Topical Antimicrobials in Burn Care: Part I – Topical Antiseptics

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Abstract

Burn wounds disrupt the body's primary defense against invasion and colonization by microorganisms. Topical antimicrobials are one component in burn wound care. These agents suppress microbial growth to advantage skin cells and wound healing. Topical antimicrobials can be divided into two superclasses: antiseptics and antibiotics. Herein we review the four main classes of topical antiseptics (emulsifiers, acids, oxidizers, and heavy metals) as well as antiseptic-impregnated dressings in current clinical use and address the mechanisms as well as the advantages and disadvantages of each antiseptic for burn wound management.

Keywords

Topical Antimicrobial; Antiseptic; Silver; Dakin's; Hypochlorous Acid; Infection; Skin; wound healing; Burn; Plurogel; Skin graft; Honey; Acetic Acid; Chlorine; Iodine; Chlorhexidine; PHMB; Antimicrobial Dressing; Hydrogel

INTRODUCTION

Post-burn, a race for wound dominance exists between the human skin cells and microbes, both of which attempt to proliferate and dominate the wound bed. Along with surgical excision and grafting, nutrition, critical care, and, when needed, systemic antibiotics, topical antimicrobials are weapons in the armamentarium of burn care providers that help tilt the balance in favor of keratinocytes and, thus, wound closure. Topical application allows directly targeted therapy to the burn wounds, can physically remove microbes, allows the use

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of systemically toxic agents, as well as the achievement of drug concentrations far above minimal inhibitory concentrations (MIC). Retained eschar and burn shock can limit the penetration of systemic antimicrobials to burn wounds. Prophylactic use of topical agents can also prevent or abrogate the colonization of invasive pathogens in the wound^{1,2}.

Antimicrobial is a broad term encompassing agents with the potential to eradicate organisms or inhibit their growth. Broadly, these can be divided into two superclasses: antiseptics and antibiotics. Antiseptics are agents that are non-selectively toxic to all biological materials and were initially developed as cleaning agents, such as bleach³. In addition to their broad spectrum of activity, microorganisms uncommonly develop resistances to them, and they rarely cause allergic reactions despite being too toxic for systemic administration⁴. Additionally, these compounds can be modified in their formulations and use to increase their efficacy in killing microbes while reducing their tissue toxicities, making them act similar to topical antibiotics. In this manuscript we will focus on antiseptic agents, while in our companion manuscript, Part 2 – Topical Antibiotics, we will focus upon those agents.

The use of topical antiseptic treatment for wound care is not a recent development. Historical documents dating back to 2500 B.C. show ancient healers and physicians used honey, plants, copper salt, and cobwebs, among a myriad of other substances, to treat wounds⁵. During the 16th century, Ambroise Paré, a French surgeon, is documented using onion paste to treat burn wounds⁶.

The goal of topical antiseptic therapy is to prevent or clear microorganism colonization, and invasion, while promoting wound healing. Studies have shown that inadequate antimicrobial therapy for infections in critically ill patients is associated with poor morbidity and mortality outcomes⁷. Topical agents should be used to dress wounds when quantitative culture counts persist at $<10^2$ /g tissue. Colony counts greater than 10^2 /g tissue warrant culture-directed antimicrobial application. It is common practice to initiate empiric broad-spectrum antimicrobials and tailor the antimicrobial regimen once culture results become available.

According to the 2015 United States National Burn Repository, burn wound infections remain among the top four leading causes of burn morbidity and mortality^{8–10}. Though various studies have found little to no evidence to support the use of topical antimicrobial therapy to prevent infections of the burn wound bed¹¹, the use of topical antimicrobials for treating burn wounds has indeed significantly reduced burn mortality^{12,13}. Application of topical antiseptics and antibiotics is an important adjunct to the early excision and grafting that is the standard of care in treating burn victims. This review presents the four main classes of topical antiseptics and addresses the advantages and disadvantages of each for optimal burn wound management.

CLASSIFICATION

In addition to the myriad of compounds currently considered too toxic for clinical use, there are four major classes of topical antiseptics in clinical use: emulsifiers, oxidizers, acids, and heavy metals (Table 1). Multiple other classes are not in clinical use. These agents differ in their antimicrobial spectrums, penetration characteristics, and toxicities. The second

superclass of antimicrobials, consisting of topical antibiotics, will be discussed in the compendium's other manuscript, Part 2 – Topical Antibiotics.

Emulsifiers

These are a broad range of compounds that disrupt cell walls and cytoplasmic membranes by serving as emulsifiers: their hydrophobic moieties enter the lipid bilayer and their polar ionic regions serve to make water soluble channels and also to create micelles which make the hydrophobic lipid membranes water soluble. Thus, the cytoplasmic contents and ionic gradients requisite to ensure cellular viability leak, and the pathogens are lysed. (Table 2) Most of these compounds are cationic in nature, while some have substantial dipoles, exerting a similar hydrophilic effect as cationic antiseptic agents.

The most ubiquitous members of this class are soaps and detergents. Soaps are cleansing and emulsifying substances consisting of sodium or potassium salts made through the action of alkali on fats or fatty acids¹⁴. Bacteria exist as two distinct biological entities: single independent cells (planktonic) or organized aggregates (biofilm). Biofilms are extremely difficult to eradicate; they allow the bacteria to form resistances to host defenses and antimicrobials by creating privileged adhesive environments, which the host is unable to penetrate, and maintaining a large reserve of pathogens in a quiescent non-replicating state that are not susceptible to many antibiotics, which require replication to exert their toxicity¹⁵. This pathogen stable can be monomicrobial or polymicrobial. Current protocols recommend that burn wounds suspected to have biofilm yet absent of clinical signs of infection should be debrided, covered with antimicrobial dressings and antiseptic soaks, and assiduously washed¹⁶. Washing the wounds with soap cleanses the wound of overlying microorganisms and disrupts the biofilm layer, decreasing the pathogen burden in the wound and periwound regions. This basic measure can cause a 2-log (99%) reduction in colony counts per gram of viable tissue over 48 hours¹⁷. Soaps are rarely used as mono-therapy as they merely wash pathogens off the surface of the wound and lack the ability to kill organisms that have penetrated the wound bed. They do not target microbial colonization selectively, but rather decrease the overall microbial load and burden on the wound. Systemic toxicity is not clinically evident, given the lack of penetration to the tissues; however, they may cause hypersensitivity reactions. Soaps play an important role in the care of burn wounds and patients with extensive open and exposed areas, e.g., wounds after debridement of soft tissue infections or necrotizing fasciitis that require a combination of therapies for optimal results.

Recently, a hydrogel, PluroGel® (PluroGen™, Norristown, PA, USA), has entered clinical use and is a non-ionic detergent consisting of an unidentified surfactant¹⁸. The suggested mechanism for wound-healing qualities by micellation of the wound bio-burden, disruption of biofilms, and a chemical debridement of the wound bed in a detergent phase transfer mechanism are based upon Pluronic™ F-68, a surfactant it is unclear if it is in this product¹⁹. There are data supporting the antimicrobial properties of surfactant proteins A and D; however, these proteins are not present in this commercially available wound product²⁰. There are limited animal data that the surfactant poloxamer-188 improved rat mesenteric microcirculation, though, again, it is unclear if this compound is in the commercially

available preparation or if these data are generalizable to human cutaneous burns²¹. There are no data to support superiority of these compounds over conventional detergents and soaps to date. Further, they lack the millennia of data and clinical experience supporting the use of soap, and they cost dramatically more. Controlled studies against other soaps and detergents as well as surgical debridement are needed to demonstrate superiority before their use could be applied in burn patients. Of the hydrogel products currently in standard use, such as DuoDERM® (ConvaTec, Deeside, Flintshire, UK) or Hydrosorb® (HARTMANN, Heidenheim, Germany), they have been of limited utility for the treatment of burn wounds and prevention of infection.

Biguanides are another major cationic emulsifier with biocidal properties. These agents similarly permeate the cell walls and cytoplasmic inner membranes. Chlorhexidine is not just the most commonly used biguanide, it is one of the most commonly used antiseptics worldwide. In fact, it is on the list of essential medicines published by the World Health Organization (WHO)²². Chlorhexidine reduced both Gram-positive and Gram-negative contamination of porcine skin graft substitutes²³, and it is also active against fungi²⁴. However, higher concentrations are requisite against Gram-negative organisms and fungi than against Gram-positive. Additionally, mycobacteria are highly resistant. A recent Cochrane Review found some evidence that preparations of chlorhexidine gluconate to be associated with lower rates of surgical site infections than povidone-iodine²⁵. In addition to its broad-spectrum activity, the low irritation associated with chlorhexidine has ensured its enduring use in burn wound care. Though it has been most used as a dental antiseptic, a recent study showed a much lower rate of hospital-acquired infections when patients bathed in chlorhexidine gluconate rather than soap and water²⁶. While it is pH dependent, the pH of the wound bed has less effect on its activity than on other antimicrobials, most likely due to its low molecular weight²⁷. However, chlorhexidine does exhibit reduced activity when exposed to some organic compounds, like soaps or anionic substances²⁸.

Polyhexamethylene biguanide (PHMB), Vantocil™ (Arch UK Biocides Ltd.™, Castleford, UK), is the most commonly used polymeric biguanide. While most health care providers are unfamiliar with the name PHMB, it is the active antimicrobial agent in Kerlix™ Antimicrobial Dressing (AMD®) (Covidien™, Dublin, Republic of Ireland). It is also commonly used as a swimming pool and hot tub algicide, though chlorine may be the better disinfectant for swimming pools²⁹. Like other biguanides, PHMB has broad-spectrum activity³⁰, with effect against *Pseudomonas aeruginosa* though less against *Proteus vulgaris*³¹. Further, PHMB-based products have been shown to not just be less cytotoxic than other antiseptics, but to aid in wound closure in comparison to other antimicrobial agents³². Additionally, bacterial resistances to PHMB have yet to be reported³⁰.

Octenidine dihydrochloride (OCT; Octenisept®, schülke™, Norderstedt, Germany), a bispyridine derivative, has broad-spectrum antimicrobial efficacy against Gram-positive and Gram-negative bacteria as well as fungi³³. While this has mostly been used as an endodontic irrigant, it has recently found utility in the topical care of burn wounds³⁴. OCT compounds have demonstrated no impairment of wound healing and lower colonization of bacteria on wound beds³⁵. In animal trials, it was found to more effectively reduce bacterial counts in eschar than silver sulfadiazine³⁶, and it has been demonstrated to be effective against

bacteria at lower concentrations than chlorhexidine^{37,38}. In a small study, octenidine dihydrochloride was found to be more effective to treat *P. aeruginosa*-contaminated burn wounds than povidone iodine³⁹, and generally more active against the other bacterial strains most commonly isolated from burn wounds than most topical antimicrobials, including silver sulfadiazine, Betadine® (Purdue Products LP, Stamford, CT, USA), and Acticoat® (Smith & Nephew™, London, England, UK)⁴⁰. However, mild skin irritations and rare allergic reactions that include severe anaphylaxis have been reported^{41,42}. Its lower cytotoxic side-effect profile, broad-spectrum antimicrobial activity, and lower minimum inhibitory concentration make OCT a promising adjunct⁴³.

Quaternary ammonium compounds are cationic emulsifiers that have little clinical utility as topical antimicrobials in the setting of burn wound care due to their irritating natures^{44,45}. These are primarily used as preoperative disinfectants on unbroken skin, as surface disinfectants, or as cleaning agents, such as Lysol® (Reckitt Benckiser, Inc.™, Slough, England, UK). In fact, they are the most commonly used hard surface disinfectants in animal laboratories⁴⁶. However, as antimicrobial resistance patterns evolve, further investigation into their clinical use may be warranted.

Oxidizers

Oxidizers are the second broad class of antiseptics (Table 3). These agents work through a free radical mediator to breakdown biofilms, cell walls, cytoplasmic membranes, proteins, and DNA and can also oxidize intracellular metals such as iron. These compounds have broad-spectrum activity. However, due to their high reactivity and host toxicity, they have a narrow therapeutic index and care must be taken to limit host toxicity.

Peroxygens are a subclass of oxidizers. Hydrogen peroxide, H₂O₂, is the most commonly applied member of this class and is generally used as a 3% aqueous solution with broad activity against bacteria, yeasts, and viruses⁴⁷. Catalase provides a resistance mechanism to *Staphylococcus*⁴⁸. The utility of hydrogen peroxide is limited in burn care due to its extremely short half-life; however, it is commonly used to remove blood and clots from excision and graft sites to reduce the bio-burden available for bacterial colonization.

The subclass of oxidative halides consists mainly of four topical agents: sodium hypochlorite (Dakin's solution), hypochlorous acid, povidone-iodine (Betadine®), and cadexomer iodine (Iodosorb®, Smith & Nephew™, London, England, UK). Chemically, oxidative halides are compounds composed of a halogen, or salt-producing element, and a less electronegative element or radical, either part having been combined with oxygen.

During World War I, Noble laureate Alexis Carrel, with the help of English chemist Henry D. Dakin, used sodium hypochlorite to create an antiseptic for heavily-contaminated battle wounds obtained from trench warfare⁴⁹. The original Carrel-Dakin's solution diluted 5.25% sodium hypochlorite (NaOCl) found in household bleach with water to create a concentration of 0.5%^{3,50}. Sodium hypochlorite has been widely used due to its effectiveness in dissolving biofilms and its broad bactericidal coverage, which includes: *P. aeruginosa*, *S. aureus*, methicillin-resistant staphylococci (MRSA), enterococci, and other Gram-negative and Gram-positive organisms^{51,52}. However, studies have shown that the

0.5% NaOCl solution, more commonly known as full-strength Dakin's solution, or even half- or one-quarter strength Dakin's solution is toxic to tissues and inhibit epithelialization⁵³. As such, Heggors and coworkers studied the efficacy of a Dakin's solution at one-twentieth the strength of the original, full-strength Dakin's⁵⁴. Their study demonstrated that buffered 0.025% Dakin's solution, which was formulated to mimic normal human physiology, to be as effective a broad-spectrum antimicrobial as full-strength Dakin's but with less toxicity to fibroblasts and less impedance to wound healing. While searching for an agent with less tissue toxicity, a longer tissue half-life, and neutral pH, Drs. Carrel and Dakins developed another sodium-derived oxidative halide, oxychlorasene (Clorpactin®, United-Guardian, Inc., Hauppauge, NY). Available as a powder, this agent is intended for use as a solution by mixing it with water. Irrigation of wounds with this solution has been shown to be nontoxic to skin grafts⁵⁵. In resource-limited environments, Full-Strength Dakin's solution can be made by diluting 95 ml of regular unscented household bleach (sodium hypochlorite solution 5.25%) and ½ teaspoon of baking soda (sodium bicarbonate) into 1 liter of sterilized or purified water.⁵⁶ At Shriner's Hospital for Children - Galveston, one-twentieth buffered Dakin's solution is the main therapy for wound care in the presence of open, contaminated, or infected wounds, including abscess drainage, soft tissue infection debridement, and pressure ulcers. It can also be used in combination with vacuum assisted dressings, since new devices now allow for periodic infusion and irrigation of the wound through the vacuum assisted dressing⁵⁷.

In recent years, interest in chlorine-containing topicals has resurged with a proliferation of formulations containing hypochlorous acid (HOCl). While it was introduced to combat wound infections in 1831, it fell from favor following the widespread introduction of antibiotics after World War II. However, given the increasing resistances of many pathogens to antibiotics as well as the toxic side effects of various agents, HOCl has re-emerged as an adjunct in wound care⁵⁸. Produced naturally by neutrophils to fight pathogens, various studies have shown hypochlorous acid to have broad-spectrum activity against many fungal, bacterial, and viral human pathogens⁵⁹ with less detrimental effects on fibroblasts and wound healing as well as less pain on application than other antiseptics^{60,61}. Agents containing chlorine, such as Dakin's, exert their bactericidal activity primarily by forming HOCl⁶². Challenges faced in maintaining the stability of hypochlorous acid diminished its potential as a wound care agent^{61,63}. However, recent studies have established methods by which HOCl can be prepared and stored to ensure it remains within an effective pH range^{61,64}. Once stabilized, pH-neutral HOCl has remarkable efficacy against biofilms^{58,65,66}. At concentrations greater than 1%, topical application of HOCl can cause an irritant or allergic contact dermatitis⁵⁹. After World War II, hypochlorous acid continued in commercial production for the food preparation industry and was thus readily available for later study to re-enter clinical use. It has been formulated for topical antimicrobial use due to its extended tissue half-life and decreased tissue toxicity. Of caution, the current preparations of hypochlorous acid are only approved as mechanical wound irrigants due to tissue toxicity and any further dilutions of the current preparations ensure loss of all effectiveness⁶⁷. Additionally, one recent study indicated complete inactivity against *S. aureus* in a wound bed with a heavy bio-burden, indicating HOCl might be affected by the pH of the wound bed⁶⁷. While these novel formulations lack the centuries' experience and

data collection enjoyed by Dakin's solution, they provide a promising balance between efficacy and toxicity that may enhance wound care in this new millennium, proving what is past is prolog.

Another oxidative halide with topical antimicrobial utility is povidone-iodine (PVP-I), commonly known as Betadine®. This agent is a stable chemical complex consisting of polyvinylpyrrolidone (PVP) and 9–12% elemental iodine (I)²⁸. Iodine is less electronegative thus less reactive than chlorine but is similarly broad in its antimicrobial spectrum, enjoying over 150 years of clinical experience. Betadine® is available in two different preparations: liquid and ointment formulations. The principle advantage of this agent is its broad-spectrum antimicrobial coverage that extends beyond Gram-negative and Gram-positive bacteria to include fungi and yeast⁶⁸. However, this agent is cytotoxic to fibroblasts and keratinocytes, which may lead to delayed wound healing⁶⁹. Iodine toxicity (e.g., hypothyroidism), renal failure, acidosis, and dermatitis are among the complications reported after application to burn wounds and, therefore, it is not used routinely^{70–72}. The active component of this agent (iodine) is absorbed less through intact skin; as such, Betadine® is a common agent used to prep the skin for surgery^{68,73}. However, recent human studies suggest that PVP-I reduces bacterial load, decreasing infection rates, which ultimately benefits the healing process⁷⁴. A study published in 2002 showed that PVP-I significantly reduced the time of wound healing in a population of patients with chronic leg ulcers by 2–9 weeks when compared to chlorhexidine digluconate or silver sulfadiazine⁷⁵. However, it must be noted that what is effective clinically to treat chronic wounds does not always correspond to efficacy in burn wound management²⁵.

Cadexomer iodine (Iodosorb®) is another oxidative halide and is available as a paste dressing, an ointment, or a gel with 0.9% iodine. Cadexomer iodine is a chemically-modified starch that contains elemental iodine within its structure. This agent is used commonly for chronic venous leg ulcers⁷⁶. It has been shown to be most effective against methicillin-sensitive and -resistant *S. aureus*⁷⁷. The cadexomer component of this compound causes sloughing of the wound while providing broad-spectrum antimicrobial coverage through sustained release of iodine, thereby accelerating wound healing by increasing epidermal regeneration⁷⁸. Although rare, the main disadvantage of this agent is the potential for systemic absorption and toxicity of iodine, which has limited its use as a topical antimicrobial⁷⁹. In addition, Iodosorb® and similar products are relatively expensive compared to other agents in the oxidative halide category.

Bromine compounds are also available as topical antimicrobials, though their clinical use is uncommon. There are limited citations available describing its clinical use. However, its chemistry, lying between chlorine and iodine, portends promise for the future. The remaining halogen, fluoride, is too electronegative for use as a topical antimicrobial. It immediately chelates free serum calcium and can cause heart failure and death⁸⁰.

A bacteriotoxic foam dressing of gentian violet (crystal violet) and methylene blue dyes, commonly known as Hydrofera Blue® (Hollister Inc., Libertyville, IL, USA), was recently approved for use on chronic and burn wounds, though its use in burn care has thus far been limited. This adjunct is a less expensive alternative to the popular silver or other biocidal

dressings, though it lacks the experiential data that have made silver-impregnated dressings so enduring. Though the exact mechanism is unknown, it is theorized that these dyes exert their bacteriostatic and bacteriocidal activities by interfering with redox reactions and decoupling oxidative phosphorylation, distinct from other oxidizers⁸¹. At low concentrations, gentian violet is very effective against Gram-positive bacteria and fungi, with moderate action against Gram-negative bacteria^{82,83}. In addition to its antiseptic properties, methylene blue has demonstrable efficacious activity against Gram-negative bacteria⁸⁴. The dyes work synergistically to provide a broad spectrum of activity against Gram-negative and Gram-positive bacteria as well as fungi, but they have no documented effect on biofilms⁸⁵. These dyes are delivered bonded to either polyvinyl alcohol foam or polyurethane foam dressings, the latter of which simultaneously provides a moist environment to wound beds to promote wound healing⁸¹. Neither is typically used on burn wounds in our practice, though other practitioners have found them not only effective but facile to apply and change⁸¹. Unlike other antimicrobials, the active agents in this dressing exert themselves against only the pathogens and proteins found in a wound bed, not against all tissues and microbes found therein, extending the half-life of this product⁸¹. Their effective spectrum against resistant organisms, low cost, ease of use, and effective action at lower concentrations than other antimicrobials against many pathogens portend potential for the future.

Acids

Weak acids have been utilized for wound care throughout human history. In modern burn management, acetic acid, honey, and boric acid are the principle acidic antiseptics used in wound care (Table 4).

Acetic acid (AA), the active component of vinegar, has been used as a topical antimicrobial since antiquity; its use was described by Hippocrates⁸⁶. This agent is available only as solution preparations and is particularly bactericidal to Gram-negative bacteria, most importantly *Pseudomonas aeruginosa*⁸⁷. A minimum inhibitory concentration of 0.5% is required for this agent to be an effective antibacterial drug⁸⁸. Halstead et al. showed that exposure to AA for 3 hours leads to eradication of biofilms and planktonic bacteria, including *Pseudomonas* spp., *Acinetobacter* spp., *E. coli*, MRSA, *Proteus* spp., *Enterobacter* spp., and *Klebsiella* spp.⁸⁹. It can be used in the treatment of skin and soft tissues infections, such as hot tub folliculitis or foot infections, and burns, and it also has a synergistic effect with systemic antibiotics in patients with documented *Pseudomonas* wound infections⁹⁰. Cortesia et al. showed that 6% acetic acid successfully eradicated *Mycobacterium tuberculosis* after bacterial cultures were exposed to the solution for 30 minutes⁹¹. In addition to its bactericidal properties, acetic acid is inexpensive and universally available. However, its cytotoxicity to fibroblasts and hindrance of cell viability are the primary disadvantages of this agent as it resultantly impedes successful healing of skin grafts. These effects increase with the acetic acid concentration. In our burn center in Galveston, AA is used in the treatment of burn wounds with culture-proven multi-drug resistant *Pseudomonas* in combination with systemic antibiotic treatment. Patients undergo dressing changes three times daily with AA-soaked gauzes to allow for acetic acid activity against biofilms.

However, a surgeon should be aware of potential cytotoxic effects when applying acetic acid, especially on fresh skin grafts.

Boric acid is another acid demonstrated to have potentially protective effects for wound healing. Even though it has limited direct antimicrobial properties, a recent study demonstrated that it may play a significant role in wound healing by decreasing DNA damage in environments of oxidative stress⁹². Thus, boric acid may be a useful adjunct along with other antimicrobials, but additional study is indicated.

HONEY

Given the rise of microbes resistant to antimicrobials, interest in honey in the setting of burn wounds to prevent infection has surged once more. Since antiquity, honey has been utilized as a topical agent; while it fell from clinical use in industrialized nations with the advent of modern antibiotics, honey has remained popular in low-resource settings⁹³. Honey does have a broad-spectrum activity, particularly against *Pseudomonas* spp. and *Proteus* spp., maintains a moist environment crucial for wound healing, and has been shown to stimulate faster healing, as well as being less toxic than silver, and to date no major resistances to honey have been reported^{94–96}. These antimicrobial attributes arise from its acidity, inhibines, and osmotic gradient⁹⁷, or possibly its high sugar content and low pH⁹⁸. Given its unclear mechanism of action, we are currently classifying honey as an acidic antiseptic. However, honey may warrant its own class in the future. A recent study indicated similar efficacy in using honey-based or honey-coated dressings when compared to silver-impregnated dressings for use on burn and chronic wounds but with less pain on application⁹⁹. However, its inherent stickiness makes assessment of wound healing difficult without prior painful cleansing, in a manner similar to silver sulfadiazine. A meta-analysis and a Cochrane review did substantiate the use of honey as a topical application for wounds as a useful adjunct for partial-thickness burns when compared to conventional treatment, but found low-quality evidence to validate its use when compared to silver or other antimicrobials^{100,101}. A newer Cochrane review found moderate certainty evidence that burn wounds treated with honey healed faster than those treated non-surgically with topical antibiotics or with conventional non-antimicrobials¹⁰². While emerging studies have reported quicker wound healing, superior infection control, and improved outcomes with regards to hypertrophic scars and contractures when comparing honey-based dressings to mafenide acetate or silver sulfadiazine in the setting of partial-thickness burns, further investigation is warranted to determine the mechanism of action and effectiveness of honey against all commonly found pathogens in burn wounds^{103–106}. To date no good data support the use of medical honey in conjunction with allografts or skin grafts. We would be concerned that the adhesive nature of the agent could cause an unacceptable degree of graft dislodgement with dressing change or cleansing. Though the United States Food and Drug Administration has approved various honey products for use in the human patient population, few studies have examined differences in the various products and so we cannot recommend one at this time. While honey is an easily accessible product with data, we do not recommend other home remedies such as but not limited to cinnamon, eggs, flour, or yellow mustard.

Heavy Metals

The class of heavy metal antiseptics mainly consists of four metals: ionic silver, bismuth, copper ions, and mercury (Table 5). Of these, ionic silver is the most commonly applied antimicrobial in burn wound management, exemplified by the use of silver nitrate¹⁰⁷. In the 18th century, silver nitrate was commonly referred to as “lunar caustic”, and its beneficial antimicrobial properties were well established¹⁰⁸. While bismuth and copper both have limited utility, mercury has largely fallen out of clinical use due to concerns for systemic toxicity.

In the United States, silver is the most commonly employed topical antimicrobial and is available as a liquid solution of silver nitrate (AgNO_3), ointments such as silver sulfadiazine (Silvadene®, Pfizer, Inc.™, New York, NY, USA), and on impregnated dressings. The silver ion component has the potential to bind to DNA, proteins, and enzymes and cause destruction via an oxidative pathway. It can induce catalase production, apoptotic body formation, and DNA fragmentation^{109,110}. Silver nitrate is particularly bacteriostatic to *Staphylococcus aureus*, *Escherichia Coli*, and *Pseudomonas aeruginosa*, while *Klebsiella* spp., *Providencia* spp., and other Enterobacteriaceae have proven less susceptible to 0.5% AgNO_3 . Silver sulfadiazine is not only effective against *Pseudomonas* spp. and enteric bacteria, but it also provides coverage against fungi, including *Candida albicans*, with antimicrobial effects lasting up to 24 hours¹¹¹. While both silver drugs have less toxicity to regenerating epithelium than oxidative halides, their capacities to penetrate into the wound bed is limited to the surface epithelium due to the binding of silver ions to surface proteins¹¹². Recent studies have cast the non-toxic nature of silver into question, and caution might be warranted in the future when applying this topical antimicrobial¹¹³.

Silver nitrate comes in solution with various concentrations, ranging from 0.5% to 50%. The standard concentration is 0.5%; however, more concentrated solutions can be applied, if necessary, in deep wounds with resistant microorganisms. Additionally, miconazole powder can be combined with AgNO_3 to generate an aqueous solution of 0.5% silver nitrate and 2% miconazole for greater activity against bacteria and fungi in burn wounds¹¹⁴. For comparison, the concentration of silver nitrate tissue applicators used to cauterize burn wound have a concentration of 75%. Silver oxynitrate [$\text{Ag}(\text{Ag}_3\text{O}_4)\text{NO}_3$] is a novel formulation of silver with promising in vitro data showing eradication of biofilms at lower equimolar concentrations than silver nitrate, but clinical data are lacking¹¹⁵.

Silver sulfadiazine is a combination of silver ions and the sulfa antibiotic sulfadiazine. This agent is typically used in 1% cream. The silver ion synergistically causes DNA damage while the inhibition of DNA synthesis from sulfadiazine limits repair. Our extensive experience with burn patients at the Shriners Hospital for Children® - Galveston has proven that silver nitrate and silver sulfadiazine provide excellent antimicrobial protection, decreasing the rates of superinfection, as well as maintaining a moist environment that promotes wound healing. Further, they prevent the adhesion of the dressings to open wounds and are not painful or irritating on application. Wound penetration is poor, particularly in the presence of eschar. In this setting, different modalities should be utilized for optimal effects. The disadvantages of silver nitrate are hyponatremia and hypochloremia, necessitating the monitoring of serum electrolytes¹¹⁶. Furthermore, although rare, AgNO_3 can cause

methemoglobinemia and hemoglobinemia, particularly on wounds growing nitrate-positive organisms¹¹⁷. On the other hand, silver sulfadiazine can cause reversible neutropenia¹¹¹. While the application of Silvadene® or other silver sulfadiazine products are soothing, multiple applications of this agent can cause a pseudo-eschar on the wound bed, limiting its utility by hindering assessments of wound depths¹¹⁸. Katzner et al. created a compound that combines silver nitrate with β -glucan (an immune-stimulating agent); this compound could act as both an antimicrobial agent and an immune modulator¹¹⁹.

Bismuth is another heavy metal with antimicrobial properties. The most commonly used formulation of bismuth for wound care is bismuth subgalactate, found in Xeroform® (Covidien™, Dublin, Republic of Ireland) gauze. This heavy metal disrupts biofilm formation by inhibiting polysaccharide capsule production in bacteria⁶². This agent is particularly bacteriostatic against enteric microorganisms, such as *C. diff* and *E. coli*¹²⁰. Additionally, bismuth is not cytotoxic to fibroblasts and does not hinder wound healing¹²¹. Studies suggest that bismuth thiols are more effective than conventional antibiotics in the topical treatment of chronic wounds, particularly against MRSA and *P. aeruginosa* infections¹²². Bismuth's antimicrobial efficacy is greatly enhanced when compounded with thiol chelators¹²³. Bates et al. invented a matrix with bismuth compounds and small intestine submucosa that not only dissolves biofilms but also promotes wound healing by supplying a rapidly vascularized matrix to the lesion¹²⁴. Another variation of bismuth is bismuth iodoform paraffin paste (BIPP), which not only has antimicrobial properties but also promotes granulation tissue formation. This paste should not be applied to wound areas greater than 1% TBSA due to the risk of bismuth toxicity^{125–127}. In our experience, BIPP prevents infections from developing and promotes the formation of granulation tissue, allowing split-thickness skin grafting over wound beds conventionally deemed ungraftable.

As with silver, copper possesses inherent antimicrobial properties and was used in antiquity as a topical antimicrobial¹²⁸ but has not been exploited for use in modern topical antimicrobials. Due to concerns for mercury's toxic profile, mercurical compounds are not in current use as topical antimicrobials, though they were widely utilized for the majority of the previous century.

DRESSINGS

Often used yet seldom discussed in the literature, antimicrobial dressings and biocide-impregnated dressings are routinely used in the management of burn patients, either as prophylaxis or to treat an established infection¹²⁹. Typically, these dressing contain antiseptics and are commonly referred to in the literature as AMDs. However, this is not to be confused with the Kerlix AMD®, and, to avoid the confusion, in this paper we will not refer to antimicrobial dressings broadly as AMD. Many burn centers utilize antimicrobial-based dressings, particularly silver, bismuth or PHMB, rather than applying topical antimicrobials because the dressings are easier to manage, have more consistent antimicrobial levels, and are generally less messy. While silver-based dressings may be the most common wound dressing commercially available, neither the literature nor much data support their use or that of other antimicrobial-impregnated dressings in the management of burn wounds^{14,112,129–132}. Only recent have studies examined the efficacy of antimicrobial

dressings in inhibiting the growth of pathogens on wounds. Several of these studies have examined the use of negative-pressure wound therapy in conjunction with antimicrobial dressings. However, they did not examine the effects of just the negative-pressure devices or just antimicrobial dressings of infections in wounds^{133,134}. A recent animal study indicated that silver-based antiseptic dressings dramatically retarded the growth of MRSA in the early stages post-burn¹³⁵. However, a Cochrane review of 56 studies found only moderate evidence to support the use of silver-impregnated dressings over Vaseline gauze in terms of healing time, and low evidence as a benefit in cost, number of dressing changes, and nursing time¹⁰². Despite the low-quality evidence, in our experience in wounds not exuding, silver-impregnated dressings are useful adjuncts in terms of duration of wound healing and infection control. Each product's dressing substrate and particular antimicrobial formulation provide varying dressing characteristics worthy of an entire review; however, there are to date no large-scale studies determining the most efficacious product, so preference of the practitioner and cost typically define use. When comparing silver-impregnated dressings to membranous dressings, such as Biobrane® (Smith & Nephew™, London, England, UK) or skin substitutes (e.g., amnion membrane), the antimicrobial dressings were inferior in infection control, pain for healing, epithelialization rate, and length of hospital stay in the setting of pediatric burns¹³⁶. Of note, what has shown to be clinically effective in the management of chronic wounds does not always translate to the care of thermal wounds, and care must be taken before applying a product to a burn wound with no prior experiences covered in the literature¹³⁶.

It is important to remember that no dressing, no matter how well marketed, replaces the tenets of burn surgery: aggressive and early debridement of all devitalized tissue, coverage of wounds with skin, assiduous wound cleansing to remove pathogens and contaminants, and physical examination. It is also critical to remember, regardless of the advertising campaign used, the utility and spectrum of a particular impregnated dressing are limited to that of the antiseptic it contains.

NOT USED IN BURN WOUND CARE

The preceding sections covered antiseptics used in the management of burn wounds. In this section, we briefly cover others that, while being powerful disinfectants, are generally too toxic for use clinically (Table 6).

Alcohols, such as isopropyl alcohol, are widely used surface disinfectants and skin antiseptics, exerting their actions possibly through protein denaturation or inhibition and uncoupling of mRNA and protein synthesis^{137,138}. However, they have little use in the setting of burn wounds given their irritating side profiles, despite their broad spectrum of activity, particularly against sessile bacteria. Triclosan and other bisphenols exert their activities by arresting the fatty acid biosynthesis within cells, halting the synthesis of lipopolysaccharides, lipoproteins, and phospholipids, leading to the degradation of the cell membrane¹³⁹. However, given the notice issued by the United States Food and Drug Administration that beginning September 2017 triclosan would be banned in consumer antiseptic products due to a lack of efficacy in soaps,¹⁴⁰ we cannot recommend the use of this antiseptic in the setting of burn wounds. Triclorocarban is an agent used in soaps and

lotions, with less data accumulated than on triclosan or Dakin's, but with potentially grave environmental impact. While it has been shown to be effective against *S. aureus*¹⁴¹, its carcinogenic byproducts could have other grave implications in medical and environmental safety¹⁴². As a result, we cannot recommend this antiseptic at this time. Formaldehyde, a monoaldehyde, is not just a bactericidal disinfectant, but sporocidal and virucidal as well¹³⁸. However, given its toxic side effect profile, it is not recommended for use in the setting of burn wound infection prophylaxis. Glutaraldehyde, a dialdehyde, has broad-spectrum activity against bacteria, fungi, and viruses and is a commonly used disinfectant of surgical equipment¹³⁸. As with formaldehyde, exposure limits from glutaraldehyde are recommended due to its toxicity¹⁴³.

CONCLUSION

Topical antimicrobials can be categorized into antiseptics and antibiotics. Each agent in contained in these superclasses possesses its own advantages and disadvantages that have been extensively discussed in this article. Despite some topical antiseptics' ability to dissolve biofilm and provide broad-spectrum antimicrobial coverage, the value of surgical excision and grafting should be emphasized. Early surgical removal of the infected tissue is the most effective method to eliminate invasive infection^{144,145}. In severe cases, such as severe burns and necrotizing soft tissue infections, surgical debridement can be life-saving. Topical agents then are chosen based upon the challenges of each wound, including biofilms, eschar, bioburden, the need for epithelialization, and specific microbes. Healing and fibroblast proliferation are heavily dependent on adequate nutrition. Each wound and each patient is unique, and different factors related to the wound should be considered when deciding which topical antimicrobial to employ while taking into account the risks and benefits of each agent and discussing them with the patient.

Further work is needed to more comprehensively define the in vivo use of these agents. Synergies and interferences of these agents commonly applied to wounds in a polypharmacy have been tested in very limited manner. Drug concentrations have not been adjusted as microbes have evolved ever-increasing resistances. There is a paucity of data regarding total patient dosing or absorption. Once believed immune from developed and acquired resistances, antiseptics now face pathogens not susceptible to their antimicrobial activities¹³⁸. Researchers and health care professionals have lagged in innovation. Novel topical classes or agents have not been developed in an unacceptably long time. Historically, antiseptics too toxic for clinical use, such as iodine and chlorine, were modified to enable safe and effective administration. Perhaps with time and effort, currently available but clinically unusable disinfectants, such as quaternary ammonium compounds; phenols; anillides; and aldehydes, can be made safe for topical use and expand our arsenal in the unending arms race against microbes. Topical antimicrobials are critical tools in the armamentarium of burn and wound care, and failing to match the evolution of pathogenic resistances leaves patients underserved and exposed.

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Table 1

Topical Antiseptic Classification

Class	Burn Wound Use	Example
Emulsifiers	Yes	Soap
Oxidizers	Yes	Dakin's Solution
Acids	Yes	Acetic Acid
Heavy Metals	Yes	Silver Nitrate
Alcohols	No	Isopropyl Alcohol
Aldehydes	No	Formaldehyde
Anilides	No	Triclorocarban
Bisphenols	No	Triclosan
Phenols	No	Cresol

Table 2**Emulsifying Topical Antiseptics**

Emulsifier	Agents	Commercial Product
Soap, Detergents	Sodium Dodecyl Sulfate	Dial ® , Ivory ® , Etc.
	Cocamidopropyl betaine	Johnson's ® Baby Shampoo ®
Surfactants	Surfactant	PluroGel ®
Biguanides	Chlorhexidine	Betasept ® , Chloraprep ® , Peridex ™
	Polyhexamethylene biguanide	Vantocil ™ , Kerlix AMD ®
	Alexidine	Biotrue ®
Bispyridine	Octenidine dihydrochloride	Octenisept ®
Quaternary ammonium	Benzalkonium Chloride	Lysol ®

Dial® (Henkel Corporation™, Stamford, CT), Ivory® (Procter & Gamble, Cincinnati, OH), Johnson's Baby Shampoo® (Johnson & Johnson, New Brunswick, NJ), Betasept® (Purdue Products LP, Stamford, CT, USA), Chloraprep® (Becton Dickinson, Franklin Lakes, NJ), Peridex™ (3M™ ESPE™ AG, Seefeld, Germany), Biotrue® (Bausch & Lomb™, Rochester, NY)

Table 3**Oxidizing Topical Antiseptics**

Oxidizer Class	Agent	Commercial Agent
Peroxygens	Hydrogen peroxide	3% Hydrogen peroxide
Oxidative Halides	Sodium hypochlorite (NaOCl)	Dakin's Solution, Heggers' Solution
	Oxychlorosene	Clorpactin®
	Hypochlorous acid (HOCl)	PhaseOne®, Vashe®, Puracyn®
	Iodine (I ₂)	Povidone-iodine, Betadine®, Iodosorb®
Redox Dyes	Gentian violet and methylene blue	Hydrofera Blue®

PhaseOne® (IHT™, Franklin, TN), Vashe® (SteadMed™, Fort Worth, TX), Puracyn® (Innovacyn, Inc., Rialto, CA)

Table 4

Acidic Topical Antiseptics

Acid Class	Agent	Commercial Agent
Organic Acid	Acetic Acid	0.5%–3% Acetic Acid Solution
Acidic Colloidal Suspension	Honey	MEDIHONEY®
Inorganic Weak Acid	Boric Acid	3% Boric Acid Solution

MEDIHONEY® (Integra LifeSciences™, Ellicott City, MD)

Table 5**Heavy Metal Topical Antiseptics**

Heavy Metal Class	Agent	Commercial Agent
Silver Compounds	Silver Nitrate	5% Silver Nitrate
	Silver sulfadiazine	Silvadene®
	Silver ion releasing dressings	Acticoat®, KerraContact® & Exsalt®
	Silver oxynitrate	Ag Oxysalts™
Bismuth Compounds	Bismuth Subgalactate	Xeroform®
	Bismuth Iodine Paraffin Paste	BIPPs (Compounded)
Other Heavy Metals	Copper, Mercury	Not Currently Available

KerraContact® & Exsalt® (Crawford Healthcare, Knutsford, UK), Ag Oxysalts™ (Exciton Technologies, Inc., Edmonton, Canada)

Table 6

Topical Antiseptics Not Used in Burn Wounds

Class	Type
Other Heavy Metals	Copper, Mercury
Alcohols	Ethanol Isopropanol
Aldehydes	Glutaraldehyde Formaldehyde
Anilides	Triclorocarban
Bisphenols	Triclosan Hexachlorophene
Phenols	Phenol Cresol