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Current Treatment Recommendations for Topical Burn Therapy

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Summary

Infections in burn patients continue to be the primary source of morbidity and mortality. Topical antimicrobial therapy remains the single most important component of wound care in hospitalised burn patients. The goal of prophylactic topical antimicrobial therapy is to control microbial colonisation and prevent burn wound infection. In selected clinical circumstances topical agents may be used to treat incipient or early burn wound infections. At the present time silver sulfadiazine is the most frequently used topical prophylactic agent; it is relatively inexpensive, easy to apply, well tolerated by patients, and has good activity against most burn pathogens. In patients with large burns the addition of cerium nitrate to silver sulfadiazine may improve bacterial control. Mafenide acetate has superior eschar-penetrating characteristics, making it the agent of choice for early treatment of burn wound sepsis. However, the duration and area of mafenide application must be limited because of systemic toxicity associated with prolonged or extensive use. Other agents, such as nitrofurazone or chlorhexidine preparations, may be useful in isolated clinical situations. The undesirable side effects of silver nitrate solution limit its use by most clinicians at the present time.

Burn wound infections are the primary source of morbidity and mortality in burn patients (Yurt et al. 1984). Burn injury disrupts both the normal skin barrier and many of the systemic host defence mechanisms that prevent infection, so that burn wounds are potentially susceptible to colonisation and infection by the multitude of environmental microorganisms with which the human body nor-

mally coexists. In the wound, the surface microflora changes after burn injury, with eventual predominance of more pathogenic organisms. The burn patient thus remains vulnerable to invasive microbial infections of all kinds until complete epitheliasation has occurred.

Complete early closure of the burn wound should theoretically eliminate the risk of serious infection. There is now a large body of literature – nearly all of it uncontrolled, however – supporting aggressive surgical wound excision and closure, even in patients with massive injuries (Burke et al. 1976; Chicarelli et al. 1986; Demling 1985; Feller et al. 1980; Gray et al. 1982; Herndon et al. 1989; Hunt & Sato 1982) but clear evidence that this approach decreases mortality in patients with massive burns has not appeared. Without effective topical antimicrobial therapy to minimise the risk of infection, these excisional techniques would carry a prohibitive mortality. Thus, at present, topical antimicrobial therapy remains the single most important component of wound care in all hospitalised burn patients.

1. Therapeutic Principles

Microscopic examination of full thickness burn injury demonstrates coagulative necrosis of the epidermis, variable degrees of dermal and subcutaneous fat necrosis, as well as vascular thrombosis involving arterioles, venules and capillaries (Order & Moncreif 1965). This devitalised tissue, the burn 'eschar', consisting of denatured protein and avascular cellular debris, provides an ideal environment for proliferation of microorganisms. Partial thickness burns are associated with more superficial injury when examined histologically; dermal thrombosis is limited to the outer dermis and circulation to the subcutaneous tissues is preserved. The dermal circulation is restored gradually, and during this healing interval infection of partial thickness burns can convert them to full thickness injuries. With restoration of the dermal circulation, eventual healing of the partial thickness burns is likely.

Systemically administered antimicrobial agents do not achieve reliable levels in the burn eschar because diffusion from the perfused wound margins into the avascular eschar is variable. In contrast, topical application of antimicrobials ensures that adequate concentrations are achieved on the wound surface, where microbial numbers are the greatest (fig. 1). Selected topical agents penetrate the eschar to a greater extent; these diffusible agents may also achieve effective concentrations at the interface between viable and nonviable dermis, thereby protecting against the infrequent occurrence of haematogenous eschar infection.

The bacterial flora of normal skin consist of a resident, relatively constant population of microbes residing in protected skin crevices and hair follicles, and a transient population that arises from the environment of the host and can be highly variable (Simmons & Ahrenholz 1988). Transient microbes are loosely attached and tend to disappear with time or can be easily washed away. The resident microflora are comparatively resistant to removal, but in most instances consist of relatively avirulent species.

Gram-positive, aerobic species predominate in the resident microflora, with diphtheroids (*Corynebacterium* species) being most abundant. Staphylococcal species are the next most common type of resident skin microorganism, with *Staphylococcus epidermidis* most typically present. *S. aureus* is found less often on normal skin but is frequently responsible for superficial infections and burn wound colonisation, and can be isolated from most hospitalised patients at discharge. Streptococcal species are not part of the normal skin microflora and therefore streptococcal infections, when they occur, are secondary to exogenous contamination (Noble & Sommerville 1974). Gram-negative bacteria are unusual residents of normal skin (Simmons & Ahrenholz 1988), but colonisation with pathogenic Gram-negative species, such as *Pseudomonas*, *Enterobacter* and *Serratia*, is frequent after admission to hospital (Pruitt & Lindbergh 1979). Fungi or yeasts such as *Candida* species (e.g. *C. albicans*) are unusual on exposed skin, but may be present on mucous membranes or in skin folds. The normal bacterial flora inhibit *C. albicans*, but

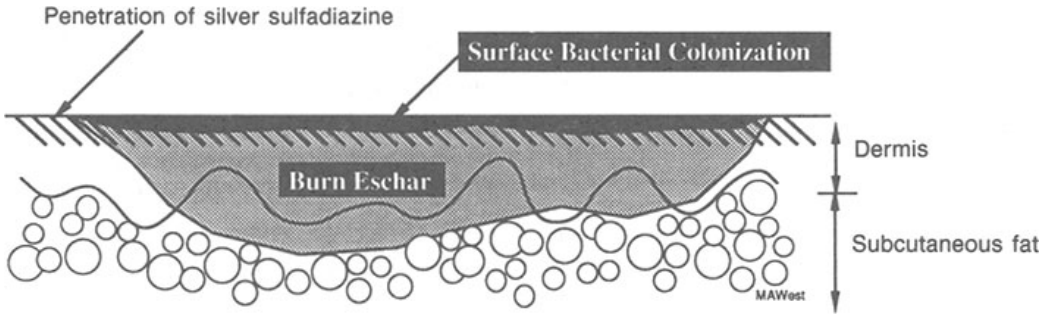

Fig. 1. Schematic cross-section of a full thickness burn wound showing surface bacterial colonisation. With appropriate use of prophylactic topical agents, bacterial colonisation can be limited and controlled in most patients. The figure shows that the moderate penetration of silver sulfadiazine (hatched lines) affords good control of superficial bacterial growth, although extensive burns will eventually become colonised. It should be clear that systemically administered antibiotics will not control bacterial growth at the surface.

antibiotic treatment can result in rapid overgrowth.

The density of microorganisms present on the skin surface is controlled by a number of host defence mechanisms: the skin surface is dry, limiting bacterial survival and multiplication; its outermost layers are continually lost via desquamation, with the loss of the attached colonising microbes; the skin surface is relatively nutrient-poor; and the presence of a nonpathogenic flora inhibits growth of other species. In addition, the acidic pH of the skin surface and the fatty acids in it further inhibit bacterial proliferation. These host defence mechanisms limiting microbial survival and growth are disrupted after burn injury. Heat from the burn injury destroys the most superficial nonpathogenic bacteria, favouring more virulent species residing in deep skin appendages or on mucous membranes. Burn injury converts skin from a dry to a moist environment, destroys the keratinised layers containing inhibitory fatty acids and raises the pH. With admission to hospital, the injured areas become further colonised by nosocomial pathogens. In the absence of topical antimicrobials, the burn wound can become colonised with up to 100 million Gram-positive bacteria per gram of tissue in less than 48 hours (Curreri 1988).

The bacteria isolated from burn wounds change with time and the therapeutic modalities employed. Initially, Gram-positive organisms predominate, but they are gradually superseded by Gram-negative opportunistic species (Pruitt & Lindbergh 1979). The Gram-negative organisms which are isolated most commonly include *Pseudomonas, Proteus* and *Klebsiella* species (Pruitt & McManus 1984). Invasive Gram-negative burn sepsis is associated with the extent of burn injury (Bowser-Wallace et al. 1984), as well as the presence of motile bacterial forms (McManus et al. 1980). With routine use of topical antimicrobial therapy directed against Gram-negative species, an increasing incidence of burn sepsis with *Staphylococci* has re-emerged recently (Bowser-Wallace et al. 1984). At present, the major problem with bacterial isolates following antimicrobial prophylaxis is the frequency of antibiotic resistance.

The goal of prophylactic topical antimicrobial therapy is to control microbial colonisation and thereby prevent burn wound infection. Prophylactic usage must be distinguished from therapy designed to *treat* established infection. Prophylactic agents do not need to penetrate the burn eschar deeply and should have a broad spectrum of activity against common pathogens. Topical antimicrobials used prophylactically should not retard wound healing and they should have minimal or no toxicity, implying that systemic absorption is nil. This modality has been universally adopted during the past 25 years because its efficacy and cost effectiveness are plain. The characteristics of

an ideal prophylactic antimicrobial agent are shown in table I. None of the topical antimicrobials, alone or in combination, will eliminate colonisation of burn wounds, but invasive infections are infrequent. The benefits of effective prophylactic topical treatment are listed in table II.

Use of topical antimicrobial agents for treatment implies that a specific infection is present. The goal of treatment is eradication of the infection, and the spectrum of activity of a therapeutic agent must include the responsible organism(s). Concerns about toxicity, cost, patient comfort and other factors must be weighed against the therapeutic goals. In most cases, eradication of an established invasive infection with a topical agent requires that it penetrate the eschar deeply, as invasion of tissue at the eschar-viable tissue interface has occurred. Development of burn wound sepsis is *prima facie* evidence of resistance to the prophylactic agent previously employed. Systemic or subeschar antibiotics are then administered, but these have the potential for significant systemic toxicity and also exert additional selection pressure on the patient's and burn unit's bacterial flora. Most clinicians treating burn patients have made use of the eschar penetrating properties of topical mafenide acetate to interdict incipient burn sepsis with staphylococcal or pseudomonal species (see fig. 2). More recently, reports of the successful eradication of established clinical burn wound sepsis with other topical agents have appeared (Munster 1984; Rode et al. 1988).

Table I. Characteristics of an ideal prophylactic topical antimicrobial agent

Activity against Gram-positive, Gram-negative and fungal species
Easy to apply
Painless
Penetrates eschar
No systemic absorption
Nontoxic
Speeds wound healing
Long-lasting
Inexpensive
Easy to store

Table II. Benefits of prophylactic topical antimicrobial agents

Delay initial bacterial colonisation
Maintain lower density of colonising bacteria for several weeks
Result in a less diverse wound flora
Prevent conversion of superficial injuries to full thickness wounds
Permit spontaneous healing of deep partial thickness wounds
Decrease the frequency of bacteraemic episodes

2. Specific Agents

The topical agents which have been or are currently most widely used are discussed in detail individually below. The basic principles which have been discussed regarding the pathophysiology of the burn wound, the goals of prophylactic therapy and treatment with topical antimicrobials should be used to select the appropriate agent in a given clinical setting. Failure with one agent does not preclude a response with another. Frequent clinical observation remains the best method of assessing the therapeutic response. Wound culture results, both quantitative and qualitative, require clinical correlation because the distinction between wound colonisation (which nearly always occurs) and wound infection (which is relatively uncommon) remains fundamentally clinical, although wound biopsy may be helpful to identify organisms invading unburned tissue. It is important to emphasise that topical agents cannot substitute for the meticulous wound care that is the mainstay of burn therapy. Debridement of devitalised tissue must be performed expeditiously and be repeated as necessary to limit bacterial proliferation.

2.1 Silver Sulfadiazine

At present, silver sulfadiazine is by far the most frequently used topical prophylactic agent. Silver sulfadiazine, a white, highly insoluble compound synthesised by Fox (1968) from silver nitrate and sodium sulfadiazine, is available as a 1% preparation in a water soluble cream base. The advantages of silver sulfadiazine include an excellent

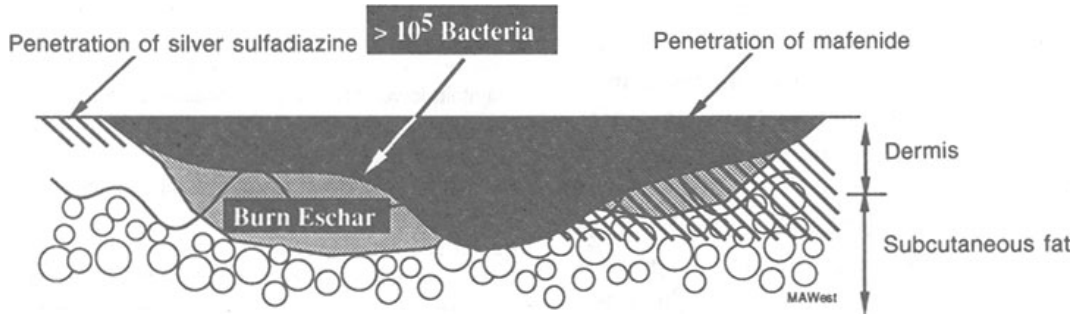

Fig. 2. Cross-section of a colonised and infected full thickness burn. Burn wound infection usually implies that > 10^5 bacteria per gram of tissue are present in the burn eschar. In the figure, variable depths of bacterial infection are depicted, with focal areas of bacterial invasion into unburned tissue. The limited penetration of silver sulfadiazine provides inadequate therapy for infected wounds. In contrast, the greater penetration of mafenide, shown on the right, may permit control of early burn sepsis. Once bacterial invasion into normal tissue has occurred, systemic antibiotic therapy can be effective. Inability to control focal burn sepsis with topical agents may necessitate surgical debridement.

antimicrobial spectrum of activity, low toxicity, ease of application and minimal pain with application.

Silver sulfadiazine has *in vitro* activity against a wide range of burn wound microbial pathogens including *S. aureus, Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Proteus* species, other *Enterobacteriaceae* and *C. albicans.* The mechanism of action of silver sulfadiazine is thought to be via 2 mechanisms: inhibition of DNA replication and modification of the cell membrane. Penetration into the eschar by silver sulfadiazine is intermediate between the lack of absorption seen with silver nitrate and the deep penetration of mafenide.

Adverse effects usually associated with sulphonamides, such as crystalluria or methaemoglobinaemia, are rare after silver sulfadiazine treatment. The most common adverse effect encountered clinically with the use of silver sulfadiazine is transient leucopenia (Smith-Choban & Marshall 1987). The leucopenia typically appears 2 to 3 days after initiation of therapy and is associated with a disproportionate decrease in the neutrophil population. Despite a 5 to 15% incidence of this phenomenon, there have been no reports of an increased incidence of infectious complications (Fuller & Engler 1988). The leucocyte count tends to recover whether or not the agent is withdrawn (Smith-Choban & Marshall 1987). This transient leucopenia may be an intrinsic response to burn injury and unrelated to the use of silver sulfadiazine (Fuller & Engler 1988). Cutaneous sensitivity reactions, typically a maculopapular rash, occur in less than 5% of patients and rarely require stopping the use of silver sulfadiazine.

Clinical trials have shown that silver sulfadiazine is efficacious at reducing bacterial numbers and delaying burn wound colonisation with Gram-negative bacteria. Treatment failure with continued use in large burns [>50 to 60% of body surface area (bsa)] still occurs with silver sulfadiazine (and other agents), however. Silver sulfadiazine may be applied in an 'open' manner or used with dressings. The 1% cream is reapplied every 24 to 48 hours. With extensive burns, it should be applied at least every 24 hours; treatment should commence as soon after the burn injury as possible. Twice daily application of the drug has also been suggested as being useful as an adjunct to central venous catheter maintenance in central line sites placed through eschar, granulation tissue or healing grafts (Bentivegna 1990). Use of silver sulfadiazine is frequently associated with the development of a 'pseudoeschar' within 2 to 4 days due to interaction of the drug with proteinaceous exudate in the wound. The yellow-grey pseudoeschar can be confused with full thickness injury, but it sep-

arates readily within several days, exposing the true wound surface.

2.2 Cerium Nitrate-Silver Sulfadiazine

The lanthanides or 'rare earth' elements all have antimicrobial activity *in vitro*. Fox et al. (1977) reported that the modification of silver sulfadiazine by the incorporation of cerium nitrate resulted in enhanced clinical efficacy in patients with large burns (greater than 50% bsa). Theoretically, cerium nitrate-silver sulfadiazine cream provides several potentially antimicrobial substances *in vivo*: silver and cerium ions and sulfadiazine. The antimicrobial activity of cerium nitrate-silver sulfadiazine is similar to that of silver sulfadiazine or silver nitrate. Another theoretical advantage of the inclusion of cerium nitrate is reversal of postburn injury immunosuppression. Peterson et al. (1985) showed that treatment of burned mice with cerium nitrate alone or in combination with silver sulfadiazine prevented postburn alterations in cell-mediated immunity. Cerium nitrate-silver sulfadiazine provides excellent coverage for most Gram-positive and Gram-negative organisms, good antifungal activity, and may be superior to silver sulfadiazine alone. The compound is commercially available in some Western European countries; it is easily prepared by adding a concentrated aqueous solution of cerium nitrate [$Ce(NO_3)3.6\ H_2O$] to silver sulfadiazine cream (Fox et al. 1977). (The concentrated cerium solution does not appreciably dilute the 1% silver sulfadiazine.)

Adverse effects with the combination are similar to those seen with silver sulfadiazine. Methaemoglobinaemia from reduction of nitrate to nitrite has been observed, as seen with silver nitrate, but no other toxicity related to the cerium nitrate has been reported. Cerium nitrate-silver sulfadiazine cream is not associated with the electrolyte disturbances seen with 0.5% silver nitrate (see below).

Clinically, use of cerium nitrate-silver sulfadiazine cream is identical to that of silver sulfadiazine cream. The combination is used most frequently in conjunction with dressings, but can be applied without dressings if preferred. A prospective randomised clinical trial by Munster et al. (1980) comparing cerium nitrate-silver sulfadiazine to silver sulfadiazine alone showed no difference in mortality, but a decrease in the density of colonising bacteria in the cerium nitrate-silver sulfadiazine group. Other studies show superior control of bacterial levels with this combination (Hermans 1984). In our view, this is an important prophylactic agent in patients with life-threatening injuries.

2.3 Mafenide

Mafenide (alpha-amino-*p*-toluene sulphonamidemonoacetate) is a methylated sulphonamide introduced in the mid-sixties as a topically applied cream (Lindbergh et al. 1968). It was the most common topical agent used prophylactically for burns of all degrees of severity prior to the development of silver sulfadiazine. Topical mafenide is formulated as an 11.1% suspension in a water soluble cream base. It has excellent bacteriostatic activity (Schuck et al. 1975) against most Gram-positive species, including *Clostridia* species, but has limited activity against some *S. aureus*, particularly methicillin-resistant strains. It possesses a broad spectrum of activity *in vitro* against most Gram-negative burn pathogens, but has little antifungal activity (Pruitt & Goodwin 1987). The mechanism of action of mafenide is not precisely known. The concentrations of the drug used clinically are bacteriostatic, with much higher levels being necessary for bacteriocidal activity. Despite this, the drug is quite effective clinically. Morbidity and mortality from the side effects of mafenide (see below), as well as reports of resistant *P. stuartii* infection and fungal superinfection, led to the abandonment of mafenide for routine burn prophylaxis during the 1970s.

Mafenide penetrates the burn eschar rapidly and is metabolised to an inactive acid salt which is excreted in the urine (Harrison et al. 1971). It is a potent inhibitor of carbonic anhydrase; this effect, combined with the osmotic effects of the breakdown product, results in a significant osmotic diuresis. Drug absorption through the burn wound

is so rapid that after 3 to 4 hours low concentrations are present on the wound surface, whereas concentrations of 1.5 mg/dl are present in the wound (Harrison et al. 1972). After 8 to 10 hours, levels in the wound drop below the effective concentration and topical application must be repeated. Following absorption into the blood stream the active compound is deaminated; therefore, no systemic antimicrobial effects are seen.

The carbonic anhydrase activity and the diuresis associated with mafenide application produce significant electrolyte abnormalities (White & Asch 1971). Hyperchloraemic metabolic acidosis is typically seen, with moderate to severe tachypnoea from the associated respiratory compensation. The pCO_2 is frequently reduced and a minute ventilation as high as 50 L/min may occur. The compensated metabolic acidosis decreases the blood buffering capacity and predisposes to decompensated acidosis. Pulmonary complications are seen with an unacceptable frequency after prolonged use of mafenide in burns of greater than 40% bsa. It should be discontinued promptly in this setting, with the expectation that these adverse effects should resolve within 24 to 36 hours (Moncrief et al. 1966). Another disadvantage of mafenide is that application is quite painful, possibly due to its high osmolarity. The pain is most marked in the early postburn period and decreases somewhat with continued use. A maculopapular rash is seen in approximately 50% of patients, but this reaction is usually readily controlled with antihistamines. Experimental studies indicate that mafenide inhibits epithelial regeneration, a property which is probably shared by all topical agents, however (McCauley et al. 1989).

Clinical use of mafenide has decreased significantly in the past decade, although it may still be the most useful agent for treatment of invasive burn wound infection because of its superior eschar penetration. Because of its rapid absorption it must be applied twice daily; more frequent applications, however, result in toxic complications. Careful monitoring of pulmonary function and acid-base status is critical. Mafenide may safely be used to control invasive burn wound infection, but should be used for as short a period as possible. The risk of toxicity increases significantly in proportion to the size of the area treated and the duration of treatment (Moncrief 1978).

2.4 Silver Nitrate Solution

Silver nitrate has been used since antiquity as an antiseptic agent. In concentrated form it is highly toxic to tissues, as can be seen with the silver nitrate granules used to cauterise hypertrophic granulation tissue. Silver nitrate formulated as a 0.5% solution retains significant antimicrobial activity without tissue toxicity (Monafo & Moyer 1965). Topical use of this agent to treat burn patients was introduced by Moyer in the mid-sixties (Moyer et al. 1965), signalling the beginning of the present era of topical therapy with silver compounds. Silver nitrate is effective against most strains of *S. aureus* and *S. epidermidis*, and also has activity against *P. aeruginosa*. It has less activity against other Gram-negative species such as *Enterobacter* and *Klebsiella* species.

The precise mechanism by which silver nitrate inhibits microbial growth is unknown, but ionic silver exerts antimicrobial activity via many potential mechanisms (Moyer et al. 1965). The non-histotoxic concentrations (0.5%) used clinically are bacteriostatic, and bactericidal activity requires higher concentrations (10%). Silver nitrate does not penetrate the burn eschar to any significant degree because silver chloride and other silver salts are highly insoluble and precipitate on the wound surface (Constable et al. 1967). The agent itself is inexpensive, but clinical use is associated with significant dressing and nursing time costs.

Silver salts are extremely insoluble and 0.5% silver nitrate solution must therefore be prepared with distilled water; the resulting final solution is extremely hypotonic (29.4 mmol silver/L) [Moyer et al. 1965]. Electrolyte imbalances, secondary to this hypotonicity, are the major adverse effect of silver nitrate therapy. The 0.5% solution leaches large quantities of sodium, potassium and other solutes into the dressings. Up to 350 mmol/day of sodium may be lost per square metre of body surface area

treated with silver nitrate, necessitating continuous oral or intravenous electrolyte supplementation. Electrolyte balance must be carefully and continuously monitored, especially in infants or children with major burns (Bonder et al. 1967). Methaemoglobinaemia is another potential complication of therapy with silver nitrate, but is fortunately rare. It occurs via bacterial reduction of nitrate to nitrite, which is subsequently absorbed (Moyer et al. 1965). The diagnosis should be suspected if the skin or blood appear cyanotic or 'grey' in the presence of a normal arterial pO_2. The diagnosis can be confirmed with measurement of the blood methaemoglobin level. The silver nitrate should be discontinued if this complication occurs. Rarely, treatment with reducing agents may be required.

Application of silver nitrate is relatively painless. Thick cotton dressings saturated with 0.5% silver nitrate are applied to thoroughly debrided areas. The dressings must be rewetted every 2 to 3 hours with fresh 0.5% solution to prevent development of histotoxic concentrations (2 to 3%) at the wound surface (Moyer et al. 1965). The bulky dressings prevent evaporative losses from patients with major burns and thus provide an added metabolic advantage. A major disadvantage of silver nitrate is that it stains everything it touches brown-black. The bulky dressings also limit patient movement and the required frequency of dressing soaks consumes valuable and expensive nursing time. Properly used, silver nitrate is still an effective prophylactic agent, but the lack of eschar penetrating ability makes it an inappropriate choice for established infections.

2.5 Other Agents

Nitrofurazone topical cream contains 0.2% nitrofurazone in a water soluble cream base. Nitrofurazone has bacteriocidal activity for a number of important burn pathogens, including *S. aureus, E. coli, Enterobacter cloacae* and *Proteus* species, but does not have significant activity against *P. aeruginosa* or fungi. It acts via inhibition of several bacterial enzymes involved in carbohydrate metabolism. Nitrofurazone cream can be applied in an 'open' fashion or used with a variety of dressings and should be applied daily or every other day. Adverse reactions with the cream preparation are unusual, but 1% of patients develop local skin reactions or pruritus.

Chlorhexidine preparations have been used clinically in moderate burn injuries and are the subject of continuing evaluations. Chlorhexidine gluconate combined with 0.5% silver nitrate is comparable in terms of usefulness to silver sulfadiazine (Lawrence et al. 1982). A newer conjugate, chlorhexidine diphosphanilate, shows greater promise as a clinically useful topical antimicrobial, but pain on application has been noted in clinical trials (McManus et al. 1984). Chlorhexidine phosphanilate has excellent activity against Gram-negative enteric pathogens as well as most species of *S. aureus, S. epidermidis* and *P. aeruginosa.* In contrast to sulfonamide agents, plasmid-mediated resistance has not been demonstrated with chlorhexidine.

Povidone iodine (Hunt et al. 1980) has not proved useful as a topical antimicrobial treatment for burn patients, although its antimicrobial spectrum *in vitro* is excellent, including most of the common Gram-positive and Gram-negative pathogens, as well as fungi and viruses. Povidone iodine is inactivated by wound exudate, however, which significantly limits its clinical effectiveness. Clinical use of this preparation is also limited by the release and systemic absorption of iodine, with resultant renal and thyroid dysfunction (Hunt et al. 1980; Rath & Meissl 1988).

3. Conclusions

Silver sulfadiazine is currently the initial topical antimicrobial of choice for prophylactic use in most patients. It is relatively inexpensive, easy to apply, well tolerated by patients, and has good activity against most burn pathogens. In patients with large burns (greater than 40 to 60% bsa), the addition of cerium nitrate to silver sulfadiazine appears to enhance bacterial control. The superior eschar-penetrating characteristics of mafenide make it the agent of choice for early topical treatment of burn wound sepsis. However, the duration and area of

mafenide application must be limited because prolonged or extensive use is associated with systemic toxicity. Agents such as nitrofurazone or chlorhexidine preparations may occasionally be useful in isolated clinical situations. 0.5% silver nitrate solution is presently used infrequently by most clinicians because of its undesirable side effects. In the future, new agents (Holder et al. 1986; Rode et al. 1988), new combinations of existing topical antimicrobials (Heggers et al. 1989), and new delivery methods of established topical agents (Deitch et al. 1987) will continue to appear. However, clear evidence of their clinical efficacy should be forthcoming before established therapies are abandoned.

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