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BURNS (N NAMIAS, SECTION EDITOR)

The Current State of Topical Burn Treatments: a Review

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Abstract

Purpose of Review The purpose of this review is to discuss commonly used dressings for burn treatments, including short-acting topicals and long-acting silver dressings.

Recent Findings Recent literature supports the use of long-acting silver dressings over traditional daily use topical treatments. Longer acting topical dressings result in less frequent dressing changes, less pain, and greater ease of use, but have similar results in wound healing and infection prevention.

Summary There are many topical agents on the market for use on burn wounds. Short-acting topicals can be divided into 3 generalized classes: antiseptics, antimicrobials, and enzymatic debridement agents. Longer acting applied dressings include silver-bonded nylon and fiber (Silverlon® Argentum, Clarendon Hills, IL); multilayer rayon, polyester silver-coated mesh polyethylene (Acticoat™ Smith & Nephew London, UK); silver sodium carboxymethylcellulose (Aquacel® Ag, ConvaTec, Greensboro, NC); silver-containing soft silicone foam (Mepilex® Ag; Mölnlycke Health Care, Gothenburg); soft silicone silver (Mepitel Ag® Mölnlycke Health Care, Gothenburg). Tradition and surgeon preference are major influences on frequency of use. While recent literature supports using long-acting silver-based dressings over short-acting topicals, more research, particularly randomized controlled trials, is needed to provide evidence-based recommendations regarding their use.

Keywords Burn topicals · Silver burn dressing · Silver sulfadiazine · Mepilex Ag · Aquacel Ag · Acticoat · Mepitel Ag

Introduction

From its origins, humanity has had a persistent and compelling urge to apply all types of materials to burn wounds. John A. Moncrief, third president of the American Burn Association, described how early Egyptians used oily strips of linen, Chinese in the fifth and sixth centuries utilized tea leaves, and old Jewish cultures of the Middle East used ink, and the devastating period of topical tissue poisons such as picric acid, carbolic acid, and tannic acid among others through the mid-twentieth century [1].

There are many topical agents on the market for use on burn wounds. They include both short-acting topicals, with a 24-h or less action of duration, and long-acting topicals. The short-acting topicals can be divided into 3 generalized classes: antiseptics, antimicrobials, and enzymatic debridement agents. The difference between antiseptics and antibacterial agents is that the antiseptics are non-selectively toxic to all biologic matter and may have significant toxic manifestations. Antimicrobial agents have significantly less cytotoxic effect and more specific antibacterial, antifungal, and antiviral activity. Enzymatic topicals act to debride wounds.

Although this discussion will focus on topical short-acting and long-acting antimicrobials, a brief synopsis of antiseptics and enzymatic agents will more fully acquaint the reader to topical agents used in burn care.

This article is part of the Topical Collection on *Burns*

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Short-Acting Topicals

The most common antiseptics in burn care include emulsifiers, peroxygens, oxidizers, halides, and organic acids.

The most typical emulsifying agents in burn care are soaps, surfactants, and biguanides.

Soaps are cleansing and emulsifying substances which consist of sodium or potassium salts produced by the reaction of alkali on fats or fatty acids [2].

Soaps are used to cleanse the wound of surface microorganisms and to disrupt biofilm layer which may produce a 2-log (99%) decrease in colony counts [3].

Biguanides are cationic emulsifiers with biocidal properties and permeate cell walls and cytoplasmic inner membranes. Chlorhexidine is the most commonly used biguanide [4].

PluroGel is a non-ionic detergent consisting of a surfactant which apparently disrupts biofilms [5].

Oxidizers are a broad class of antiseptics which produce a free radical mediator that disrupts biofilms, cell walls, cytoplasmic membranes, proteins, and DNA. These materials have broad spectrum activity, but because of their high reactivity and host toxicity have a narrow therapeutic index. They should be used with caution due to this toxicity [4].

The subclass of oxidative halides includes sodium hypochlorite (NaOCl; Dakin's Solution), hypochlorous acid (HOCl; PhaseOne, Vashe, Puracyn), and iodine (I_2; povidone–iodine, betadine, iodosorb).

Sodium hypochlorite (Dakin's) is effective in dissolving biofilms and has broad bactericidal coverage against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, MRSA, and enterococci [6].

Betadine (povidone–iodine), the active principle of which is iodine, is another oxidative halide with broad antimicrobial spectrum activity including gram-negative and gram-positive bacteria as well as fungi and yeasts in burns [7].

Blanco pooled the clinical experience of 39 investigators who used povidone–iodine to treat 1079 patients [8]. Several studies related an effective reduction in surface wound quantitative cultures, especially when povidone–iodine was applied every 6 h [9]. The disturbing implication of cell organ toxicity with high serum iodine levels from absorption through wounds was not demonstrated [10, 11]. This topical is cytotoxic to fibroblasts and keratinocytes which may lead to inhibition of wound healing [12].

Peroxygens are a subclass of oxidizers. Hydrogen peroxide (H_2O_2) is the most commonly applied constituent of this class and is generally used as a 3% aqueous solution with broad activity against bacteria, yeasts, and viruses [13].

Weak acids include acetic acid (AA), the active ingredient of vinegar, which has been used as a topical antimicrobial since antiquity with a description by Hippocrates [14]. It is distinctly bactericidal to gram-negative bacteria especially *P. aeruginosa* [15].

Bismuth is a heavy metal with antimicrobial action. Xeroform (Covidien) gauze is a formulation of bismuth subgalactate which disrupts biofilm formation by inhibiting bacterial polysaccharide capsule production [16]. It is bacteriostatic against *Clostridium difficile* and *Escherichia coli* [17]. Bismuth does not inhibit fibroblasts and is not cytotoxic to wound healing [18].

Enzymatic Debridement Agents

Enzymatic debridement agents, though not technically antibiotics or antiseptics, may influence microbial growth by eradicating necrotic tissue from wounds.

The quest for the perfect non-surgical enzymatic debridement medium has produced both non-selective agents, which digest all material to which they are applied, and selective products, which digest only necrotic tissue while sparing viable tissue. These agents include streptokinase-streptodornase, subtilisin, and trypsin [19]. Collagenase (Santyl® Smith & Nephew London) is the most commonly used selective enzymatic debridement agent in the USA and is extracted from *Clostridium histolyticum* [20]. Although Hansbrough claimed collagenase produced improvement in rate of wound healing [21], most experts feel the rate of healing is not increased. It does, however, evoke a more rapid removal of the eschar thus enabling earlier visual confirmation of wound depth.

Bromelain, which produces selective debridement much more rapidly, is synthesized from the stem or fruit of pineapples. Nexobrid® (MediWound, Yavne, Israel) has been used extensively in Israel and Europe and is in phase III trials in the USA [22, 23] (see Table 1 for a summary of these short-acting topical agents).

Longer Acting Topicals

The revolution in burn care topical management has been the introduction of longer acting mostly silver-based topical agents. These products have decreased the time and cost of daily dressing changes, as well as improving compliance and decreasing the pain and morbidity of daily dressing changes. Table 2 summarizes these longer acting agents and describes some advantages and disadvantages of each.

Our discussion will center initially on the older and established topical agents which are still widely used worldwide.

Many studies have attempted to demonstrate an outcome difference with each of these agents; however, no survival outcomes difference has ever been definitively determined.

Silver Nitrate

Carl A. Moyer introduced the burn world to silver nitrate [24].

The silver component binds to DNA, proteins, and enzymes and causes destruction by an oxidative pathway. It can induce catalase production, apoptotic body formation, and DNA fragmentation [24, 25].

Table 1 Short-acting topical agents

Short-acting topicals		
Class	Category	Example
Antiseptic	Emulsifiers	Soaps
		Surfactants (PluroGel)
		Biguanides (Chlorhexidine)
	Oxidizer: peroxygens	Hydrogen peroxide
	Oxidizer: halides	Sodium hypochlorite (Dakin's)
		Hypochlorous acid (PhaseOne, Vashe, Puracyn)
		Iodine (povidone–iodine, betadine, iodosorb)
	Organic acids	Acetic acid (vinegar)
Antimicrobial	Heavy metal	Bismuth (Xeroform)
Enzymatic debriders		Collagenase
		Bromelain

Silver nitrate is particularly bacteriostatic to *S. aureus*, *E. coli*, and *P. aeruginosa*, whereas *Klebsiella* species, *Providentia* species, and other *Enterobacteriaceae* have proven less susceptible to 0.5% $AgNO_3$ [26].

$AgNO_3$ has a limited ability to penetrate through eschar because of the binding of the silver ions to surface proteins. The disadvantages of $AgNO_3$ are hyponatremia and hypochloremia, necessitating the monitoring of serum electrolytes [27].

Additionally, $AgNO_3$ can rarely cause methemoglobinemia, in the presence of wounds growing nitrate-positive organisms [28].

Moyer pioneered a dressing technique utilizing 20 thicknesses of course mesh gauze wet with 0.5% silver nitrate solution with a dry outer layer. His original report contained a series of 21 patients ranging in age from 13 months to 69 years and with burns ranging from 30 to 90% total body surface area burned, with one-half ultimately dying [29].

Table 2 Longer acting topicals

Longer acting topicals		
Topical	Advantages	Disadvantages
Silver nitrate	Penetrates eschar	Hyponatremia, hypochloremia
	Bacteriostatic to *S. aureus*, *E. coli*, and *P. aeruginosa*	Methemoglobinemia
		Impaired wound healing
Mafenide	Broad antibacterial properties	Discomfort on application
	Penetrates eschar	Non-gap acidosis
Silver sulfadiazine	Broad antibacterial properties	Allergic reactions (sulfa)
	No pain on application	Hyperosmolality
		Hemolysis
		Argyria
		Pseudo-eschar formation
Gentamicin sulfate	Antibacterial	Drug resistance
		Not recommended on large burns
Cerium	Decreased infection	May interfere with silver sulfadiazine
	Improved survival	
Bactroban	Effective against MRSA	Bacterial resistance rising
Bacitracin	Availability	Can be used on facial wounds Alternative o silver sulfadiazine in sulfa-allergic patients
Polysporin	Broad antibacterial properties	Can be used on facial wounds
Honey	Broad antibacterial properties	Poor-quality studies for use

Polk and Monafo published survival data on 225 consecutive burned humans treated with dilute silver nitrate demonstrating a survival improvement over a historical control [30].

Lewis et al. found that 0.5% silver nitrate did not alter survival when compared with historical controls. They did find a qualitative change in the bacterial flora of the wounds [31].

Only a few centers use silver nitrate currently because of the paucity of survival outcome data. Disadvantages include its apparent ineffectiveness on established infection [32], impairment of wound healing [33], hypertonicity of the solution resulting in transient electrolyte depletion [24], methemoglobinemia [29], objectionable staining, bulky expensive dressings, and the question of argyria [34, 35].

It remains in the burn toolkit for patients who have a significant sulfa allergy.

Mafenide

Mafenide was synthesized in the USA in 1938 [36] and initially used by German surgeons in World War II to treat anaerobic infection in battle wounds [37]. Its use on 4 burned patients was reported in 1944 by the British [38] and when rediscovered by Moncrief was being used by Mendelson and Lindsey as a treatment of wounds massively infected with *Clostridium perfringens* [39]. It was realized that mafenide provided additional antibacterial spectrum against common burn pathogens, most importantly, *Pseudomonas aeruginosa* [39].

Although it was initially felt that mafenide decreased mortality based on historical controls [1, 40–44], other researchers could not confirm the mortality results [31]. However, they did note a reduction in the bacterial density of wounds treated with mafenide.

The problems associated with the use of mafenide include discomfort on application of the drug [45], a 5 to 7% hypersensitivity rate [46, 47], and production of a non-anion gap acidosis caused by inhibition of carbonic anhydrase [48, 49•].

It is applied as a thick butter and because of its ability for penetration is recommended for third- and fourth-degree burns, as well as burns involving bone, joint, or tendon.

It remains the second most commonly utilized topical throughout the world.

Silver Sulfadiazine (AgSD)

This is by far the most commonly utilized topical worldwide and is a combination drug utilizing the antibacterial properties of silver as well as a sulfa component used in the form of creams such as Silvadene® (Keltman Pharmaceuticals, Inc., Flowood, MS), Flamazine® (Smith & Nephew, Hull), and Geben® (Mitsubishi Pharma, Tokyo). It was synthesized by Charles L. Fox, Jr. [50] with Baxter reporting the initial experience with treatment of 345 consecutive patients in 1968 and 1969 [51].

Silver sulfadiazine binds with serum and other extracellular fluids and binds to the cell membrane with disruption of the membrane producing bactericidal action [50]. The silver component as ionic silver is slowly released producing DNA damage. Further disruption of DNA synthesis occurs by inhibition of folate metabolism by the sulfadiazine component [27].

The half-life of silver sulfadiazine is 10 h and can be prolonged with renal disease [52]. It provides good coverage against susceptible *Pseudomonas* species and other gram-negative enteric flora as well as some fungal species including *Candida albicans* [27].

Most commercial preparations of silver sulfadiazine (Thermazene®, Silvadene®, SSD Cream®) seem to produce a cooling, soothing sensation to the early burn wound as contrasted to the pain experienced by most after application of mafenide.

The side effects of silver sulfadiazine include methemoglobinemia, hyperosmolality, and hemolysis in those with G6PD deficiency. It may cause lactic acidosis in some because of the propylene glycol emulsifier [53].

Rarely, argyria can occur, a clinical condition associated with very high tissue silver levels associated with blue, black, or gray discoloration of the eyes, skin, and mucocutaneous membranes. Additionally, it can be toxic to the liver and kidney.

It was initially thought that early post burn leukopenia (EPBL) was a result of AgSD. However, further studies have shown that it is not the causative agent of EPBL and silver sulfadiazine should not be discontinued because of the presence of EPBL because the white blood cell count corrects regardless of whether or not the agent is discontinued [54].

Another troublesome aspect of silver sulfadiazine is that it does not penetrate the eschar and creates a thin glazed pseudoeschar over the wound making visual inference of depth difficult [55].

Cerium

In 1976, Monafo [56] reported his experience with the rare earth lanthanon, cerium, with silver sulfadiazine to enhance bacteriologic control of the burn wound. He reported a prompt increase in the incidence of sterile cultures and the sparse recovery of gram-negative bacteria in wound surface cultures. His conjectures on the improvement of incidence in sepsis and survival were based on historical controls. There are several reports which seem to indicate that cerium may interfere with the action of silver sulfadiazine in reducing the latter's efficacy [57, 58].

Gentamicin Sulfate

Topical gentamicin has a long history of usage for the topical treatment of burns. Stone reported a clinical experience with

1182 patients that gentamicin was effective in reducing both the incidence of burn wound colonization by virulent organisms and the frequency of life-threatening sepsis plus a striking reduction in mortality [59]. However, with extended use, gentamicin-resistant organisms emerged, and the drug has never been recommended by the manufacturer for use on large burns [60••]. It may be used alone or in combination with another agent in a situation where the wound demonstrates an aminoglycoside-sensitive pseudomonas or other gram negative.

Bacitracin

Bacitracin is a relatively old topical antibiotic, first isolated in 1945 and found to inhibit cell wall and peptidoglycan synthesis [61]. It was initially used systemically in burns, but found to have nephrotoxicity [62].

Its penetrance against staph is considerably less than mupirocin [63].

Many centers use it on facial wounds because of its consistency (not too thick) and ability to cling to the face. Additionally, some centers use it as a topical for donor sites with other minimally adherent dressings.

It is a potential replacement for silver sulfadiazine in those with sulfa allergies [64].

Polysporin

Polysporin is a combination of two antibiotics: bacitracin and polymixin B sulfate.

Polymyxin B is an antibiotic which inhibits bacterial cell wall synthesis as well as interfering with the production of tetrahydrofolic acid. It has bacteriostatic activity against a wide range of both skin flora and other organisms, including gram-negative bacteria [65]. It has also been used in attempts at eradication of MRSA [66].

MacMillan compared 454 patients treated with occlusive polysporin, 0.5% silver nitrate, mafenide, gentamicin, or silver sulfadiazine and found a greater number of gram negatives populating wounds treated with polysporin compared to mafenide and silver sulfadiazine [67].

It may have some utility in facial burns [68].

Bactroban (Mupirocin)

Mupirocin (Bactroban) or pseudomonic acid is a natural crotonic acid derivative drug extracted from *Pseudomonas fluorescens*. It inhibits protein synthesis through binding to bacterial isoleucyl-tRNA synthetase [69]. Mupirocin has been used on burn wounds and to prevent skin and soft tissue infections caused by *S. aureus* isolates and where the MRSA isolates are epidemic [70].

However, the rate of mupirocin resistance among MRSA strains is continuously rising [71].

It appears that resistance to mupirocin is conferred by plasmid transfer resistance genes from the historically and mistakenly less important coagulase-negative staphylococci. It was demonstrated that 12% of *Staphylococcus hemolyticus* was resistant to mupirocin and this phenotype was correlated with the presence of plasmids [72•].

Honey

Preparations of honey have been used since ancient times. It has been demonstrated to provide antimicrobial control by enzymatic release of H_2O_2 or the presence of active components like methylglyoxal (MGO) [73]. Honey has been shown to have broad spectrum bacteriologic coverage and has been shown to be synergistic with linezolid against *S. aureus* [74].

Different kinds of honey, including Gelam, Tualang, and Manuka, have been tested and found to have similar properties. Currently, Medihoney is marketed in the USA [75].

At least 8 randomized controlled trials, although methodologically poor-quality studies, demonstrated that honey was found to be more effective than comparators, typically silver sulfadiazine, in healing rates, presence of contractures, and number of sterile swabs [76].

Long-Acting Silver Applied Dressings

A revolutionary change in topical burn care has occurred over the last decade, which includes the use of long-acting silver-based dressings. These dressings have become the mainstay in many centers because of improved compliance, decreased pain during dressing changes, decrease in time consumed during dressing changes, and improved cost-effectiveness. The long-acting dressings are in part directly responsible for a decrease in daily census in many burn centers as patients who would have been admitted for once to twice daily dressing changes now may be re-evaluated on a weekly basis. While some papers do exist regarding the use of applied burn dressings, very few randomized controlled trials have been conducted to research their use. Several synthetic dressings are available for partial thickness burns, including silver-bonded nylon and fiber (Silverlon® Argentum, Clarendon Hills, IL); multilayer rayon, polyester silver-coated mesh polyethylene (Acticoat™ Smith & Nephew, London, UK); silver sodium carboxymethylcellulose (Aquacel® Ag, ConvaTec, Greensboro, NC); silver-containing soft silicone foam (Mepilex® Ag; Mölnlycke Health Care, Gothenburg); and soft silicone silver (Mepitel Ag® Mölnlycke Health Care, Gothenburg) [77, 78]. Table 3 lists some available applied dressings and their length of use per application.

Table 3 Long-acting applied silver dressings

Long-acting applied silver dressings	
Dressing	Length of use
Silverlon	7 days
Acticoat	3–7 days
Aquacel Ag	21 days
Mepilex Ag	7 days
Mepitel Ag	8 days

Silverlon

This dressing was one of the initially introduced and is a nylon fabric with a polymeric silver–plated substrate surface. The dressing releases silver in the ionic AG^{+1} form. During the first 24 h, 10% of the total amount of silver is released into the wound and the remaining silver continues to be released until the dressing is removed. Ionic silver has penetrance on gram negatives including *Pseudomonas* species, *Klebsiella*, and *Acinetobacter*, and most gram positives including MRSA as well as some fungal and yeast species and certain viruses. It was initially used in Iraq and Afghanistan because of its ease of use compared to the short-acting topicals as well as its comparably much lighter weight per unit, ease of storage, and stability in environmental extremes [79]. Although initially used for forward operations burn care, these silver-nylon dressings have been implemented in treating blast injuries, traumatic amputations, open fractures, and large tissue loss wounds and the wounds would require change only every 3–7 days [80]. BARDA has this stockpiled for burn mass casualties and radiation disasters.

Acticoat

Acticoat became available in the 1990s. It is a multilayered barrier dressing which employs the use of silver for antimicrobial properties. It is frequently employed in burn care, for donor and recipient graft sites. Acticoat consists of three layers: two outer layers of silver-coated non-adherent polyethylene net surrounding an absorbent core of rayon and polyester. The dressing can remain in place for 3 days [81]. Acticoat 7, which touts an additional absorbent layer of rayon and polyester as well as an additional silver-coated non-adherent polyethylene net, can remain in place for 7 days [82]. It can be secured to tissues using staples or sutures to prevent shear forces from disrupting the dressings and underlying grafts during repositioning of the patient [83]. It is important to realize that for activation of the ionic silver, sterile water must be used as opposed to saline which precipitates silver chloride. It may also be used as an interface between a graft and the negative pressure wound sponge.

A multicenter randomized controlled trial of 166 burn wounds comparing Acticoat to sulfadiazine found that Acticoat use resulted in statistically significant higher bacterial clearance of the wound at day 6 and day 12, although bacterial clearance was 100% for both groups at the end of the study. This included clearance of MRSA. Several other studies have concluded that Acticoat was more effective in terms of greater bacterial clearance, less infections, and improved healing time with minimal wound handling when compared to silver nitrate, sulfadiazine, and mafenide acetate. However, Acticoat has been associated with greater duration for re-epithelialization, including donor sites.

While more widely studied than other long-acting agents, a review published on Acticoat and silver dressings revealed only 2 of 31 articles abstracted being randomized controlled trials and just one considered level 1 [81].

Aquacel Ag

Aquacel is a hydrofiber dressing of sodium carboxymethylcellulose with embedded silver manufactured by Convatex Inc. [84,85•]. It consists of a silver-embedded hydrofiber which creates a gel within the wound bed to promote a moist environment conducive to healing, while fighting infection with a wide antibacterial activity. Contours created by the dressing eliminates dead space where potential pathogens could multiply [84]. A prospective, randomized controlled trial published in 2014 comparing Aquacel Ag and Acticoat dressings in burns found that both silver applied dressings had similar healing times and bacterial control. Aquacel Ag did have statistically significant difference in ease of use and decreased reported patient pain [85]. It looks like soft felt when applied, but firms when it dries. The only issue with this material is that it is occasionally difficult to remove and has to be soaked off or needs the use of an emollient oil to loosen it.

Mepilex Ag

Mepilex Ag is distributed by Mölnlycke. It is a soft and pliable silver-containing foam dressing designed to absorb exudate from low to medium exuding wounds to decrease bacteria, minimize the need for dressing changes, and provide a moist environment for wound healing while protecting surrounding skin from wound drainage. It begins to inactivate wound pathogens within 30 min, with effects lasting up to 7 days [86]. These silver foam dressings can also be cut into various shapes for use in covering many different wounds [87•]. A randomized controlled trial published in 2011 compared Mepilex Ag with silver sulfadiazine in children over 5 years of age and adult burn patients. This study found that the Mepilex Ag group had a decreased cost to treat, which included the cost of analgesia for dressing changes, decreased pain, and shorter healing times [87•]. Studies have also found

decreased infections when using Mepilex Ag versus petroleum gauze in donor sites [88] and have also found decreased serum inflammatory markers, IL6 and IL-10, using Mepilex Ag versus other dressings [89]. This is one of the easier to use long-acting silver-based dressings as it is both easy to apply and easy to remove.

Mepitel Ag

This is the newest silver-based long-acting dressing. This is a silver-bonded soft silicone dressing providing a broad spectrum of antimicrobial coverage lasting up to 8 days. The dressing is very compliant and is a good material for joints and mobile areas [90].

Conclusion

In the USA each year, there are estimated to be 700,000 people treated for burns, with 45,000 requiring hospitalization [88]. There are many options available for wound dressings for burn wounds, including older and shorter acting agents, as well as more contemporary longer acting silver-based dressings. Where available, the new technology of long-acting silver dressings appears more comfortable and cost effective. At present, silver is the predominant antimicrobial agent in the longer acting products. This review article summarizes the most current information regarding these options. The future is wide open for new developments in topicals with regard to duration of application and specificity of action.

Compliance with Ethical Standards

Conflict of Interest Dr. Haith has nothing to disclose. Dr. Hashmi has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Moncrief JA. The development of topical therapy. J Trauma. 1971;11:906–10.
2. Brady JE, Russell JW, Holum JR. Chemistry: matter and its changes. 3rd ed. New York: Wiley p924; 2000.
3. Barret JP, Herndon DN. Effects of burn wound excision on bacterial colonization and invasion. Plast Reconstr Surg. 2003;111:744–50.
4. Cambiaso-Daniel J, Boukovalas S, Bitz GH, Branski LK, Herndon DN, Culnan DM. (2018). Topical antimicrobials in burn care. Ann Plast Surg. 2018;00:1–9.
5. Plurogel Product Information https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/ldetails.cfm?lid=184268. Accessed March 2019
6. Moore GA. The Carrel-Dakin method of treating septic wounds; its application to civil surgery. Boston Med Surg J. 1918;178:109–16.
7. Georgiade NG, Harris WA. Open and closed treatment of burns with povidone-iodine. Plast Reconstr Surg. 1973;52:640–4.
8. Blanco, C: 1079 hospitalized burn patients treated topically with betadine ointment. Scientific exhibit, 4th International Congress of Burn Injuries, Buenos Aires, Argentina, 1974;15-21.
9. Robson MC, Schaerf RH, Krisel TJ. Evaluation of topical povidone-iodine ointment in experimental burn wound sepsis. Plast Reconstr Surg. 1974;54:328–34.
10. Hunt JL, Sato R, Heck EL, et al. A critical evaluation of povidone – iodine absorption in thermally injured patients. J Trauma. 1980;20:127–9.
11. Pietsch J, Meakins JL. Complications of povidone – iodine absorption in topically treated burn patients. Lancet. 1976;1:280–2.
12. Thomas GW, Rael LT, Gar-Or R, et al. Mechanisms of delayed wound healing by commonly used antiseptics. J Trauma. 2009;66:82–90.
13. Omidbakhsh N, sattar SA. Broad-spectrum microbicidal activity, toxicologic assessment, and materials; the side compatibility of a new generation of accelerated hydrogen peroxide-based environmental surface disinfectant. Am J Infect Control. 2006;34:251–7.
14. Johnston CS, Gaas CA. Vinegar: medicinal uses and antiglycemic effect. MedGenMed. 2006;8:61.
15. Madhusudhan VL. Efficacy of 1% acetic acid in the treatment of chronic wounds infected with Pseudomonas aeruginosa: prospective randomized controlled clinical trial. Int Wound J. 2016;13:1129–36.
16. Sevgi M, Toklu A, Vecchio D, et al. Topical antimicrobials for burn infections – an update. Recent Pat Antiinfect Drug Discov. 2013;8:161–97.
17. Pitz AM, Park GW, Lee D, Boissy YL, Vinjé J. Antimicrobial activity of bismuth subsalicylate on Clostridium difficile, and E. coli 0157:H7, norovirus, and other common enteric pathogens. Gut Microbes. 2015;6:93–100.
18. Chattopadhyay A, Chang K, Nguyen K, Galvez MG, Legrand A, Davis C, et al. An inexpensive bismuth – petrolatum dressing for treatment of burns. Plast Reconstr Surgery Globe Open. 2016;4:e737.
19. Ramundo J, Gray M. Collagenase for enzymatic debridement: a systematic review. J Wound Ostomy Continence Nurs. 2009;36(6 suppl):S4–S11.
20. Payne WG, Salas RE, Ko F. Enzymatic debriding agents are safe in wounds with high bacterial bioburdens. Eplasty. 2008;8:e17.
21. Hansbrough J, Achauer B, Dawson J, et al. Wound healing in partial-thickness burn wounds treated with collagenase ointment versus silver sulfadiazine cream. J Burn Care Rehabil. 1995;16(3):241–7.
22. Pavan R, Jain S, Shraddha KA. Properties and therapeutic application of bromelain: a review. Biotechnol Res Int. 2012;2012:976203.
23. Loo YL, Goh BKL, Jeffery S. An overview of the use of bromelain-based enzymatic debridement (Nexobrid®) in deep partial and full thickness burns: appraising the evidence. J Burn Care Res. 2018;39(6):932–8.
24. Moyer CA, Brentano L, Gravens DL, et al. Treatment of large human burns with 0.5% silver nitrate solution. Arch Surg. 1965;90:812–67.

25. Duran N, Duran M, de Jesus MB, et al. Silver nanoparticles: a new view on mechanistic aspects on antimicrobial activity. Nanomedicine. 2016;12:789–99.
26. Kumar Pandian SR, Deepak V, Kalishwaralal K, et al. Mechanism of bactericidal activity of silver nitrate – a concentration dependent bi – functional molecule. Braz J Microbiol. 2010;41:805–9.
27. Greenhalgh DG. Topical antimicrobial agents for burn wounds. Clin Plast Surg. 2009;36:597–606.
28. Aziz Z, Abu SF, Chong NJ. A systematic review of silver – containing dressings and topical silver agents (used with dressings) for burn wounds. Burns. 2012;38:307–18.
29. Ternberg JL, Luce E. Methemolglobinemia: a complication of the silver nitrate treatment of burns. Surgery. 1968;63:328–33.
30. Polk HC Jr, Monafo WW Jr, Moyer CA. Human burn survival: study of the efficacy of 0.5% aqueous silver nitrate. Arch Surg. 1969;98:262–5.
31. Lewis SR, Lynch JB, Blocker TG Jr, et al. Evaluation of topical burn therapy over the past 20 years. In: Matter P, Barclay TL, Konickova Z, editors. Research in burns. Stuttgart: Hans Huber; 1971. p. 111–5.
32. Monafo WW, Ayvazian VH. Topical therapy. Surg Clin No Am. 1978;58:1157–71.
33. Branemark PL, Breine U, Joshi M, et al. Microvascular pathophysiology of burned tissue. Ann N Y Acad Sci. 1968;150:474–94.
34. Bader JE. Organ deposition of silver following silver nitrate therapy of burns. Plast Reconstr Surg. 1966;37:550–1.
35. Marshall JP, Schneider RP. Systemic argyria secondary to topical silver nitrate. Arch Dermatol. 1977;113:1077–9.
36. Moore ML, Miller CS, Miller E. Substituted sulfanilamides: III. N^{4}-acyl-N^{1}-hydroxy derivatives. J Am Chem Soc. 1940;62:2097–9.
37. Jelenko C III, Jelenko JM, Mendelson JA, et al. The marfanil mystery. Surg Gynecol Obstet. 1966;122:121–7.
38. Mitchell GA, Rees VS, Robinson CN. Marfanil and marfanil prontalbin. Lancet. 1944;1:627.
39. Mendelson JA, Lindsey D. Sulfamylon (mafenide) and penicillin as expedient treatment of experimental massive open wounds with C. perfringens infection. J Trauma. 1962;2:239–61.
40. Lindberg RB, Moncrief JA, Switzer WE, et al. The successful control of burn wound sepsis. J Trauma. 1965;5:601–16.
41. Moncrief JA, Lindberg RB, Switzer WE, et al. Use of topical antibacterial therapy in the treatment of the burn wound. Arch Surg. 1966;92:558–65.
42. Moncrief JA. The status of topical antibacterial therapy in the treatment of burns. Surgery. 1968;63:862–7.
43. Pruitt BA. Multidisciplinary care and research for burn injury: 1976 Presidential Address, American Burn Association Meeting. J Trauma. 1977;17:263–8.
44. Haynes BW, Gayle WE, Madge GE. Sulfamyalon therapy in severe burns: 246 cases compared to previous experience. Ann Surg. 1969;170:696–704.
45. Harrison HN, Shuck JM, Caldwell E. Studies of the pain produced by mafenide acetate preparations in burns. Arch Surg. 1975;110:1446–9.
46. Pruitt BA, Curreri PW. The burn wound and its care. Arch Surg. 1971;103:461–8.
47. Yaffee HS, Dressler DP. Topical application of mafenide acetate: its association with erythema multiforme and cutaneous reactions. Arch Dermatol. 1969;100:277–81.
48. Schaner P, Shuck JM, Ritchey CR. A possible ventilatory effect of carbonic anhydrase inhibition following topical sulfamylon in burn patients. Anesthesiology. 1968;29:207–8.
49.• White NG, Asch MJ. Acid-base effect of topical mafenide acetate in the burn patient. N Engl J Med. 1971;284:1281–6.
50. Fox CL. Silver sulfadiazine-a new topical therapy for pseudomonas in burns. Arch Surg. 1968;96:184–8.
51. Baxter CR. Topical use of 1.0% silver sulfadiazine. In: Polk HC, Stone HH, editors. Contemporary burn management. Boston, Little: Brown; 1971. p. 217–25.
52. Kulick MI, Wong R, Okarma TB, Falces E, Berkowitz RL. Prospective study of side effects associated with the use of silver sulfadiazine in severely burned patients. Ann Plast Surg. 1985;14:407–19.
53. Willis MS, Cairns BA, Purdy A, et al. Persistent lactic acidosis after chronic topical application of silver sulfadiazine in a pediatric burn patient: a review of the literature. Int J Burns Trauma. 2013;3(1):1–8.
54. Fuller FW. The side effects of silver sulfadiazine. J Burn Care Res. 2009;30(3):464–70.
55. Koller J, Orsag M. Our experience with the use of cerium sulfadiazine in the treatment of extensive burns. Acta Chir Plast. 1998;40:73–5.
56. Monafo WW, Tandon SN, Ayvazian VH, et al. Cerium nitrate: a new topical antiseptic for extensive burns. Surgery. 1976;80:465–73.
57. Heggars JP, Ko F, Robson MC. Cerium nitrate/silver sulfadiazine synergism or antagonism as determined by minimum inhibitory concentration. Burns. 1979;5:308–11.
58. Salisbury RE, Bevin AG, Steinkraus GE, et al. Burn wound sepsis: effect of delayed treatment with topical chemotherapy on survival. J Trauma. 1980;20:120–2.
59. Stone HH. Wound care with topical gentamicin. In: Polk HC, Stone HH, editors. Contemporary burn management. Boston, Little: Brown; 1971. p. 203–16.
60.•• Hartford CE, Topical therapy of burns: 1981 ABA Presidential Address The J Trauma; 21:827–834. **Although nearly 40 years old this detailed essay on the history and clinical efficacies of short acting topicals is classic and has stood the test of time**.
61. Storm D. Mechanism of bacitracin action: a specific lipid-peptide interaction. Ann N Y Acad Sci. 1974;235(1):387–98.
62. Moncrief JA, Rivera J. The problem of infection in burns by resistant micro-organisms with a note on the use of bacitracin. Ann Surg. 1958;147(3):295–312.
63. Soto NE, Vaghjimal A, Stahl-Avicolli A, Protic JR. Bacitracin versus mupirocin for staph aureus nasal colonization. Infect Control Hosp Epidemiol. 1999;20(5):351–3.
64. Johnson B, Anker H, Meleney F. Bacitracin: a new antibiotic produced by a member of the B. subtilis group. Science. 1945;102(2650):376–7.
65. McQuillan RF, Chiu E, Nessim S, et al. A randomized controlled trial comparing mupirocin and polysporin triple ointments in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2012;7(2):297–303.
66. Fung S, O'Grady S, Kennedy C, Dedier H, Campbell I, Conly J. The utility of polysporin ointment in the eradication of methicillin-resistant Staphylococcus aureus colonization: a pilot study. Infect Control Hosp Epidemiol. 2000;21:653–5.
67. MacMillan BF. Comparison of topical antimicrobial agents. In: Polk Jr HC, Stone HH, editors. Contemporary burn management. Boston, Little: Brown; 1971. p. 227–44.
68. Leon-Villapalos JMG, Herndon DN. Topical management of facial burns. Burns. 2008;34(7):903–11.
69. Strock LL, Lee MM, Rutan RL, Desai MH, Robson MC, Herndon DN, et al. Topical Bactroban (mupirocin): efficacy in treating burn wounds infected with methicillin-resistant staphylococci. J Burn Care Rehabil. 1990;11(5):454–9.
70. Khoshnood S, Heidary M, Asadi A, Soleimani S, Motahar M, Savari M, et al. A review on mechanism of action, resistance, synergism, and clinical implications of mupirocin against Staphylococcus aureus. Biomed Pharmacother. 2019;109:1809–18.

71. Mahmoodzadeh Hosseini H, Kiyani N, Amin M, Hedayati Ch M, Imani Fooladi AA. Distribution of high-level mupirocin resistance among clinical MRSA 2017. J Chemother. 2017;29(4):215–9.
72.• Rossi CC, Ferreira NC, Coelho ML, et al. Transfer of mupirocin resistance from Staphylococcus haemolyticus clinical strains to Staphylococcus aureus through conjugative and mobilizable plasmids. Microbiol Lett. 2016;363(14). **This study describes how plasmid transfer of from innocuous organisms to other bacteria produces virulence**.
73. Burlando G, Cornara L. Honey in dermatology and skin care: a review. J Cosmet Dermatol. 2013;12(4):306–313.
74. Hayes G, Wright N, Gardner SL, Telzrow CL, Wommack AJ, Vigueira PA. Manuka honey and methylglyoxal increase the sensitivity of Staphylococcus aureus to linezolid. Lett Appl Microbiol. 2018;66(6):491–5.
75. Yaghoobi R, Kazerouni A, Kazerouni O. Evidence for clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory, anti-oxidant and anti-viral agent. Jundishapur J Nat Phar Prod. 2013;8(3):100–4.
76. Wijesinghe M, Weatherall M, Perrin K, et al. Honey in the treatment of burns: a systematic review and meta-analysis of its efficacy. In: Database of abstracts of reviews of effects (DARE): quality-assessed reviews [Internet]. York: Centre for Reviews and Dissemination (UK); 2009. 1995-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK78502. Accessed March 2019
77. Heggars J, Goodheart R, Washington J, et al. Therapeutic efficacy of three silver dressings in an infected animal model. J Burn Care Rehab. 2005;26(1):53–6.
78. Sheridan R. Burns. A practical approach to immediate treatment and long-term care: Manson Publishing; 2012.
79. Barillo DJ, Pozza M, Margaret-Brandt M. A literature review of the military uses of silver – nylon dressings with emphasis on wartime operations. Burns. 2014;40:S24–S29.
80. Cancio LC, Horvath EE, Barillo DJ, Kopchinski BJ, Charter KR, Montalvo AE, et al. Burn support for Operation Iraqi Freedom and related operations, 2003-2004. J Burn Care Rehabil. 2005;26(2):151–61.
81. Khundkar R, Malic C, Burge T. Use of Acticoat dressings in burns: what is the evidence? Burns. 2010;36(6):751–8.
82. Acticoat information guide from Smith and Wesson http://www.smith-nephew.com/key-products/advanced-wound-management/acticoat/. Accessed April 2019
83. Hamnett M, Chandra A, Chamaidi E, Farroha A. Improving and maintain the conformity of Acticoat dressings with shear reducing transfixion suture. J Burn Care Res. 2016;37(4):e398–9.
84.• Verbelen J, Hoeksema H, Heyneman A, Pirayesh A, Monstrey S. Aquacel Ag dressing versus Acticoat dressing in partial thickness burns: a prospective, randomized controlled study in 100 patients. Part 1: burn wound healing. Burns. 2014;40(3):416–27. **Excellent study demonstrating differences between two long acting silver dressings**.
85. Aquacel Ag Product information guide https://www.convatec.com/wound-skin/aquacel-dressings/aquacel-ag-extra/. Accessed April 2019
86. Mepilex Ag Product Information Guide https://www.molnlycke.us/products-solutions/mepilex-ag/. Accessed April 2019
87.• Silverstein P, et al. An open, parallel, randomized, comparative multicenter study to evaluate the cost-effectiveness, performance, tolerance, and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. J Burn Care Res. 2011;32(6):617–26. **Brilliant multicenter study that demonstrated superiority of long acting silver dressings to short acting topicals**.
88. Sanji N et al. Silver impregnated silicon foam dressing leads to fewer donor site infections compared to petroleum gauze: a retrospective review. American Burn Association 51st Annual Meeting. https://academic.oup.com/jbcr/article-abstract/40/Supplement_1/S150/5371873. Accessed April 2019
89. Demercan M, Gurunluoglu. The IL-6, TNF-alpha, and TGF-ß levels in serum and tissue in children with treated by different burn dressings. American Burn Association 51st Annual Meeting. https://academic.oup.com/jbcr/article-abstract/40/Supplement_1/S154/5371950. Accessed April 2019
90. Hallerstig LM, Granath P, Lindgren L, Tranberg M. Determination of silver in soft silicone wound dressings using dodecylbenzene sulfonic acid digestion and inductively coupled plasma optical emission spectroscopy. Anal Methods. 2017;9(1):149–53.