

Prevention of Chronic Wound Infection in Clinical Practice

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Abstract

The notion of prevention includes all procedures by which a disease-infection is being inhibited and its development and spreading is halted.

For an efficient implementation of preventive procedures, we must be familiar with the basic comorbidity of the patient and treatment, phases of physiological healing of the wound, risk factors which cause delayed healing, pathophysiological features of the chronic wound, a continuous development of infection with a particular emphasis on biofilm.

Prevention of chronic wound infection includes a range of active procedures by which the development of infection and its progression is halted. The key moment is the recognition of the patient with a chronic wound in phase of colonization and with a timely intervention the development of infection is prevented.

We live in a modern world characterized by an increasing proportion of the elderly among the overall population, increase of body weight, malnutrition, diseases of the circulatory system, neoplasms, major surgical interventions in which ischaemia is the predominant risk factor.

The best wound care is the prevention of the development of the chronic wound, followed by prevention of infection which is the complication of the basic endogenous disease. Prevention of the chronic wound infection represents a successful management of the chronic contaminated or colonized wound.

Chronic wound infection can be prevented by a quality and targeted medical care provided it assists the physiological healing with an optimal immune response on the part of the host. At the same time, the number of microbes in the wound is reduced and active measures are undertaken to destroy the biofilm. In addition, it is unavoidable to carry out general preventive measures which will prevent a recolonization of the bacteria, and thereby the reconstruction of the biofilm.

The aims of the prevention are to avert the development of infection as well as the spreading of a local into systemic infection and delay the onset of infection for as long as possible. The infection of the wound is defined by the quantity of microbial colony forming units (CFU) in gm/ml, overall virulence of the microbes with the domination of biofilm and the composition of the microbial community, all against the background of the immune response of the host, quantity of exudate and necrotic tissue.

Modern preventive procedures and methods are multimodal, because the infection is multi-factorial. The development of infection depends on the cumulative effect of risk factors in relation to the host's defensive system.

Bacteria are the leading causative agents, and the biofilm as the virulence factor determines the infection and its chronicity. All types of bacteria develop biofilm, and it is not an exclusive feature of dominant agents such as *Staphylococcus spp*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, anaerobes of the skin.

The approach to the prevention, care and treatment of the chronic wound must be holistic, whereby we perceive the patient as a whole, not only his wound.

Prevention or efficient management of the wound infection includes the optimization of the host's immune response through the treatment of the basic disease and control of successfulness of the treatment. The reduction of the number of microbes in the wound is achieved by the application of aseptic techniques, hygiene of the hands, moisture control and the control of exudate. The optimization of the wound bed is achieved by means of efficient cleaning procedures, application of antibiofilm-active antiseptics, supportive dressings and debridement. General preventive measures include also the education of the patient, treatment plan, psychosocial assistance and team work.

The prevention and treatment of chronic infected wounds is still an area prone to confusion, especially in the light of knowledge about the role of biofilm.

It is crucial to know that the application of individual preventive procedures will not prevent the infection of a chronic wound. Prevention of infection also implies a successful management of the contaminated or colonized wound.

Keywords

prevention, infection, chronic wound, strategies, biofilm.

Introduction

“Health is the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [1].

Under the notion of prevention, we imply all procedures with which a disease, in our case infection is being prevented and its development and spreading are disabled [1].

The word originates from the Latin word *preventio* which means to precede. In its broader sense the prevention of infection implies its suppression, recognition, treatment and patient care. So, the prevention of infection reflects the principles of best clinical practice. In order to achieve this, we use the procedures of observation, identification and risk assessment along with control and surveillance. All preventive procedures must be evidence-based and include representation, proof, causes, interventions and consequences [2].

The importance of the acute and chronic wound prevention of infection is also referred to the document issued by the World Health Organization in 2015, which also enumerates the essential principles of prevention [3].

In order to be able to carry out preventive procedures and measures, we must know the essential phases of the physiological healing of the wound, factors which hinder healing or cause a delay in the process, specific features of the chronic wound and a continuous development of infection. Prevention of the chronic wound infection contains a range of active measures with which the progression of the chronic wound and the development of local or systemic infection are disrupted [4]. Moreover it represents secondary prevention because it relates to the recognition of the patient in the phase of contamination or colonization of the wound, whereas a timely intervention halts the development of infection [5].

We apply preventive procedures only when we know what needs to be prevented and which process should be targeted by prevention [6].

Chronic Wound

Chronic wound is a wound whose process of healing is sluggish or which manifests time-wise an intermittent, delayed or completely obstructed healing.

The definition of the Wound Healing Society is that a chronic wound is one which lags behind of an orderly and timely process of regeneration, one that would result in an anatomic and functional integrity. From clinical observation we can say that the chronic wound is one in which the healing lasts longer than three weeks [7]. The absence of healing depends on numerous intrinsic and extrinsic factors of the patient and wound itself. Today, a chronic non-healing wound is a paradigm for biofilm, a dominant virulent bacterial factor in the absence of healing and infection, whereby an underlying pathology such as ischaemia should be excluded (6,8). Complicating risk factors which hinder the healing are numerous and are shown in Table 1 (9,10).

Systemic	Local – wound
<ul style="list-style-type: none"> • Insufficient perfusion (ischaemia) • Inflammatory components • Diet • Metabolic diseases • Immunosuppression • Habits (smoking, alcohol) • Age • Mental status • Immobility • Hormones • Genetics • Medication 	<ul style="list-style-type: none"> • Mechanical injury / pressure • Ischaemia / necrosis of tissue • Oedema / lymphatic oedema • Infection • The balance of moisture in the wound • Low oxygen tension in tissue • Molecular factors • Microcirculation • Foreign body presence • Topical substances

Table 1: Risk factors influencing the healing of the wound (11,12).

Chronic wounds mainly develop from acute ones, when the physiological course of healing in any given phase is disrupted: this may occur in the haemostatic, inflammatory, proliferative or remodeling phase [13]. Finally, the chronic wound lags behind in the inflammatory phase which is characterized by high levels of proinflammatory cytokines [14,15].

At the same time, in the micro-environment of the wound, high levels of protease are present, along with a low level of protease inhibitors, whose ratio is key for successful healing [16, 24]. The result of the disbalance is the breakdown of the tissue matrix, reduction of growth factors and a drop of mitogenic activity [17,25]. When we add to this the activity of microbes, predominantly bacteria and their proteinases, the breakdown of the wound is complete [18].

The activity of bacterial proteinases is multi-potent and is manifested in the activation of matrix metalloproteinases (MMPs), toxins, degradation of extracellular matrix (ECM) protein and immunoglobulin, inactivation of proteinase inhibitors and a disbalance in the activation and inactivation of cytokines and complement factors [26]. On the molecular level, the processes create an ideal foundation for the spreading of infection and a delay in healing [3,19].

Chronic wounds are a present-day global epidemic [17]. For this reason, the primary aim is to prevent the development of the chronic wound, its progression and complications with an emphasis on infection (3,20-23). The treatment strategy is based on the establishment of cellular balance and a return of the wound into the healing phenotype, targeting etiological factors [17].

Infection of the Chronic Wound

Infection of the chronic wound is an expected further complication, provided we accept the fact that the wound itself is a consequence of endogenous and exogenous pathophysiological processes along with the degeneration of the natural protective cover–skin [27, 37]. The consequence of infection is the absence of healing and an increase in the risk of loss of extremities or even of a lethal outcome. Between 2008 and 2016, significant advances were made in the scientific and clinical understanding of the chronic wound infection [27-37].

We live in a predominant world of microbes and human body itself contains around 10¹⁴ microbial units in its physiological flora. The physiological flora in man covers the skin and the mucosa, differing in its composition and concentration and plays an important role in the maintenance of health. When the balance between the microbes and macro-organisms is disrupted, conditions favourable for the development of infection arise [37, 38].

The etiologic agents of infection are predominantly bacteria, primarily gram-positive cocci, but in the chronic wound we also find gram-negative rods and anaerobes in varying combinations [42]. The proof of bacterial capability to excrete biofilm, along with the understanding of its influence and role in delayed healing, maintenance of chronicity, persistence of inflammation and development of infection, represent the greatest achievement of modern medicine related to the problem of chronic wound [6, 30-32].

Primary determinants of the pathophysiological process taking place in the wound are:

1. Quantity of microbes (bacteria) [33]
2. Type of bacteria which determines the type and quantity of virulence factors, with a predomination of biofilm [34-36, 87]
3. Ability of the host to defend itself from potential pathogens (immunocompetence) [6].

Definition of wound infection (6,42)

$$\begin{array}{r}
 \text{Number of microbes} \quad + \quad \text{virulence} \quad + \\
 \text{combination of bacteria} \\
 \text{CFU/gm/mL} \quad \quad \quad \text{biofilm} \\
 \text{aerobes / anaerobes} \\
 \\
 \text{Host immune response} \quad + \quad \text{quantity of necrotic tissue} \quad + \quad \text{exudate}
 \end{array}$$

Table 2 : A summarized definition of wound infection is shown

Chronic wound infection is a continuous process which develops in several stages and is defined by the relationship of microbes with the host.

A continuous process of wound infection goes by several developmental stages: contamination, colonization, local infection, spreading of infection and systemic infection [40,41,43,44] (Fig 1).

These stages are characterized by clinical symptoms and developmental stages of microbes and biofilm (6, 98).

Having insight into the individual stages of chronic wound infection, along with a recognition of primary and secondary clinical signs of infection pointing to the biofilm, it is possible to implement

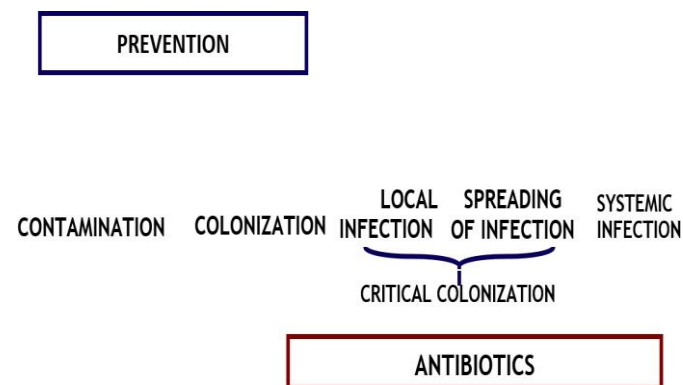


Fig. 1: Continuity of wound infection (40,41,43,44).

successful strategies for prevention, care and control [6, 27, 39].

For the understanding of individual stages of chronic wound infection, we apply the definitions accepted in 2016, which describe the relationship between the host, microbes and virulence factors (6). A brief description of the stages is the following:

- ◆ Contamination is a stage in which non-proliferative microbes are present in the wound and the host's immune response cannot be proven.

Contaminants of the wound are members of exogenous and endogenous physiological flora including that from the environment, which appear as a consequence of poor hygiene, especially of hands and exposure to the environment. Essential preventive measures are: hygienic washing of hands, aseptic procedures, washing, rinsing, dressing, other procedures indicated by the appearance of the wound bed, the presence of exudate, risk factors and care of the wound's environment [6, 45, 46].

- ◆ Colonization is a stage in which the microbes are successfully established and multiply, along with the forming of biofilm. Reason: abundance of nutritive products (necrosis, exudate).

All chronic wounds are colonized, but not necessarily infected. Colonization is a consequence of poor hand hygiene, absence of aseptic procedures and an incorrect application of dressings and antiseptics. Essential preventive measures: hand hygiene, aseptic procedures, firm cleaning and rinsing of the wound, sharp or filamentous debridement, dressing, taking care of the exudate.

The definition of critical colonization, due to lack of clarity and inherent vagueness, was broken down into local infection and the spreading of infection [40,43,48].

- ◆ Local infection is a stage of the chronic wound in which the bacteria from the surface penetrated into the tissue and caused an immune response in the host. Infection is localized on one site, structure or system. Primary signs of infection are seen. Preventive measures, although late, are necessary because a further spreading of infection must be halted. In addition, targeted treatment, debridement and oral antibiotics are indicated [6,28].

- ◆ The spreading of infection defines the invasion of microbes into the surrounding tissue, all the way to the edges of the wound. Proliferation is characterized by the immune response of the host and primary and secondary signs of infection. Preventive measures are belated or failed. In spite of that, it is necessary to prevent the spreading and development of systemic infection. Targeted oral or intravenous antibiotics are indicated, depending on the severity of infection, along with repeated rinsing, debridement, dressing and other measures (43).

- ◆ In systemic infection, microbes are spreading beyond the edges of the wound through vascular and lymphatic circulation. Systemic inflammatory response is present. The consequence is the development of sepsis and organ dysfunction, even death.

Preventive measures are belated or failed and the outcome of targeted treatment with antibiotics and debridement had a dubious action and outcome [43].

Continuity of development of chronic wound infection is caused by biofilm [6,19,30,49].

The recognition of biofilm as the dominant bacterial virulence factor and its developmental phases is essential for the strategies of prevention and treatment [43,50,51]. The goal of preventive and at the same time therapeutic procedures is the prevention of adherence of plankton bacteria to the destroyed surfaces of the wound-tissue, the destruction of the quorum sensing factor, prevention of phenotype changes in the bacteria, destruction of sessile bacteria and the disrupting of the renewal of biofilm with bacteria from the environment.

Stages in the development of biofilm are the following:

- ◆ Plankton reversible phase of attachment.
Prevention: destruction or killing of the microbes [52,53]
- ◆ Irreversible attachment
Enabled by the secretion of extracellular polymer substance (EPS) secreted by adhered microbes, which envelops the bacterial colonies. Prevention: destruction of EPS, quorum sensing molecules and adhesins [54,55].
- ◆ Cellular proliferation
After a successful irreversible attachment, the bacteria build a complex structure of a biofilm by means of the quorum sensing molecules. They organize the transport of nutrients, elimination of byproducts and control the density of bacterial population inside the biofilm along with the formation of microcolonies.
Prevention: destruction of quorum sensing molecules, specific receptors on the surfaces and adhesion [56].
- ◆ Maturation
Biofilm is structured in a complex formation. The defence of the host recognizes the biofilm. The result of the reaction is the presence of excessive number of neutrophils, pro-inflammatory cytokines and extensive secretion of host's proteases. This, in turn, causes the destruction of tissue, significantly increased permeability of the capillaries and the development of oedema [53].
Prevention: combination of strategies along with the application of efficient biocides (antiseptics) and reduction of oedema [31].
- ◆ Dispersion
A mature biofilm can be actively or passively dispersed / spread into the surrounding tissue. The main cause of spreading is an abundance of nutritive products on the wound's surface.
Prevention: mechanical strong cleaning of the wound, sharp debridement, application of negative wound pressure therapy (NWPT), antibiofilm-active biocides and dressings, combination of procedures and methods indicated by the state of the wound bed, wound environment and the host [6,47,53,54,57].

It is significant that all types of bacteria and fungi in the wound are capable of forming a biofilm, not only the predominant agents of infection such as *Staphylococcus spp*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, skin anaerobes [42].

Goals Of Prevention

The comprehensive care of the patient with a chronic wound must be such as to include all preventive procedures which will:

- Prevent the chronic wound infection
- Prevent the development of a local infection into a systemic one
- Postpone the development of infection for as long as possible [39,61].

The procedures of prevention of infection have the following goals:

- Removal of necrotic tissue, abundant exudate and microbes from the wound
- Reduce the quantity of microbes in the wound
- Remove and/or destroy the biofilm
- Interrupt the synergy of microbial communities in the wound
- Disable the recolonization of microbes and renewed formation of biofilm
- Interrupt the continuity of the development of infection by raising the immunocompetence of the host [57,60,61].

Understanding the risk factors, development of the wound, life cycle of microbes and features of the biofilm are a precondition for the application and carrying out of efficient preventive measures which will prevent the development of a chronic wound infection [6,11,21,60,98].

The factors related to the frequency of chronic wound infection are the following:

- Characteristics of the host: comorbidity and risk factors, targeted treatment of comorbidity and supportive therapy, acting on the risk factors [58]
- Characteristics of the wound bed and the environment of the wound, phases of wound development, care of the wound's environment [54,58]
- Characteristics of the environment of the patient, general hygienic measures, predominantly hygiene of hands [57-59]

It is significant that the environmental factors in the patient are directly connected with medical care, depending on the knowledge and skill of medical personnel, as well as on the organization and financial capabilities to carry out the preventive and organizational strategies. [57-59].

The basic principles and goals in the prevention of wound infection have been accepted and applied for decades along with revisions and additions proceeding from scientific discoveries, clinical results and technological advancement.

Present-Day Strategies In The Prevention Of Chronic Wound Infection

The development of infection is multi-factorial and depends on the cumulative effects of risk factors related to the host's defence mechanisms, along with external factors which increase the risk of wound infection. Bacteria are the predominant agents of infection, and virulent factors such as the biofilm determine the infection and chronicity [6]. For this reason, a holistic approach to care and treatment is mandatory, because in such an approach we observe the patient as a whole, not only the wound (Greek *hólos* = full, complete, whole). In order to reach the set goal, the cooperation of a multidisciplinary team is necessary, along with a comprehensive knowledge of risk factors, chronic wound development, continuity of infection and a recognition of biofilm as the predominant virulent bacterial factor [6,53,54,58,62]. Measures applied in prevention of infection are multimodal, meaning that no single measure is powerful enough to prevent such a complicated process [6,39,57].

We distinguish several types of measures which must be combined and repeated. These are:

- ◆ General measures – goal: control and elimination of causes
 - anamnesis
 - degree and type of comorbidity (diagnosis)

- targeted treatment of the basic disease including control and treatment
- determination of risk factors and their elimination (e.g. load, pressure)
- hand hygiene
- aseptic procedures.
- ◆ Special or local measures – directed at the wound; therapeutic window [54]
 - strong washing and cleaning
 - irrigation
 - antiseptics which act upon the biofilm
 - sharp debridement
 - dressings which act upon the biofilm, respective of the wound bed and exudate
 - elimination of dead spaces, pain and odor
 - care about the surrounding skin
 - moisture control
- ◆ Supportive measures – reduction of existing and potential risk factors
 - resolving of ischaemia
 - optimal nutrition
 - compensation of liquid
 - reduction of the oedema
 - systemic support in resolving other risk factors [6,27,54,78].

Prevention of infection or a crucial preventive measure in averting local infection of the chronic wound is a recognition of delayed healing and progression of wound disintegration, because secondary clinical signs are not clearly visible [40,41].

Prevention of the spread of infection includes general, special and supportive measures along with an intensive repeated debridement and a targeted use of antibiotics. The applied antiseptics and dressings must possess anti-biofilm characteristics [39].

Integral skin, in anatomical and physiological sense, is the best prevention against the development of acute and chronic wound and infection. The skin possesses numerous functions, and some of them are the consequence of the presence and activity of physiological flora which colonizes the skin with numerous bacterial species. Molecular researches into the physiological flora have resulted in the discovery of biofilm and its role in the integral community and architecture of the skin [53].

Health Roadmap for Medical Research investigated the role of the biofilm of physiological microflora in the processes which characterize the physiological state of healthy skin, but also in the processes of absence of healing of wounds, chronicity and development of infection. In these researches the dominant agents of chronic wound infection were discovered, as well as the dominant virulence factor – the biofilm [63,64].

For the above reason, the care of integral skin is an essential factor in the prevention of wound development. This includes the risk factors, along with specific application of products, aids and materials [67-69]. A general prevention is the hygiene of the skin along with moisture control and the application of medical lotions and creams [65].

The goal of preventive procedures is to avert the development of chronic wound infection, and thus to disable a continuous development of infection [6, 40]. Here it is of essence to prevent or reduce the influence of bacteria from the environment, such as hands, non-sterile objects and environment itself, as well as the physiological flora of the skin and mucosa in the patient [70].

The key procedures are hand hygiene, cleaning and rinsing of the wound, application of antiseptics and dressings with anti-biofilm activity and debridement [6,39,57].

- ◆ Hand hygiene is the single most important procedure in preventing the transmission of microbes and contamination of the wound. This procedure is mandatory: before contact with the patient or wound and aseptic and clean procedures; after contact with the patient and the wound and after exposure to secretions and excretions [71]. The carrying of gloves is not a substitute for hand hygiene [71]. Clean hands – clean wound [66].

- ◆ Cleaning of the wound is significant because in such a way the free, loose tissue is being removed, along with remains of the dressing, and excoriation of exudate into the surrounding tissue is prevented. Clean procedures are mechanical cleaning and irrigation [57].

Mechanical cleaning, irrigation and debridement open the “therapeutic window” for an efficient activity of antiseptics and dressings (Table 3).

Table 3. Therapeutic window (54)

- ◆ Mechanical strong cleaning with no-touch techniques, using
 - sterile physiological solution
 - sterile water
 - sterile irrigation solutions
 - antiseptics
 - (tap water only under certain conditions, as it is not a controlled medical procedure)
- ◆ Debridement and sterile techniques
 - conservative, sharp
 - surgical / hydro-surgical
- ◆ Monofilament according to recommendation by the *National Institute for Health and Care Excellence* (NICE) 2015. (90)
- ◆ Techniques of cleaning used in preventive and therapeutic procedures, in the preparation or treatment of the wound depend on the status both of the patient and the wound (39). They are all listed within the group of aseptic techniques, so we distinguish:
 - sterile techniques
 - no-touch techniques
 - clean techniques (70,72,92,94)
- ◆ The aim of the application of solutions in showering – rinsing – irrigation of the chronic wound is to efficiently remove the debris, necrotic tissue, remains of dressings and bacteria without damaging healthy tissue below and around the wound. This also represents the basic procedure in the prevention of local infection (57,73,74) (Table 4).

Solution	Type	Action on biofilm	Note
sterile physiological 0,9% sodium chloride	isotonic	none	rinsing
sterile water	hypotonic	none	rinsing
Tap water*	variable	none	non-sterile

Table 4: Solutions for the rinsing and irrigation of the wound (39) .

Decision to apply tap water is taken on the basis of water quality, immune competence of the patient, characteristics of the wound (72,92)

All solutions before use must be warmed up to bodily temperature [73].

Antiseptics are surface-active substances of varied chemical composition. They are classified as drugs and are effective bactericides. They differ in the spectrum of activity on the microbe cell, efficiency, cytotoxicity, teratogenicity, induction of resistance and activity on the biofilm [77]. They are applied in the form of solutions, creams or are incorporated into dressings. They are used both in preventive and therapeutic settings.

The goals of preventive application of antiseptics on wounds are the following:

- To prevent undesirable colonization of microbes from the environment (skin) into uncolonized areas of the body – tissue, wound

- To prevent the spreading of pathogenic microbes, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) or multiple-resistant enzymes strains such as Extended spectrum beta-lactamases (ESBL) strains from the families *Enterobacteriaceae*, *Acinetobacter anitratus*, *Pseudomonas aeruginosa* and other into the areas colonized by physiological flora, which occurs in the second stage of the chronic wound.
- To prevent the development of local infection from the phase of colonization of chronic wound.
- Their application is especially significant in immunocompromised and immunologically incompetent hosts with chronic wounds [31,77].

Targeted application of antiseptics in therapeutic purposes is to be a support to targeted treatment in cases such as:

- Clinically proven locally defined chronic wound infection up to the phase of granulation
- Clinically and laboratory proven infection up to the moment of granulation
- Colonization of immunologically incompetent host [31,77].

The reason for the use of antiseptics in preventive and therapeutic purposes is because there is no single therapeutic or preventive procedure which is effective on its own, but they must be combined. We ought to stress that there is no antiseptic which is efficient for all phases of development and forms of bacteria in the biofilm, which today is the paradigm for a chronic and chronic infected wound. For this reason, the application of a combined approach and use of different anti-biofilm active compounds is imperative [6,31,77] (Table 5).

ANTISEPTIC	BIOFILM
Octenidine dihydrochloride (79)	Destruction of EPS, alteration of phospholipids and change of the cell wall, during 3-72 hours
Polyhexanides (PHMB) (43)	Penetration through the biofilm matrix; kills sessile bacteria
Povidone iodine (31)	Action on the glycocalyx, matrix; penetration to the lower layers of a biofilm
Cadexomer iodine (31)	Destruction of mature (maturation) biofilm
Nanocrystal silver (80)	Disruption of biofilm matrix, lower layers of a biofilm and sessile bacteria
Manuka honey (31)	Penetration through the biofilm matrix; kills sessile bacteria
Ion silver + ethylenediamine tetraacetic acid (EDTA) + benzethonium chloride (BEC) (80,81)	Synergy of anti-biofilm and antimicrobial action, Prevention of renewed formation of biofilm
* Surfactants (82) (*application after and between debridements, during 5 days)	Prevention of the creation of biofilm Eradication of mature biofilm Prevention of renewed formation of biofilm * application after and between debridements, during 5 days

Table 5 : Action of antiseptics on biofilm structures (31,43,79-82).

- ◆ Debridement, conservative, sharp is both an aseptic preventive and therapeutic procedure by which adhering necrotic tissue from the wound along with bacteria and biofilm is being removed [39,57,76]. With a reduction of the quantity of necrotic tissue and microbes in the wound, active substances can act as bactericides and anti-biofilm agents [54,89]. Cleaning of the wound is not always indicated for all types of wounds; the need and goal should be defined [75].

It is one of a procedures range which enables healing by reducing the quantity of microbes in the wound, controls and prevents wound infection, especially of the chronic wound, visualizes the wound bed and walls, and on the molecular level destroys the process of wound chronicity by lowering the levels of protease, cytokines as well as biofilm, and turns the wound from the chronic into acute one [88].

With regard to the era of biofilm it is good to orient oneself how much a certain type of debridement is successful as an anti-biofilm procedure (Table 6).

Type	Method	Efficacy on biofilm
Conservative - sharp	No-touch	Removes and destroys a biofilm on the wound surface
Surgical	Sterile	Destroys a biofilm on the surface and deeper layers of the wound
Mechanical	Non-selective, depends on the operator <ul style="list-style-type: none"> • therapeutic irrigation • monofilament debridement • low frequency ultrasound • hydro-surgical 	Certain levels of destruction and removal of biofilm, as well as the possibility of biofilm dispersion
Autolytic	Selective, dressings with antiseptics	Variable action, depending on the product and phase of a biofilm
Enzymatic / chemical surfactants	Exogenous enzymes and chemical compounds <ul style="list-style-type: none"> • alginogel • enzymatic debridement • wound cleaning agents with varied concentration of enzymes 	Certain levels of biofilm destruction
Bio-surgical	Larvae	Destroys and removes a biofilm and bacteria

Table 6: Types of debridement and action on a biofilm (6,27,83-86,91).

Debridement is a targeted procedure which plays a significant role in the prevention of the spreading of infection in the chronic wound. Efficacy depends on the timing, repetition of the procedure and change in the type of debridement. The latter depends on the state of the wound bed, walls and edges. The state of the wound is never static, it changes dynamically and should be carefully monitored and documented [78].

All types of debridement are efficient when applied immediately or on time, which is significant also in the light of its action on the biofilm [66,69].

Surface management of a wound is actually a manipulation with the aim of eliciting from the wound a positive response to the physiological process of healing. This type of care must be comprehensive and holistic in order to optimize the patient's capability of healing through creating a physiological environment for the wound [6,39,57].

Discussion

Prevention, as well as treatment of infected chronic wounds are still subject to a certain confusion, because the terminology used to describe the bacterial environment on the wound's surface is still not clearly defined. For this reason, even the term "infection" should be redefined in the light of new knowledge about the presence and prevalence of the biofilm phenotype. The preventive procedures themselves must be assessed in accordance with the above [18].

Different definitions and descriptions of the techniques and procedures in the application of dressing in the context of wound care often also lead to confusion. The terminology used varies and often depends on individual interpretation. Therefore, it is justifiable to ask the question about the meaning of clean, versus sterile techniques in wound care [92]. This is especially important in the application of dressing [93].

There are no definitive data which would prove that sterile techniques are superior to clean ones in the care of chronic wounds, because the data are still insufficient to differentiate the incidence of infection [92]. Dominant disputes relate to the infected chronic wound and decubitus where the issue is being raised on the recolonization of bacteria and renewed formation of biofilm (95). In addition, a dispute is going on about the use of tap water by contrast to sterile physiological solution, in the context of frequency of infection. For the moment, a difference between the two **means** in the application on chronic wounds has not been proven (92).

Discussion is going on also about the use of sterile and non-sterile gloves. The factors which determine the choice between the two are: type of wound, exposed bone or tendon, immunosuppression, and non-specific ones are: knowledge, education, type of dressing, drainage (96).

The use of clean techniques in wound care saves time, whereas a higher incidence of infection in comparison to sterile techniques has not been proven (92,96).

We also find a certain controversy in the definition of the chronic wound infection with regard to clinical symptoms and microbiological findings concerning the biofilm (27).

The quantity of microbes expressed as CFU in g of tissue or the quantity of exudate of $\geq 10^5$ CFU/g/mL is nowadays taken to be questionable in the definition of chronic wound infection. The question also arises in relation to biofilm as well as the agents of infection *Streptococcus pyogenes*, *Clostridium spp* (42).

As regards the biofilm, classical microbiological diagnostic procedures are inefficient. The infection is present and causative agents are trapped within the biofilm structure and escape microscopic proof and cultivation. The result of a classical microbiological examination: preparation stained according to Gram without visible microbes, culture is sterile and targeted antimicrobial therapy inefficient (27). Today, the presence of biofilm is being proven by qualitative and quantitative methods, the speed and strength of adhesion along with the sensitivity to antibiotics and antiseptics, depending on the type of bacterium. In this process, various cultivation methods are used (TCP, TM, CRA), latex agglutination, bioluminescent and molecular methods (ESEM) (99,100,101).

Unfortunately, all of the above is still not available in daily clinical practice [6]. Therefore, the chronic wound infection should be defined as the presence of bacteria in any given quantity, provided the secondary clinical symptoms of infection are present, the breakdown of the wound progresses and healing is delayed [84,92,97].

Concluding, we wish to raise the question whether a mere removal of microbes is sufficient for healing and whether it is a proof of efficacy of the topic antimicrobial substance (dressing). The relation of the total quantity of microbes, inflammatory response and clinical outcome is perceived to be of essence [22].

There are as yet no clinical data that only the application of antiseptics will prevent the infection of a chronic wound, and a recurrence of infection [22,27]. The same is true for all other preventive procedures taken individually.

Conclusion

The basic process in the prevention of chronic wound infection is the standardization of educational programs for all medical personnel which takes care of the wound. When a general consensus is reached, minimal educational programs should be defined [67].

In the light of multiple resistance of bacteria to antibiotics, it is of essence to undertake all preventive measures in order to arrest the development of infection in the chronic wound, because in such a manner treatment is made possible without the use of antibiotics.

The prevention of chronic wound infection is multimodal, because the presenting factors are numerous, with a predominance of biofilm. The basic preventive measure is "clean hands – clean wound". Therefore, medical care must be comprehensive and holistic in order to optimize the patient's capability of healing and to create a physiological environment around an acute wound. The application of preventive procedures results in a successful care of an infected chronic wound or an efficient management of the same. The key to prevention is the recognition of the colonization of a chronic wound and immediate multimodal preventive action.

We expect the future researches to focus predominantly on biofilm. This includes diagnostic tests for clinical use, understanding of the efficacy of debridement in the destruction of biofilm and its efficient removal with the breakdown of quorum sensing molecules.

"The prevention of infection lies in a successful care of contaminated or colonized chronic wound".

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