# Topical Antibacterial Agents for Wound Care: A Primer

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**Although often overlooked, topical antibiotic agents play an important role in dermatology. Their many uses include prophylaxis against cutaneous infections, treatment of minor wounds and infections, and elimination of nasal carriage of *Stapylococcus aureus*. For these indications, they are advantageous over their systemic counterparts because they deliver a higher concentration of medication directly to the desired area and are less frequently implicated in causing bacterial resistance. The ideal topical antibiotic has a broad spectrum of activity, has persistent antibacterial effects, and has minimal toxicity or incidence of allergy.**

*C. T. SPANN, MD, W. D. TUTRONE, BS, J. M. WEINBERG, MD, N. SCHEINFELD, MD, AND B. ROSS, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.*

THE MAJOR advantage in the topical use of an antibiotic is the ability to achieve high local drug concentrations with minimal systemic absorption, thereby minimizing the risk of systemic adverse effects. Topical antibacterial agents are generally divided into two major categories: those used primarily for wound care and those used primarily for acne and rosacea. This article focuses on the former. The dermatologic indications for and the mechanism of action of some of the most commonly used topical antimicrobials, including mupirocin, neomycin, bacitracin, polymyxin, erythromycin, gentamycin, and silver sulfadiazine, are reviewed. Several new antimicrobial agents and issues of bacterial resistance are also addressed. Table 1 gives a summary of the data presented in this article.

## Mupirocin

Mupirocin (Figure 1) is a naturally occurring antibiotic whose chemical name is (E)-(2S, 3R, 4R, 5S)-5-[(2S, 3S, 4S, 5S)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3, 4-dihydroxy-β-methyl-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid.[1] Mupirocin, available as a cream or ointment, is unusual in its origin and mechanism of action. It is also known as pseudomonic acid and is a fermentation product of *Pseudomonas fluorescens*. It inhibits protein synthesis, actively preventing the incorporation of isoleucine into protein by binding to isoleucyl transfer-RNA synthetase.[2] Because of this unique mechanism of action, there is no in vitro incidence of cross-reactivity with other antimicrobials. Mupirocin is highly effective against aerobic gram-positive cocci (namely *Stapylococcus aureus*, *Staphylococcus epidermidis*, and beta-hemolytic streptococci) and some gram-negative cocci but spares much of the normal flora.[2] Its indications include prophylaxis in ulcers, operative wounds, and burns; treatment of skin infections; and the eradication of nasal carriage of *S. aureus*. Mupirocin is the treatment of choice for nonbullous impetigo and has been shown to be as effective as an oral antibiotic.[1] In addition, mupirocin has proven useful in the management of secondary pyodermas or superinfection of chronic dermatoses.

The efficacy of the cream formulation of mupirocin in mouse surgical models with primary and secondary wounds infected with *S. aureus* and *Streptococcus pyogenes* was recently evaluated. Mupirocin cream was found to be similar in efficacy to oral flucloxacillin but significantly more effective than oral erythromycin.[3] The same study found mupirocin cream to be similar in efficacy to cephalexin against *S. pyogenes* and superior to cephalexin against *S. aureus*.[3] Colonization of chronic atopic dermatitis with *S. aureus* is frequently encountered and is effectively controlled with mupirocin if the infection is localized.[4]

Recurrent impetigo, furunculosis, or other staphylococcal infections may be a result of pathogenic nasal carriage of *S. aureus*. Mupirocin is the most effective topical antibiotic for the elimination of nasal colonization of *S. aureus* and is effective in reducing subsequent infections.[1] When applied intranasally four times daily for 5 days, it has been shown to reduce nasal carriage for up to 1 year.[1] This advantage has

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ISSN: 1076-0512/02/$15.00/0 • Dermatol Surg 2003;29:620–626

**Table 1.** Summary of Topical Antibacterial Agents

| *Antibiotic* | *Bacteriostatic Versus Bacteriocidal* | *Mechanism of Action* | *Spectrum of Activity* | *Special Indications* | *Additional Considerations* | *Resistance* |
|---|---|---|---|---|---|---|
| Mupirocin (Bactroban) | Bacteriocidal | Inhibits protein synthesis by preventing incorporation of isoleucine | Gm +, some Gm –, spares normal flora | Nonbullous impetigo, eradication of nasal carriage of *S. aureus* | | Infrequent; low levels overcome with highdose Mupirocin |
| Neomycin | Bacteriocidal | Inhibits protein synthesis by binding to rRNA | Most Gm –, some Gm + (not anaerobes or streptococci) | Superficial infections | Causes contact derm in some patients; potential for systemic toxicity if absorbed | Plasmid-mediated in Gm + and Gm – cocci |
| Bacitracin | Bacteriocidal | Blocks cell wall synthesis by inhibiting peptidoglycan synthesis | Gm +, Gm – | Superficial infections, prophylaxis | Cross-sensitization with neomycin | Uncommon, but documented in some staphylococci |
| Polymyxin | Bacteriocidal | Disrupts phospholipids in cell membranes | Some Gm – (not active against most Gm +) | Superficial infections, prophylaxis | Limited spectrum of activity | Not documented |
| Erythromycin | Bacteriocidal | Inhibits protein synthesis by binding 50s subunit of ribosome | Gram + cocci, *Corynebacterium diptheriae, Hemophilus influenzae, Chlamydiae Treponema pallidum* | Acne, ophthalmic, surgical wounds | Low incidence of sensitization | Resistant strains of *P. acnes* in antibiotic-treated acne patients |
| Gentamicin | Bacteriocidal | Inhibits protein synthesis by binding 30s subunit | Some gram +, some gram – | Ophthalmic | Cross-reactivity with neomycin; not effective against streptococci | Not documented |
| Neomycin/ Polymyxin B Sulfate/ Bacitracin zinc (Neosporin) | Bacteriocidal | See individual descriptions | Active against *S. Aureus, S. pneumoniae, E. coli, Neisseria, and P. aerugin* | Superficial infections, prophylaxis, adjunct in burns | Does not cover *Serratia marcescens*; potential for allergy | Uncommon |
| Bacitracin zinc /Polymyxin B sulfate (Polysporin) | Bacteriocidal | See individual descriptions | See individual descriptions | Superficial infections, prophylaxis, adjunct in burns | Potential for allergy if neomycin cross-sensitization | Uncommon |
| Silver Sulfadiazine (Silvadene) | Bacteriocidal | Cell wall interference | Most Gm + and Gm – (includes *P. aeruginosa* and *Staphylococcus*) | Burns, mild infections | Rare reports of neutropenia, leukopenia; frequent use may cause hyperpigmentation | Documented in *P. aeruginosa;* but stable |

Gm + = gram-positive bacteria; Gm – = gram-negative bacteria, MRSA = methicillin resistant *S. Aureus.*

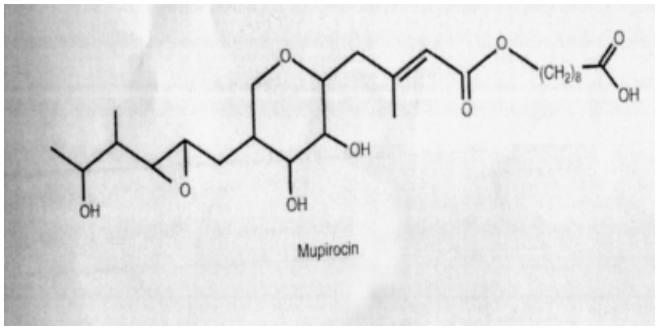


**Figure 1.** The chemical structure of mupirocin. Mupirocin inhibits protein synthesis by preventing the incorporation of isoleucine into protein.

been extended to colonized healthcare workers and other susceptible patients in an attempt to reduce postoperative complications. Double-blind, placebo-controlled trials showed that mupirocin eradicated 78% of the original strains of *S. aureus* at 4 weeks and reduced nasal and hand carriage for up to a year after 5 days of intranasal application.[2,5] These results were corroborated in a recent study that examined immunocompetent staphylococcal carriers who experienced recurrent skin infections. The study concluded that an initial 5-day course of mupirocin followed by a 5-day course of nasal mupirocin every month for 1 year reduced the incidence of nasal colonization and in turn lowered the risk of skin infection.[6] It is important to realize that mupirocin has only proven beneficial in the reduction of methicillin-sensitive *S. aureus*. In a randomized, placebo-controlled, double-blind trial to evaluate mupirocin in the setting of endemic methicillin-resistant *S. aureus*, nasal mupirocin was only marginally effective in the eradication of multisite methicillin-resistant *S. aureus* carriage.[7]

Although the incidence of adverse reactions to mupirocin is typically low (occurring in less than 1.5% of patients), several local side effects have been reported. These include burning, stinging, or pain in 1.5% of patients and itching in 1% of patients.[8] Rash, nausea, contact dermatitis, erythema, dry skin, tenderness, swelling, and increased exudate are reported in less than 1% of patients.[8]

Resistance to mupirocin has been reported but is not common. Some strains of bacteria have a low level of resistance but succumb to high-dose mupirocin.[9] Infrequently, strains have a high-level plasmid-mediated resistance that is not responsive to high-dose mupirocin.[9] Recently, mupirocin use over 10 years was followed, and it was noted that short courses of treatment, even when repeated, were associated with remarkably little resistance.[10] As with all antibiotics, judicious use will help prevent resistance.

## Neomycin

Neomycin sulfate, the sulfate salt of neomycin B and C, is one of the most commonly used topical antibiotics. It is an aminoglycoside antibiotic produced by the growth of *Streptomyces fradiae*.[8] Its mechanism of action is to inhibit protein synthesis by binding with ribosomal RNA, causing misreading of the bacterial genetic code.[8] With the exception of *P. aeruginosa*, it is bactericidal against most gram-negative bacteria; however, it lacks activity against anaerobes.[2] It is active against some gram-positive bacteria, including staphylococci, but is not effective against streptococci.[2]

Commercially, neomycin is available as 20% neomycin sulfate in a petrolatum vehicle and is frequently combined with other topical antimicrobials to improve its coverage against gram-positive bacteria. Its indications include the treatment of superficial infections, prophylaxis against infection in minor wounds and postoperative wounds, adjunctive treatment of burns, and management of superinfection in chronic dermatoses. Although it is frequently used in the management of stasis dermatitis and chronic leg ulcers, caution must be exercised, as application to compromised skin can lead to sensitization, systemic absorption, and potentially systemic toxicity.[2,8] Allergic contact dermatitis is another adverse effect of neomycin that occurs in intact skin in 1% to 6% of the population; the incidence is even higher in damaged skin.[2] In patients with stasis dermatitis or leg ulcers, the incidence of contact dermatitis reported is as high as 30%.[11] The potential for delayed hypersensitivity, IgE-mediated reactions, and anaphylactic reactions to neomycin also exists. The potential for resistance in neomycin is a further disadvantage. Resistance can be plasmid mediated and has been reported in gram-positive cocci (including staphylococci) and gram-negative cocci, including *Escherichia Coli*, *Klebsiella*, and *Proteus*.[2]

## Bacitracin

Bacitracin (Figure 2) is an inexpensive, low risk for toxicity, and readily available topical antibiotic. Therefore, it is one of the most popular topical antibiotics. It is produced by growth of an organism of the *lichenformis* group of *Bacillus subtilis*.[8] Bacitracin is bactericidal for a variety of gram-positive and gram-negative organisms. It blocks bacterial cell wall synthesis by inhibiting the regeneration of phospholipid receptors involved in peptidoglycan synthesis. Resistance is uncommon but has been reported in some strains of staphylococci.

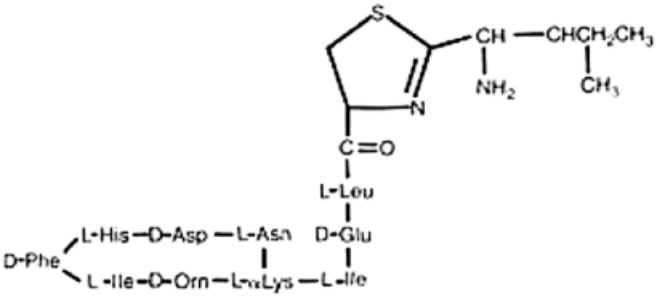


**Figure 2.** The chemical structure of bacitracin.

Bacitracin is indicated in prophylaxis and treatment of local infections, treatment of secondary pyodermas, as an adjunct in burn treatment, and as prophylaxis in operative wounds. Along with neomycin, it is not indicated in the treatment of chronic ulcers because of the increased risk of sensitization.[2] Although neomycin allergy may predispose to bacitracin-induced allergic contact dermatitis, the incidence of allergy to bacitracin itself is low. The risk of allergy should not be disregarded, however, as there are rare occurrences of delayed hypersensitivity, acute IgE-mediated allergic reactions, and anaphylactic reactions to bacitracin documented in the literature.[12–16] One study suggests that white petrolatum is a safe and effective wound care alternative to bacitracin, which may be especially useful in patients with known sensitizations. The study demonstrated that in 922 patients, 9 (2%) patients in the white petrolatum group versus 4 (0.9%) in the bacitracin group developed postprocedure infections.[17] In addition, there was no clinically significant difference in healing between the groups on Days 1, 7, or 28.[17] The study reported no incidence of allergic contact dermatitis in the petrolatum group and allergic contact dermatitis in four (0.9%) of patients in the bacitracin group.[17] Therefore, white petrolatum is a reasonable alternative to bacitracin in patients with known sensitivity and chronic wounds.

## Polymyxin

Polymyxins are decapeptides that are isolated from *Bacillus polymyxa*.[2] Because bacitracin is similarly isolated from *Bacillus* sp., there is potential for allergic cross-reactivity between polymyxin and bacitracin. However, cutaneous sensitization is rare, and systemic absorbance and toxicity are unlikely.

The mechanism of action is to disrupt the phospholipid component of the cell membranes through a surfactant-like action, resulting in increased permeability of the bacterial cell.[2,8] They are bactericidal against some gram-negative bacteria, but their spectrum of activity is limited. Polymyxins are largely inactive against most gram-positive bacteria and *Providencia*.[2] In contrast, polymyxins are bactericidal against *P. aeruginosa*, *Proteus mirabilis*, *Serratia marcescens*, *E. coli*, *Enterobacter*, and *Klebsiella*. Combinations of polymyxin with zinc, bacitracin, and neomycin comprise some of the more common antibacterial ointments (i.e., Neosporin and Polysporin) and increase the spectrum of activity.

Similar to the other topical antibiotics, polymyxins are indicated in prophylaxis and treatment of superficial wounds, in the treatment of secondary pyodermas, as adjunctive measures in burns, and for prophylaxis in the surgical wound. They are generally well tolerated and are most frequently used in combination with other topical antimicrobials for maximum efficacy.

## Erythromycin

Topical erythromycin is used most frequently in the treatment of acne vulgaris and ophthalmic preparations; however, an ointment formulation is also useful in postsurgical wound care.[11] Erythromycin is a macrolide antibiotic that is derived from *Streptomyces erythraeus*. It is a bactericidal drug against gram-positive bacteria, which works by irreversibly binding to the 50s subunit of the bacterial ribosome, thereby inhibiting protein synthesis.[8] Because of the expensive of other topical antibiotics and the potential for sensitization, erythromycin 2% powder was compounded in white petrolatum to form erythromycin 2% ointment.[11] This ointment proved to have a very low incidence of sensitization at 0.022% in surgical procedures.[11] In addition, the rate of wound infection was 0.586%.[11] Erythromycin 2% ointment was therefore deemed to be a worthy substitute for other topical antibiotics.[11]

## Gentamicin

Topical gentamicin is an aminoglycoside isolated from *Micromonospora purpurea*. It is bactericidal against some gram-positive bacteria and gram-negative bacteria. Reportedly, gentamicin is not effective against streptococci. It works by irreversibly binding to the 30s subunit of the ribosome, thereby inhibiting protein synthesis. Gentamicin sulfate has been reported to have a true cross-reactivity, as high as 40%, with neomycin.[11] Because of this cross-reactivity, its use is limited mainly to ophthalmic preparations for the treatment of bacterial conjunctivitis.

## Combination Topical Antibiotics

As previously mentioned, the most frequently used topical antibiotic agents contain compounds of several

medications for more adequate antibacterial coverage. Neomycin, polymyxin B sulfate, and bacitracin zinc in combination (Neosporin) are considered active against *S. aureus, Streptococcus pneumoniae, E. coli, Neisseria,* and *P. aeruginosa*. However, the combination does not provide adequate coverage against *Serratia marcescens*.[8] Because of the neomycin component of this combination, caution must be exercised, as the potential for allergic sensitization does exist.

Bacitracin zinc and polymyxin B sulfate are other commonly used compounds of topical antibiotics. They have a similarly extended spectrum of action but do not contain the neomycin component. However, as previously discussed, patients with a neomycin allergy may be predisposed to bacitracin sensitivity. In these patients, this compound must be used cautiously.

## Silver Sulfadiazine

Silver sulfadiazine (Figure 3) is indicated for the treatment of mild infections such as pseudomonas cellulitis, toe web infections, ecthyma gangrenosum, and most commonly for the prevention of wound sepsis in second- and third-degree burns.[1] Silver sulfadiazine is currently available in a polypropylene glycol vehicle and in a water-soluble gel. It is a sulfa drug and, therefore, is an inhibitor of folic acid synthesis and the folic acid coenzymes required for the synthesis of precursors of RNA and DNA (purines and pyrimidines). Because of this, silver sulfadiazine is bactericidal for a broad range of gram-positive and gram-negative bacteria, including *P. aeruginosa* and *S. aureus*; its mode of destruction against bacteria is interference with the cell wall. Although it is the most frequent topical antibiotic used in the treatment of burns, several studies have recently demonstrated other formulations to produce superior responses in burns. Iodophors,[11,18,19] a combination of povidone-iodine with neomycin, polymyxin, and bacitracin (neosporin),[2,20] and silver sulfadiazine-cerium nitrate cream[21] have all yielded results superior to silver sulfadiazine in recent studies. However, because of its low toxicity, relatively low hypersensitivity, and low incidence of resistance, silver sulfadiazine continues to be frequently used. Rare cases of neutropenia, leukopenia, and kernicterus have been reported in connection with the use of silver sulfadiazine. Therefore, caution should be exercised during its use, and it should be avoided in pregnant women and newborns. In addition, it should be avoided in patients with a known hypersensitivity to sulfa drugs.

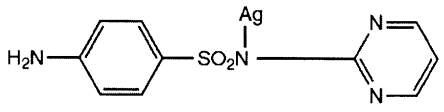


**Figure 3.** The chemical structure of silver sulfadiazine. As a sulfa drug, its mechanism of action is to inhibit folic acid synthesis and therefore inhibit formation of RNA and DNA.

## New Antimicrobial Agents

### *Protegrin-1*

The high incidence of morbidity and mortality in burn victims and the emergence of resistance to topical agents currently used for wound care have led to the search for more powerful topical antimicrobials. Protegrins (PGs) are naturally occurring, broad-spectrum antimicrobial peptides that were initially identified in porcine neutrophils.[22] Similar structures have been identified in humans, mice, rats, and sheep.[23–26] The PGs (Figure 4) are highly homologous cations, are cystine rich, and assume a β-sheet structure stabilized by two disulfide bonds between the cystine residues at positions C-6-C15 and C8-C13 for optimal antimicrobial activity.[22] In vitro studies have demonstrated that PG-1 acts rapidly to kill log- and stationary-phase gram-positive and gram-negative bacteria, including methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus faecalis*, and *Enterococcus faecium*.[22,27]

Although the mechanism of action by which PGs exert their antimicrobial power is not completely understood, they appear to create voltage-dependent ion channels in the bacterial membrane.[22,28–30] PGs bind with moderately high affinity to components of the bacterial cell membrane, such as the lipopolysaccharide component of gram-negative bacterial membranes and the lipoteichoic acid component of gram-positive membranes. When a sufficient concentration of PGs is bound to the membrane, voltage-dependent channels are formed that rapidly result in the death of the microbe.[22,27,30,31] In addition to its

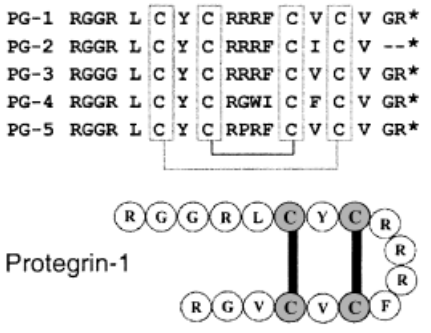


**Figure 4.** The chemical structure of PG-1. Note that the β-sheet structure is stabilized by two disulfide bonds between the cystine residues at positions C-6 to C-15 and C-8 to C-13.

broad antimicrobial activity and rapid killing action, PG-1 is promising because of its stability. It retains activity in the setting presence of serum and at physiologic salt concentration and has proven to be active against a range of multiple drug-resistant microorganisms in a recent study.[22]

## Pexiganan

In recent years, attention has been given to a new antibiotic isolated from the skin of frogs, which showed potential in in vitro studies. Although the original antimicrobial peptide, magainin, has not made it to market, there is an analogue of magainin known as pexiganan that appears to offer great promise. Pexiganan is a 22-amino acid peptide that is isolated from the skin of the African clawed frog.[32] Its broad range of activity includes *Staphylococcus*, *Streptococcus*, *Enterococcus faecium*, *Corynebacterium*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, and some of the *Enterobacteriaceae*, *Bacteroides*, *Peptostreptococcus*, and *Propionibacterium* species.[32] It is rapidly bactericidal against *Pseudomonas* in vitro, eliminating $10^6$ organisms per milliliter within 20 minutes of treatment.[32] Clinical trials have been conducted examining its efficacy in bacteria isolated from diabetic foot ulcers.[33] Pexiganan demonstrated a broad spectrum of activity in the foot ulcer isolates. In addition, it did not exhibit cross-resistance with other commonly used antibiotics, including β-lactams, quinolones, macrolides, and lincosamides, effectively reducing the strains than were known to be resistant to oxacillin, cefalosporins, imipenem, ofloxacin, ciprofloxacin, gentamicin, and clindamicin.[32,33] Further studies are underway to validate the efficacy of pexiganan as a topical antimicrobial.

## Conclusion

Topical antimicrobials offer an important option in the treatment of mild infections. They have a lower incidence of toxicity, adverse effects, and resistance than systemic antibiotics and have proven to be very valuable in wound prophylaxis, localized infections, treatment of primary and secondary pyodermas, and burns. Their potential benefits should not be discounted in favor of systemic antibiotics in cases of mild infection. However, to maintain their low levels of resistance, they should be used judiciously.

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