Topical Antimicrobial Therapy for Treating Chronic Wounds

Benjamin A. Lipsky[1,2] and Christopher Hoey[1]

[1]Veterans Affairs Puget Sound Health Care System and [2]University of Washington, School of Medicine, Seattle

Various agents have been applied topically to treat infected wounds for millennia, but their proper role remains unclear. Topical therapy affords many potential advantages but also has disadvantages. Opinions differ on which clinical signs define wound infection and on whether quantitative microbiological studies are useful. Clinically infected wounds usually require systemic antibiotic therapy, whereas clinically uninfected wounds that are healing as expected do not require antimicrobials. There is controversy over how to treat poorly healing wounds with "secondary" signs suggesting infection; these may benefit from topical antimicrobial agents. Some evidence supports using topical agents for malodorous or burn wounds. Meta-analyses and systematic reviews suggest there are few proven indications for topical antimicrobials. Use of a newer, relatively nontoxic antiseptic (eg, cadexomer iodine or silver dressings) is preferable to use of topical antibiotics, especially agents that are available for systemic use. We provide clinically relevant information on currently available topical antimicrobial agents.

> Perhaps the most deceptively simple of all therapeutic procedures is the treatment of cutaneous infection with topical medication. Despite the unique accessibility of the skin to scientific investigation, it has for too long been the playground of crude empiricism.
>
> —Professor Sydney Selwyn, 1981[1]

Chronic skin wounds affect ~3% of persons aged >60 years [2] and are usually related to neuropathy (eg, diabetic foot or pressure ulcers), vasculopathy (venous stasis or arterial insufficiency ulcers), or trauma. Patients with chronic wounds are frequently treated with either systemic or topical antimicrobial therapy. Two studies in Europe found that >60% of these patients had received some form of antibiotic therapy in the previous 6–12 months, typically for a prolonged duration [3, 4]. In the nearly 3 decades since Professor Selwyn's summary of the state of the art of topical therapy [1], we still know surprisingly little about the role of antimicrobials applied to infected wounds. This paper briefly reviews the concepts germane to considering topical antimicrobial therapy, describes the agents currently available, and offers suggestions about when they may be useful. We will not deal with topical antimicrobials for treating non-bacterial infections, acne, noncutaneous (eg, optical, otic, or mucosal) conditions, or for hand hygiene or prophylaxis to prevent wound infection. We must begin by defining when a wound is infected.

HOW SHOULD WE DEFINE WOUND INFECTION?

Virtually all open wounds are colonized with microorganisms, but this usually has no clinical consequences, because they show no evidence of infection and heal as expected [5]. Some wounds are clearly infected; they have purulent secretions or some of the cardinal manifestations of inflammation (erythema, warmth, pain or tenderness, or induration) that have classically defined the host response to tissue damage caused by pathogenic and invasive microorganisms [6]. The likelihood that a wound will become infected is related directly to the inoculum size and virulence of the colonizing organisms and inversely related to local and systemic host resistance [7]. But some wounds occur in patients with neuropathy (which may obscure or cause pain), ischemia (which may reduce erythema, warmth, or induration), or venous insufficiency (which may mask warmth or cause in-

Received 24 May 2009; accepted 26 June 2009; electronically published 20 October 2009.
Reprints or correspondence: Dr Benjamin A. Lipsky, VA Puget Sound Health Care System, S-111-PCC 1660 S Columbian Way, Seattle, WA 98108 (balipsky@u.washington.edu).

Clinical Infectious Diseases 2009; 49:1541–9

1058-4838/2009/4910-0015$15.00
DOI: 10.1086/644732

Table 1. Bacterial Species Isolated from Various Types of Wounds in 3 Studies Using Optimal Culture and Molecular Techniques

	Type of wound (specimen)					
	Mixed[a]		Venous ulcers (tissue specimens)[b]		Chronic wounds[c]	
Bacterial genus	Chronic (tissue)	Acute (biopsy)	Healers	Nonhealers	Swab culture	Tissue PCR
Staphylococcus	65	60	100	100	28	68
Enterococcus	62	80	…	…	12	18
Pseudomonas	35	20	88	70	32	28
Proteus	24	20	25	30	126	…
Citrobacter	24	20	…	…	8	28
Enterobacter	24	20	…	…	…	…
Streptococcus	22	0	25	60	…	…
Micrococcus	…	…	25	90	…	…
Escherichia	14	0	…	…	…	…
Morganella	8	0	…	…	…	…
Klebsiella	5	0	…	…	…	…
Acinetobacter	5	0	…	…	…	…
Serratia	3	0	…	…	…	…
Corynebacteria	…	…	…	…	0	68
Anaerobes	…	…	50	40	0	70

NOTE. Data are from [12, 13].

[a] Diabetic foot, pressure, or venous stasis ulcers (77 chronic and 16 acute); several anaerobic organisms detected by molecular methods but none were isolated by culture [12].

[b] Specimens from 8 healing and 10 nonhealing chronic venous leg ulcers; 40% of species detected by molecular methods were not detected by standard culture [13].

[c] Specimens from 19 wounds (all but 1 of the lower extremity) [14].

duration). Because these conditions limit the expression of inflammation, some define infection by "secondary" signs of local infection, (eg, nonpurulent exudate, discolored or friable [easily bleeding] granulation tissue, breakdown or "pocketing" at the wound base, or an abnormally foul odor) [6, 8]. A Delphi approach by an international group of 54 wound care experts produced consensus on criteria they deemed common to infection in all chronic wounds: "cellulitis," malodor, pain, delayed healing, deterioration or breakdown, and increased exudate [9]. Some of these criteria have purportedly been validated by studies of various wounds in several settings, but the findings are limited by the fact that they compare the clinical criteria to inadequately validated microbiological definitions of infection [10]. Furthermore, the "additional" (if not the "traditional") evidence of infection likely varies for different types of chronic wounds [6].

Others approach the diagnostic problem by defining infection microbiologically, suggesting that apparently uninfected but nonhealing wounds may demonstrate either "critical colonization" with certain virulent species or a heavy bacterial "bioburden," usually defined as $\geqslant 10^5$ colony forming units per gram of tissue [11]. This concept remains controversial, and recent studies suggest it is less the density of organisms than the presence of particular species (eg, *Pseudomonas aeruginosa, Peptostreptococcus* species, or *Morganella morganii*) [11], the diversity of bacteria, or the patient's response to colonization that lead to a nonhealing but uninflamed wound [2]. Cultures of wound specimens usually grow aerobic gram-positive cocci, which are often mixed with gram-negative bacilli and sometimes anaerobes, but molecular diagnostic studies have shown a greater microbial complexity than had previously been recognized (Table 1). Furthermore, recent studies have demonstrated that, in many chronic wounds, bacteria persist in adhesive, polymeric matrix biofilm communities, in which they induce chronic inflammation that delays healing and that they are more resistant to antimicrobial therapy [15]. These findings have led to suggestions that, in wounds that are apparently properly treated but that fail to heal, the clinician should consider topical antimicrobials.

WHY CONSIDER TOPICAL THERAPY?

With many systemic antibiotics available, why consider topical antimicrobial therapy for an infected wound? Even if the in-

Table 2. Potential Advantages and Disadvantages of Using Topical Antimicrobial Therapy for Infected Chronic Wounds

Advantages
High and sustained concentration of antimicrobial at the site of infection
Limited total amount of antimicrobial needed
Limited potential for systemic absorption and toxicity
Can use novel agents not available for systemic use
May enable avoidance of using systemic antibiotics, thereby reducing development of antibiotic resistance
Directs attention of both patient and providers to the wound
Easily applied as outpatient, by patient or caregiver, potentially reducing the need for institutional care
Often better adherence to treatment, especially for children
Disadvantages
Few agents have been proven to be effective in clinical trials
Minimal penetration limits use to open wounds without cellulitis or deep soft-tissue spread of infection
Systemic absorption of some agents may occur if used on large wounds
Some cause local hypersensitivity or contact dermatitis reactions
May interfere with wound healing processes
Possible alteration of normal cutaneous flora
Difficult to accurately dose
Frequent reapplications may be needed
May be difficult to apply or esthetically unacceptable to some patients
Can become contaminated during recurrent use of multidose container

fection remains confined to superficial tissues, it may cause delayed healing, exudation, or malodor. Although some wound infections will heal with no antimicrobial therapy, many—particularly in immunocompromised or anatomically compromised hosts—will progress to involve deeper tissues and potentially cause systemic infection. These processes are largely mediated by toxins and metabolic wastes produced by microorganisms but also by the host response to infection [16]. For millennia, healers have applied various compounds to infected wounds, some of which (eg, silver and honey) we still use today. Compared with systemic antibiotic therapy, topical application has many potential advantages, as well as some disadvantages, as outlined in Table 2 [17, 18]. To overcome known deficiencies, clinicians and industry have defined the ideal potential topical agent, as summarized in Table 3 [19]. Topical antimicrobials have traditionally been formulated as ointments, which are more occlusive, often contain petrolatum, and are best for dry lesions; and creams, which are less occlusive, wash off with water, are less messy, and are best for moist lesions. One gram of cream covers ~100 cm^2 of skin, whereas ointments cover a 5%–10% larger area. Newer technologies incorporate antimicrobials into dressings, such as alginates, foams, and sponges, allowing controlled release at the wound surface. One major problem with topical therapies is that there are no specific tests of these agents that have been standardized and approved by any official oversight agency for evaluating their efficacy.

WHAT TYPES OF TOPICAL ANTIMICROBIALS ARE AVAILABLE?

Disinfectants are agents with activity against virtually all disease-causing microorganisms, including spores; they are used primarily for sterilizing inanimate surfaces and may be toxic to tissues. Most topical antimicrobials can be divided into 1 of 2 major groups:

- ***Antiseptics.*** Antiseptics are disinfectants that can be used on intact skin and some open wounds to kill or inhibit microorganisms. They often have multiple microbial targets, a broad antimicrobial spectrum, and residual anti-infective activity but are often toxic to host tissues (eg, fibroblasts, keratinocytes, and possibly leukocytes).
- ***Antibiotics.*** Antibiotics are chemicals produced either naturally (by a microorganism) or synthetically that in dilute solution inhibit or kill other microorganisms. They usually act on one specific cell target, have a narrower spectrum of activity, are relatively nontoxic, and are more susceptible to losing their effectiveness to bacterial resistance.

Antiseptics. These compounds have antibacterial and desloughing actions and are generally safe when applied to intact skin. Most agents can cause some toxicity to host cells in vitro, such as prolonging the acute inflammatory response or delaying the production of collagen, but these effects are not usually noted in vivo [16, 20]. Some older agents (eg, sodium hypochlorite and hexacholorphene) are now infrequently used for infected wounds. Commonly used antiseptics (see Table 4) include hydrogen peroxide, which has limited bactericidal and debriding activity; chlorhexidine, which has long-acting activity

Table 3. Properties of an Ideal Topical Antimicrobial for Treating Chronic Wounds

Properly targeted antimicrobial spectrum for the particular type of infected wound
Rapid bactericidal activity
Persistent or residual skin activity, allowing infrequent dosing
Activity in the presence of body fluids and proteins in wound exudate
Low likelihood of inducing bacterial resistance
Some local skin penetration but no systemic absorption
No associated toxic (to host tissue) or allergic reactions
Acceptable cosmetic and aesthetic qualities
Low cost

Table 4. Topical Antiseptic Products Available for Treating Chronic Wounds

Product and formulations	Formulation(s)	Bacterial spectrum	Advantages	Disadvantages	Cost[a]	Indications[b] and comments
Acetic acid	0.25%, 0.5%, and 1% solutions	Bactericidal against most gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*	Inexpensive Shown to eliminate *P. aeruginosa* colonization from burns	Cytotoxic in vitro although maybe not in vivo; limited activity against biofilm	$	No longer as widely used as it was in the past
Cadexomer idine	Gel,[c] ointment, and dressing	Polysaccharide starch lattice; active agent is slowly released free iodine; broad spectrum of activity (same as iodine)	Reduced local toxicity compared to iodine; elemental iodine released on exposure to exudate	Application may cause stinging and erythema but less tissue damage than other iodine products; effect may not persist, and efficacy may be reduced in body fluids	$$	Indicated for use in cleaning wet ulcers and wounds and reducing microbial load in the wound environment
Cetrimide	Solution, 40%	Active against bacteria and fungi; not active against *P. aeruginosa*	May be less toxic to wound tissues than other antiseptics	May be corrosive and is potentially harmful if swallowed	…	Not available in the United States
Chlorhexidine gluconate	Solution, 2% and 4%; liquid, 2% and 4%; hand rinse, 0.5%; wipes, 0.5%; sponge/brush, 4%; and foam, 4%	Active against gram-positive bacteria (eg, *Staphylococcus aureus*) and gram-negative bacteria, including *P. aeruginosa*	Persistent activity up to 6 h after application; few adverse effects	Hypersensitivity, including anaphylaxis, generalized urticaria, bronchospasm, cough, dyspnea, wheezing, and malaise; may cause serious injury to the eye and middle ear; avoid contact with face or head; some resistance reported	$	2% Chlorhexidine indicated as surgical hand scrub, hand wash, preoperative skin, skin wound cleanser, and skin cleaner; polyhexanide is a similar newer biguanide
Hexachlorophene	Liquid, 3%; foam, 0.23% with 56% alcohol	Biguanide that is bacteriostatic against *Staphylococcus* species and other gram-positive bacteria	May retain residual effect on skin for several days	Rapidly absorbed and may result in toxic blood levels; application to burns has resulted in neurotoxicity and death; may cause central nervous system stimulation and convulsions, dermatitis, and photosensitivity reactions	$$$	Not recommended for routine use on wounds because of potential toxicity
Iodine compounds and iodine tincture[c]	Solution, 2% and 2.4%; and NaI strong iodine (Lugols), 5% and 10% KI; for iodine tincture, 2% and 2.4% NaI with 47% alcohol; and 7%, 5% KI in 83% EtOH	Microbicidal against bacteria, fungi, viruses, spores, protozoa, and yeasts	Broad spectrum	Highly toxic if ingested or significantly absorbed; do not use with occlusive dressings; causes pain and stains skin and clothing; use cautiously in patients with thyroid disorders	$	Iodine compounds are now rarely used for wound management; cadexomer iodine and povidone iodine products are less toxic
Povidone iodine[c]	Ointment, 1%, 4.7%, and 10%; solution, 1% and 10%; and wash, scrub, cleanser, gel, aerosol, gauze pad, swab, and others	Broad spectrum includes *S. aureus* and enterococci; active ingredient is liberated free iodine; shares spectrum but is less potent than iodine	Less irritating to skin and allergenic than iodine. Can be covered with dressings. Clinically significant resistance very rare	Antibacterial action requires at least 2 min contact; may cause stinging and erythema; effect may not persist, and efficacy may be reduced in body fluids; prolonged use may cause metabolic acidosis; stains skin and clothing; possible interaction with starches in dressings	$	Indicated for perioperative skin cleansing and for cleansing and prevention of infection in superficial burns, incisions, and other superficial wounds
Sodium hypochlorite[c] (Dakin's solution and EUSOL)	Solution, 0.0125%, 0.125%, 0.25%, and 0.5%	Vegetative bacteria, viruses, and some spores and fungi	Inexpensive. No known systemic toxicity	May require prolonged contact for antibacterial action; inactivated by pus; toxic to fibroblasts and keratinocytes, and may cause pain or lyse blood clots	$	Concentrations ⩽0.025% may be useful to reduce bioburden
Hydrogen peroxide[c]	Solution, 1% and 3%; and cream, 1%	Oxidizing agent active against many gram-positive and gram-negative bacteria	Broad-spectrum, bactericidal, inexpensive; no known resistance	May cause some discomfort	$	Commonly used, but few clinical studies
Silver nitrate	Solution 0.5%, 10%, 25%, and 50%; ointment, 10%; and swabs, 25%–50%	Silver ions are bactericidal against a broad spectrum of gram-positive and gram-negative bacteria	Low cost; easily applied	Painful on application; stains tissues; may delay healing; concentrations >0.5% cause cauterization; inactivated by wound exudates and chlorine	$	Although it was previously widely used, it has now been largely replaced by other compounds, including newer silver dressings
Sliver dressings	At least 6 approved products with different properties	Slowly released silver ions have broad-spectrum, including MRSA and VRE	Provide sustained levels of active silver ions; microbial resistance is rare; less painful and few adverse effects than silver nitrate; variety of products adaptable to different types of wounds; infrequent application required	Levels of silver ions at wound interface not well defined; may cause silver staining of tissues; may delay epithelialization; relatively expensive; few published comparative trials	$$	Should not substitute for nonmedicated dressings for uninfected wounds; may be useful for subclinically infected, highly colonized wounds or for wounds being prepared for skin grafting

NOTE. EUSOL, Edinburgh University Solution of Lime; MRSA, methicillin-resistant *S. aureus;* VRE, vancomycin-resistant enterococci.

[a] Costs are approximate in US$ per day for treating 100-cm^2 wound, as follows: $, <$3; $$, $3–$15; and $$$, >$15.

[b] US Food and Drug Administration–approved indications.

[c] Available without prescription.

against a wide range of both gram-negative and gram-positive bacteria; and iodophors, which release free iodides but may be cytotoxic. Iodines have been used for >150 years without bacteria developing resistance [21]. Newer formulations, such as cadexomer iodine, offer sustained delivery of bactericidal concentrations to moist wounds without apparent tissue damage. Silver compounds (metallic, nanocrystalline, and ionic) have a broad bactericidal spectrum and have enjoyed a recent resurgence as topical antiseptics in various types of wound dressings. Silver ions kill bacteria by several mechanisms, including damaging their cell walls, membranes, respiratory enzymes, and ribonucleoproteins [22, 23]. Because they are rapidly inactivated in the wound environment, they require a sustained delivery formulation. Silver has proven efficacy against several common wound pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase producers. Resistance is rare but has been reported, mostly with gram-negative species [19]. Adverse effects are infrequent, and silver may be active against biofilm. Silver compounds in various wound products differ in the manner and speed with which they release the bactericidal silver ions [22]. Although silver dressings have been the subject of many anecdotal reports and case series, they have been used in few well-designed clinical trials.

Another newly popular topical remedy for wound infections is honey. Its beneficial actions are related to the osmotic effect produced by the high sugar content but also to the presence of an enzyme that produces hydrogen peroxide, as well as to nonperoxide antibacterials [24]. Honey has an inhibitory effect on >50 species of bacteria, including clinical strains of MRSA and VRE, and there is no reported microbial resistance. It has demonstrated clinical effectiveness for various types of wound infections; dramatically decreases skin colonization with many bacteria, including MRSA [25]; hastens wound healing; and rarely causes adverse reactions. Medical grade honey (eg, Manuka) is approved in many countries and there are several sterile, irradiated, antibacterial (Unique Manuka Factor–rated) brands available [24, 26, 27]. Clinicians should avoid using nonmedical honeys that may contain viable spores (including clostridia) and have unpredictable antibacterial activity.

Because chronic wounds are so common, it is not surprising that new agents are frequently introduced. Super-oxidized water is a recently approved antiseptic, one brand of which (Microcyn; Oculus) is available without prescription. This pH-neutral sterilant with reactive species of chlorine and oxygen in a stable formulation is rapidly bactericidal, has broad-spectrum coverage, does not appear to facilitate bacterial resistance or damage host tissues, and may be active in the presence of biofilm [28]. It can be applied directly to wounds or be combined with dressings or other wound products, and several small, nonrandomized studies suggest it is effective in treating infected diabetic foot ulcers [29–31]. Antimicrobial peptides are another novel approach to topical therapy. These small (<100–amino acid), cationic, amphipathic compounds are stored in granules of polymorphonuclear leukocytes and epithelial cells in most eukaryotes [32, 33]. They are rapidly bactericidal against a broad spectrum of organisms and synergistic with—although unrelated to—other antimicrobials. Acquired resistance rarely develops. Pexiganan, a peptide awaiting US Food and Drug Administration approval that is applied in a 1% cream, is bactericidal for most aerobic and anaerobic, gram-positive and gram-negative pathogens [34–36], and there are no reports of cross-resistance to other antibiotics. In 2 randomized, controlled trials that enrolled patients with a mildly infected diabetic foot ulcer, topical pexiganan proved overall to be similarly effective clinically and microbiologically to oral ofloxacin, with fewer adverse events [37].

Antibiotics. Clinically infected wounds should usually be treated with systemic antibiotic therapy. The first topical antibiotics were derived from agents developed for systemic use (ie, sulfonamides in the mid-1930s), followed in the next decade by topical penicillins, bacitracin, gramicidin, aminoglycosides (including neomycin), polymixin, tetracyclines, and choloramphenicol. Agents introduced later include fusidic acid, clindamycin, metronidazole, mupirocin and retapamulin. Only a few topical antibiotics are commonly used in the US (Table 5). Neomycin is active against most aerobic gram-negative rods (excluding most *Pseudomonas* species) and staphylococci (but not most other gram-positive cocci); resistance develops relatively frequently, as does contact dermatitis. Polymixin is active against some gram-negative rods (including *Pseudomonas* species) but not gram-positive cocci; systemic absorption is uncommon, and dermatitis is rare. Bacitracin is active against most gram-positive organisms, and resistance and toxicity are uncommon. These 3 antibiotics are combined in a nonprescription ointment commonly used on wounds by patients and some providers. It is best to avoid using topical antibiotics that are available for systemic therapy when treating wound infections, because they can provoke delayed hypersensitivity reactions, favor superinfections, and select for resistant pathogens. One exception is metronidazole, which can reduce the fetid odor of (presumably) anaerobically colonized wounds [38].

Antibiotics used only in topical formulations may be appropriate for treating some infected wounds. Mupirocin is active against aerobic gram-positive cocci (except enterococci) and has minimal toxicity, and cross-resistance is uncommon. Although it is sometimes used off-label for treating or decolonizing (especially if MRSA is present) chronic wounds [39], published studies supporting this indication are lacking, and the incidence of resistance is increasing. Retapamulin, which was approved in 2007, is a 1% semisynthetic pleuromutilin compound with in vitro activity against most gram-positive

Table 5. Topical Antibiotic Products Available for Treating Chronic Wounds

Product	Formulation(s)	Bacterial spectrum	Advantages	Disadvantages	Cost[a]	Indications[b] and comments
Bacitracin[c]	Ointment, 500 units/g; and powder combinations with neomycin, polymixin B, and zinc	Many gram-positive organisms, including aerobic staphylococci and streptococci, corynebacteria, anaerobic cocci, and clostridia; inactive against most gram-negative organisms	Activity not impaired by blood, pus, necrotic tissue, or large bacterial inocula; resistance is rare but increasing among staphylococci; no cross-resistance with other antibiotics; minimal absorption	May cause allergic reactions, contact dermatitis, and (rarely) anaphylactic reactions; may lead to overgrowth of drug-resistant organisms, including fungi	$	Widely used for many years; indicated for prevention of infection in minor skin injuries
Fusidic acid	Cream, 2%; ointment, 2%; and gel, 2%	*Staphylococcus aureus*, streptococci (in topical concentrations), corynebacteria, and clostridia	Penetrates intact and damaged skin as well as crust and cellular debris	Occasional hypersensitivity reactions; resistance among staphylococci is emerging; must apply 3 times daily	$$	Not available in the United States
Gentamicin	Cream, 0.1%; and ointment, 0.1%	Streptococci, staphylococci, *Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli, Proteus vulgaris,* and *Klebsiella pneumoniae*	Broad spectrum; inexpensive	Must be applied 3–4 times daily; may drive resistance to an agent used systemically	$	Indicated for primary skin infections (pyodermas) and for secondary skin infections, including infected excoriations, and for bacterial superinfections
Mafenide acetate	Solution, 5%; and cream, 85 mg/g	A sulfonamide that is bacteriostatic against many gram-negative organisms, including *P. aeruginosa*, and some gram-positive organisms, but minimal activity against staphylococci and some obligate anaerobes	Remains active in the presence of pus and serum, and its activity is not affected by acidity of environment	Systemic absorption may occur; dug and metabolites may inhibit carbonic anhydrase, potentially causing metabolic acidosis; use cautiously in patients with renal impairment; pain on application; hypersensitivity reactions	$$$	Indicated as adjunctive therapy in second-nd and third-degree burns; may be used in rapidly progressing bacterial necrotizing fasciitis; limited use in other wounds
Metronidazole	Cream, 0.75%; gel, 1%; lotion, 0.75%	Many clinically important anaerobic bacteria	May reduce odor associated with anaerobic infections; application only 1–2 times daily	Relatively expensive; systemic formulations available; could drive resistance to these	$–$$	Indicated for inflammatory papules and pustules of rosacea
Mupirocin and mupirocin calcium	Ointment, 2%; for mupirocin calcium, cream, 2.15%;[c] and nasal ointment, 2.15%;[c] (equivalent to 2% mupirocin)	Gram-positive aerobes, including *S. aureus* (most MRSA), *Staphylococcus epidermidis, Staphylococcus saprophyticus,* and streptococci (groups A, B, C, and G) but not enterococci, some gram-negative aerobes (not *P. aeruginosa),* corynebacteria, and obligate anaerobes	Minimal potential for allergic reactions	Rare local burning and irritation; applying ointment to large wounds in azotemic patients can cause accumulation of polyethylene glycol; long-term use can lead to resistance among staphylococci, which is increasing	$$	Indicated for topical treatment of impetigo and eradication of nasal colonization with *S. aureus*
Neomycin sulfate[c]	Powder; cream, 0.5%, combinations with polymixin B and pramoxine; and ointment, 0.5%, combinations with bacitracin, polymixin B, lidocaine, and pramoxine	Good for gram-negative organisms but not *P. aeruginosa;* active against some gram-positive bacteria, including *S. aureus,* but streptococci are generally resistant; inactive against obligate anaerobes	Low cost; applied only 1–3 times daily; may enhance reepithelialization	Topical powder in wound irrigating solution may cause systemic toxicity (FDA banned); use other formulations cautiously on large wounds, especially with azotemia; hypersensitivity reaction in 1%–6%, often with chronic use or history of allergies	$	Use of topical powder alone or in solution is not recommended; cream and ointment, in combination with other agents are indicated for prevention of infection in minor skin injuries
Nitrofurazone	Solution, 0.2%; ointment, 0.2%; and cream, 0.2%	Broad gram-positive and gram-negative activity, including *S. aureus* and streptococci, but not *P. aeruginosa*	Used mainly for burn wounds	Hypersensitivity reactions; polyethylene glycols (in some formulations) may be absorbed and can cause problems in azotemic patients	$$	Indicated as adjunctive to prevent infections in patients with second- and third-degree burns
Polymixin B[c]	Cream, 5000 units/g or 10,000 units/g, in combination with other agents	Bactericidal against many gram-negative organisms, including *P. aeruginosa;* minimal activity against gram-positive bacteria; activity may be neutralized by divalent cations	Inexpensive	Some hypersensitivity and neurological or renal adverse reactions reported; may show cross-reaction with bacitracin	$	Only available in combination with other agents, including bacitracin and neomycin; indicated for prevention of infection in minor skin injuries
Retapamulin	Ointment, 1%	Active against staphylococci (but uncertain for MRSA) and streptococci and some obligate anaerobes	May be active against some mupirocin-resistant *S. aureus* strains; broader activity than mupirocin	Not evaluated for use on mucosal surfaces; may cause local irritation	$$$	Indicated for impetigo, due to *S. aureus* (methicillin-susceptible only) or *S. pyogenes*
Silver sulfadiazine	Cream, 1%	A sulfonamide; the released silver ions are the primary active ingredient; active against many gram-positive and gram-negative organisms, including *P. aeruginosa*	Applied only once or twice daily; soothing application; low rate of hypersensitivity reaction	Potential cross-reaction with other sulfonamides; may rarely cause skin staining	$	Indicated as adjunctive treatment to prevent infections in patients with second- and third-degree burns.
Sulfacetamide Na^+	Lotion, 10%	Bacteriostatic against many gram-positive and gram-negative pathogens	Broad spectrum; can be combined with sulphur	Systemic absorption and rarely severe side effects occur with application to large, denuded areas; hypersensitivity reactions may occur	$$$	Indicated for secondary bacterial skin infections due to susceptible organisms and for acne vulgaris in adults

NOTE. There are no published studies supporting the use of topical erythromycin, clindamycin, aminoglycosides other than neomycin, gramicidin, or tetracyclines for treating chronically infected wounds. FDA, US Food and Drug Administration; MRSA, methicillin-resistant *S. aureus.*

[a] Costs are approximate in US$ per day for treating 100-cm^2 wound, as follows: $, <$3; $$, $3–$15; and $$$, >$15.

[b] FDA-approved indications.

[c] Available without prescription.

Table 6. Recommended Approach to Using Topical Antimicrobials for Treating Chronic Wounds in Various Clinical States

Infection status	Definition	Consequences	Antimicrobial therapy
Uninfected	No classical[a] or secondary[b] clinical evidence of infection	None	None
Uncertain	Only secondary clinical evidence of infection or quantitative culture with $\geq 10^5$ cfu/g of tissue	Possibly slowed or absent wound healing; malodor; discomfort	Consider short-term topical antiseptic therapy
Infected	Classical[b] clinical signs or symptoms of inflammation	Progression of infection; failure of wound healing; discomfort	Systemic[c] antibiotic therapy (with or without topical antiseptic)

NOTE. In addition to usual required wound care (eg, debridement, off-loading, proper dressings, correcting critical ischemia, malnutrition, hyperglycemia, or other metabolic problems).

[a] Purulent discharge, or erythema, warmth, pain or tenderness, or induration.

[b] Nonpurulent (serous or sanguineous) exudate, discolored or friable (easily bleeding) granulation tissue, breakdown or "pocketing" at the base of the wound, or abnormally foul odor.

[c] Oral or parenteral, depending on severity of infection and agent(s) required.

bacteria (and anaerobes). Although it is indicated for impetigo in both the United States and the European Union, only the latter has also approved it for treating wounds (small lacerations, abrasions, or sutured wounds) infected with *Streptococcus pyogenes* or *S. aureus* (excluding MRSA strains). Although retapamulin has good in vitro activity against MRSA, it has not yet been proven to be clinically effective [40]. It has a low potential for organisms to develop resistance and has not shown cross-resistance to other antimicrobial classes. Retapamulin has been shown to be similar in efficacy to topical fusidic acid and to oral cephalexin for treating impetigo or infected traumatic lesions [40–42], but there are no data on use of this agent for chronic wounds.

WHAT IS THE EVIDENCE FOR USING TOPICAL ANTIMICROBIALS FOR TREATING CHRONIC WOUNDS?

Available data make it difficult to assess the efficacy of topical antimicrobials for chronic wounds. Most studies are suboptimal and have varying designs that are not easily comparable. To start, specifications for in vitro testing of these agents are not standardized among countries [43]. Animal models also yield inconsistent evidence, depending on the experimental species, type of wound induced, and microorganisms used; many are probably irrelevant to chronic wounds in patients, who often have underlying medical conditions. Although the anecdotal reports and case series involving humans provide some information, clinical trials are the test of efficacy. Unfortunately, many of the published trials do not define the types of patients and wounds included, select inappropriate control groups, or have inadequate sample sizes. Because wound infection is ill-defined, comparison of study outcomes is difficult. So what do the published clinical trials tell us about the efficacy of these agents?

A 2001 systematic review of controlled trials of antimicrobial agents for chronic wounds (diabetic foot ulcers, pressure ulcers, chronic leg ulcers, etc.) found 30 studies (25 randomized trials) with a total of 1436 patients that met the inclusion criteria [44]. The authors concluded that few systemic agents improved outcomes, but several topical substances hastened healing, including silver-containing compounds for venous ulcers and oxyquinoline ointment for stage 1–2 pressure ulcers. A 2008 Cochrane systematic review of antibiotics and antiseptics for venous leg ulcers concluded that some evidence supports using topical cadexomer iodine, but further research is required to determine the effectiveness of povidone iodine, peroxide-based preparations, ethacridine lactate, and mupirocin for healing venous leg ulcerations [45]. Similarly, a 2008 systematic review of the effectiveness of various interventions for enhancing the healing of chronic diabetic foot ulcers found a single study that demonstrated no benefit of cadexomer-iodine in cavitary wounds and one suggesting that zinc oxide tape improved necrotic wounds more than a hydrocolloid [46]. A 2006 Cochrane review of silver-based wound dressings and topical agents for treating diabetic foot ulcers found no controlled trials that met basic design requirements and that reported outcomes on healing rates or infection resolution [47]. Likewise, a 2007 Cochrane review of silver-containing dressings or topical agents for treating infected or contaminated chronic wounds concluded there was insufficient evidence, on the basis of 3 randomized, controlled trials (each with a short follow-up duration), to recommend this treatment [48]. Use of honey for treating wounds was the subject of a 2008 Cochrane systematic review. On the basis of data from 19 trials (totaling 2554 patients) that met the inclusion criteria, the authors concluded that, compared with some conventional

dressings, honey may reduce the healing time for mild-to-moderate superficial and partial thickness burns but did not significantly hasten leg ulcer healing; for other uses, there was insufficient evidence to guide clinical practice [49].

WHAT CAN WE CONCLUDE ABOUT TOPICAL ANTIMICROBIAL THERAPY FOR CHRONIC WOUNDS?

Although some take strong positions on either side of the debate, most clinicians are confused about whether and when to use topical antimicrobials for chronic wounds and which topical antimicrobial to use. Wound care should always begin with ensuring adequate debridement, removal of any foreign bodies, pressure off-loading, and proper dressings, then assessing for (and treating when needed) any arterial or venous insufficiency, or metabolic derangements. Then, classify the wound to determine the approach to antimicrobial therapy (Table 6). Clinically infected wounds usually require systemic antibiotic therapy, with the exceptions mentioned previously. Topical antimicrobial therapy, although not currently advisable for most clinically uninfected chronic wounds, does have a role in specific circumstances. Evidence upholds its use for burn wounds in which blood vessels to the skin are often destroyed, both to prevent sepsis and help treat infection [50]. Some data support use of topical agents for eradicating wound bacteria prior to skin grafting or for reducing odor associated with nonhealing, necrotic wounds. Clinicians could consider adding topical antimicrobials, which achieve high local levels, to systemic antibiotics in a patient with an infected ischemic wound who cannot undergo revascularization. One can reasonably argue for trying a short course of a topical antiseptic (preferably one of the newer, safer preparations, such as iodine or silver dressings) for an otherwise properly managed wound that is failing to heal and has some secondary findings suggesting subclinical infection. Another potential application might be to help in the removal of biofilms, which have been implicated in persistent infections. Some in vitro tests of iodides, silver, and hydrogen peroxide (and, thus, peroxide-generating honey) compounds show inhibition or disruption of biofilm [43]. Topical treatments may also prove helpful with the increasing problem of multidrug-resistant organisms that are untreatable with most systemic agents. A recent study of 47 multidrug-resistant organisms from burn wounds found that most were susceptible to 11 commonly used topical antibiotics and antiseptics, although the rates of resistance were higher than to non–multidrug-resistant organisms [50].

The main arguments against using topical antiseptics are the lack of adequate proof of efficacy and residual concerns about their potential toxicity to healing wounds. A compound's toxicity risk depends on the particular formulation, concentration of active ingredient, and duration of exposure. Newer formulations and methods of applying topical antiseptics appear to reduce the risk. Antiseptics should not be used in solutions, because they are more likely to cause cell damage and have no demonstrated benefit over saline irrigation [5]. Newer topical creams, ointments, gels, and dressings appear to provide adequate, sustained, and apparently nontoxic levels of antiseptics. Unfortunately, there is little information on systemic absorption of the agents, and evidence of clinical efficacy is meager. Thus, clinicians should currently use these products very selectively and only for a short duration. Investigators and the industry are seeking other ways to deal with chronic wound infections, including various innovative nonantimicrobial approaches. In light of the size and importance of the problem of chronic wound infection, we expect crude empiricism to continue to give way to creative entrepreneurship.

Acknowledgments

We thank Mia Hannula (medical librarian at Veterans Affairs Puget Sound Healthcare System) for assisting with our systematic review of the literature on this topic, as well as the following authorities who responded to our request to provide their written opinions on the topics covered in this article: Keith Cutting (High Wycombe, England) Michael Edmonds (London, England), John Embil (Winnipeg, Canada), Lawrence Eron (Honolulu, HI), Keith Harding (Cardiff, Wales), Jan Hirschmann (Seattle, WA), Alberto Piaggesi (Pisa, Italy), L. Neal Sharpe (Louisville, KY), and Luc Téot (Montpelier, France).

Potential conflicts of interest. B.A.L. has received recent research funding from Ortho-McNeil Janssen, Merck, and Cubist; has served as a consultant for Pfizer, Wyeth-Ayerst Laboratories, and Coloplast; and has served as a speaker for Pfizer. C.H.: no conflicts.

References

1. Selwyn S. Microbial interactions and antibiosis. In: Maibach H, Aly R, eds. Skin microbiology: relevance to clinical infection. New York: Springer-Verlag, **1981**:63–74.
2. Davies CE, Hill KE, Newcombe RG, et al. A prospective study of the microbiology of chronic venous leg ulcers to reevaluate the clinical predictive value of tissue biopsies and swabs. Wound Repair Regen **2007**; 15:17–22.
3. Howell-Jones RS, Wilson MJ, Hill KE, Howard AJ, Price PE, Thomas DW. A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. J Antimicrob Chemother **2005**; 55:143–9.
4. Tammelin A, Lindholm C, Hambraeus A. Chronic ulcers and antibiotic treatment. J Wound Care **1998**; 7:435–7.
5. White RJ, Cutting K, Kingsley A. Topical antimicrobials in the control of wound bioburden. Ostomy Wound Manage **2006**; 52:26–58.
6. Cutting KF, White RJ. Criteria for identifying wound infection—revisited. Ostomy Wound Manage **2005**; 51:28–34.
7. Heinzelmann M, Scott M, Lam T. Factors predisposing to bacterial invasion and infection. Am J Surg **2002**; 183:179–90.
8. Gardner SE, Frantz RA, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. Wound Repair Regen **2001**; 9:178–86.
9. Moore Z, Cowman S. Effective wound management: identifying criteria for infection. Nurs Stand **2007**; 21:68, 70, 72.
10. Gardner SE, Hillis S, Frantz R. Clinical signs of infection in diabetic foot ulcers with high microbial load. Biol Res Nurs **2009**; 11:119–28.
11. White RJ, Cutting KF. Critical colonization—the concept under scrutiny. Ostomy Wound Manage **2006**; 52:50–6.

12. James GA, Swogger E, Wolcott R, et al. Biofilms in chronic wounds. Wound Repair Regen **2008**; 16:37–44.
13. Davies CE, Hill KE, Wilson MJ, et al. Use of 16S ribosomal DNA PCR and denaturing gradient gel electrophoresis for analysis of the microfloras of healing and nonhealing chronic venous leg ulcers. J Clin Microbiol **2004**; 42:3549–57.
14. Frank DN, Wysocki A, Specht-Glick DD, et al. Microbial diversity in chronic open wounds. Wound Repair Regen **2009**; 17:163–72.
15. Rhoads DD, Wolcott RD, Percival SL. Biofilms in wounds: management strategies. J Wound Care **2008**; 17:502–8.
16. Drosou A, Falabella A, Kirsner R. Antiseptics on wounds: an area of controversy. Wounds **2003**; 15(5). Available at http://www.medscape.com/viewarticle/456300. Accessed 7 October 2009.
17. Lio PA, Kaye ET. Topical antibacterial agents. Infect Dis Clin North Am **2004**; 18:717–33.
18. Gelmetti C. Local antibiotics in dermatology. Dermatol Ther **2008**; 21: 187–95.
19. Patel PP, Vasquez SA, Granick MS, Rhee ST. Topical antimicrobials in pediatric burn wound management. J Craniofac Surg **2008**; 19:913–22.
20. Lineaweaver W, Howard R, Soucy D, et al. Topical antimicrobial toxicity. Arch Surg **1985**; 120:267–70.
21. Cooper RA. Iodine revisited. Int Wound J **2007**; 4:124–37.
22. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol **2008**; 58:185–206.
23. Castellano JJ, Shafii SM, Ko F, et al. Comparative evaluation of silver-containing antimicrobial dressings and drugs. Int Wound J **2007**; 4: 114–22.
24. Molan PC. Honey as a topical antibacterial agent for treatment of infected wounds. World Wide Wounds **2001**; November. Available at http://www.worldwidewounds.com/2001/november/Molan/honey-as-topical-agent.html. Accessed 7 October 2009.
25. Kwakman PH, Van den Akker JP, Guclu A, et al. Medical-grade honey kills antibiotic-resistant bacteria in vitro and eradicates skin colonization. Clin Infect Dis **2008**; 46:1677–82.
26. Molan PC, Cooper RA. Honey and sugar as a dressing for wounds and ulcers. Trop Doct **2000**; 30:249–50.
27. Cooper RA, Molan PC, Harding KG. The sensitivity to honey of gram-positive cocci of clinical significance isolated from wounds. J Appl Microbiol **2002**; 93:857–63.
28. Gonzalez-Espinosa D, Perez-Romano L, Guzman-Soriano B, Arias E, Bongiovanni CM, Gutierrez AA. Effects of pH-neutral, super-oxidised solution on human dermal fibroblasts in vitro. Int Wound J **2007**; 4: 241–50.
29. Goretti C, Mazzurco S, Nobili LA, et al. Clinical outcomes of wide postsurgical lesions in the infected diabetic foot managed with 2 different local treatment regimes compared using a quasi-experimental study design: a preliminary communication. Int J Low Extrem Wounds **2007**; 6:22–7.
30. Zahumensky E. Infections and diabetic foot syndrome in field practice. Vnitr Lek **2006**; 52:411–6.
31. Kaehn K. Dermacyn on the infected foot ulcers of 10 patients. J Wound Care **2007**; 16:232.
32. Ulvatne H. Antimicrobial peptides: potential use in skin infections. Am J Clin Dermatol **2003**; 4:591–5.
33. Reddy KV, Yedery RD, Aranha C. Antimicrobial peptides: premises and promises. Int J Antimicrob Agents **2004**; 24:536–47.
34. Ge Y, MacDonald D, Hait H, Lipsky B, Zasloff M, Holroyd K. Microbiological profile of infected diabetic foot ulcers. Diabet Med **2002**; 19:1032–4.
35. Ge Y, MacDonald DL, Holroyd KJ, Thornsberry C, Wexler H, Zasloff M. In vitro antibacterial properties of pexiganan, an analog of magainin. Antimicrob Agents Chemother **1999**; 43:782–8.
36. Lipsky BA. Pexiganan acetate [commentary]. Drugs **1999**; 56:1053.
37. Lipsky BA, Holroyd KJ, Zasloff M. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clin Infect Dis **2008**; 47:1537–45.
38. Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. Ostomy Wound Manage **2008**; 54:18–27; quiz 28–9.
39. Terpenning MS, Bradley SF, Wan JY, Chenoweth CE, Jorgensen KA, Kauffman CA. Colonization and infection with antibiotic-resistant bacteria in a long-term care facility. J Am Geriatr Soc **1994**; 42:1062–9.
40. Yang LP, Keam SJ. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. Drugs **2008**; 68:855–73.
41. Jacobs MR. Retapamulin: a semisynthetic pleuromutilin compound for topical treatment of skin infections in adults and children. Future Microbiol **2007**; 2:591–600.
42. Odou MF, Muller C, Calvet L, Dubreuil L. In vitro activity against anaerobes of retapamulin, a new topical antibiotic for treatment of skin infections. J Antimicrob Chemother **2007**; 59:646–51.
43. Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. World Wide Wounds **2004**; February:1–11. Available at http://www.worldwidewounds.com/2004/february/Cooper/Topical-Antimicrobial-Agents.html. Accessed 7 October 2009.
44. O'Meara SM, Cullum NA, Majid M, Sheldon TA. Systematic review of antimicrobial agents used for chronic wounds. Br J Surg **2001**; 88: 4–21.
45. O'Meara S, Al-Kurdi D, Ovington LG. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev **2008**; (1):CD003557.
46. Hinchliffe RJ, Valk GD, Apelqvist J, et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev **2008**; 24(Suppl 1): S119–44.
47. Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst Rev **2006**; (1): CD005082.
48. Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT. Topical silver for treating infected wounds. Cochrane Database Syst Rev **2007**; (1):CD005486.
49. Jull AB, Rodgers A, Walker N. Honey as a topical treatment for wounds. Cochrane Database Syst Rev **2008**; (4):CD005083.
50. Neely AN, Gardner J, Durkee P, et al. Are topical antimicrobials effective against bacteria that are highly resistant to systemic antibiotics? J Burn Care Res **2009**; 30:19–29.