An Overview of the Topical Antimicrobial Agents Used in the Treatment of Burn Wounds

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Burn victims are susceptible to a wide array of infectious complications. Overall, care in burn centers with dedicated specialists in all aspects of burn care has led to advances in the medical and surgical management of burn victims leading to decrease in infectious complications. Medical improvements include: advances in resuscitation and intensive care specifically management of fluids and shock, recognition of the role of early enteral feeding, use of topical antimicrobials and adherence to strict infection control practices. Surgical advances include: early debridement and excision of the wound and improved grafting techniques and materials. Despite these remarkable advances, burn wound infection (BWI) continues to be an important source of morbidity and mortality in burn patients. Although the Microbiology Laboratory is rarely called upon to help in selection of topical antimicrobial agents, we need to understand how these agents are similar to, and different from, the kinds of antimicrobial agents more commonly tested and reported so that we can contribute to the care of these critically ill patients, when needed. This review is designed to familiarize Laboratory Technologist/Scientists with some of the more common antimicrobial agents used in the topical care of burn patients and to introduce the basic medical concepts needed to understand how these agents are used by clinicians.

Classification of Burns

Burns are classified according to the degree of dermal damage and the ability of the skin to epithelialize. Partial thickness wounds consist of superficial and deeper thermal burns which have a remnant of dermal appendage and are therefore capable of re epithelialization. In full thickness wounds, no dermal appendages are left and the skin is incapable of re epithelialization.

Partial thickness wounds may be further subdivided into 3 categories: 1) superficial (partial thickness or first degree) burns involve the epidermis and part of the superficial dermis. Common features include a red surface which blanches upon pressure, discharge, and pain with temperature changes and pressure stimuli. Healing is spontaneous and rapid. 2) Deep dermal (partial thickness or second degree) burns destroy both epidermis and the superficial dermis showing a dark red surface with moderate discharge. They are less sensitive to stimuli and demonstrate a slow spontaneous rate of healing. 3) Deep (full thickness or third degree) burns destroy both epidermis and dermis. They have a dry pearly white or charred surface which may be depressed from the surrounding skin. They are often less painful or insensitive to stimuli (although the surrounding areas of lesser degree burns may be painful). They demonstrate no spontaneous healing. To prevent scarring and contractures skin grafting is necessary.

Skin Defense Mechanisms

The skin has many natural protective defense mechanisms which deter invasion of microorganisms. These mechanisms include: a dry skin surface which limits bacterial survival and proliferation, continual skin desquamation, a nutritionally poor composition (acidic pH and fatty acids) which inhibit bacterial multiplication and the presence of non pathogenic normal flora which inhibits the growth of potentially pathogenic organisms.

The Burn Wound

Burn injury disrupts the skin’s natural protective barrier, which serves to protect the body from invading environmental bacteria. The skin’s surface flora changes after burn injury, resulting in the eventual overgrowth of pathogenic organisms. Until a complete epithelialization occurs, the burn patient is susceptible to bacterial invasion and infection.

Burn wounds are targets for bacterial colonization and subsequent tissue invasion. The burn wounds provide an excellent medium to cultivate bacteria due to their warm surface temperature, moist environment and availability of nutrients. The microorganisms that colonize the burn wound may originate from the patient’s normal flora or from the environment.

During the first hours post burn, wounds are generally sterile or are at the stage of superficial bacterial colonization. The first organisms to colonize the wound are staphylococci. By the fourth to fifth day post burn, extensive bacterial involvement of the wound itself is evident and Gram-negative organisms are present. By the end of the first week, the damaged skin is thoroughly permeated by the increased number of organisms and more virulent organisms begin active invasion of the unburned tissue. The avascular nature of the burn predisposes the burn site to bacterial invasion by impeding effective delivery of the bod-
ies own defenses and preventing systemic antibiotics from penetrating the damaged area.

Organisms which are frequently isolated from burn wounds include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacteriaceae* (*Klebsiella, Enterobacter, Providencia, Serratia*, and *Proteus* spp.) and *Candida* spp. In 1987, Winkler demonstrated that Gram-positive organisms accounted for 62.5% of bacterial isolates from 122 patients with burns > 40% total body surface area (TBSA); *S. aureus* was the most frequent isolate. Subsequently, Laursen described 253 patients admitted to the Copenhagen Burn Center. *S. aureus* was the most frequently isolated organism. Infection by Gram-negative bacteria tended to be found later in the course of hospitalization in this series. Predominant organisms may vary by institutions due to differences in resident microflora and antibiotic utilization.

Microbial factors involved in colonization and invasion include: bacterial adhesion and attachment properties, the production of exotoxins, endotoxins, permeability factors and enzymes. Consequences of bacterial invasion include: impairment or delay of the healing process, destruction of viable epithelial cells which may convert partial thickness wounds to full thickness wounds, decreased graft survival, development of generalized symptoms or systemic inflammatory response secondary to production of bacterial toxins and invasion of deeper tissue leading to local infection and or bacteremia.

**Goal of Topical Antimicrobial Treatment**

The burn eschar is the affected full thickness burned tissue which consists of coagulative necrosis of the epidermis, dermal and subcutaneous fat necrosis as well as vascular thrombosis involving the arterioles capillaries and venules. The denatured proteins and cellular debris along with the relative avascularity of the eschar provides an ideal environment for proliferating microorganisms. Although topical antimicrobial agents do not sterilize the burn wound, their goal is to limit bacterial proliferation below the threshold required to invade underlying viable tissue and cause burn wound infection. This converts a “dirty” open wound to a “clean” closed one. Since systemically administered antimicrobial agents lack adequate access to the damaged eschar, topical agents are thought to be useful in providing therapeutic levels on the wound surface where microbial numbers are the greatest.

**Choosing Topical Agents**

Topical antimicrobial agents are often chosen based on physician preference and experience. The optimal topical agent should be: a broad spectrum agent and include activity against organisms endemic to the burn unit, easy to apply, painless upon application, able to penetrate eschar, lack systemic absorption, able to penetrate eschar, lack systemic absorption and not impede it, long lasting, inexpensive and easy to store. Unfortunately, the ideal topical agent does not exist. Most important in choosing an agent is its activity against pathogens in the patient and in the burn unit. This is usually based on known susceptibilities of the topical agent because susceptibility testing of individual isolates is rarely performed outside of the research setting. Therefore it may be useful in patients at highest risk of infection (>30% TBSA) to perform routine surveillance cultures to know what their colonizing organisms are and base topical therapy on these results. Although skin surface cultures are more widely used due to the ease of performance, culture of burn wound biopsies provides the most reliable information as to the bacterial species and density. Isolation of pathogenic organisms on surface cultures does not establish a diagnosis of infection but identifies colonizing organisms that if in high density (>100,000org/gram of tissue) may invade underlying unburned, viable tissue causing burn wound infection. Frequent clinical observation is needed for assessing the therapeutic response in burn wound therapy. Use of an active topical agent decreases the organism density to prevent possible invasion. Once a burn wound infection is established, topical therapy plays an adjunctive role since management includes surgical debridement and excision and systemic antibiotic therapy.

**Acquired Resistance**

Acquired resistance to topical antimicrobials has been documented, particularly for topical gentamicin (possibly reflecting the routine use of susceptibility testing of gentamicin vs. other topical agents), although resistance to silver containing antimicrobials in *S. aureus, Providencia stuartii*, and *Enterococcus* spp. has been reported. Resistant organisms may pose a problem particularly in a setting where the patient numbers are large and isolation facilities are inadequate. As a general rule, antimicrobials that are to be used systemically should not be used topically due to the rapid emergence of resistance and possible transmission of these organisms in the burn unit.

**Summary of Specific Agents**

**Bacitracin** (Generic) is available as water soluble solutions and suspensions in petroleum bases. The mechanism of action is the interruption of cell wall synthesis. Bacitracin spectrum of activity is primarily against Gram-positive organisms with limited effectiveness against Gram-negative organisms and no antifungal activity. Bacitracin has limited eschar-penetrating ability. It is used for outpatient burns and shallow partial thickness burns, in particular on the face. A white petroleum base allows for soothing and comfortable application that makes it useful for small burns. It is also used on grafted wounds and donor sites. Due to bacitracin’s limited eschar penetrating ability. It is used for outpatient burns and shallow partial thickness burns, in particular on the face. A white petroleum base allows for soothing and comfortable application that makes it useful for small burns. It is also used on grafted wounds and donor sites. Due to bacitracin’s limited eschar penetrating ability. It is used for outpatient burns and shallow partial thickness burns, in particular on the face. A white petroleum base allows for soothing and comfortable application that makes it useful for small burns. It is also used on grafted wounds and donor sites. Due to bacitracin’s limited eschar penetrating ability. It is used for outpatient burns and shallow partial thickness burns, in particular on the face. A white petroleum base allows for soothing and comfortable application that makes it useful for small burns. It is also used on grafted wounds and donor sites. Due to bacitracin’s limited eschar penetrating ability. It is used for outpatient burns and shallow partial thickness burns, in particular on the face. A white petroleum base allows for soothing and comfortable application that makes it useful for small burns. It is also used on grafted wounds and donor sites. Due to bacitracin’s limited eschar penetrating
ability, it should not be used on deep burns. Adverse effects to topical application and are very rare; but include hypersensitivity reactions and fungal overgrowth.

**Cerium Nitrate Silver Sulfadiazine** (Flammac-erium). Since the mid-1970s, silver sulfadiazine modified by the addition of the lanthanide salt cerium nitrate has been used in the control and treatment of burn wounds. The ‘rare earth’ elements, one of which is the relatively non-toxic cerium, all have antimicrobial activity in vitro. The antimicrobial spectrum of cerium nitrate-silver sulfadiazine in vitro is similar to that of silver sulfadiazine or silver nitrate. Some investigators have suggested that the efficacy of the cerium nitrate-silver sulfadiazine combination might be due in part to an effect on immune function. The cell-mediated immune response appears to be preserved in burned mice treated with cerium nitrate alone or in combination with silver sulfadiazine. Methemoglobinemia, due to the absorption of reduced nitrate from the combination cream, has been only rarely seen. Cerium nitrate-silver sulfadiazine cream is not associated with electrolyte disturbances. Absorption of cerium has been documented in patients with large burns treated continuously with it for several weeks, but is minimal.

**Gentamicin** (Garamycin, Gentamar, et al). Gentamicin is usually applied as a 0.1% in a water miscible ointment. Its mechanism of action is it binds irreversibly to the 30s ribosome and inhibits protein synthesis. Gentamicin is a bacteriocidal, aminoglycoside with activity against Gram-negative organisms such as *Pseudomonas* sp., although *Pseudomonas* sp. can develop resistance. The drug is readily absorbed when applied topically which can result in significant blood levels and systemic toxicity including ototoxicity and nephrotoxicity. Other adverse affects include overgrowth of non-susceptible organisms such as fungus and *Pseudomonas* sp. Due to the rapid emergence of resistance of Gram-negatives and its marked toxicity when applied topically it should not be used routinely.

**Mafenide Acetate** (Sulfamylon). Mafenide (a- amino-p-toluene sulfonamide monoacetate) was introduced as a topical burn treatment in the mid-1960s. It is available in a water-soluble cream base containing 0.2% nitrofurazone and its marked toxicity when applied topically it should not be used routinely. Absorption of cerium has been documented in patients with large burns treated continuously with it for several weeks, but is minimal.

**Nitrofurazone** (Furacin). A water-soluble cream base containing 0.2% nitrofurazone is available. The mechanism of action is that it inhibits several bacterial enzymes involved in carbohydrate metabolism. It is bacteriocidal. Its spectrum of activity includes a variety of different Gram-positive and Gram-negative organisms, including *S. aureus*, *Escherichia coli*, *Enterobacter cloacae* and *Proteus spp.*, but does not have significant activity against *P. aeruginosa* or fungi. Nitrofurazone has good penetration into burn eschar and can be used with a variety of dressings.
Hypersensitivity reactions in the patient are rare. The adverse effects such as burning sensation, irritation, etc. are mainly due to the polyethylene glycol which is used in the preparation.

**Povidone Iodine** (Betadine). Povidone iodine is often used to treat minor burns. It is a water soluble complex formed by the interaction of iodine with the polymer polyvinyl pyrrolidone. On contact with the skin, it releases iodine slowly from the complex providing a mild antimicrobial effect. Although not completely understood, it seems most likely that iodine acts by oxidizing the sulfhydryl group of the amino acid cysteine. The spectrum of action of free iodine is very wide and includes both gram-positive and gram-negative organisms, including staphylococci and *Streptococcus pyogenes*. Acquired resistance has been reported for *Pseudomonas alcaligenes* and *Alcaligenes faecalis*. The adverse effects include pain, discomfort and secondary effects on thyroid function secondary to systemic absorption, alterations in renal function, which may include renal failure and/or serious electrolyte alterations mainly in severely burned children. Therefore, when using povidone careful monitoring of the patient for electrolyte imbalances is necessary.

**Silver Nitrate** (Generic). 0.5% silver nitrate solution was introduced as an effective topical burn therapy in the mid-1960s. This began the present era of topical therapy with silver compounds. The antibacterial action of silver nitrate is unknown but is probably dependent on free silver ions. It is bacteriostatic at lower concentrations (0.5%) and bacteriocidal at higher concentrations (10%). As a topical agent silver nitrate is effective against most strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* and also has activity against *Pseudomonas aeruginosa*. It has less activity against other Gram-negative species such as *Enterobacter* and *Klebsiella* spp. It does not penetrate the skin eschar to any significant degree because silver chloride and other silver salts are highly insoluble and precipitate on the wound surface. Adverse effects seen with silver nitrate are electrolyte imbalances secondary to hypotonicity. Methemoglobin is a rare complication. Application is relatively painless however the dressing must be changed every 2–3 hours to prevent development of histotoxic concentrations. The agent itself is inexpensive, but clinical use is associated with significant dressing changes and nursing time costs. Another major disadvantage of silver nitrate is that it stains everything brownish black.

**Silver Sulfadiazine** (Silvadene, SSD, Theramaze). Silver sulfadiazine is the most frequently used topical prophylactic agent. Silver sulfadiazine is a white, highly insoluble compound which is synthesized from silver nitrate and sodium sulfadiazine. It is available in 1% concentration in a water-soluble cream base. Sulfadiazine acts independently and is a competitive inhibitor of para aminobenzoic acid. Silver has been reported to act on the bacterial cell membranes. Silver binding may also impaire bacterial DNA replication. Although bacteriostatic, it has in vitro activity against a wide range of microbial pathogens including *S. aureus*, *E. coli*, *Klebsiella* spp., *P. aeruginosa*, *Proteus* spp., other Enterobacteriaceae and *C. albicans*. The advantages of silver sulfadiazine include a broad spectrum of activity, low toxicity, ease of application and minimal pain with application. Penetration of silver sulfadiazine into the skin eschar is intermediate. Adverse effects usually associated with sulfonamide are rare. The most common adverse effect with use is transient leukopenia, and on rare occasion a maculopapular rash. The use of silver sulfadiazine may also cause a “pseudoeschar” to develop within 2–4 days due to interaction of the drug with proteinaceous exudate in the wound. Although clinical trials suggest that silver sulfadiazine reduces wound bacterial numbers and delays colonization with gram-negative bacteria, treatment failures still occur with some frequency in large burns. The agent is usually applied on a daily or twice daily basis. When it is used on superficial second degree burns, a yellow-gray barrier may form after several days.

**References**


Questions for STEP Participants

Answer questions only on the official STEP answer sheet. If you do not have the official STEP answer sheet, a year’s supply can be obtained (at no cost), simply by writing to: STEP Program Answer Sheets, American Medical Technologists, 710 Higgins Road, Park Ridge, IL 60068-5765, or by fax: 847/823-0458, or by e-mail: paula.simoncini@amt1.com

In addition to marking your answers, be sure to include all the required information on the answer sheet and a processing fee of $3.00 per article.

In the following, choose the one best answer for each question.

1. The first organisms to colonize a burn wound are:
   A. Staphylococci
   B. Gram-negative bacilli
   C. Environmental organisms such as *Pseudomonas* spp.
   D. Gram-positive bacilli

2. The mechanism of action of the sulfadiazine portion of silver sulfadiazine is:
   A. inhibition of cell wall synthesis
   B. inhibition of protein synthesis at the ribosome
   C. inhibition of para-aminobenzoic acid metabolism
   D. bacteriocidal binding to mRNA.

3. The antibacterial action of silver nitrate is derived from:
   A. the release of nitric acid, a mild bacteriocidal agent
   B. Inhibition of cell wall synthesis
   C. the rapid penetration of silver nitrate through the eschar
   D. the release and subsequent action of free silver

4. An important side effect of the use of povidone iodine is:
   A. the selection of multiply resistant bacteria.
   B. the development of a yellow-gray barrier following use.
   C. electrolyte imbalance.
   D. negative effects on thyroid function.

5. The mechanism of action of nitrofurazone is:
   A. the inhibition of enzymes involved in carbohydrate metabolism.
   B. inhibition of protein synthesis at the ribosome
   C. inhibition of para-aminobenzoic acid metabolism
   D. bacteriocidal binding to mRNA.

6. Mupirocin action is mainly against:
   A. *Pseudomonas aeruginosa*
   B. *Escherichia coli*
   C. Gram-negative bacilli
   D. *Staphylococcus aureus*

7. Mafenide acetate mechanism of action is:
   A. the inhibition of enzymes involved in carbohydrate metabolism.
   B. inhibition of protein synthesis at the ribosome
   C. inhibition of para-aminobenzoic acid metabolism
   D. bacteriocidal binding to mRNA.

8. Gentamicin is a bacteriocidal agent of the class:
   A. aminoglycosides
   B. penicillins
   C. cephalosporins
   D. aminopepsidase

9. In addition to its antimicrobial activity, Cerium Nitrate Silver Sulfadiazine may effect:
   A. thyroid function.
   B. cell mediated immunity.
   C. kidney function.
   D. electrolyte balance.

10. The mechanism of action of bacitracin is:
    A. inhibition of cell wall synthesis
    B. inhibition of protein synthesis at the ribosome
    C. inhibition of para-aminobenzoic acid metabolism
    D. bacteriocidal binding to mRNA.