PREVENTION OF INFECTION, EFFECTIVE CONTROL AND TREATMENT OF INFECTED BURN WOUNDS – THE ROLE OF A NURSE IN AN INTERDISCIPLINARY TEAM

ZAPOBIEGANIE ZAKAŻENIOM, SKUTECZNA KONTROLA I LECZENIE ZAKAŻONYCH RAN OPARZENIOWYCH – ROLA PIELĘGNIARKI W ZESPOLE INTERDYSCYPLINARNYM

Aleksandra Głowacka, Grażyna Bączyk, Agnieszka Ulatowska

Department of Nursing Practice, Chair of Nursing, Faculty of Health Sciences
Poznan University of Medical Sciences, Poland

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ABSTRACT

Wound infection is one of many, but at the same time the most serious complication in the treatment of burns. The development of infection particularly concerns patients with deep burns of intermediate and full thickness of skin. In severe thermal, chemical or electrical burns the skin immune system (SIS) in the burn wound is damaged or destroyed. The SIS phenomenon is one of the causes of post-traumatic immunosuppression in the burn wound and systemic anti-infectious response.

The risk of burn wound infection and systemic infection is correlated with the burn area.

The aim of the study is to discuss the currently used methods of prevention, effective control and treatment of an infected burn wound. It discusses criteria for infection recognition, immunosuppressive limiting methods, standards and newly introduced methods of removing dead tissues, antimicrobial agents and methods to reduce the risk of bacterial transfer between patients.

Prevention, control and treatment of an infected burn wound requires a multidisciplinary approach, including close cooperation between a nurse and a physician. The patient's deep and extensive burn care process is designed to reduce the risk of developing burns and prevent critical infection that not only prolongs the healing process but also can lead to generalized infection. The patient care plan should be based on up-to-date medical knowledge and updated regularly.

KEYWORDS: burn, burn wound, immunosuppression, infection, prevention, infection control, antiseptics, dressings.

STRESZCZENIE

Zakażenie rany oparzeniowej jest jednym z wielu, ale równocześnie najgroźniejszym powikłaniem w leczeniu oparzeń. Na rozwój zakażenia w sposób szczególny narażeni są pacjenci z głębokim oparzeniem pośredniej i pełnej grubości skóry. W głębokim oparzeniu termicznym, chemicznym lub elektrycznym w ranie oparzeniowej zostaje uszkodzony lub zniszczony układ odpornościowy skóry (ang. skin immune system – SIS). Zjawisko SIS stanowi jedną z przyczyn pourazowej immunosupresji w ranie oparzeniowej oraz systemowej odpowiedzi przeciwzakaźnej.

Ryzyko zakażenia rany oparzeniowej oraz infekcji ogólnoustrojowej jest skorelowane z powierzchnią oparzenia. Celem pracy jest omówienie aktualnie stosowanych metod zapobiegania, skutecznej kontroli i leczenia zakażonej rany oparzeniowej. Omówiono w niej kryteria rozpoznawania zakażenia, metody ograniczające immunosupresję, standardowe i nowo wprowadzone metody usuwania tkanek martwych, środki przeciwdrobnoustrojowe oraz metody ograniczające ryzyko transferu bakterii między pacjentami.

Zapobieganie, kontrola i leczenie zakażonej rany oparzeniowej wymaga podejścia wielodyscyplinarnego, w tym ścisłej współpracy pielęgniarki z lekarzem. Proces pielęgnowania realizowany na rzecz pacjenta z głębokim i rozległym oparzeniem ma na celu ograniczenie ryzyka rozwoju infekcji w ranie oparzeniowej oraz zapobieganie krytycznemu zakażeniu, które nie tylko wydłuża proces gojenia się rany oparzeniowej, ale także może doprowadzić do uogólnionego zakażenia. Plan opieki nad pacjentem powinien być oparty na aktualnej wiedzy medycznej i bieżąco aktualizowany.

SŁOWA KLUCZOWE: oparzenie, rana oparzeniowa, immunosupresja, zakażenie, zapobieganie, kontrola infekcji, antyseptyki, opatrunki.

Introduction

One of the most important and still current problems in the treatment of deep burns are infection, which significantly impedes wound healing, can cause bacteremia and sepsis, which is always a serious threat to life [1]. Patients with deep to severe burns and full thickness of the skin are particularly at risk for infection. In deep burns of intermediate skin thickness, superficial dermis is destroyed, burns are characterized by superficial necrosis, when the destruction crosses the der-

mis, deep necrosis is present in the clinical picture [2]. In severe thermal, chemical or electrical burns the skin immuno-system (SIS) in the burn wound is damaged or destroyed. Consequently, the active protective barrier of the skin is destroyed. It results in the damage to or destruction of the guard function of the skin. The skin loses its ability to react to foreign antigens, especially of bacterial origin. The SIS phenomenon is one of the causes of post-traumatic local immunosuppression in the burn wound and systemic anti-infectious resistance. The gates of contamination, colonization and infection are open [3]. The results of multicentre studies in different countries have demonstrated the microbiological dynamics of burn wound. During the first three days after burns the wound is settled by coagulase-negative staphylococci, mainly Staphylococcus epidermidis as well as Stapchylococcus aureus, including methicillin-resistant Staphylococcus aureus. At 3–4 day the dominant etiological factor of septic complications in patients with burn wounds are Pseudomonas aeruginosa and Acnetobacter baumani [4].

The mechanism of burn wound infection can be divided into three stages: colonization, invasion and generalized infection. The stage of colonization is divided into critical colonization and the formation of the biofilm structure. The condition for the biofilm formation is the adhesion of bacterial cells to the burned surface. In the next stage of the biofilm formation, the multiplication and accumulation of cells in the form of multiple layers is followed by the formation of a cluster immersed in the polymer matrix. Bacteria in the biofilm community adapt their metabolic processes according to the availability of nutrients and provide themselves protection from harmful conditions [4]. In the guidelines of the Polish Society for Wound Management (Polskie Towarzystwo Leczenia Ran) from 2012 on local and general management of wound infections, it was emphasized that microorganisms in the biofilm exhibit exceptional (resistance) tolerance to topical antibiotics. Therefore, there is an urgent need for therapeutic agents that allow eradication of microorganisms before they form the biofilm [5].

The risk of burn wound infection and systemic infection is correlated with the extent of burn wound assessed as a percentage of the total body surface area (TBSA). It is believed that the immune system is destroyed by burns over 30% of TBSA [5], but sepsis can develop in deep thermal burns covering less than 30% of TBSA, especially in the presence of additional factors increasing the risk of infection development [1]. The risk of wound infection associated with the need for topical antibiotic treatment may be assessed on the basis of the wound-at-risk scale, created by the team of clinicians from Germany, Italy, and Austria, and presented in the Polish scientific literature. Indication for topical treatment is given after calculation of the parametric value of individual risk factors to which 1, 2 or 3 points are attributed. The initiation of antimicrobial treatment is justified when the combined value of individual risk factors is equal to or greater than 3. However, it should be noted that regardless of the number of points awarded, topical treatment should be undertaken in the presence of multiresistant microbes even if the risk score is less than 3 [5, 7]. Particular risks of infection in the burn according to the WAR scale (Wound at risk scale) are: local and general immune suppression, surface of the burn wound greater than 15% of TBSA, burn location, very young or old age of the patient, comorbidities, e.g. diabetes [2]. Prevention, effective control and treatment of the infected burn wound requires a multidisciplinary approach, including close cooperation between a nurse and a physician.

The aim of the thesis

The purpose of this paper is to discuss the currently used methods of prevention, effective control and treatment of an infected burn wound. It discusses criteria for infection recognition, methods of immunosuppressive reduction, standards and newly introduced methods of removing dead tissues, antimicrobial agents, and methods to reduce the risk of bacterial transfer between patients.

Methods of infection recognition

Accurate, clinical assessment of the condition of the wound during each dressing change allows to early identify the deterioration of the local condition. Deep infection is shown by the change of the macroscopic appearance of the wound. The most common symptom of profound infection is a change in the depth of burns from incomplete skin thickness to full thickness burns (burn conversion) or an unexpected change in coloration of necrosis, which from pale or whitish turns dark brown, black or violet. Rapid separation of the burn eschar in the first week after burn is the most common and easily noticeable symptom suggesting a deep infection. General symptoms that may be associated with infection are fever, hypothermia, hypotension, oliguria, hyperglycemia, mental disorders [8, 9]. The presence of these symptoms may signal the infection, but confirmation of this condition requires a microbiological examination. It is believed that methods of recognition and following registration of infections should be based on standardized criteria and clear programs.

Around the world, infection control programs are being developed and implemented for years, taking into account the specificity of burn injuries. According to the definition

of Centers for Disease Control and Prevention (CDC), for skin and soft tissue infections, one of the following criteria must be met to identify a burn wound infection:

1. Change of a burn wound appearance or character, such as: rapid eschar separation or dark brown, black or violaceous discoloration of the eschar or edema at the wound margin and invasion of the organisms into the adjacent viable tissue shown in the histologic examination of burn biopsy.
2. Change of a burn wound appearance or character, such as: rapid eschar separation or dark brown, black or violaceous discoloration of the eschar or edema at wound margin and both of following:
   a) organisms cultured from blood in the absence of other identifiable infections,
   b) isolation of HSV (Herpes simplex virus), histologic identification of inclusions by light microscopy or visualization of viral particles in electron microscopy in biopsies or lesions scrapings.
3. Patient with a burn has at least two of the following signs or symptoms with no other recognized cause: fever, hypothermia, hypotension, oliguria, hyperglycemia, mental confusion and at least one of the following conditions:
   a) histopathologic examination of burn biopsy shows invasion of organisms into the adjacent viable tissue
   b) organisms cultured from blood,
   c) isolation of HSV, histologic identification of inclusions by light microscopy or visualization of viral particles in electron microscopy in biopsies or lesions scrapings [9].

It is believed that cultures from the swabs surface have limited usefulness in the diagnosis of infection, but can be used to monitor trends in the epidemiological center or burn treatment departments [8].

Reduction of immunosuppression

The period between the burn and clinical signs of infection with Pseudomonas aeruginosa can be used for active immunization. Prophylactic use of Pseudomonas in patients with extensive and severe burns offers the ability to acquire active immunity against infections caused by cyanobacterium and significantly reduces the risk of infection spreading in all tissues and organs of the body. The treatment regimen consists in increasing doses of the preparation. The preparation is administered by intramuscular injection [10].

Modification of the immune response under the influence of nutrients

Nutrients may modify and positively influence physiological processes. The use of preparations which, apart from their basic purposes (satisfying the caloric needs, the supply of building substances) may to a greater extent than previously affect the immune system is referred to as immunomodulating nutrition [11]. Early and continuous nutritional interventions using high protein, high carbohydrate and low fat nutritional supplements, and adequate vitamin and trace elements supplementation [12] may reduce the effects of hypermetabolism in burns and support wounds healing. However, with the recognition of the intestines as immune-regulatory organs several key substances have been identified to modify physiological functions, alleviate oxidative stress and act as signaling molecules when administered enterally. Examples of such substances are amino acids: glutamine, arginine, cysteine, taurine, omega-3 unsaturated fatty acids, nucleotides, vitamins C and E, micronutrients such as zinc and selenium [11]. Glutamine is the major source of energy for macrophages, fibroblasts, lymphocytes and enterocytes, which prevents spreading of the bacteria from the digestive system into the body [12]. The clinical benefits of supplementation of glutamine in patients with burns include a reduced infection rate, reduced hospital stay, and lower mortality. It is believed that glutamine supplementation is relatively safe, which makes it worth considering as an element of prophylaxis of infections in severely burned patients. The role of arginine supplementation in burn patients is still under investigation [13]. Arginine accelerates healing of wounds, but it contributes to an increase of urea production and a massive loss of nitrogen from the organism, which often excludes it from clinical practice [12, 13]. The potential benefits of arginine in terms of wound healing can be seen particularly in malnourished patients, which also indicates its importance in the nutritional therapy of burn patients [13]. Among micronutrients, a significant role in the immune response modulation and burn wound healing has been demonstrated with respect to copper, selenium and zinc. A large escape of these trace elements with wounds exudate continue until their definitive closure. The time of supplementation depends on the surface of the open burn injuries [12].

After identifying the demand for individual nutrients and determining the composition of the diet the way to deliver nutrients which meet patient's metabolic and clinical needs best should be defined. Given the importance of maintaining intestinal mucous membrane integrity and benefits of enteral nutrition, especially in reduction of increased catabolism effects, most clinicians opt for enteral nutrition as the preferred form of therapy. [13]. It is recommended that enteral nutrition is introduced as soon as possible using a naso-gastric tube or a naso-intestinal tube [12, 13]. Parenteral nutrition is

treated as a supplement to enteral nutrition, and often at the initial stage of treatment it is carried out simultaneously with enteral nutrition [12, 13]. In the course of intensive nutritional therapy, one of the main problems of care is the infection associated with both enteral and parenteral nutritional interventions. Industrial enteral diets are manufactured in a standardized and sterile manner. The diet may be contaminated during the collection, filling, administration, and such contamination can cause local and general infection. Proper storage and administration of the diet guarantees microbiological safety [9]. Central vascular lines used in parenteral nutrition are often colonized by microorganisms, becoming the starting point for catheter-related infections. The problem of catheter-associated infections in patients with severe burns is particularly important for two reasons. Firstly, burn-induced immunosuppression limits the defenses of the patient's organism, and secondly, the location of the central vascular line, often near the wound, increases the risk of colonization by microorganisms. As far as possible, a central puncture should be performed through not burnt skin, preferably in an appropriate distance from the wound to prevent infection at the catheter site. Because it is not always possible in case of extensive burns, it may be necessary to frequently change the central access site. Handling a central puncture area near or through a burn wound is a challenge because occlusive dressing cannot be used. In such cases non-occlusive anti-microbial dressings changed every 2–4 hours are recommended [6]. An important part of prophylaxis is aseptic treatment during the use of the central vascular line.

Surgical and enzymatic methods of dead tissue removal

The standard procedure in the case of deep burns is early surgical excision of necrosis [14]. Excision of dead tissue and the replacement of the burn wound to a pure surgical wound closed with autologous transplants of intermediate thickness skin or its substitutions closes the gates of infection and reduces the risk of systemic infection [15].

What is important is the time of application. The treatment should be performed quickly, before the burn wound infection and multi-organ failure development. Although early cut and closure of wounds are considered to be the main factors reducing the incidence of burn wound infections, questions have been raised in the literature on the effectiveness and safety of treatments performed during the first 24 hours of burn treatment. The quantitative study evaluating the effect of time on the degree of bacterial colonization of burn injuries showed that the incidence of wound infection was lower in patients treated within the first 24 hours of injury compared to surgical patients treated in a deferred mode – 6 days after injury [16].

However, in the case of extensive wounds, surgical treatment may be distributed in time and the patient may require several treatments. Until all dead tissues have been removed, an important part of the nursing process is to protect the wound from burn conversion and infection. Antimicrobial agents are used for this purpose. The characteristics of antimicrobial agents used in the prevention and treatment of burn infections are presented in the following section.

Recently, for the treatment of the burn wound, hydrocephalic treatment has been introduced. Hydrosurgical procedures allow for a safe transfer during the procedure of cleaning a dead wound tissue. The method involves the use of a Versajet apparatus delivering physiological saline to the surgical tip, at supersonic speed, at about one atmosphere pressure. The fluid jet cuts off the dead tissues that are immediately aspirated together with a bacterial aerosol, the biofilm from the wound surface is also removed. The operator can control the depth and strength of the tissue aspirations. Hydro-surgical treatment guarantees a precise cleaning of the wound, especially in inaccessible areas to the expected depth and its decontamination and preparation of the wound to the free graft of the intermediate skin thickness - the next stage of surgical burn treatment. The authors emphasize the high safety of such a method for both the patient and the staff [1, 17].

An alternative method for surgical procedures is the enzymatic purification of burn wounds with NexoBrid [18]. NexoBrid is the first of a new generation of non-surgical treatment agents for burn wounds. NexoBrid is used in adults with deep thermal burns of intermediate and full-thickness of the skin. The formulation contains a mixture of enzymes called "bromelain-enriched proteolytic enzyme concentrate," which comes from the stalk of the pineapple plant. NeksoBrid removes a dead tissue without damaging the living tissue, in most cases after one 4-hour local application. Efficacy in removing dead tissues is obtained without additional damage to surrounding living tissues, mainly dermis. NexoBrid dramatically reduces the time of effective removal of the burn wound, allowing for faster treatment and the possibility to move to the next step of wound closure by autogenic skin graft [19, 20, 21].

Time control of the wound after surgical or enzymatic debridement with skin transplantation

Free skin grafts of intermediate thickness are the basic way to close wounds after the removal of dead tissues, in the treatment of burns of full thickness of the skin.

Free skin grafts of intermediate thickness excision sites heal spontaneously within seven to fourteen days. Dressings play a protective role both in the free skin grafts of intermediate thickness donor sites and in skin transplants, allowing or even facilitating and accelerating the healing of the wound. Wet treatment is most commonly used in these locations so that it does not interfere with the natural healing process, as the growth factors, proteins and other active substances in the wound healing are retained in the exudate fluid.

Unfortunately, the warm environment of wounds and water, electrolytes and proteins is not only a condition for reproducing the epidermis in the donor field of free skin grafts of intermediate thickness and for grafting, but also for the development of bacteria [22]. Therefore, transplanted areas and transplant sites require the observation and evaluation of both transplant conditions and wound healing after transplantation. Clinical manifestations of infection include present or increasing pain, a change in appearance and increased or changed exudate [23]. Antiseptics and modern silver-containing dressings are recommended for treatment of dermatitis [22, 23]. In the case of changes of care and wounds treatment, it is important to regularly update the patient care plan.

Use of antiseptics with a broad spectrum of antimicrobial activity

The aim of care assuming maximization of preventive measures is important when choosing the optimal antimicrobial agent. The choice of the local antimicrobial agent should be based on its ability to inhibit the development of microorganisms, in controlled microbiological tests and the monitoring of infections within a burn treatment site [24].

When selecting an antimicrobial agent, we also need to be sure of its local and systemic safety. At present antiseptic, which remains a safe therapeutic option in the prevention and treatment of septic complications of burns, is octenidine. For over 30 years of octenidine use, the resistance mechanism has not been developed by microorganisms. Octenidine is characterized by high antimicrobial activity, the activity spectrum includes Gram-negative and Gram-positive bacteria, fungi and protozoa. Octenidine dihydrochloride also has a high activity against microorganisms in the biofilm form. In addition, octenidine dihydrochloride has not been shown to be absorbed, whereas phenoxyethenol, which is an excipient in octenidine-containing formulations, is safely excreted from the body in the form of phenoxyacetic acid. Up to now, no case of allergy to octenidine has been reported in the scientific literature [4]. The choice of recommended antiseptic depends also on its individual form, e.g. liquid, gel or cream [24].

Liquid antiseptics have a short duration of antimicrobial activity limited to a few hours. In studies on the effectiveness of various antiseptics, it has been shown that the octenidine gel has a longer and more effective bactericidal effect compared to liquid antiseptics [25].

Another compound used in burn antiseptics is povidone iodine (PVP-1). The mechanism of action of this antiseptics is to penetrate the free iodine particles through the cell wall of the microorganisms and to irreversibly combine them with the proteins, lipids and nucleic acids. PVP-1 has a strong and wide range of both antimicrobial and antifungal properties. However, its use on the wound causes pain, and the brown color can mask the wound infection in the wound. For this reason, PVP-1 was included in the 2012 group of antiseptics that should not be used in the treatment of chronic wounds. What is more, in case of extensive burns iodine can affect the thyroid. Iodine compounds are absorbed by the wound and penetrate into the serum. Accumulation of elemental iodine in the thyroid can lead to thyroid dysfunction. The antiseptics still used to combat septic complications in burns include chlorhexidine and polyhexadine. However, according to microbiologists, their use may not lead to satisfactory therapeutic effects due to the high resistance of microorganisms [4]. However, it needs to be emphasized that antimicrobial therapy alone in case of deep and extensive burns using antimicrobial agents (antiseptics and silver-containing dressings) cannot protect the patient from invasive burn wound infections. The purpose of antimicrobial preparations is to support surgical or enzymatic treatment.

Dressings containing silver

Silver has a broad spectrum of antimicrobial, antiviral and antifungal effects. It is currently widely used in wound dressings, and its use has increased in recent years, probably due to the resistance of bacteria to traditional antibiotics. The use of silver can provide effective antimicrobial effects in critically colonized wounds or infected wounds [26]. Hydrofiber dressings with silver ions and foam dressings with ionic silver are recommended for the use in infected wounds. Hydrocarbon dressings with silver ions have a mechanism for absorbing exudates and closing bacteria in the structure of the dressing fibers. They easily adapt to the wound, forming a gel under the influence of absorbed exudate. They are antibacterial. Foam dressings with silver ions have strong absorption properties and ensure optimal moist environment in the wound. They are antimicrobial and prevent penetration of microorganisms from the outside [27]. The well controlled and long silver release process to the wound allows less frequent dressing changes, reducing the risk of the tissue damage, infection and patient's discomfort [24]. If the dressing is dry,

it should be changed after time recommended by the manufacturer, if it leaks with exudate from the wound, it should be removed earlier, then re-evaluation of the depth of the wound and the local condition should occur [27]. Although extensive clinical experience proves the safety and therapeutic efficacy of silver-containing dressings, however, this has not been proven in randomized prospective clinical trials. Most of the publication applies only to the clinical case reports or case series [28, 29]. In a recent study, the advantages and disadvantages of various dressings used for the temporary dressing of the burn wound, including nanocrystalline silver dressings, were analyzed [30]. It showed a high clinical efficacy of all tested dressings. However, it should be remembered that nanocrystalline silver is toxic to human cells [28]. According to the guidelines of the Polish Society for Wound Management on local and general treatment of infected wounds, it is important to use medicinal products that should be pharmaceutically compatible. Iodine based antiseptics cannot be used with silver-containing dressings. One should not combine antiseptics, containing octenidine and iodine since a chemical reaction of pure iodine release can be observed. We can use octenidine-based antiseptics and silver-based dressings to treat wounds at risk of infection and infected ones [5]. The recommendations of the Group of Experts representing the Polish Society for Wound Management allow to focus diagnostic and therapeutic procedures in a particular clinical situation and are important not only in the selection of the appropriate antimicrobial agent. but also throughout the decision-making process in the diagnosis and treatment of wound infections. The recommendations focus on the diagnosis of the microbiological condition of the wound, the route of entry of microorganisms into the wound, the clinical stages of wound infection development, the principles of local treatment of infected wounds and the risk of infection [5].

Antibiotic prophylaxis and antibiotic therapy

According to experts dealing with the treatment of burns place of antibiotics is not recommended because it promotes resistance of strains [14], whereas systemic antibiotic prophylaxis is debatable. It is believed that the routine prophylactic use of antibiotics before the results of the bacteriological test is not justified [31]. Some authors recommend perioperative prophylaxis. It is suggested that antibiotics can be administered immediately prior to the procedure of the dead tissue removal, during and one or two doses following the procedure, especially in patients with extensive burns [24]. Targeted antibiotic therapy is carried out with the bacteriological findings [14].

Practices of controlling infection

Nursing care is an important part of environmental control in burn treatment. Nurses and other medical staff should be assigned to the care of a particular patient or a group of patients as a team, and contacts with other patients should be limited to a minimum and strictly controlled.

Cross-contamination is additionally minimized within hospitals by treating patients in single rooms. Modern burn treatment centers provide the ability to perform all intensive care and treatment procedures, including patient operations and all aspects of care within the ward in which the patient is treated. Infection control programs developed in burn treatment departments require strict compliance with strict rules, including strict adherence to hand washing procedures and the use of personal protective equipment such as overalls, gloves and masks. Staff are required to wear disposable overalls and gloves during each visit to an isolated room where the patient is present [24, 32]. Particularly strict rules apply during a dressing change procedure. A strict aseptic technique should be used when handling open wounds and dressings. What is more, the frequency of dressing change should be adjusted to the clinical condition of the wound. It is essential to use sterile gloves and masks during the dressing procedure, and it is also advisable to minimize open wound exposure time [6].

When applying gel or cream preparations, it should be first applied on dressings prior to the application to the wound, in order to eliminate the possibility of contamination with the flora of the burn wound [24]. Studies assessing the impact of prophylaxis on nosocomial infections and treatment costs indicated that multidirectional prophylaxis against nosocomial infections provide beneficial results in terms of reduction of time and cost of treatment [32].

Recapitulation

The purpose of this study was to present the latest knowledge on the prevention, effective control and treatment of an infected burn wound essential for optimal nursing care. Providing a wide range of burn prevention prophylaxis methods requires a multidisciplinary approach, including close cooperation between the nurse and the doctor. The use of antimicrobial agents significantly reduces the microbial load on the wound and reduces the risk of infection, but it is used adjunctively with the early removal of dead tissues by surgical, mechanical or enzymatic methods. The use of procedures to reduce the risk of bacterial transfer between patients ensures patient safety and is important in reducing the risk of hospital infections. The patient care plan should be based on up-to-date medical knowledge and should be regularly updated.

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Address for correspondence:
Aleksandra Głowacka
Dąbrowskiego 79
60-959 Poznan, Poland
phone: (+48) 61 854 68 64
e-mail: aglowacka@ump.edu.pl
Department of Nursing Practice, Chair of Nursing, Faculty of Health Sciences, Poznan University of Medical Sciences