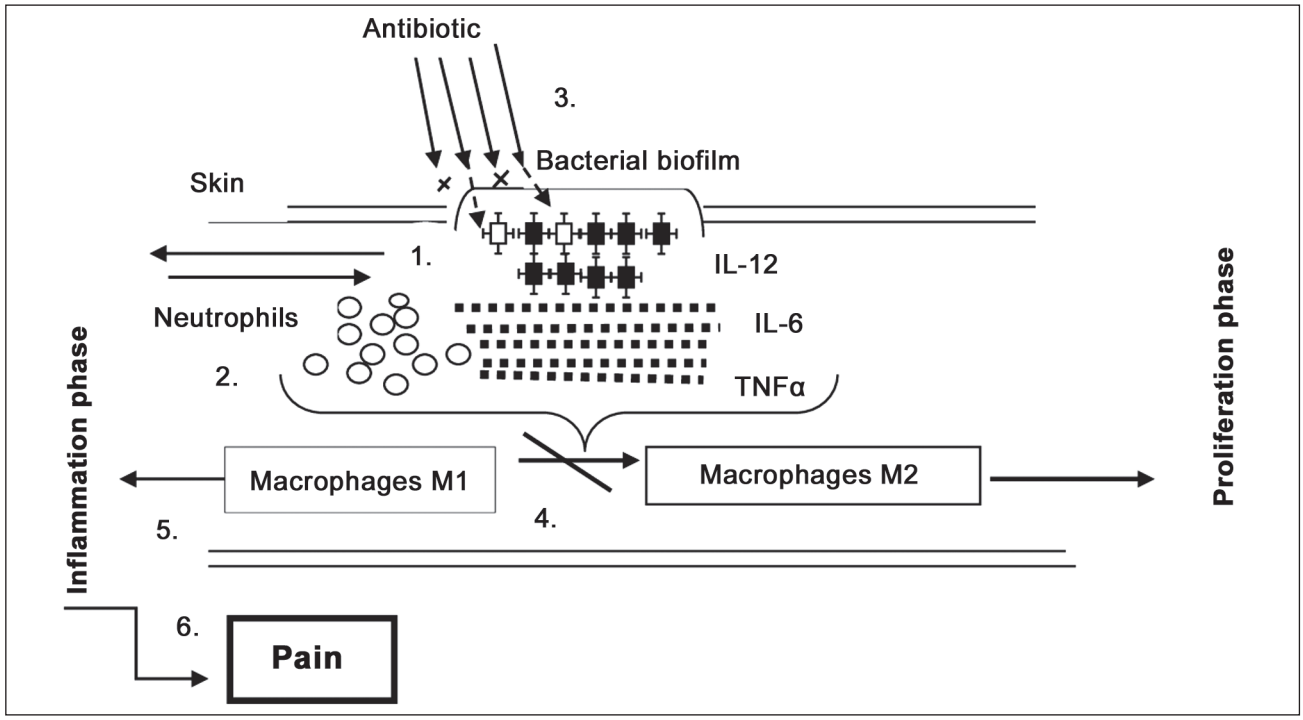

Figure 5. The biofilm role in altered wound healing: connections between prolonged inflammation phase and pain

number of pro-inflammatory cytokines such as chemokine ligands, IL-1B and IL-6, CXCL1, and TNFα. Pathogenic microorganisms also directly affect the wound-healing process. For example, group A *Streptococcus* can contribute to re-epithelialization and the colonization of epithelial tissue by the opportunistic *Pseudomonas* spp. with different clinical manifestations depending on the microbial loads. A small amount of these microorganisms contributes to the acceleration of epithelization, however, under the condition of a high microbial load of *Pseudomonas* spp., stimulates the TAK1/MKK/p38 signaling pathway, which induces cell apoptosis and inhibits tissue regeneration [18].

There are different states in which microorganisms can exist on the surface of damaged wound tissues, namely in the planktonic and biofilm states. Each of these forms affects the healing process, plays a certain role in delaying it, and causes infectious complications of both acute and chronic wounds. However, based on the analysis of open sources of information, the virulent state of the biofilm is the main cause that the normal course of wound healing is disturbed, and its duration is prolonged (Kim et al., 2018). According to the literature data, the biofilm presence in chronic wounds is detected in more than 80 % of patients. Biofilms are structured, organized groups of bacteria, limited by a common protective polymer membrane, and able to attach to any surface. Such bacteria are characterized by higher resistance to antibiotic therapy and immune response [19–21].

Although microorganisms can be found in every open wound, their presence does not necessarily manifests in a wound infection. The latter is provoked by the immunological response of the host and is characterized by local inflammation, swelling, erythema, or pain. The wound microbiome consists of bacterial pathogens as well as fungi that either interact with the bacteria and can promote resistance to antibacterial therapy or are even primary pathogens themselves. The bacterial strains mostly found in infected wounds are *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and the most common fungal genus is *Candida* spp. The course of infection in the wound can be different and varies from colonization of the wound without impaired healing to systemic infection with sepsis and organ dysfunction [22, 23]. According to the data of the study, which consisted in conducting a molecular analysis of samples from wound surfaces, gram-positive bacteria were found in the upper layers of the biofilm bacteria, and in deep ones — gram-negative and microbial associations. Anaerobic microorganisms such as *Prevotella* spp., *Porphyromonas* spp. were also detected in samples from chronic wounds. In general, *Staphylococcus* spp. is detected in 65 and 60 % of chronic and acute wounds, respectively; *Enterococcus* spp. — 62 and 80 %; *Pseudomonas* spp. — 35 and 20 %; *Proteus* spp., *Enterobacter* spp. and *Citrobacter* spp. — 24 and 20 %; *Streptococcus* spp. — 22 and 0 %; *Escherichia* spp. — 14 and 0 %; *Morganella* spp. — 8 and 0 %; *Klebsiella* spp., *Acinetobacter* spp. — 5 and 0 %; *Serratia* and *Xanthomonas* — 3 and 0 %, respectively. The results of conducted experiments showed that biofilms significantly prevail in chronic wounds and are rarely found in acute wounds [24].

The US Centers for Disease Control and Prevention estimates that 65 % of human infectious diseases are caused by bacteria with a biofilm phenotype, and the National Institutes of Health estimate is closer to 80 %. It remains unclear whether all bacteria can form biofilms. However, environmental factors are known to induce genetic changes and biofilm growth [25].

Signs of biofilms are established *in vivo* based on the criteria outlined by Parsek and Singh: a cluster of bacteria that are embedded in the matrix of an extra polymeric substance; the ability of adhesion to the surface or to each other; persistent and localized infection; resistance to antibacterial therapy [26].

The human body perceives the biofilm as a foreign body on the wound surface, which stimulates the immune response. Neutrophils, which begin to actively move to damaged tissues, are not able to phagocyte associated bacterial cells but continue to release enzymes and oxygen metabolites. These substances damage the surrounding tissues, while conditionally pathogenic bacteria function in the form of a biofilm [27].

Infected chronic wounds are observed in many patients. Biofilm bacteria are about 1,000 times more resistant to conventional antimicrobials than planktonic cells. Antimicrobial resistance refers to the ability of bacteria to resist the effects of antibiotics. This interferes with proper healing and, as a result, prolongs the wound healing and hospital stay. A violation of the physiological wound healing significantly affects the functional capacity and, as a result, the quality of life [28].

Multidrug-resistant bacterial isolates are defined as those resistant to 3 or more classes: penicillins/cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides. Commonly isolated pathogens include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Acinetobacter baumannii, Enterobacteriaceae, Pseudomonas aeruginosa*, which produce extended-spectrum beta-lactamases or carbapenemases and are resistant to carbapenems [29].

The true frequency of anaerobic microorganisms in surgical wounds remains to be fully understood, which is associated with different methods of bacterial cultivation, and different types of samples taken for analysis. However, anaerobes are predominantly found in wounds that are deeper, more chronic, and associated with ischemia, gangrene, or foul odor. In February 2017, to focus research and development on finding new antibiotics, the World Health Organization published the list of pathogens for which new antimicrobials are urgently needed. ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) received priority status in this broad list. After analyzing the available literature, it turned out that these bacteria are quite common in biofilms of chronic wounds and are highly virulent and resistant to antibiotics. While much attention has been paid to the study of various bacterial pathogens in the chronic form of the wound, the role of fungi (especially *Candida* species) in wound biofilms is also gaining importance [30, 31].

Because the clinical signs and symptoms of chronic wound infection can be subtle, there are difficulties in diagnosing it. For example, when conducting microbiological

research, a dubious assessment of the microbial load is possible. Today, new technologies are known, which are used as additional means of determining the microbial load in the wound and the status of infection. Fluorescence imaging is a modern method that allows visual determination of the location of wound tissue with an increased bacterial load ($> 10^4$ CFU/g), as well as detection of biofilm *in vitro* [32].

There is research evidence that the presence of anaerobic bacteria (eg, *Peptoniphilus*) at the initial stage of infection has been associated with poorer healing outcomes. Certain features of the patient's genetics contribute to the colonization of some species, that is, they can affect the composition of the microbiome, its stability, and resistance. For example, in wounds in which *S.epidermidis* was detected, *P.aeruginosa* was more likely to be cultured. The wound microbiome containing *Pseudomonas aeruginosa* in which the use of topical antibiotic combination therapy is assumed reflects that it has less bacterial diversity, and such wounds have a longer healing time. Also, the results of a recent study on the features of the healing process under local therapy with combinations of antibiotics show that *Pseudomonas aeruginosa* dominates in the composition of the microbiome of wounds, which heal longer compared to those in staphylococcal infections. Comparing different models of wound healing duration helps understand the importance of the influence of specific microorganisms on likely patient outcomes. Wounds infected with the gram-negative pathogen *Pseudomonas aeruginosa* are characterized by poor outcomes. *P.aeruginosa* readily formed biofilms on the biological wound dressing within 48 hours of incubation *in vitro* at 30 °C [33].

According to the recommendations of the World Union of Wound Healing Societies, it is considered that "all unhealed chronic wounds" potentially contain biofilms, and the main principle of treating such wounds is targeted destruction of biofilms and prevention of their regeneration. The results of a longitudinal prospective study on the composition of the microflora of diabetic foot ulcers demonstrate that the microbial "genetic signature" of the biofilm directly affects clinical outcomes [30, 32].

Therefore, it is quite important to monitor wound condition and assess all phases of healing promptly. Proper care of the wound surface includes early application of local antiseptics, vacuum systems, and the use of dressings that help prevent the prolongation of the healing inflammatory phase, the formation of strong interbacterial connections in the biofilm, and, as a result, the formation of secondary pain [16, 34].

Chronic pain reflects not only changes in the physical components of the health but also affects the emotional-volitional, cognitive-behavioral spheres of the personality, and social relationships, which leads to a violation of adaptation mechanisms in everyday life. These factors contribute to disability, anxiety, depression, sleep disturbances, poor quality of life, and increased healthcare costs [11, 35].

Pain is a stress factor and leads to sleep problem, their influence on each other is considered bidirectional. Although the causes and effects of chronic pain are well known, the flip side is that factors such as emotional support and the absence of psychological health impairment can promote healing and reduce the likelihood of chronic pain. Quality of life indicators and neuroplastic changes can also be reversible with adequate pain control, so treatment is usually complex and combines pharmacotherapy, psychotherapy, integrative treatment, and invasive procedures [19].

Discussion and conclusions

The problem of chronic pain is significant and is actively studied all over the world. Our literature search carried out over the last 10 years reflects the growing dynamics of publications, and thus the increasing interest in studying the causes, mechanisms of pain, and means of its control. The World Health Organization defines health as a state of complete physical, mental, and social well-being, and not only as the absence of diseases and physical defects. Indeed, chronic pain is a significant factor affecting every component of health and ultimately reducing quality of life. The combination of various mechanisms of chronic pain formation causes the greatest difficulties in finding effective means of achieving the main therapeutic goal — the ability to control chronic pain. Among all the factors that lead to the formation of secondary postoperative and post-traumatic chronic pain, the microbiota of the wound plays an important role. The processes that occur as a result of the presence and vital activity of microorganisms can have both a beneficial effect and be burdensome for the prognosis. Therefore, microorganisms belonging to the group of commensals contribute to the epithelization and help ensure the normal process of physiological healing of damaged tissues. At the same time, there are several microorganisms, mainly opportunistic, which, in comparison with others, can harm the wound healing process, primarily extending the duration of the wound closure. An additional prognostically unfavorable factor is the resistance of bacteria to antibacterial agents, which creates difficulties in providing effective treatment. Such factors, which are the cause of disruption of the normal healing of damaged tissues, destabilize metabolic processes at the cellular and tissue levels and affect the state of the dermatome as a whole. This is considered one of the possible factors in the formation of chronic pain.

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Information about authors

Kateryna Ksenchyna, Assistant, Department of Internal and Family Medicine, Vinnytsya National Pirogov Memorial Medical University, Vinnytsia, Ukraine; e-mail: zaluzhna.katia@gmail.com; phone: +380 (97) 524-45-21; https://orcid.org/0009-0008-1506-2673

Oleh Ksenchyn, PhD, Assistant, Department of Internal and Family Medicine, Vinnytsya National Pirogov Memorial Medical University, Vinnytsia, Ukraine; e-mail: vinshura@gmail.com; https://orcid.org/0000-0001-8438-5320

Olexandr Nazarchuk, MD, DSc, PhD, Professor, Department of Microbiology, Vinnytsya National Pirogov Memorial Medical University, Vinnytsia, Ukraine; e-mail: nazarchukoa@gmail.com; https://orcid.org/0000-0001-7581-0938

Dmytro Dmytriiev, MD, DSc, PhD, Professor, Department of Anesthesiology, Intensive Care and Emergency Medicine, Vinnytsya National Pirogov Memorial Medical University, Vinnytsia, Ukraine; e-mail: mddmytriiev@gmail.com; https://orcid.org/0000-0001-6067-681X

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Ксенчина К.В., Ксенчин О.О., Назарчук О.А., Дмитрієв Д.В.
Вінницький національний медичний університет імені М.І. Пирогова, м. Вінниця, Україна

Роль мікробної контамінації рани в розвитку хронічного болю в пацієнтів із травмою

Резюме. З початком бойових дій в Україні кількість постраждалих зросла і продовжує збільшуватися. Безумовно, одним із головних завдань, яке стоїть перед медичними працівниками, є запобігання ускладненням і достатнє відновлення працездатності. Біль є одним із захисних механізмів організму людини; його тривале відчуття є однією з найважливіших причин зниження якості життя та обмеження працездатності. Гострий біль позиціонується як основний сигнал організму про допомогу, зазвичай симптом хвороби, тоді як хронічний біль може бути самостійною нозологічною одиницею і здебільшого виникає після першопричини. Оцінено вірогідність впливу видового складу мікробіоти рани на формування передумов для розвитку хронічного болю. Проведено оцінку сучасної літератури щодо зв'язків ранової мікробіоти й механізмів розвитку хронічного болю. Ми здійснювали пошук матеріалів в електронних базах даних PubMed, Google Scholar і Cochrane. Вторинний хронічний біль є одним із наслідків травми, що може виникнути та значно погіршити прогноз пацієнта й знизити якість життя. Профілактика формування вторинного хронічного болю можлива, якщо відомі всі передумови. Крім того, людський організм взаємодіє зі складною спільнотою бактерій, грибків і вірусів. Різні мікроорганізми створюють мікробіом шкіри, який забезпечує її бар'єрну функцію та відіграє важливу роль в імунній відповіді в рані. Ці процеси не завжди передбачувані, і можна спостерігати як позитивний, так і негативний вплив на загоєння ран. Тривалість останнього безпосередньо залежить від виду мікроорганізмів та їхньої чутливості до лікування антибіотиками. Довгий процес загоєння ранової поверхні може призвести до порушення всіх фізіологічних процесів у цій частині тіла, що може бути досить важливим фактором у виникненні хронічного болю.

Ключові слова: хронічний біль; інфікована рана; біоплівки; загоєння; післяопераційний біль; мікробіота шкіри