ANTISEPTICS FOR BURNS: A REVIEW OF THE EVIDENCE
ANTISEPTIQUES CHEZ LES BRÛLÉS: REVUE DES DONNÉES FACTUELLES

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SUMMARY. The burn patient is easily subject to colonization by microorganisms and infection, due to reduced defence capabilities and immune dysfunction. Moreover, burn units and intensive care units are characterized by a selection of resistant bacterial strains. If the burn patient is not adequately cared for in terms of infection prevention and control, sepsis is inevitable. Nowadays, several different antiseptics and antiseptic dressings are used in the topical treatment of burns, each with positive and negative effects. Topical antiseptics allow control of bacterial load, but they can also cause cytotoxicity and reduce healing rate. Choosing the most effective antiseptic is crucial to preventing infection from compromising wound healing. The present study aims to review the available literature in order to highlight evidence on the use of topical antiseptics in burns.

Keywords: antiseptics, burns, infection control, wound care, wound cleansing, wound healing

***RÉSUMÉ**. Les patients brûlés sont facilement colonisés et infectée, en raison de diminution des capacités de défense et de la fonction immunitaire. En outre, les services de réanimation et les CTB ont une prévalence élevée de bactéries multirésistantes. Si les mesures préventives et les soins sont mal conduits, la survenue d'infection est inéluctable. Actuellement, de nombreux antiseptiques et pansements antiseptiques sont disponibles, chacun avec ses avantages et inconvénients. Ils ont en effet la capacité de diminuer la charge bactérienne locale, mais sont susceptibles d'obérer la cicatrisation par cytotoxicité. Le choix de l'antiseptique peut donc être crucial. Cette revue de la littérature a pour but de dégager des données factuelles concernant l'usage des antiseptiques chez les brûlés.*

***Mots-clés**: antiseptiques, brûlure, prévention de l'infection, soins locaux, détersion, cicatrisation*

Introduction

Infection is the main cause of death in severe burn trauma: the destruction of the cutaneous barrier and concomitant immune depression are key factors in the onset of infectious complications.[1]

The burnt surface is sterile immediately after injury, but is soon colonized by microorganisms: endogenous bacteria that survive the insult, such as *Staphylococci* located in the sweat glands and in hair follicles, colonize the wound surface within the first 48 hours unless topical antimicrobial agents are used.[2] After approximately 5-7 days, burns are colonized by Gram-positive bacteria, Gram-negative and yeasts derived from the gastrointestinal and respiratory tract of the host and/or exogenous microorganisms from the external environment or from the operators ("cross-infection"). If therapeutic measures are inadequate or delayed, microbial invasion of tissues occurs, resulting in burn infection. The bacterial organisms that are most frequently responsible for burns infection are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*. Methicillin-resistant *S. aureus* (MRSA) is currently the most common pathogen in many burns, and *Enterococcus spp.,* resistant to vancomycin, although not as common, is highly virulent.[3-6]

Antiseptics are agents that destroy or inhibit the growth and development of microorganisms in living tissues. Unlike antibiotics, which selectively act on a specific target, antiseptics have multiple targets and a broader spectrum of activities, including bacteria, fungi, viruses, protozoa, and even prions.

The usefulness of antiseptics on intact skin is well established and widely accepted. However, the use of antiseptics as prophylactic anti-infectious agents for open wounds, such as lacerations, abrasions, burns and chronic ulcers, has been an area of intense debate for several years.[7-8] The strongest argument against the use of antiseptics on the lesions is that antiseptics have been found, mainly *in vitro*, to be cytotoxic for the cells essential to the wound healing process, such as fibroblasts, keratinocytes and leukocytes.[9-10] However, cytotoxicity appears to be dependent on concentration. Another reason against the use of antiseptics on open wounds is that they are not as effective against bacteria *in vivo* as they are *in vitro*, due to the presence of exudate, serum and blood, which seems to diminish their activity. Nevertheless, several studies have shown that antiseptics can reduce bacterial count in wounds.[11]

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The ideal topical antimicrobial agent should have a wide spectrum of activity, with a long duration of action, low toxicity and the ability to penetrate the eschar without being absorbed by the body. Furthermore, it should not hinder epithelial regeneration, guaranteeing the maximum concentration of active principles on devitalized and necrotic lesions, helping to provide an environment conducive to healing.

In the field of burn care, it is possible to use antiseptics in different formulations. The British National Formulary (BNF) divides applications into two categories: lotions used for irrigation and/or wound cleaning with a short contact time; and prolonged contact-products such as creams, ointments and impregnated dressings.[12] The agents used primarily for irrigation/wound cleaning are generally made from povidone-iodine, chlorhexidine and peroxide agents. Longer-contact creams and ointments include fusidic acid, mupirocin, neomycin sulfate and iodine. Some of these are rarely used in clinical practice. Silver-based products such as silvery sulfadiazine and silver-impregnated dressings are increasingly used, as well as honey-based products. Aloe Vera is sometimes also used as an antiseptic, although a sterile source is currently not available.

The objectives of burn wound care are removal of non-vital tissue, prevention of infections, promotion of wound healing, and pain control. Once the wound bed is clean, the debate on the best topical agent or dressing begins. Unfortunately, there are relatively few significant studies regarding the topical treatment of burn wounds. Therefore, we decided to review the most recent evidence from the literature on the current use, action and validity of antiseptics in the treatment of burns.

Materials and methods

A review of the literature on studies concerning the use of antiseptics in the field of burns was carried out. Medline (PubMed) and Cochrane Database of Systematic Reviews were consulted and a free search was made with Google Scholar in May and June 2018. The main international guidelines on wound care for burn injuries were also examined. Documents were considered if published from January 1st 2008 (10-year retrospective research).

The following key words were entered for bibliographical research:

- Antiseptic-burn.

The following search strings were compiled:

- "Antiseptic in Burns";
- "Anti-Infective Agents, Local"[Mesh] AND "Burns"[Mesh].

The studies and documents included had the following characteristics:

- Meta-analyses, systematic revisions, randomized clinical trials;
- Articles published in the last ten years;
- Articles available in full text;
- Articles concerning adult human subjects with uninfected or infected burns.

Studies and documents were excluded if:

- Not available in full text;
- Conducted more than ten years ago;
- Conducted on animals or *in vitro*;
- Concerned paediatric subjects (age <18 years) or other types of injury.

Results

Applying the search filters to the PubMed survey, the string "Antiseptic in Burns" reported 115 results; the string "Anti-Infective Agents, Local"[Mesh] AND "Burns"[Mesh] reported 54 results, many of which overlapped with the previous ones. Twenty-three articles complying with the criteria were included.

Some studies compare the use of different antiseptics (topical disinfectants, antiseptic dressings) in burns. Other studies compare antiseptic formulations with traditional or advanced dressings. Most studies used Silver Sulfadiazine (SSD) as a control for comparison with other topical treatments.

It has been demonstrated from individual studies and with a low level of evidence that the use of antiseptics based on sodium hypochlorite (e.g. Amukine Med ® solution 0.05%) could reduce the average time of healing when compared with SSD.[13]

Acetic acid (solution to 0.25%) is useful in decreasing colonization by *Pseudomonas spp.* in infected burn wounds, but it is generally acknowledged that it should not be left on the lesion for a prolonged period of time as it tends to cause excessive dryness.[14]

The efficacy of chlorhexidine is proportional to its concentration: at 0.5% the effectiveness is similar to SSD, while at a concentration of 2% it has a higher efficacy.[15] However, chlorhexidine can also be toxic to epithelial cells and delay the regeneration and healing of tissues.[16]

Topical iodine-based antimicrobials are active against a wide variety of bacteria, fungi, protozoa and viruses. Povidone-iodine has excellent healing properties when applied to burns or other wounds, and has a protective function for the growth of healing tissues.[13,17] Cadexomer iodine is a slow-release antimicrobial agent that can absorb excess wound exudates while offering a sustained level of iodine in the wound bed; it has shown efficacy *in vivo* against *S. aureus* and MRSA.[15] The use of povidone-iodine reduces the average time of healing when compared to chlorhexidine (low level of evidence). It has been shown with a moderate level of evidence that there is no difference in rate of infection between iodine-based treatments and non-antibacterial treatments such as soothing ointments.[13] A systematic revision was carried out in 2010 in order to evaluate the effects of povidone-iodine on various types of lesions, including burns. The main outcome parameters were wound healing, bacterial count, and adverse effects. Iodine did not entail a reduction or extension of wound healing time compared with other wound medications or antiseptics. Adverse effects, including derailment of thyroid function, did not occur any more frequently with iodine. Based on the evidence available from clinical trials, iodine was regarded as an effective antiseptic agent, and no impairment in wound healing was reported.[18]

Choice of dressing should be based primarily on its effects on healing, but it is also necessary to consider ease of application and removal, costs, and comfort of the patient.[19]

Silver-based dressings have a long history and remain a mainstay of topical burns treatment. Silver ions interrupt DNA replication and the electron transport chain, resulting in bactericidal activity against a wide spectrum of microorganisms including gram-positive and gram-negative bacteria, fungi and some viruses. The SSD remains the best-known and most widely used silver antimicrobial agent in burns. It is often referred to as "gold standard" in the treatment of partial thick-

ness burns due to its excellent antibacterial properties and wide availability, especially in developed countries.[20] A recent poll shows that most burns experts continue to use SSD.[14] Nevertheless, in recent years, several studies have shown that this gold standard of treatment also involves a number of substantial disadvantages.

There is a shortage of high quality papers concerning the effects of different dressings on the healing of superficial and partial thickness burns. It is impossible to draw firm and safe conclusions on the efficacy of specific dressings, however SSD has consistently been associated with poorer healing outcomes than biosynthetic dressings, silicon and silver coated, while burns treated with hydrogels have shown better healing results compared to standard care.[19] A meta-analysis involving 52 trials conducted in 2016 compares the use of SSD with thirty different types of medications in burns (viscose, solid and biological, silver and without silver). The study concluded that the use of SSD in the treatment of burns can no longer be considered the gold standard of topical therapy. The results of this systematic review clearly showed that faster healing is achieved with the newly conceived burns dressings. In addition, these new dressings tend to be more comfortable for patients and easier to use for caregivers. No medication, however, was able to show a clear advantage over SSD regarding the incidence of infection.[21]

Another problem associated with SSD remains bacterial resistance to the sulfonamide antibiotic component. Species of *Pseudomonas* have been reported to be resistant. A special patent was issued to address these species, consisting of a combination of SSDs with piperacillin.[15]

The efficacy of SSD with added cerium nitrate is debated. It seems that this combination reduces mortality and morbidity in severe burns. However, it has been seen that cerium nitrate has minimal antimicrobial action and benefits from its direct action on the burn eschar.[22] Burnt skin produces a lipid protein complex that causes immunosuppression in the burn patient, leading to increased susceptibility to infections (and consequent morbidity and mortality). Cerium nitrate binds and thus denatures this lipid protein complex, preventing immunosuppression.

Silver nitrate is the most commonly used silver salt, has antibacterial action at concentrations of 0.5% and has a significant toxic effect at concentrations >1%. Its use remains controversial in burns, as nitrate is toxic to tissues and reduces wound healing, damaging re-epithelialization and reducing the benefits of silver.[15]

All these formulations represent old silver-based solutions that need an application on gauze to act on the wound. Silver-based dressings are newer products incorporating silver to the dressing itself.

Over the last few decades, there has been an increase in nanocrystalline silver-based dressings, which possess better antimicrobial activity (even against MRSA), since they provide a more rapid and prolonged release of ions of silver. Nanocrystalline silver can be incorporated into a network of high-density polyethylene (Acticoat™), hydrofiber (Aquacel® AG), or soft silicone foam (Mepilex® AG). Several studies have shown that these formulations are equally effective in preventing infections compared to previous formulations (such as silver sulfadiazine) and allow faster re-epithelialization. Moreover, a longer interval between dressing changes leads to an increase in patient comfort and decreases the total costs.[23]

In a prospective, randomized controlled study conducted with 100 patients, the effectiveness of Acticoat™ and Aquacel® Ag dressings in healing partial thickness-burns was compared, and the wounds were assessed by laser Doppler between 48 and 72 hours after the burn. Healing time and infection control were comparable, but Aquacel® Ag dressing significantly increased comfort: it was associated with a greater ease of use and with lower overall costs when compared to Acticoat™.[24] Similar results were reported by studies comparing SSD and Aquacel® Ag,[25] and silver hydrofiber dressing versus 1% SSD for the treatment of partial thickness-burns.[26] Several studies suggested that Acticoat™ improves bacterial clearance compared to other silver-containing dressings, is easy to use, and has a prolonged release of silver, which allows for less frequent renewal of the dressing. All this, combined with its low toxicity levels, makes it a possibly ideal medication for burn wounds. However, the evidence regarding its use in burns is weak.[27]

A comparative study evaluating the efficacy of Mepilex® Ag and SSD showed no difference in healing time, with good tolerance for both products. The longer interval for changing Mepilex® Ag dressing promotes undisturbed healing of the lesions and makes it easier for patients to lead a normal life.[28]

A comparison between the efficacy of a nanocrystalline silver nylon dressing (Agicoat®) and SSD cream was carried out by randomizing 185 patients affected by partial thickness-burns (total body surface area burns between 10 and 40%). The efficacy of treatment, use of analgesics, number of dressing changes, wound infection rate and overall costs were assessed. The study showed that silver nylon dressing significantly reduces length of hospital stay, the use of analgesics, and wound infection rate.[29] The use of antiseptic dressings based on silver nanocrystals seems to reduce the average time for burn wounds to heal when compared to Vaseline gauze at 14 days post-burn; however, the level of evidence is low.[13] On a 28-day follow-up, silver-based antiseptic seemed to reduce the average time of healing compared to SSD.[13] With regard to the toxicity of nanocrystals, evidence was found *in vitro* but not confirmed *in vivo*.[15]

A prospective, randomized, controlled, single-centre study was designed to evaluate the clinical efficacy of a polyhexanide-containing bio-cellulose dressing when compared to SSD cream. The bio-cellulose dressing was demonstrated to be safe and effective, and showed no problems regarding resistance, typically associated with SSD.[30]

Urgotul SSD®, a hydro-colloidal dressing containing SSD, was compared with 1% SSD in the treatment of partial-thickness burn wounds, showing a significantly shorter healing time, more efficient pain control, a reduced follow-up, and lower overall costs. Also, infection rate was comparable between the two different dressings.[31]

A randomized controlled clinical trial comparing SSD with Polihexanide/betaine gel showed no significant differences in healing time, rate of infection/colonization, and cost of treatment.[32]

SSD has also been compared with Procutase® for the treatment of partial-thickness burns with total body surface area burns <10%. Procutase® is an ionic hydrogel consisting of natural hydrophilic polymers in an active ionic solution, together with a matrix metalloproteinase inhibitor. The result of this study showed a significant decrease in pain level and a significantly shorter wound healing time with Procutase®.[33]

Petroleum gel (Petrolatum/Vaseline) may be as effective as

SSD gauze with regard to time of re-epithelialization, incidence of infection, and allergic contact dermatitis. Petrolatum appears to be an effective, accessible and widely available alternative for the treatment of minor superficial burns of partial thickness in adults.

Honey most likely inhibits bacterial proliferation by means of its high osmolality and through a direct antimicrobial activity. Various studies show that burns treated with honey have shorter healing times than conventional dressings such as SSD.[13,23] Aziz et al.[34] confirmed through a meta-analysis that there is evidence that honey dressings promote burn healing more efficiently than SSD. The Cochrane Revision 2015 aimed to assess the effects of honey on the healing of acute and chronic wounds compared to various medications and topical treatments. The review concluded that there is strong evidence that honey dressing can promote healing in partial-thickness burns. It is unclear, however, if differences with conventional dressings exist with regard to adverse events and infection rates.[35] Studies reporting that burns treated with honey heal faster than those treated with SSD are low quality. However, the overall risk of adverse events seems to be lower with honey compared to SSD. A comparison between honey-based antiseptics and non-antibacterial treatments (including Vaseline gauze, silicone dressing, and sterile gauze)/non-conventional treatments (e.g. potato peel) showed a significant reduction in average time to healing with honey-based dressings.[13]

Compared to SSD, Centella Asiatica (Centidem®) was shown to improve local symptoms associated with burns, and was reported to allow faster re-epithelialization in the absence of infection.[36]

Aloe Vera did not show any advantage in healing burns when compared to SSD. Currently, there is no evidence supporting the use of topical Aloe Vera agents/dressings as a treatment for acute and chronic wounds.[37]

Table I shows the main antiseptics/antiseptic dressings taken into account in the review, and their main characteristics.

Table II shows evidence of action (wound healing time, infection rate, and interval of dressing change, pain and costs) for the different antiseptics/antiseptic dressings in the treatment of burns in relation to the standard of care, SSD.

Antiseptic	Characteristics	Reference(s)
Silver sulfadiazine	Poorer healing outcomes than other topical products and dressings, both with and without antiseptic activity. Need for frequent renewal of dressing. Pain associated with removal from the wound bed. Possibility of adverse reactions and resistance to the antibiotic sulfonamide component.	14, 19, 21
Silver sulfadiazine + cerium nitrate	It acts directly on the eschar, but holds minimal antibacterial activity.	15
Silver nitrate	Controversial use in burns. Cytotoxic when concentration is >1%.	15
Acetic acid	Useful to decrease colonization by *Pseudomonas spp.* in infected burn wounds.	14
Centella Asiatica	Improves local symptoms associated with burns. Seems to allow for a faster re-epithelialization in the absence of infection.	37
Aloe Vera	No evidence that it provides advantages in healing burns.	38

Table I - The main antiseptics taken into account by the review and their main characteristics.

Antiseptics/Antiseptic dressings	Healing time	Infection rate	Dressing change interval	Pain perceived	Costs of care	Reference(s)
Hydro-colloidal dressing containing SSD	<SSD	=SSD	>SSD	<SSD	>SSD	31
Povidone-iodine	<SSD <Chlorhexidine <Non-antimicrobial dressings					13, 18
Chlorhexidine		<SSD				15
Sodium hypochlorite	>SSD					13
Nanocrystalline silver	<SSD =vaseline gauze	=SSD	>SSD	<SSD	<SSD	13, 23, 25, 26, 28, 29
Polyhexanide-containing bio-cellulose	<SSD	=SSD	>SSD	<SSD	<SSD	30
Ionic hydrogel (natural hydrophilic polymers in an active ionic solution + matrix	<SSD			<SSD		33

Table II - Evidence of action (wound healing time, infection rate, and interval of dressing change, pain and costs) available for the different antiseptics/antiseptic dressings in the treatment of burns in relation to the standard of care, silver sulfadiazine (SSD).

Discussion

The search disclosed a fair number of articles addressing the use of antiseptics in burn wounds. Most studies compared the action of different antiseptics with SSD, a product combining the antibiotic action of sulfadiazine and the antiseptic action of silver. All reports agreed on the need for accurate debriding and cleansing of the wound surface before applying any material.

With regard to liquid antiseptic agents, the present review confirms that povidone-iodine is a widely used antiseptic for the treatment of burn wounds. Its spectrum of action is wide, and no effect on wound healing was shown. When in combination with liposomes, it promotes the creation of a moist environment and therefore facilitates re-epithelialization. Cadexomer iodine shows efficacy towards resistant bacteria especially. Overall, povidone-iodine reduces the average time of healing when compared to chlorhexidine, SSD and non-antiseptic dressings.[13,15,17,18]

Chlorhexidine proved to be effective in relation to its concentration: when greater than 2%, its action is more effective than SSD. Sodium hypochlorite, however, seems to reduce the average time to healing when compared to SSD.[15,16]

Acetic acid is still regarded as a useful tool for decreasing colonization by *Pseudomonas spp.*[14]

Silver is undoubtedly the most important antiseptic agent for the topical treatment of burn wounds. Among silver-based products, SSD still appears to be the most widely used, despite being associated with poor healing outcomes. Other limitations reported are the need for frequent change of dressing, the pain associated with removal from the wound bed, chances of adverse reactions and resistance to sulphonamide.[14,15,19-21] In order to reduce the side effects associated with SSD, different combinations with active agents have been created; cerium nitrate, for example, exerts a direct effect on the eschar.[22]

Among classic silver-based dressings is silver nitrate, even if its use in burns remains controversial due to its cytotoxicity in concentrations that exceed 1%.[15]

In recent years, the use of nanocrystalline silver-based dressings incorporated in high-density polyethylene, hydrofiber, soft silicone foam, and nylon mesh has increased. These dressings show excellent antimicrobial activity, faster re-epithelialization, a longer interval between dressing changes, increased comfort for the patient, greater ease of use, and positive economic implications when compared to SSD, as well as comparable efficacy in terms of infection control. It also seems that crystalline silver dressings promote faster healing than Vaseline gauze. However, cytotoxicity is still debated.[13,15]

More products showing proven efficacy are bio-cellulose dressing containing polyhexanide and hydro-colloidal dressing containing SSD: in addition to a shorter healing time, these products were associated with more efficient pain control and cost reduction compared to SSD.[30]

Ionic hydrogel showed statistically lower pain and a shorter wound healing time than SSD. Instead, biguanide and oil gel were comparable to SSD in terms of recovery time, rate of infection and bacterial colonization, and costs of treatment.[33]

Recently, natural products such as honey, Centella Asiatica and Aloe Vera have experienced a rapid increase in use in the development of new products. However, evidence of their action is still limited. While it seems that honey and Centella Asiatica act as an excellent agent for healing superficial, uncomplicated wounds, there is still insufficient evidence for routine clinical use.[36,37]

All things considered, the literature provides no evidence on the use of one particular antiseptic compared to another. The individual studies showed great variability with regard to data collection methods and statistical analysis. The evidence provided was not always strong, and results were often conflicting between different reports. Also, studies often focused on different outcomes, variably taking into account healing time, incidence of infection, patient comfort, or ease of use. Moreover, the extent, degree, etiology and characteristics of burn injuries are not uniform, making clinical outcomes difficult to compare when different treatments are used. There are no studies specifying if patients affected by conditions known to directly or indirectly affect healing (immune compromised patients, diabetics, smokers, etc.) were excluded. Another limitation is the fact that treatment is strictly operator-dependent, and unfortunately is it impossible to standardize behaviours such as the amount of antiseptic used, the accuracy of cleansing, sterility during dressing changes, compliance with protocols, etc. among the different studies. No data are available on the risk of infection with antiseptics/antiseptic medications and topical antibiotics, and it is uncertain whether infection rate differs between burns treated with silver or natural products and non-antimicrobial treatment. Undoubtedly, antiseptic dressings carry advantages regarding comfort and ease of use, and control of pain at dressing change.

The limitations of the present study are that it took into consideration only studies published in the last ten years, available online in full-text, and involving adult human subjects affected by burn injuries only.

Conclusion

Nowadays, there are several topical antimicrobial agents that have been approved, tested or proposed for the topical treatment of burns. However, at the present moment it is still uncertain whether the different products used on burn wounds are associated with different healing rates. The present review aimed to provide an updated tool for healthcare professionals for a conscious choice and use of antiseptics in the proper management of burn wounds. The conclusions drawn from the studies from the literature taken into consideration here indicate that further efforts are needed in order to provide stronger evidence.

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