Article's History: Received: 24.07.2024; Revised: 06.11.2024; Accepted: 26.11.2024

Bulletin of Medical and Biological Research

Vol. 6, No. 4
2024

DOI: 10.63341/bmbr/4.2024.64

Journal homepage: https://bmbr.com.ua/en

UDC 616.5-006.6: 616.5-007.4

Optimisation of treatment of chronic wounds in bullous epidermolysis and the influence of microflora: A literature review

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Abstract. The study was conducted to find the most effective approaches to the treatment of chronic wounds in bullous epidermolysis, addressing the influence of the wound microbiome on the healing process. The study reviewed relevant scientific sources in dermatology, pharmacology, genetics, immunology, and microbiology, established the role of the wound microbiome in the healing of chronic wounds in bullous epidermolysis and analysed modern treatment strategies to accelerate the healing of these wounds. The results of the study showed that the wound microflora has a significant impact on the healing process. Epidermolysis bullosa provokes constant skin trauma, contributing to the creation of conditions for the growth of pathogenic bacteria in wounds, which leads to the development of dysbiosis and complicates the healing process. The wound microbiome in bullous epidermolysis is significantly affected by the patient's immune status, antibiotic use, location, depth, and duration of the wound. Weakened immunity provokes the development of multidrug-resistant bacteria, an enhanced immune response and autoimmune processes create conditions for the development of microorganisms that can multiply in conditions characteristic of an inflamed wound. The use of antibiotics is a highly effective method of treating infections, but prolonged or irrational antibiotic therapy can provoke the emergence of resistant bacterial strains. Depending on its location, the wound microbiome is influenced by skin characteristics in different parts of the body, such as the level of moisture, the presence of sweat and sebaceous glands, and hair. The influence of the wound depth on the microbiome is realised by creating conditions for the reproduction of the relevant microorganisms at the appropriate depth. The duration of the wound increases dysbiosis in the wound, complicating healing. Modern treatment strategies to accelerate the healing of chronic wounds in bullous epidermolysis include personalised medicine, an integrated approach and the use of modern dressings. The results obtained indicate the need to research and develop new effective methods of eliminating wound dysbiosis to normalise its microbiome and accelerate the healing process

Keywords: healing; pathogenic bacteria; dysbiosis; antibiotics; resistance; personalised medicine

Suggested Citation:
Fedorets Ye, Golubovska O, Pinsky L. Optimisation of treatment of chronic wounds in bullous epidermolysis and the influence of microflora: A literature review. Bull Med Biol Res. 2024;6(4):64–75. DOI: 10.63341/bmbr/4.2024.64

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INTRODUCTION

Epidermolysis bullosa (EB) is a common name for a group of rare complex genetic pathologies that occur as a result of genetic mutations that lead to a disruption in the structure of proteins responsible for the strength of the connection between different layers of the skin. This makes the skin vulnerable to any damage and leads to the formation of chronic wounds, causing pain that leads to restrictions on physical activity and psychological discomfort that can provoke social isolation. Despite significant advances in medicine, the treatment of EB remains a challenge, as there is still no universal and effective method of healing chronic wounds. However, the development of new technologies in the field of healthcare and an increased understanding of the role of microflora in the healing process was used to review existing therapeutic strategies and analyse the possibilities of optimising the treatment of chronic wounds in EB.

Currently, the main challenge facing doctors and scientists involved in the treatment of EB is to find ways to reduce the time it takes for wounds to heal. To address this issue, C. Guttmann-Gruber *et al.* [1] conducted a randomised, double-blind, placebo-controlled trial to evaluate the effect of low-dose calcipotriol ointment on wound healing in patients with dystrophic epidermolysis bullosa. According to the results, the researchers determined that topical treatment with a low dose of calcipotriol (a vitamin D3 analogue) can significantly reduce wound area and itching on the 14th day of therapy without affecting serum calcium levels. Promising treatments for EB were reviewed by P.-C. Hou *et al.* [2]. The authors assessed the high potential of therapeutic areas aimed at primary genetic abnormalities and secondary inflammatory trace of EB, the effectiveness of which is confirmed at various stages of trials of gene, cell and recombinant protein therapy. The efficacy of topical treatments for EB was investigated by M. Pabón-Carrasco *et al.* [3]. Scientists concluded that, according to the criteria of healing speed and reduction of itching, the most effective topical treatment for EB is Oleogel S10 and allantoin, diacerein 1% followed by fibroblasts, and B-VEC gene therapy.

After reviewing new treatments for EB, N.M. Bermudez *et al.* [4] analysed the effectiveness of symptomatic and gene therapy. Investigating the problems of wound healing, scientists determined that the improvement of this process is effectively achieved by a recently approved treatment method using drugs based on natural compounds of birch bark (*Fisulvez*), which have anti-inflammatory, antioxidant and wound healing effects. Among the gene therapy areas, the drug beremagene geperpavec (*Vyjuvek*) demonstrates high performance, a treatment method aimed at correcting the genetic defect underlying EB. In the above works, based on theoretical and practical research, the authors determined the effectiveness of various methods of wound healing in EB, but the analysis of the impact of wound microflora on the process of wound healing was not carried out. An important problem associated with the search for effective treatments for EB is the complications that arise from damage to the skin. Among the common complications of severe EB, researchers identify anaemia. The difficulty in its treatment was noted by C. Liy-Wong *et al.* [5], who studied the problem and presented the first consensus recommendations for the diagnosis and treatment of this complication. In particular, the authors emphasised the importance of an individual approach to therapy, noted the importance of dietary measures as an important part of the treatment process, and suggested the use of iron supplements orally or by infusion, depending on the severity of anaemia.

Based on the results of a multicentre retrospective clinical analysis, E. Raboei *et al.* [6] identified the most common complications in children with EB. Patients with the recurrent-dystrophic subtype of EB (RDEB) most often had complications associated with skin and musculoskeletal diseases. Oesophageal stenosis and pyloric atresia were less common. The prevalence of otological complications in inverse RDEB type was studied by S.J. Robertson *et al.* [7]. Previous reports indicated a low prevalence among patients in this group, but researchers found that 44% of patients with RDEB had otological complications, 90.9% of whom were diagnosed with recurrent otitis externa. These results demonstrate a higher prevalence rate than previously reported and indicate that this group of patients is at high risk of hearing problems.

In a prospective study of 26 patients with EB, Y. Yavuz *et al.* [8] determined complications in patients that included anaemia, growth retardation, gastrointestinal dysfunction, deformity of hands and nails, hair thinning, vision problems, and kidney disease. The most common among them were dental problems, in particular caries, which indicates the importance of preventive and therapeutic measures aimed at improving the condition of the teeth and oral cavity in patients with EB. In the analysed studies, the authors primarily focused on the identification and methods of effective treatment of complications arising from EB, but they did not include an analysis of how these complications can affect wound healing in patients with this disease.

The study aimed to determine the most effective methods of treatment of chronic wounds in EB, addressing modern medical advances. Study tasks included analysis of the role of wound microflora in the wound healing process and assessing the impact of anaemia, vitamin D3 and zinc levels on wound healing in patients with RDEB.

The study was conducted based on the analysis of thematic scientific sources in dermatology, genetics, pharmacology, microbiology, immunology and regenerative medicine published in PubMed, Google Scholar and Scopus databases. The stages of source selection included the formation of an initial sample, screening by titles and abstracts, detailed analysis of the full text, and assessment of the quality of research. The initial sample was formed from keyword searches: “bullous epidermolysis”, “epidermolysis”, “rare skin diseases”, “chronic wounds”, “wound healing”, “vitamin D3”, “zinc”, “anaemia”, “microflora”, “treatment/therapy”. After screening by titles and abstracts, articles that did not correspond to the research topic were excluded.

A detailed analysis of the full text was conducted with sources that met the inclusion criteria, namely containing the results of theoretical and clinical studies written in Ukrainian or English and published from 2016 to 2024. The quality of trials was determined by assessing clinical relevance – the extent to which results can be useful in clinical practice. The methods of processing the sources included thematic analysis, synthesis, identification of general

trends, and data visualisation for a clear presentation of the results (figure, table). A total of 60 relevant publications were selected for review.

ROLE OF THE WOUND MICROBIOME IN THE EB HEALING DYNAMICS

Several key factors have contributed to the growing interest in the wound microbiome. The development of DNA sequencing technologies was used to conduct a detailed analysis of the composition of the microbiome, identify new species of microorganisms and study the interaction between them, identify infection markers and detect genes encoding antibiotic resistance factors. The scientific and medical community has grown increasingly aware that the microbiome plays a crucial role in many physiological processes, including immune and metabolic processes, which has further study. An additional impetus for the search for new approaches based on a deep understanding of the mechanisms of wound healing, accounting for the peculiarities of its microbiome, was the decline in the effectiveness of antibiotic therapy caused by the spread of antibiotic-resistant bacterial strains. In 2022, 30% of urinary tract infections and 19% of recurrent wound infections became resistant after antibiotic treatment [9]. This is primarily due to the misuse of these drugs in medicine – up to 50% of all antibiotic prescriptions are clinically unjustified [10]. The development of personalised medicine, which involves an individual approach to patient treatment, was also an impetus to a more detailed study of the microbiome as a tool for developing more accurate diagnostic methods and more effective and safe treatments using its modulation.

The main value of the wound microbiome, which allows it to be used to develop new therapeutic strategies, is its uniqueness, as the wound microflora of a patient with EB differs significantly from that of a healthy person. These differences are due to both the characteristics of the disease itself and the impaired barrier function of the skin. In the wounds of patients with EB, an increased number of pathogenic bacteria (*Staphylococci*, *S. aureus*), fungi (*Candida*) and viruses are often found that can produce toxins that destroy tissue and impede healing [11]. Favourable conditions for their reproduction are provided by the moist environment under the blisters, constant skin trauma that provokes re-infection, impaired immune response and prolonged use of antibiotics, which leads to the development of resistant strains of bacteria. This intensive multiplication of pathogenic microorganisms leads to the displacement of beneficial bacteria, which reduces the diversity of the wound microflora of a patient with EB compared to that of a healthy person.

The imbalance between pathogenic and beneficial bacteria (*dysbiosis*) has a negative impact on the healing process, as it inhibits important functions of beneficial microorganisms, which include the creation of a protective barrier (biofilm formation) aimed at preventing the penetration of pathogens into deeper tissue layers; activation of the immune response; production of substances that promote healing (growth factors, antimicrobial peptides, etc.), stimulating regeneration and regulation of the inflammatory response, which prevents excessive inflammation that can be harmful to healthy tissues [12, 13]. Such functions are performed by certain types of staphylococci, in particular, *Staphylococcus epidermidis*, which are part of the normal skin microflora and can play a protective role by preventing the colonisation of pathogenic microorganisms; certain types of streptococci, which contribute to the production of substances that stimulate regeneration; *Propionibacterium* involved in the production of lactic acid, an important component for inhibiting the growth of pathogenic microorganisms; certain non-pathogenic species of pseudomonas, which produce antimicrobial substances (pseudomonas) with a wide range of antimicrobial activity that inhibit the growth of other bacteria, fungi and some viruses [14, 15]. Dysbiosis caused by genetic features, immune disorders and concomitant diseases characteristic of EB is the main factor in slowing down the healing process and, as a result, chronicity of wounds, so its elimination should be part of the therapeutic strategy for treating this disease. The combination of different wound surface microorganisms and the nature of their interaction depends on many factors, the main ones being the patient's immune status, antibiotic use, location, depth and duration of the wound.

The wound microbiome constantly interacts with the body's immune system, so the immune status of a person significantly affects its composition and functioning, particularly the process of healing chronic wounds in EB. Immunodeficiency provokes a decrease in the body's defence functions, creating favourable conditions for the reproduction of pathogenic microorganisms. This causes an imbalance in the microbiome in favour of pathogens. In this case, opportunistic pathogens are most active – microorganisms that do not usually cause disease in healthy people but can cause infection in people with weakened immune systems. Examples of such pathogens are pneumocystis, candida, aspergillus, etc. In anaerobic conditions, which can occur in deep or poorly drained wounds, anaerobic bacteria, in particular clostridia, actively multiply. Immunodeficiency favours the development of bacterial strains, which makes infection treatment and wound healing much more difficult [16].

An enhanced immune response can provoke chronic inflammation, providing conditions for the growth of bacteria that can survive and multiply in conditions of elevated temperature, low pH, the presence of antimicrobial substances and other adverse factors characteristic of an inflamed wound. In chronic inflammation, an increase in staphylococci, in particular *Staphylococcus aureus* and *Pseudomonas aeruginosa*, is particularly common, as they can form biofilms that protect them from antibiotics and the immune system, facilitating their survival and reproduction [17] (Fig. 1).

Inflammation also increases the number of pseudomonas, which colonise wet wounds and can cause severe infections, *Escherichia coli*, *Klebsiella* spp., *Proteus* spp. and other aerobic and facultative anaerobic Gram-negative bacilli [18]. Anaerobic bacteria such as *Clostridium* spp., *Bacteroides* spp. and *Fusobacterium* spp. are commonly found in closed wounds [19].

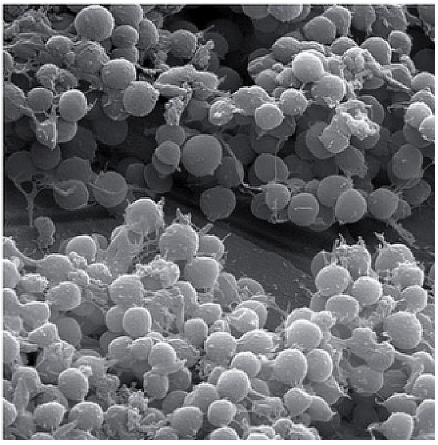

Figure 1. An image of *Staphylococcus aureus* biofilms obtained by electron scanning
Source: compiled by the authors based on J. Azeredo *et al*. [12]

Although autoimmune diseases and an enhanced immune response are similar in their impact on the wound microbiome, they have significant differences that affect the composition and function of the wound surface microbiota. In autoimmune diseases, inflammation is more specific, while in other causes of an enhanced immune response, it can be more diffuse. The imbalance of the microbiome in the case of activation of autoimmune processes can be more complex and include a greater number of different pathogenic and opportunistic microorganisms, including staphylococci, in particular *Staphylococcus aureus*, streptococci, *Escherichia coli*, pseudomonas, including *Pseudomonas aeruginosa*, anaerobic bacteria and fungi of the *Candida* genus [20]. In addition to the colonisation of the wound by pathogens, wound healing in autoimmune diseases can be complicated by the development of repeated infections and the formation of severe scars.

Identification of the differences between the wound microbiome in immunocompromised, immune-enhanced and autoimmune conditions is an important step in developing effective strategies for the treatment of chronic wounds in EB. Antibiotics are an important tool in the treatment of infections, but their use can have both positive and negative effects on the wound microbiome and the healing process. First, antibiotics effectively destroy pathogenic microorganisms, helping to reduce inflammation, and pain and accelerate healing. The timely use of these drugs helps prevent the spread of infection, the development of sepsis and other complications. At the same time, prolonged or irrational use of antibiotics can cause dysbiosis, promoting the growth of resistant strains of bacteria, fungi and other pathogens and thus disrupting normal wound healing processes, including epithelialisation, angiogenesis and collagen synthesis [21].

Wound localisation is one of the key factors affecting the wound microbiome and the healing process in EB. Different areas of the body have their unique microflora, due to the characteristics of the skin, hair, sweat and sebaceous glands, and the level of hydration. The head and neck areas have a rich microflora, including both resident and transient microorganisms. A breach of skin integrity in these areas can lead to wound colonisation by staphylococci, streptococci and *Candida* fungi [22]. The torso skin usually has a lower number of microorganisms on its surface compared to the skin of the head, neck and extremities. However, in patients with EB, torso wounds can be colonised by both local and exogenous microorganisms (staphylococci, streptococci, pseudomonas, E. coli, anaerobic bacteria, *Candida* fungi) [23]. The skin of the extremities, especially the hands and feet, is exposed to constant mechanical stress and contact with various surfaces. This contributes to the colonisation of wounds by gram-negative bacteria, in particular *Pseudomonas aeruginosa* [24]. Wounds in the skin folds create favourable conditions for the growth of anaerobic bacteria that can cause deep infections [25].

The location of the wounds determines the presence of factors that affect their healing, including the level of hydration, mechanical stress, the presence of hair and the intensity of blood supply. Wet wounds in the skin folds or in areas of constant friction heal more slowly due to maceration and increased risk of infection. These areas include the groin and groin area in general, the popliteal fossae, the interdigital space, especially on the feet, the behind the ears, the folds of the abdominal skin and the area under the breasts. Wounds on body parts subjected to constant mechanical stress (extremities, especially feet and palms, elbows, knees, armpits, places of fixation of medical devices – catheters, drains, plasters, etc. Hair in the wound area complicates its cleaning and creates conditions for the development of infection. Areas of the body with insufficient blood supply (lower extremities, pressure ulcers, areas with large scars, diabetic angiopathy and areas where vascular surgery was performed) heal more slowly due to insufficient oxygen, nutrient deficiencies and slow removal of waste products.

The depth of the wound is a substantial factor that affects its microbiome, as different wound depths create different conditions for the development of microorganisms and affect the speed and quality of tissue regeneration. Superficial wounds are usually colonised by microorganisms that are part of the normal skin microflora, such as staphylococci, streptococci and other gram-positive bacteria, and therefore heal faster and with less risk of complications if they are clean and uninfected [26]. Deep wounds have less access to oxygen, which creates conditions for the growth of anaerobic bacteria (clostridia, bacteroides, etc.) and the development of serious infections [27]. Deep wounds take longer to heal and are sometimes accompanied by complications, the most common of which are infection, bleeding and scarring. The subcutaneous wound microbiome can include aerobic bacteria and fungi. Damage to the subcutaneous tissue is dangerous due to the formation of abscesses and requires surgical intervention.

The duration of a wound has a significant impact on its microbiome and the healing process. The longer the wound exists, the more complicated the processes occurring in it become. In the initial stages, the wound is usually colonised by microorganisms that are part of the normal skin microflora – staphylococci, streptococci and other gram-positive bacteria. Over time, the composition of the microflora changes, and chronic wounds create conditions for the development of more resistant and aggressive microorganisms (pseudomonas, anaerobic bacteria and fungi)

that can form biofilms that protect them from antibiotics and the immune system [28]. Therefore, the healing of chronic wounds takes longer and is accompanied by complications due to impaired regeneration processes and constant tissue irritation. Chronic wounds in EB are characterised by changes in the microenvironment (pH, temperature and oxygen tension), impaired regeneration processes due to the impact on the proliferation and migration of cells necessary for healing, and the formation of scar tissue. In a study conducted by N. Harris *et al.* [29], the average time to closure for chronic wounds was 14.6 weeks compared to recurrent wounds (8 weeks), and spontaneous closure was observed in 26% of chronic wounds, while the same percentage for recurrent wounds was 86.

It is important to note that wound microbiomes may differ depending on the subtypes of EB. Although all forms of EB are characterised by increased skin fragility and a tendency to blistering, certain features affect the composition of the microflora in wounds. For instance, RDEB, the most common subtype of EB, which in some studies reaches 70% of all cases in a study by C.I. Thien *et al.* [30], is usually characterised by deeper and more extensive skin lesions, which can create conditions for the colonisation of a more diverse and potentially pathogenic microflora. In RDEB, colonisation of the wound by fungi, viruses and anaerobic bacteria capable of penetrating deeper layers of the skin is observed, compared to other subtypes of EB, which are mostly superficial infections caused by gram-positive cocci (staphylococci, streptococci) [31]. Due to the prolonged use of antibiotics and the presence of chronic wounds, antibiotic resistance can develop in the microflora of RDEB, while in other types of this pathology, resistance may be less pronounced, as infections are more often acute and treated faster. This is attributed to the fact that the microorganisms of the wound microbiome in RDEB have a higher tendency to form biofilms compared to other subtypes of EB [32]. The difference between the impact on the wound microbiome, depending on the subtypes of BE, is also evident through the association with other diseases. RDEB is often accompanied by atopic dermatitis, which has a negative impact on the wound microbiome, increasing the number of pathogenic microorganisms (*Staphylococcus aureus, Pseudomonas aeruginosa, Candida*) and provoking dysbiosis [33].

In a prospective study, A. Horev *et al.* [34] analysed temporary changes in the skin microbiome of patients with EB after the use of wound dressings. The authors emphasised the importance of determining the characteristics of the skin microbiome of patients with EB to determine the pathophysiology of the processes that occur in it and the factors that affect them. Practical confirmation of this thesis was demonstrated by the results of a study by scientists who found that a decrease in the diversity of bacteria in the wound microbiome due to the potential impact of a topical dressing accelerated the healing process. The authors' findings are notable, and it is worth emphasising the importance of monitoring temporary changes in the microbiome, depending on different treatment methods, to optimise the treatment of chronic wounds in EB.

Based on the results of a case-control study, J. Bar *et al.* [35] provided evidence of skin dysbiosis in patients with dystrophic BE. In addition to the prevalence of staphylococcal species in the affected skin of patients with EB, the results showed that the unaffected skin of patients also had an increased content of staphylococci and significantly different microbial diversity compared to the skin of healthy people. This observation indicates the existence of the influence of EB not only on the wound microflora but also on the microflora of the patient's skin in general. These results indicate the need to expand the impact on the signature of the microbiome associated with dystrophic EB employing specific pathogen-directed therapy. The authors' findings regarding the presence of wound dysbiosis in patients with a dystrophic type of EB are noteworthy, but additional studies should be conducted to confirm the presence of dysbiosis in the intact skin of patients. Understanding the processes occurring in the wound microbiome under the influence of EB and recording the differences inherent in different subtypes of this disease will allow timely identification of the pathogens present, which will help avoid severe complications such as sepsis and select more effective treatment regimens for chronic wounds.

MODERN THERAPEUTIC STRATEGIES TO ACCELERATE CHRONIC WOUND HEALING IN EB

Current trends in the treatment of chronic wounds in EB include 3 main areas: personalised medicine, an integrated approach and the use of modern dressings. The use of each of them separately in medical practice makes it possible to improve the effectiveness of treatment, and their rational combination allows for optimising the treatment process in general and improving the quality of life of patients with this disease. An additional and important area of research in the field of EB is the study of new therapeutic strategies of gene and mRNA therapy, the use of stem cells and other promising treatments aimed at eliminating the causes (correction or modification of mutated genes) and consequences (repair of damaged skin) of this disease. Difficulties in developing therapeutic strategies for the treatment of chronic wounds in EB are primarily related to the rarity of the disease. A study by German authors found that the overall incidence of EB in the country is 45 per million newborns, of which 15.58 live births occurred in RDEB [36]. Despite its low prevalence, this genetic disease is an important problem for the healthcare industry in general and significantly worsens the quality of life of each patient.

Personalised medicine in the context of EB involves an individual approach to each patient based on knowledge of the subtype of this genetic pathology, the patient's immune status, location, depth of lesions, presence of comorbidities, the effectiveness of previous therapy, including antibiotic therapy, etc. According to this principle, treatment is planned accounting for the individual wound microbiome, genetic characteristics of the patient and the patient's general health. The wound microbiome, as a complex ecosystem of microorganisms that change dynamically depending on many of the above factors, controls both positive (accelerating healing, protecting against pathogens, modulating the immune response) and negative (chronic wound healing, developing infections, sepsis) processes in the wound. Since negative processes occur because of dysbiosis, the main tasks of therapy are to study the microbiome and eliminate dysbiosis, taking into account the factors that cause it.

The development of medical technologies has expanded the range of methods that allow for a detailed study of the composition and interaction of microorganisms in the wound microbiome. Nowadays, in addition to the classical culture method of sowing on nutrient media, which has significant limitations since not all microorganisms can grow on artificial nutrient media, there are more accurate and informative methods for studying the microbiome [37]. Molecular genetic methods include the polymerase chain reaction (PCR) test, which allows the detection of DNA or RNA of specific microorganisms in a sample; next-generation sequencing (NGS), the most informative method that allows determining the full range of microorganisms in a sample without prior cultivation; metagenomics – the study of the totality of genomes of all microorganisms in a sample; metatranscriptomics – the study of the totality of all RNAs, which can be used to assess the activity of microbial genes; metaproteomics – the study of the totality of all proteins, which allows assessing the functional activity of the microbiome [38]. Mass spectrometry is used to identify biomarkers associated with certain types of microbiomes [39]. Different types of microscopies exist depending on the research objectives. Light microscopy is used to assess the morphology of microorganisms, fluorescence microscopy is used to visualise biofilms and the interaction of microorganisms with host cells, and electron microscopy is used to study the ultrastructure of microorganisms in detail [40]. The choice of method depends on the purpose of the study (detection of a specific pathogen, assessment of microbiome diversity, analysis of the functional activity of microorganisms, etc. Molecular genetic methods currently demonstrate the best performance. They have high sensitivity, which allows the detection of even a small number of microorganisms and are characterised by informative and fast analysis [41].

There is an increasing number of studies investigating the potential of exudates in personalised wound care [42]. P. Doerfler *et al.* [43] studied more than 800 exudates from healing and non-healing wounds and found a strong correlation (76%-90%) between wound chronicity and the inhibitory effect of individual exudates on fibroblast proliferation. The validity of the scientists' observation was confirmed by testing wound healing products, the results of which were consistent with clinical experience. In the context of a personalised approach to the treatment of chronic wounds in EB, the use of autologous keratinocyte transplants with gene correction (EB-101) demonstrates efficacy and safety. The results of the second phase of the randomised controlled trial are currently available and the results of the third phase are expected [44]. The main advantage of autologous keratinocyte transplants is their long-term efficacy and the absence of serious side effects during 5.9 years of follow-up.

Depending on the level of wound dysbiosis in EB, local therapy, systemic therapy, physiotherapy, surgery, vacuum therapy, plasmolifting, or an integrated approach combining these methods can be used to eliminate it. Topical therapy uses antiseptic solutions, antibiotic ointments and gels, antifungal drugs, and wet and honey dressings [45]. Phage therapy is a promising area in the fight against bacterial infections, especially antibiotic-resistant ones. It is based on the use of bacteriophages – viruses that infect and destroy individual bacteria [46]. The advantages of phage therapy are its high specificity (each phage infects a specific type of bacteria, which allows targeted treatment of the pathogen without damaging the beneficial microflora) and permeability (they can penetrate biofilms and destroy bacteria from the inside). Bacteriophages can be used in the form of ointments, gels, solutions for washing and as part of dressings. To restore the balance of the microbiome, systemic therapy involves the use of antibiotics prescribed for severe infections that cannot be treated locally, immunomodulators aimed at correcting the immune response, and probiotics to help restore normal intestinal and skin microflora [47]. Among the physiotherapeutic methods that can be used to eliminate dysbiosis, the most effective are laser therapy, which has anti-inflammatory and bactericidal effects, and ultrasound therapy, which aims to soften necrotic tissue and improve blood circulation [48]. Surgical treatment is used when necessary to remove necrotic tissue to create a clean bed for healing and skin grafting to repair visible defects [49]. Vacuum therapy can be used to ensure the outflow of exudate and stimulate healing, and autoplasma injection (plasmolifting) can be used to stimulate tissue regeneration [50]. Each of these methods has its advantages and disadvantages (Table 1), which can be used to optimise the treatment of chronic wounds in EB.

Table 1. Advantages and disadvantages of the main methods of treatment of chronic wounds in EB

Treatment method	Advantages	Disadvantages	Side effects	Price
Local therapy	Availability, ease of use	Insufficiently effective in severe EB, possibility of allergic reactions	Redness, itching, dryness of the skin	Relatively low
Systemic therapy	Effective in many forms of EB	Serious side effects (immunodeficiency, osteoporosis), high risk of infections	Immunosuppression, increased susceptibility to infections, growth retardation in children	High
Physiotherapy methods	An additional method of treatment promotes wound healing, reduces pain	Not a standalone treatment, effectiveness may be limited	Burns, redness of the skin	Average
Surgical treatment	An effective method for removing large blisters, restoring the skin	Invasiveness, risk of complications (infection, bleeding), long rehabilitation period	Pain, scarring, risk of transplant rejection	High

Continued Table 1.

Treatment method	Advantages	Disadvantages	Side effects	Price
Vacuum therapy	Promotes wound healing, stimulates blood circulation	Can be painful, requires special equipment	Skin redness, bleeding	Average
Plasmolifting	Stimulates tissue regeneration, reduces inflammation	Efficacy is not sufficiently studied, high cost, possible allergic reactions	Pain at the injection site, haematomas	High

Notes: the effectiveness is assessed by the speed of wound healing, pain relief, and improvement of quality of life; the most common side effects are listed; the relative cost of treatment is indicated for comparison (the exact cost may vary significantly depending on the country, clinic, and treatment method chosen)
Source: compiled by the author based on M. Titeux *et al.* [45], G.A. Suh *et al.* [46] and J. Riedl *et al.* [47]

A personalised approach to the treatment of chronic wounds in EB, accounting for the patient's genetic characteristics, can be used to determine the causes of the disease more accurately, select the optimal treatment methods and predict its effectiveness. Determining the patient's genetic characteristics defines the causes of EB, as each mutation provokes different phenotypes of the disease, which requires different treatment approaches. Genetic factors can also determine a patient's response to various types of therapy, allowing for the planning of an optimal treatment strategy in advance, avoiding complications (infections, scarring, malignant tumours), and predicting its outcome. Currently, the main areas of genetic research used in personalised medicine for the treatment of EB are pharmacogenetics – the study of the influence of genetic factors on the effectiveness of drugs, the development of gene therapy methods to correct mutations that cause the disease, and regenerative medicine based on the use of stem cells to repair damaged tissues [48]. The effectiveness of medicines in the treatment of EB can vary significantly depending on the genetic characteristics of each patient. The influence of these characteristics can be realised through changes in the metabolic rate due to variations in the genes encoding the enzymes involved in this process, the tendency to develop comorbidities and individual sensitivity to therapy. Immunosuppressants (corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine) and biological drugs (tumour necrosis factor α – TNF-α inhibitors, interleukin-1 inhibitors, integrin inhibitors) have the highest variability in effectiveness [49].

Planning the treatment of chronic wounds in EB, addressing the patient's genetic characteristics, involves several stages. The first stage involves genetic testing to determine the type of mutation. On its basis, an individual treatment strategy is developed, which includes the selection of optimal methods of local therapy, selection of systemic therapy, determination of the need for surgery and development of a rehabilitation programme. Regular monitoring of the patient's condition and, if necessary, adjustments to the treatment plan are mandatory throughout the treatment period [50]. Currently, the development of drugs based on the principles of gene therapy is ongoing. One of the most famous is Vyjuvek (B-Vec) for the treatment of dystrophic E. It contains a copy of a healthy gene encoding the protein collagen type XVII, an important component of the skin, the absence of which leads to the development of dystrophic E. To deliver the gene to cells, an adenoviral vector is used, i.e. a weakened virus that does not cause the disease but effectively delivers genetic material to cells. Vyjuvek (B-Vec) is designed as a topical medication and is applied directly to the affected skin. The introduced gene begins to produce type XVII collagen, which helps to strengthen the skin and reduce the formation of blisters [51].

An important part of planning the treatment of chronic wounds in EB based on the principle of personalised medicine is the assessment of the patient's general health and, depending on it, the correction of treatment. The course of EB can be affected by concomitant diseases and vitamin and mineral deficiencies. Due to permanent skin damage and impaired barrier function, patients with EB most often face deficiencies of vitamin D3, iron and zinc. The main factor behind this deficiency is impaired absorption of nutrients in the intestine due to the large surface area of the wound on the body, which increases the body's need for vitamins and minerals to ensure an active healing process.

Vitamin D3 is central in many physiological processes in the body, including the immune response, cell proliferation and angiogenesis, which is why its deficiency is often observed in patients with chronic skin diseases. The effect of this vitamin on wound healing is realised in several ways [52]. It activates receptors that stimulate epithelial cell division (proliferation), thereby accelerating the healing process. Additionally, it has an anti-inflammatory effect by regulating the activity of immune cells, which helps to avoid scarring during healing. The vitamin also possesses antimicrobial properties, which help to prevent wound infection, and it stimulates the formation of new blood vessels (angiogenesis), improving blood circulation in the wound and providing it with the necessary nutrients.

Vitamin D3 deficiency is often observed in patients with RDEB, as most of them try to avoid sunlight, which is the main source of this vitamin in the body, due to skin sensitivity. At the same time, as a result of constant damage and chronic inflammation, vitamin D3 is synthesised less efficiently and excreted faster. The situation is further complicated by the comorbidities that patients in this group have (e.g., celiac disease), which can further disrupt the absorption of this vitamin [53]. Elimination or correction of vitamin D3 deficiency in patients with BE is carried out by including foods rich in vitamin D in their diet (fatty fish, egg yolk, dairy products, etc.), sunbathing under medical supervision, and prescription of vitamin D3 supplements in an individually selected dosage.

Iron deficiency in EB occurs due to the depletion of iron stores in the body due to constant skin damage chronic bleeding and impaired absorption caused by

inflammatory processes in the intestine. A decrease in iron levels slows down the production of haemoglobin, leading to a decrease in the number of red blood cells and contributing to the development of anaemia. Its effect on wound healing is to reduce tissue oxygenation, which provokes a slowdown in energy processes, weakening of the immune system, delayed cell proliferation, and disruption of collagen synthesis, the main connective tissue protein that provides strength and elasticity to the skin [54]. Treatment of anaemia should begin with determining its type (iron-deficiency, B12-deficiency, folic acid-deficiency). Accordingly, iron therapy or vitamin therapy is prescribed, and a diet is developed that includes iron-rich foods (low-fat red meat such as beef, lamb, pork, dark poultry such as turkey, chicken, rabbit meat, beef and chicken liver, legumes, green leafy vegetables), with vitamin C supplemented to improve iron absorption from food. In severe cases, blood transfusion may be used. Similarly to vitamin D3 deficiency, anaemia is particularly common and acute in patients with RDEB. It is influenced by a combination of factors, including chronic bleeding, comorbidities, including inflammatory bowel disease, and impaired absorption of vitamin B12 and folic acid.

Like most trace elements in the human body, zinc is central to many physiological processes, including wound healing. It stimulates the proliferation of cells, in particular keratinocytes, which are involved in skin repair, enhances collagen synthesis, strengthens the immune system, helps maintain the integrity of cell membranes to preserve cellular functionality, and has antioxidant properties that help protect cells from free radical damage [55]. Depending on the severity of the type of BE, zinc deficiency is also more acute, so patients with RDEB are the most sensitive to a decrease in zinc levels. The process of eliminating its deficiency has the same strategy as for most other trace elements – developing a diet with the inclusion of foods rich in zinc (seafood, beef, lamb, pork, dark poultry meat – chicken, turkey, nuts, legumes), prescribing zinc preparations in the form of tablets or capsules, taking into account the required dosage, and monitoring its blood level to assess the effectiveness of treatment and timely dosage adjustment. Considering the wound microbiome, the patient's genetic characteristics and general health allows to increase the effectiveness of treatment of chronic wounds in EB, using an integrated approach, for example, combining local and systemic therapy or surgical methods and physiotherapy procedures.

Modern therapeutic strategies to improve the effectiveness of local treatment of chronic wounds in EB are aimed at the development and use of dressings that provide optimal conditions for healing. The main requirements for such materials are softness and elasticity, high hygroscopicity, air permeability, and antibacterial properties, ensuring painless dressing changes [56]. Following these requirements, modern dressings have been developed that are effectively used in the treatment of EB. Hydrocollagen dressings create a moist environment, promote the detachment of necrotic tissue and stimulate healing. Hydrogel dressings contain a large amount of water, which helps to moisten the wound and reduce pain during healing. Silver-containing dressings have antibacterial properties and prevent wound infection. Polyurethane foam dressings absorb a large amount of exudate, ensuring long-term use. Alginate dressings made from algae also effectively absorb exudate and create a moist environment that is optimal for healing. Thin, transparent dressing films, called "films" because of the material properties that allow for observation of the healing process, protect the wound from external influences and allow for visual assessment of tissue repair dynamics [57, 58]. When choosing a particular type of material, the stage of wound healing (acute, subacute, chronic), wound depth (superficial, deep), the presence of infection (absent, mild, moderate, severe) and the amount of exudate (dry wound, moderately moist, very moist) should be addressed.

In the context of the study of dressings, the study by M. Nita *et al.* [59], in which scientists reviewed the latest treatments for EB, including the use of the BIOOPA dressing, is noteworthy. The authors analysed the achievements in the field of tissue engineering, which was used to create a material that mimics the structure and natural healing process and can be effectively used to treat chronic wounds, especially in EB. Among the advantages of the modern BIOOPA dressing system, the scientists pointed out the possibility of creating an optimal moist environment for healing, providing protection against infections, reducing pain, resistance to maceration, and ease of application and removal. The authors' conclusions regarding the effectiveness of using the BIOOPA dressing for the local treatment of chronic wounds are notable, as they meet the requirements for dressings specified in this study.

Integrated treatment strategies for EB were investigated by H. Sait *et al.* [60]. The authors' study and the present study have a common problem related to the difficulty in identifying a single approach to wound care in EB. The results of both studies coincide with the importance of comprehensive therapy, and their differences are related to the view of the prospects of the direction of treatment. H. Sait *et al.* [60] expect promising approaches of gene, mRNA and cell therapy aimed at the main cause of the disease, while this paper, in addition to the importance of researching ways to eliminate or correct genetic mutations that lead to severe skin diseases, emphasises the need for improved treatments to alleviate the symptoms and consequences associated with chronic wounds (pain, infection, scarring). The wide range of scientific interests and the increasing technical and information potential of the medical industry make it possible to develop both areas with equal intensity. This will help improve the quality of life of patients with different types of EB now and avoid severe consequences of this disease in the future.

CONCLUSIONS

The diversity and interaction of microorganisms in the wound microbiome allow it to be used in the development of therapeutic strategies for the treatment of chronic wounds in EB. The moist environment under the blisters and constant skin trauma creates favourable conditions for the growth of pathogenic bacteria in the wounds of patients with EB, provoking dysbiosis, which slows down the healing process.

The main factors affecting the wound microbiome in EB are the patient's immune status, antibiotic use, location, depth and duration of the wound. A weakened immune system leads to the development of multidrug-resistant bacteria, making it difficult to treat infections and slowing down the healing process. An enhanced immune response and

the presence of autoimmune diseases provoke chronic inflammation, promoting the growth of staphylococci, pseudomonas, *Escherichia coli*, *Klebsiella*, *Proteus*, *Clostridium*, bacteroides, fusobacteria, *Candida*, etc. Antibiotic therapy is a traditional method of treating infections, but its irrational use can lead to the development of resistant strains of pathogens, complicating the wound-healing process. The microbiome differs in different parts of the body due to the characteristics of the skin, sweat and sebaceous glands, its moisture level and the presence of hair. Depending on the depth of the wound, appropriate conditions are created for the growth of certain microorganisms, so superficial and deep wounds have significant differences in their microbiome. The composition of the wound microflora is also influenced by the duration of its existence – an increase in duration increases dysbiosis, complicating the healing process.

The main directions in the treatment of chronic wounds in EB are personalised medicine, an integrated approach and the use of modern dressings. The area of personalised medicine is based on the study of the individual wound microbiome, understanding of genetic characteristics and assessment of the overall health of each patient. An integrated approach to therapy allows combining different methods of treating EB to increase their effectiveness. Modern dressing materials include hydrocolloid, hydrogel, silver-containing, polyurethane foam, alginate dressings and thin transparent films (films). Based on the results of the study, the methods of personalised medicine, an integrated approach and the use of modern dressings can be recommended for involvement in the clinical practice of a dermatologist to work with patients with EB.

The limitation of this review was the difficulty of assessing the long-term effects of chronic wound treatment in EB due to the short duration of follow-up in most studies on this disease. Given the difficulty of healing chronic wounds in EB, it is worth continuing to research methods of treating this disease in two directions: correcting mutated genes to eliminate the causes of increased skin vulnerability and finding methods to eliminate wound dysbiosis based on the study of its microbiota.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

REFERENCES

[1] Guttmann-Gruber C, Hofbauer JP, Tockner B, Reichl V, Klausegger A, Hofbauer P, et al. Impact of low-dose calcipotriol ointment on wound healing, pruritus and pain in patients with dystrophic epidermolysis bullosa: A randomized, double-blind, placebo-controlled trial. Orphanet J Rare Dis. 2021;16:473. DOI: 10.1186/s13023-021-02062-2
[2] Hou PC, Wang HT, Abhee S, Tu WT, McGrath JA, Hsu CK. Investigational treatments for epidermolysis bullosa. Am J Clin Dermatol. 2021;22:801–17. DOI: 10.1007/s40257-021-00626-3
[3] Pabón-Carrasco M, Caceres-Matos R, Roche-Campos M, Hurtado-Guapo MA, Ortiz-Romero M, Gordillo-Fernández LM, et al. Management of skin lesions in patients with epidermolysis bullosa by topical treatment: Systematic review and meta-analysis. Healthcare. 2024;12(2):261. DOI: 10.3390/healthcare12020261
[4] Bermudez NM, Warp PV, Hargis A, Yaghi M, Schachner L. Epidermolysis bullosa: A review of wound care and emerging treatments. Cur Dermatol Rep. 2024;13:123–31. DOI: 10.1007/s13671-024-00437-9
[5] Liy-Wong C, Tarango C, Pope E, Coates T, Bruckner AL, Feinstein JA, et al. Consensus guidelines for diagnosis and management of anemia in epidermolysis bullosa. Orphanet J Rare Dis. 2023;18:38. DOI: 10.1186/s13023-022-02448-w
[6] Raboei E, Alabdali A, Owiwi Y, Yousef Y, Alsaggaf A, Bustanji N, et al. Overview of complications associated with epidermolysis bullosa: A multicenter retrospective clinical analysis of 152 cases. J Pediatr Surg. 2021;56(12):2392–8. DOI: 10.1016/j.jpedsurg.2021.05.023
[7] Robertson SJ, Prodinger C, Liu L, Skilbeck C, Petrof G, Martinez AE, et al. Otological complications in inversa type recessive dystrophic epidermolysis bullosa. Clin Exp Dermatol. 2022;47(4):717–23. DOI: 10.1111/ced.15029
[8] Yavuz Y, An I, Yazmaci B, Akkus Z, Ortac H. Evaluation of clinical and oral findings in patients with epidermolysis bullosa. Medicina. 2023;59(7):1185. DOI: 10.3390/medicina59071185
[9] Stracy M, Snitser O, Yelin I, Amer Y, Parizade M, Katz R, et al. Minimizing treatment-induced emergence of antibiotic resistance in bacterial infections. Science. 2022;375(6583):889–94. DOI: 10.1126/science.abg9868
[10] Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. Eur J Intern Med. 2022;99:7–12. DOI: 10.1016/j.ejim.2022.01.029
[11] Reimer-Taschenbrecker A, Künstner A, Hirose M, Hübner S, Gewert S, Ibrahim S, et al. Predominance of *Staphylococcus* correlates with wound burden and disease activity in dystrophic epidermolysis bullosa: A prospective case-control study. J Investig Dermatol. 2022;142(8):2117–27. DOI: 10.1016/j.jid.2022.01.020
[12] Azeredo J, Azevedo NF, Briandet R, Cerca N, Coenye T, Costa AR, et al. Critical review on biofilm methods. Critic Rev Microbiol. 2016;43(3):313–51. DOI: 10.1080/1040841X.2016.1208146
[13] Marvasi M, Monici M, Pantalone D, Cavalieri D. Exploitation of skin microbiota in wound healing: Perspectives during space missions. Front Bioeng Biotechnol. 2022;10:873384. DOI: 10.3389/fbioe.2022.873384
[14] White EK, Grice EA. The wound microbiome. Cold Spring Harbor Perspect Biol. 2023;15:a041218. DOI: 10.1101/cshperspect.a041218
[15] Żółkiewicz J, Marzec A, Ruszczyński M, Feleszko W. Postbiotics – a step beyond pre- and probiotics. Nutrients. 2020;12(8):2189. DOI: 10.3390/nu12082189
[16] Rajer F, Sandegren L. The role of antibiotic resistance genes in the fitness cost of multiresistance plasmids. mBio. 2022;13(1):e03552-21. DOI: 10.1128/mbio.03552-21

[17] Seebach E, Kraus FV, Elschner T, Kubatzky KF. Staphylococci planktonic and biofilm environments differentially affect osteoclast formation. Inflammat Res. 2023;72:1465–84. DOI: 10.1007/s00011-023-01745-9
[18] Liu C, Ponsero AJ, Armstrong DG, Lipsky BA, Hurwitz BL. The dynamic wound microbiome. BMC Med. 2020;18:358. DOI: 10.1186/s12916-020-01820-6
[19] Tipton CD, Wolcott RD, Sanford NE, Miller C, Pathak G, Silzer TK, et al. Patient genetics is linked to chronic wound microbiome composition and healing. PLoS Pathog. 2020;16(6):e1008511. DOI: 10.1371/journal.ppat.1008511
[20] Suárez LJ, Garzón H, Arboleda S, Rodríguez A. Oral dysbiosis and autoimmunity: From local periodontal responses to an imbalanced systemic immunity. A review. Front Immunol. 2020;11:591255. DOI: 10.3389/fimmu.2020.591255
[21] Singh A, Amod A, Pandey P, Bose P, Pingali MS, Shivalkar S, et al. Bacterial biofilm infections, their resistance to antibiotics therapy and current treatment strategies. Biomed Mat. 2022;17(2):022003. DOI: 10.1088/1748-605x/ac50f6
[22] Kunimitsu M, Nakagami G, Kitamura A, Minematsu T, Koudounas S, Ogai K, et al. Relationship between healing status and microbial dissimilarity in wound and peri-wound skin in pressure injuries. J Tissue Viability. 2022;32(1):144–50. DOI: 10.1016/j.jtv.2022.10.006
[23] Tang Q, Xue N, Ding X, Tsai KH, Hew JJ, Jiang R, et al. Role of wound microbiome, strategies of microbiota delivery system and clinical management. Adv Drug Del Rev. 2023;192:114671. DOI: 10.1016/j.addr.2022.114671
[24] Campbell A, Bae J, Hein M, Hillis SL, Rebeck ON, Rakel BA, et al. The heterogeneous wound microbiome varies with wound care pain, dressing type, and inflammatory gene expression. Wound Repair and Regen;2024;32(6):811–25. DOI: 10.1111/wrr.13184
[25] Durand BA, Pouget C, Magnan C, Molle V, Lavigne JP, Dunyach-Remy C. Bacterial interactions in the context of chronic wound biofilm: A review. Microorganisms. 2022;10(8):1500. DOI: 10.3390/microorganisms10081500
[26] Yang Y, Huang J, Zeng A, Long X, Yu N, Wang X. The role of the skin microbiome in wound healing. Burns Trauma. 2024;12:tkad059. DOI: 10.1093/burnst/tkad059
[27] Shibata K, Ogai K, Ogura K, Urai T, Aoki M, Arisandi, D, et al. Skin physiology and its microbiome as factors associated with the recurrence of pressure injuries. Biol Res Nurs. 2021;23(1):75–81. DOI: 10.1177/1099800420941100
[28] Thaarup IC, Iversen AKS, Lichtenberg M, Bjarnsholt T, Jakobsen TH. Biofilm survival strategies in chronic wounds. Microorganisms. 2022;10(4):775. DOI: 10.3390/microorganisms10040775
[29] Harris N, Fulchand S, Nazaroff J, Li S, Tang JY. Natural history of spontaneous wound healing in recessive dystrophic epidermolysis bullosa wound types using a mobile photography application. J Investig Dermatol. 2023;143(5):S260. DOI: 10.1016/j.jid.2023.03.1534
[30] Thien CI, Bessa VR, Miotto IZ, Samorano LP, Rivitti-Machado MC, de Oliveira ZNP. Hereditary epidermolysis bullosa: Clinical-epidemiological profile of 278 patients at a tertiary hospital in São Paulo, Brazil. Braz Ann Dermatol. 2024;99(3):380–90. DOI: 10.1016/j.abd.2023.06.009
[31] Nyström A, Bruckner-Tuderman L, Kiritsi D. Dystrophic epidermolysis bullosa: Secondary disease mechanisms and disease modifiers. Front Gen. 2021;12:737272. DOI: 10.3389/fgene.2021.737272
[32] Kondo M, Takashima S, Goto H, Habe K, Natsuga K, Yamanaka K. Dominance of methicillin-resistant *Staphylococcus aureus* in a Japanese infant with recessive dystrophic epidermolysis bullosa. Case Rep Dermatol. 2021;13(2):278–81. DOI: 10.1159/000516354
[33] Chua C, Sethi R, Ong J, Low JH, Yew YW, Tay A, et al. Late inflammatory monocytes define circulatory immune dysregulation observed in skin microbiome-stratified atopic dermatitis. J Dermatol. 2023;112(3):158–61. DOI: 10.1016/j.jdermsci.2023.10.006
[34] Horev A, Brandwein M, Vaknin A, Motro Y, Moran-Gilad J. Temporal changes in the skin microbiome of epidermolysis bullosa patients following the application of wound dressings. J Clin Med. 2023;12(20):6435. DOI: 10.3390/jcm12206435
[35] Bar J, Sarig O, Lotan-Pompan M, Dassa B, Miodovnik M, Weinberger A, et al. Evidence for cutaneous dysbiosis in dystrophic epidermolysis bullosa. Clin Exp Dermatol. 2021;46(7):1223–9. DOI: 10.1111/ced.14592
[36] Has C, Hachem ME, Bučková H, Fischer P, Friedová M, Greco C, et al. Practical management of epidermolysis bullosa: Consensus clinical position statement from the European Reference Network for Rare Skin Diseases. J Eur Acad Dermatol Venereol. 2021;35(12):2349–60. DOI: 10.1111/jdv.17629
[37] Forss R, Hugman Z, Ridlington K, Radley M, Henry-Toledo E, O'Neill B. Does the application of a semiocclusive dressing alter the microflora of healthy intact skin on the foot? J Am Podiatr Med Associat. 2021;111(1):e01. DOI: 10.7547/18-141
[38] Mudrik-Zohar H, Carasso S, Gefen T, Zalmanovich A, Katzir M, Cohen Y, et al. Microbiome characterization of infected diabetic foot ulcers in association with clinical outcomes: Traditional cultures versus molecular sequencing methods. Front Cell Infect Microbiol. 2022;12:836699. DOI: 10.3389/fcimb.2022.836699
[39] Bauermeister A, Mannochio-Russo H, Costa-Lotufo LV, Jarmusch AK, Dorrestein PC. Mass spectrometry-based metabolomics in microbiome investigations. Nature Rev Microbiol. 2022;20:143–60. DOI: 10.1038/s41579-021-00621-9
[40] Hatzenpichler R, Krukenberg V, Spietz RL, Jay ZJ. Next-generation physiology approaches to study microbiome function at single cell level. Nature Rev Microbiol. 2020;18:241–56. DOI: 10.1038/s41579-020-0323-1
[41] Schmidt BM. Emerging diabetic foot ulcer microbiome analysis using cutting edge technologies. J Diabet Sci Tech. 2022;16(2):353–63. DOI: 10.1177/1932296821990097

[42] Jozic I, Tomic-Canic M. Flipping the script: Are cellular assays and wound fluids the next frontier in personalized wound care? J Investig Dermatol. 2024. DOI: 10.1016/j.jid.2024.08.007
[43] Doerfler P, Schoefmann N, Cabral G, Bauer W, Berli MC, Binder B, et al. Development of a cellular assay as a personalized model for testing chronic wound therapeutics. J Investig Dermatol. 2024. DOI: 10.1016/j.jid.2024.05.029
[44] So JY, Nazaroff J, Iwummadu CV, Harris N, Gorell ES, Fulchand S, et al. Long-term safety and efficacy of gene-corrected autologous keratinocyte grafts for recessive dystrophic epidermolysis bullosa. Orphanet J Rare Dis. 2022;17:377. DOI: 10.1186/s13023-022-02546-9
[45] Titeux M, Bonnet des Claustres M, Izmiryan A, Ragot H, Hovnanian A. Emerging drugs for the treatment of epidermolysis bullosa. Expert Opin Emerg Drug. 2020;25(4):467–89. DOI: 10.1080/14728214.2020.1839049
[46] Suh GA, Lodise TP, Tamma PD, Knisely JM, Alexander J, Aslam S, et al. Considerations for the use of phage therapy in clinical practice. Antimicr Agen Chemother. 2022;66:e02071–21. DOI: 10.1128/aac.02071-21
[47] Riedl J, Popp C, Eide C, Ebens C, Tolar J. Mesenchymal stromal cells in wound healing applications: Role of the secretome, targeted delivery and impact on recessive dystrophic epidermolysis bullosa treatment. Cytotherapy. 2021;23(11):961–73. DOI: 10.1016/j.jcyt.2021.06.004
[48] Pânzaru M, Caba L, Florea L, Braha EE, Gorduza EV. Epidermolysis bullosa – a different genetic approach in correlation with genetic heterogeneity. Diagnostics. 2022;12(6):1325. DOI: 10.3390/diagnostics12061325
[49] Oliver J, Mason W. Gene variation: The key to understanding pharmacogenomics and drug response variability. Fusion Multidiscipl Res. 2020;1(2):97-109.
[50] Kolimi P, Narala S, Nyavanandi D, Youssef AAA, Dudhipala N. Innovative treatment strategies to accelerate wound healing: Trajectory and recent advancements. Cells. 2022;11(15):2439. DOI: 10.3390/cells11152439
[51] Khan A, Riaz R, Ashraf S, Akilimali A. Revolutionary breakthrough: FDA approves Vyjuvek, the first topical gene therapy for dystrophic epidermolysis bullosa. Ann Med Surg. 2023;85(12):6298–301. DOI: 10.1097/ms9.0000000000001422
[52] Yerlett N, Loizou A, Bageta M, Petrof G, Martinez AE. Establishing an appropriate level of vitamin D supplementation in paediatric patients with recessive dystrophic epidermolysis bullosa. Clin Exp Dermatol. 2022;47(7):1307–13. DOI: 10.1111/ced.15156
[53] Hou PC, del Agua N, Lwin SM, Hsu CK, McGrath JA. Innovations in the treatment of dystrophic epidermolysis bullosa (DEB): Current landscape and prospects. Therapeut Clin Risk Manag. 2023;19:455–73. DOI: 10.2147/TCRM.S386923
[54] Reimer A, Hess M, Schwieger-Briel A, Kiritsi D, Schauer F, Schumann H, et al. Natural history of growth and anaemia in children with epidermolysis bullosa: A retrospective cohort study. Brit J Dermatol. 2020;182(6):1437–48. DOI: 10.1111/bjd.18475
[55] Santos MLD, Monteiro AC, Nascimento A, Barbosa S, Delgado A, Zamberlan P. Nutritional profile and topic management for wound healing in children with epidermolysis bullosa: What is the evidence? A systematic review. Rec Progr Nutrit. 2024;4(3). DOI: 10.21926/rpn.2403010
[56] Konop M, Rybka M, Drapała A. Keratin biomaterials in skin wound healing, an old player in modern medicine: A mini review. Pharmaceut. 2021;13(12):2029. DOI: 10.3390/pharmaceutics13122029
[57] Nguyen HM, Le TTN, Nguyen AT, Le HNT, Pham TT. Biomedical materials for wound dressing: Recent advances and applications. RSC Adv. 2023;13:5509–28. DOI: 10.1039/D2RA07673J
[58] Mirhaj M, Labbaf S, Tavakoli M, Seifalian AM. Emerging treatment strategies in wound care. Int Wound J. 2022;19(7):1934–54. DOI: 10.1111/iwj.13786
[59] Nita M, Pliszczyński J, Kosieradzki M, Fiedor P. Review of the latest methods of epidermolysis bullosa and other chronic wounds treatment including BIOOPA dressing. Dermatol Therap. 2021;11:1469–80. DOI: 10.1007/s13555-021-00578-w
[60] Sait H, Srivastava S, Saxena D. Integrated management strategies for epidermolysis bullosa: Current insights. Int J Gen Med. 2022;15:5133–44. DOI: 10.2147/IJGM.S342740

Оптимізація лікування хронічних ран при бульозному епідермолізі та вплив мікрофлори: огляд літератури

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Анотація. Дослідження було проведене з метою пошуку найефективніших підходів до лікування хронічних ран при бульозному епідермолізі з врахуванням впливу мікробіому рани на процес її загоєння. Під час дослідження проведено огляд актуальних наукових джерел з дерматології, фармакології, генетики, імунології, мікробіології, встановлено роль мікробіому рани в загоєнні хронічних ран при бульозному епідермолізі та проаналізовано сучасні стратегії лікування для прискорення загоєння даних ран. Результати дослідження виявили, що мікрофлора рани має значний вплив на процес їх загоєння. Бульозний епідермоліз провокує постійне травмування шкіри, сприяючи створенню умов для розмноження в ранах патогенних бактерій, що призводить до розвитку дисбіозу та ускладнює процес загоєння. Значний вплив на мікробіом ран при бульозному епідермолізі має імунний статус пацієнта, застосування антибіотиків, розташування, глибина та тривалість рани. Ослаблений імунітет провокує розвиток мультирезистентних бактерій, посилена імунна відповідь та аутоімунні процеси створюють умови для розвитку мікроорганізмів, здатних розмножуватися в умовах характерних для запаленої рани. Застосування антибіотиків є високоефективним методом лікування інфекцій, проте тривала або нераціональна антибіотикотерапія може спровокувати виникнення резистентних штамів бактерій. На формування мікробіому рани, залежно від її локалізації, впливають особливості шкіри на різних ділянках тіла – рівень зволоженості, наявність потових та сальних залоз, волосяний покрив. Вплив глибини рани на мікробіом реалізується створенням умов для розмноження відповідних мікроорганізмів на відповідній глибині. Тривалість існування рани посилює в ній дисбіоз, ускладнюючи загоєння. Сучасні стратегії лікування для прискорення загоєння хронічних ран при бульозному епідермолізі включають напрямок персоніфікованої медицини, комплексного підходу та застосування сучасних перев'язочних матеріалів. Отримані результати вказують на необхідність дослідження та розробки нових ефективних методів усунення дисбіозу рани для нормалізації її мікробіому та прискорення процесу загоєння

Ключові слова: загоєння; патогенні бактерії; дисбіоз; антибіотики; резистентність; персоніфікована медицина