Topical Antibacterial Agents

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• Antiseptics • Mupirocin • Neomycin • Gentamicin
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The skin presents a first line of defense against a wide range of bacterial invaders. When the integrity of the skin is compromised accidentally or intentionally, its natural defenses weaken and a role for antibacterials emerges. The topical route of application offers several advantages over systemic administration, including the avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, and the high concentration of antibacterial agent at the site of infection. However, a treatment that must be physically applied to the skin is limited by patient compliance, local side effects such as allergic contact dermatitis, and the depth of penetration of the agent. Despite their shortcomings, topical antibacterial agents are highly versatile and can be used successfully for both prophylaxis and treatment of bacterial infections.

Outside of the hospital setting, *Staphylococcus aureus* and group A streptococci are classically considered the pathogens most often involved in infections of the skin. Recent data from hospitalized patients demonstrate that *S aureus*, *Enterococcus* spp, coagulase-negative staphylococci, *Escherichia coli* and *Pseudomonas aeruginosa* are the most prevalent pathogens involved in skin and soft tissue infections.[1]

These well-known offenders, as well as the panoply of more exotic pathogens that have been reported to cause skin infections, must be kept in mind while exploring the topical antibacterial agents at one's disposal.

PROFILES OF SELECTED ANTIBACTERIAL AGENTS

Antiseptics

Antiseptics, also known as disinfectants, are chemical agents primarily used to decrease the risk of infection in intact skin or in minor wounds. Alcohol and

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iodophors have rapid action against bacteria but little persistent activity, whereas chlorhexidine and triclosan are slower to act but persist on the stratum corneum for continued antimicrobial effects.[2,3] Most antiseptics are not suitable for open wounds as they may impede wound healing by direct cytotoxic effects to keratinocytes and fibroblasts.[4]

Hydrogen peroxide

Hydrogen peroxide is a common antiseptic agent used on intact skin and minor wounds. It is thought to kill bacteria in two distinct modes: rapidly by way of DNA damage from highly reactive hydroxyl radicals, and more slowly in a manner that may involve the inactivation of housekeeping enzymes.[5,6] It has limited bactericidal activity, however. In one study of mixed microorganism disinfection of a glass, it was found to be entirely ineffective.[7] A prospective study in human appendectomy wounds found that there was no statistical difference in the infection rate between a control group and a group receiving hydrogen peroxide.[8]

Hydrogen peroxide may be detrimental to wound healing, however, as it has been shown to be directly cytotoxic to keratinocytes, and even at very low concentrations inhibits keratinocyte migration and proliferation.[9]

Chlorhexidine

Chlorhexidine's role continues to expand as an effective and versatile antiseptic for both infection control and prevention.[10] Chlorhexidine gluconate is active against a wide range of gram-positive and gram-negative bacteria, yeast, and molds.[11] Chlorhexidine acts by disrupting cytoplasmic membranes and remains active for hours after application.[3,12,13] Its FDA indications are designated for general skin and wound cleansing, preoperative skin preparation, personnel hand wash and surgical hand scrub. Chlorhexidine is consistently superior to povidone-iodine and a number of other antiseptics in reducing colonizing flora immediately and several days after application.[2,14,15] While it is useful in decolonization of methicillin-resistant *Staphylococcus aureus* (MRSA) carriers, its ability to decrease skin and soft tissue infection is limited when used alone as a single agent, but it has been shown to reduce staphylococcal and streptococcal infections in marine recruits and MRSA infection in ICU patients when a combination of chlorhexidine bath is used along with intranasal mupirocin.[16–18] Daily chlorhexidine baths alone reduced contamination and acquisition of vancomycin-resistant enterococcus.[10,19] In addition, chlorhexidine is widely used for skin preparation before catheter insertion. More recent developments include chlorhexidine-impregnated dressings or sponges for maintenance of indwelling catheters and impregnated or coated catheters and catheter cuffs.[20,21] Finally, chlorhexidine is playing an emerging role in decontamination of the oropharynx as it impacts on nosocomial pneumonia. A meta-analysis found that chlorhexidine decontamination was responsible for a 30% decrease in the incidence of ventilator-associated pneumonia.[10,22]

Triclosan

Triclosan is a broad-spectrum cationic antimicrobial agent that is widely used in consumer products such as soaps, detergents, toothpastes, and cutting boards. Its mechanism of action is bacterial membrane disruption through blockade of lipid synthesis. This was elucidated recently when triclosan resistance was found in *E coli* strains. These strains were found to have a mutation in the *fabI* gene, which encodes an enzyme involved in fatty acid biosynthesis.[23] The emergence of resistance, although not yet clinically relevant, has sparked concern about the widespread use of this agent promoting resistance.

Iodophors

The iodophors are complexes of iodine and organic carrier compounds that have a broad spectrum of activity against bacteria and fungi. Its mechanism is thought to be by way of destroying microbial protein and DNA.[24] They were formulated to be less irritating and allergenic, but are also less active than pure iodine solutions.[25] Iodophors require at least 2 minutes of contact to release free iodine that exerts the antibacterial activity. In vitro data shows a large number of gram-positive isolates after exposure for 15 seconds but essentially none after 120 seconds of exposure.[26]

Iodophors are used most commonly for preoperative skin preparation. Povidone-iodine is a complex of the bactericidal iodine with the polymer polyvinylpyrrolidone (povidone). It is available in various commercial forms, including cleansers, surgical scrubs, and ointments. It is effective against MRSA and *Enterococcus* spp; clinically significant resistance to povidone-iodine has not been documented.[27]

The rate of adverse reactions with povidone-iodine is low although there are reports of contact dermatitis as well as metabolic acidosis with prolonged use.[28] In addition, iodine has been considered cytotoxic and deleterious to wound healing. One review concluded that in the majority of in vivo studies reviewed, povidone-iodine seemed to impair wound healing.[29]

Benzoyl peroxide and other antiacne agents

A powerful oxidizing agent, benzoyl peroxide has broad-spectrum bactericidal effects.[30] It is available in gels, creams, lotions, and washes and in various concentrations from 2.5% to 20%. Most commonly, benzoyl peroxide is used for the FDA-indicated treatment of acne vulgaris; however, in vitro tests confirm that it is effective against a wide range of organisms including *Staphylococcus capitis, Staphylococcus epidermidis, Propionibacterium avidum, Propionibacterium granulosum, and Pityrosporum ovale*, in addition to *P acnes*.[30]

Increasingly, benzoyl peroxide is being formulated in combination with antibiotics, such as clindamycin and erythromycin for the treatment of acne vulgaris. These topical combinations are more effective clinically and induce less resistance of *P acnes*.[31] Topical erythromycin alone is FDA-approved to treat acne vulgaris but has also been used in the treatment of erythrasma, pitted keratolysis, and trichomycosis axillaris caused by corynebacterium.[32]

Topical azelaic acid is a dicarboxylic acid that is used in both acne vulgaris and rosacea. It works by killing *P acnes* as well as decreasing keratin production.

Hypochlorite (Bleach)

Sodium hypochlorite (NaOCl) has historical significance as well as an emerging prominence because of its bleaching and disinfecting properties.[33] It was discovered in 1788 and used in 1820 to help embalm the decomposing body of Louis XVIII. Later, it was reformulated as Dakin's solution and used widely in World War II to treat both burns and wounds. Despite hypochlorite's broad spectrum activity against both gram-positive and gram-negative organisms, concerns have been raised about its potential for cytotoxicity.

More recently, NaOCl (bleach) has been used empirically in pediatric patients with impetiginized atopic dermatitis, most commonly in the proportion of one-half cup per full bath, for 15 minutes, twice weekly.[34,35] A series of in vitro experiments demonstrated that maximal killing of isolates of community-associated MRSA optimally requires a 5-minute exposure to hypochlorite at a concentration of 2.5 μl/mL.[36] This is equivalent to one-half cup of bleach in a quarter of a bathtubful of water. Perhaps the culmination of these findings lies in a newly released topical water-based gel

containing 0.008% hypochlorous acid, and 0.002% sodium hypochlorite. This over-the-counter agent allegedly kills 99.99% of *S aureus* within 30 seconds of topical application. Although more studies are needed to confirm these findings, there is great promise in this very inexpensive, broad-spectrum and non-resistance inducing disinfectant in all its forms.[37]

Other antiseptic agents

A number of other antiseptics find service in more limited capacities. Benzalkonium chloride is a quaternary ammonium compound traditionally used for preparation of the urethral area for catheterization. It is thought to work by binding and disorganizing the bacterial membrane.[38]

Hexachlorophene is a chlorinated bisphenol compound with bacteriostatic activity against gram-positive bacteria. Its residue remains active for several days on skin. Neurotoxicity has resulted from excessive absorption and studies have also suggested a possible teratogenic effect.[39]

A number of botanic products such as thyme oil (thymol)[40] and clove oil (eugenol)[41] have been shown to have antibacterial properties. Undoubtedly, the list will continue to grow as new compounds are discovered and tested.

Antibiotic Agents

Mupirocin

Mupirocin, known formerly as pseudomonic acid A, is the major fermentation product of *Pseudomonas fluorescens*. It works by the reversible inhibition of bacterial isoleucyl-tRNA synthetase, thereby preventing protein and, subsequently, cell wall synthesis.[30] Mupirocin is highly effective against aerobic gram-positive cocci, especially *S aureus*, for which it is bactericidal at the concentrations present with the commonly used 2% ointment.[42] It is not effective against enterococci and generally has poor activity against gram-negative bacteria.[43]

Mupirocin is FDA-approved solely to treat impetigo in adults and children. However, it is a versatile agent that has also been used for treating secondarily infected lesions and for eradication of nasal staphylococcus carriage. It rarely causes local adverse effects, such as pruritus or contact dermatitis. Systemic absorption of mupirocin or its major metabolite, monic acid, has not been detected with short courses of administration.[42]

Despite mupirocin's unique mechanism of action, resistant strains have emerged.[44] In the context of widespread mupirocin use, rates have ranged from 11% to as high as 65%. In the absence of widespread use, one study still found 13% mupirocin resistance in MRSA isolates from SICU subjects, with 9% demonstrating high levels of resistance.[45] Such reports of mupirocin-resistant MRSA[46] argues for more judicious use of this important topical antibiotic.

Retapamulin

Retapamulin is one of a new class of antibiotics called pleuromutilins, which selectively inhibit the elongation phase of bacterial protein synthesis at a unique site on the ribosome.[47] Retapamulin is FDA-approved only for the topical treatment of impetigo caused by *S aureus* (MSSA) and *S pyogenes* in both adults and children. Retapamulin shows in vitro activity against *S aureus* and *S pyogenes*, including isolates resistant to β-lactams, macrolides, quinolones, and mupirocin. In 664 isolates of *S aureus*, including many with high levels of resistance to mupirocin and fusidic acid. and 448 (73%) MRSA isolates, retapamulin demonstrated excellent in vitro activity.[48] It is also promising that retapamulin shows a low propensity to developing resistance to *S aureus*.[49] More clinical studies of retapamulin in treatment of resistant *S aureus* are needed.

Dapsone

A sulfone synthesized initially in 1908, dapsone was initially put to use as an antileprosy medication.[50] Known for its powerful antiinflammatory effects in addition to its antimicrobial abilities, it was frequently used for severe inflammatory forms of acne before the advent of systemic retinoids but was limited by systemic toxicity. Recently, a 5% topical gel formulation has been FDA-approved for the treatment of mild-to-moderate acne.[51] Early studies suggest that the topical formulation is safe and that monitoring for hemolytic anemia is not necessary, even among these with known glucose 6-phosphate dehydrogenase deficiency. Although it is in the sulfa family, it appears that dapsone may not be very effective against the bacteria that are commonly treated with topical agents. In one study, the minimum inhibitory concentration (MIC) for dapsone was measured for *S pyogenes*, *S aureus*, and *E coli*, and found to have essentially no antibacterial effects against these pathogens.[52] Despite these negative findings, it is possible that other uses for topical dapsone will be uncovered as it becomes more widely available.

Neomycin and gentamicin

Neomycin is an aminoglycoside produced by *Streptomyces fradiae*. It is bactericidal by binding the 30s subunit of the bacterial ribosome to inhibit protein synthesis.[30] Neomycin is highly active against most gram-negative bacteria but is less active against *P aeruginosa* and anaerobic species such as *Bacteroides*. It is active against staphylococci but is not effective against other gram-positive bacteria such as streptococci.[43] Resistance has been reported in staphylococci and gram-negative bacilli including *E coli*, *Klebsiella*, and *Proteus*.

Neomycin is usually formulated as 20% neomycin sulfate in petrolatum, and is widely used by itself and in combination with other antibiotics, such as bacitracin and polymyxin B. One of the major drawbacks of neomycin is the perceived high prevalence of allergic contact dermatitis, estimated at 1%–6%, but perhaps higher still in patients who have a compromised skin barrier.[53,54] A recent review, however, highlights the fact that data from thousands of subjects show the actual incidence of allergic contact dermatitis to neomycin to be 1% or less in the general population.[54] Neomycin can be systemically absorbed if applied to large body surfaces in which skin is damaged, causing systemic toxicity such as ototoxicity and nephrotoxicity.[55]

Topical gentamicin is another aminoglycoside with the same mechanism of action as neomycin. It is highly active against gram-negative organisms such as *Pseudomonas* and some gram-positive bacteria, including some staphylococcal strains. It has been used to treat wounds, anogenital infections, and pseudomonas folliculitis. It should be applied with caution because of its history of causing ear and kidney toxicity when used on burn wounds, where it is rapidly absorbed.[32]

Polymyxin

Polymyxins are cationic decapeptides that are products of *Bacillus polymyxa*. Polymyxin acts as a surfactant that disrupts bacterial membranes. Polymyxins have bactericidal activity against some gram-negative organisms including *P aeruginosa*, *E coli*, *Enterobacter* sp and *Klebsiella* sp, but do not have activity against *Proteus*, most *Serratia*, or gram-positive bacteria.[43] Polymyxins only rarely cause allergic contact dermatitis, and are most often used in combination with bacitracin, zinc, and neomycin in a petrolatum base.

Bacitracin

Bacitracin is FDA-approved in adults for the treatment of superficial bacterial infections of the skin. Bacitracin is a polypeptide produced by *Bacillus subtilis*, named

for Margaret Tracy, the 7-year-old girl from whose wound the strain was originally isolated.[33] Initially developed for systemic administration, nephrotoxicity limited its use.[30] Bacitracin A is the form most commonly used, often formulated as 20% bacitracin zinc in petrolatum. It exerts its antibacterial activity by complexing with C55-prenol pyrophosphate, a constituent of the bacterial cell wall, thus blocking cell wall formation.[30]

Bacitracin is primarily active against gram-positive organisms, including staphylococci, streptococci, clostridia, and corynebacteria. It is used for treatment of local infection and is a popular topical antibiotic for wound prophylaxis because of its low cost and low toxicity. Historically, bacitracin rarely caused sensitization[43] but, in recent years, it has become a frequent cause of allergic contact dermatitis.[56,57]

INTACT SKIN

Topical antibacterial agents can be used as prophylaxis against infection in a variety of inpatient and outpatient settings. In this capacity, antiseptics—chemicals used to disinfect, and antibiotics—biologically derived substances, serve this role.

Resident Skin Flora

The skin normally provides host to a number of bacteria, fungi, and even mites (ie, *Demodex* spp). Coagulase-negative staphylococci represent the dominant bacterial resident in the stratum corneum and on the skin surface, with a reservoir in the sebaceous glands. A number of agents successfully eradicate surface bacteria but are short-acting and are unable to clear bacteria that reside more deeply in the stratum corneum. A comparison of antiseptic agents and antimicrobial agents was performed on various sites in 14 healthy subjects.[58] The study results are summarized in **Table 1**.

Another study of 50 healthy subjects demonstrated that treatment with triple-antibiotic ointment (TAO) containing bacitracin, polysporin, and neomycin eradicated coagulase-negative staphylococci from 96% of skin surface sites versus mupirocin

Table 1
Eradication of coagulase-negative staphylococci by topical antibacterial agents

Agent	Sterilization of Skin Surface	Sterilization of Stratum Corneum	Prevention of Repopulation After 16 h
10% povidone-iodine	Yes	No	—
2% aqueous iodine	Yes	Yes	—
2% tincture of iodine	Yes	Yes	No
70% ethanol	Yes	No	—
0.5% chlorhexidine-ethanol	Yes	No	—
Iodophor	Yes	Yes	No
Silver sulfadiazine	No	—	—
Mupirocin	Yes	Yes	No
TAO	Yes	Yes	Yes
Control	No	No	No

10% povidone-iodine, 2% aqueous iodine, 2% tincture of iodine, 70% ethanol, and 0.5% chlorhexidine-ethanol were applied for 15 seconds with a gauze sponge. Iodophor, silver sulfadiazine, mupirocin, and TAO were applied and covered for 6 hours with gauze. (*Based on data from* Hendley JO, Ashe KM. Effect of topical antimicrobial treatment on aerobic bacteria in the stratum corneum of human skin. Antimicrob Agents Chemother 1991;35(4):627–31.)

ointment, which eradicated the bacteria at 40% of the skin surface sites.[58] This study also showed that without neomycin, TAO was essentially equivalent to placebo.

Hand Hygiene

Alcohols are antiseptics that exhibit significant pan-antimicrobial and bactericidal activity,[59] predominantly by way of protein denaturation.[60] In concentrations ranging from 60% to 95%, alcohol-based hand washes (usually ethyl or isopropyl alcohol with emollients often added) safely, quickly, and effectively reduce microorganisms on the skin surface. For patients with recurrent skin and soft tissue infections, clinical guidelines include the use of alcohol-based cleansers as part of the personal hygiene measures recommended to prevent further episodes.[61] As a point of reference, a 62% gel preparation of ethyl alcohol exhibited a 99.99% reduction in bacteria from baseline levels after one application.[62] A number of studies in both clinical and nonclinical settings demonstrate significant decrease in bacterial counts on hands and in infection rates, significantly better than hand washing with antiseptic soap.[63–65]

A major limitation of alcohol is the transient effect of antibacterial action. Compounding alcohol with a preservative or another antibacterial agent can overcome this normally transient reduction of bacterial counts. In one study, 70% ethyl alcohol with 0.5% chlorhexidine gluconate was compared with 4% aqueous chlorhexidine, triclosan, 7.5% povidone-iodine or vehicle control for surgical scrubbing. Although all preparations reduced flora when compared with control on day 1, the combination of alcohol and chlorhexidine outperformed other preparations when evaluated on day 5.[2]

The powerful antimicrobial effect with relatively few drawbacks has led to rapid adoption of alcohol-based hand washes by numerous medical institutions and discussions of replacing traditional surgical scrubs with alcohol-based agents.[66]

Staphylococcal Colonization

Nasal colonization of *S aureus* predisposes the carrier to *S aureus* infections. Both logic and some clinical studies support the assertion that eradication of carriage results in significantly decreased rates of infection.[67,68] A number of techniques for eliminating the bacteria have been attempted, including systemic antibacterial agents, antiseptics, and topical antibacterials. Topical antibiotics such as bacitracin, tetracycline, and vancomycin applied to the nares have resulted in only temporary eradication of *S aureus*.[69]

Mupirocin demonstrates superior efficacy against a host of antibiotic-resistant strains and significant duration of clearing. A recent review of the evidence for mupirocin in treating *S aureus* colonization[67] highlighted some of the following results:

- In one series, 5 days of intranasal mupirocin twice daily resulted in 13% positive culture results in the experimental group versus 93% in the placebo control group at 48 to 72 hours, 18% versus 88% at 4 weeks, and 53% versus 76% at 1 year.
- A comparison between intranasal mupirocin and bacitracin in health care workers demonstrated 20% carriage for mupirocin recipients versus 77% carriage for the bacitracin group at 30 days follow-up.
- Intranasal neomycin was compared with mupirocin (both thrice daily for 7 days) in a small study that showed 42% of the mupirocin group and 75% of the neomycin group had positive cultures at 3 months posttreatment.

While the data are convincing in terms of reducing carriage, subsequent differential infection rates are a more meaningful measure. Benefits of decolonization in reducing

infection have been demonstrated in patients who are undergoing surgery as well as those receiving peritoneal dialysis and hemodialysis.[70] In one large study of 4030 subjects who received intranasal mupirocin twice daily for 5 days preoperatively, 4% of nasal carriers of *S aureus* in the treated group developed surgical site infection versus 7.7% of placebo-treated carriers.[71] A recent multicenter study demonstrated that a combination of intranasal mupirocin and chlorhexidine soap used in nasal carriers of *S aureus* reduced the risk of surgical-site infections.[72] A study of 267 nasal carriers of *S aureus* on peritoneal dialysis showed that the group treated with mupirocin twice daily for 5 days per month had 14 exit-site infections versus 44 in the placebo group.[73] Other types of infections such as peritonitis were not significantly reduced. Of note, the study revealed that treating large numbers of nonnasal carriers did not affect their infection rate.

Unlike the surgical and dialysis populations, however, nonsurgical subjects did not seem to clearly benefit from mupirocin prophylaxis. 1602 nonsurgical subjects were found to be nasal *S aureus* carriers at the time of admission and treated with mupirocin or placebo ointment twice daily for 5 days. Nosocomial *S aureus* infections did not differ between the two groups.[74] While mupirocin resistance and dosing regimen may be factors that affected the results, the study suggests that nonsurgical patients do not benefit from such screening and intervention.[75] Future studies may better define subsets of individuals with identifiable risk factors that may be appropriate candidates for decolonization.

MRSA

Although there was an overall decrease in *Staphylococcal* nasal colonization in the United States between 2001 and 2004, the prevalence of nasal colonization with MRSA has increased.[76] Individuals who have newly acquired MRSA as well as individuals who have harbored MRSA for greater than 1 year are at high risk for MRSA morbidity.[77]

Traditionally mupirocin has shown efficacy against MRSA. One study used mupirocin intranasally thrice weekly as a prophylatic regimen on a ward with endemic MRSA. This was effective at decreasing serious MRSA infection and resistance to mupirocin was not seen.[78] Mupirocin resistance has emerged, however, and there is speculation that this may be due to low concentrations of mupirocin in the pharynx during intranasal administration.[79,80] In one provocative study, mupirocin resistance was overcome by the use of intranasal TAO containing bacitracin, polymyxin B, and gramicidin.[81] With reports of high rates of mupirocin resistance (see above), including high-level resistance, infection control strategies for MRSA should not rely too heavily on mupirocin alone, especially as testing for mupirocin resistance is not routine at most institutions.[45]

MRSA decolonization as a strategy for infection control is controversial, primarily because there is no clear antibacterial regimen that succeeds in long-term eradication in hospitalized patients. Previous studies of mupirocin have focused on detection and treatment of MRSA carriage in the nose; however, there is ample evidence that MRSA colonizes multiple sites which, in addition to the nose, include the throat, axilla, groin, and rectal area.[82] Therefore, it follows that effective decolonization would need to address these broad anatomic sites.[83]

While systemic antimicrobials are not recommended routinely for decolonization, refractory cases of MRSA infection may respond to a combined strategy of oral and topical treatment. In one randomized study, hospitalized subjects who had MRSA received a 7-day course of chlorhexidine washes, intranasal mupirocin, rifampin

and doxycycline.[84] 92% of these subjects were cleared of MRSA from all sites and 74% remained clear at 3 months. A previous study used a similar combined regimen of topical and oral antimicrobial agents and achieved 90% in the subjects followed up at 3 months.[85]

Although these studies imply that there may be effective regimens, likely including topical antibacterial agents, for long-term *S aureus* eradication there are still many important questions. The optimal dosing regimen remains unclear and its ability to alter infection rates needs to be better elucidated. It may even be argued that widespread MRSA decolonization may be detrimental as it might select for more virulent strains.

Although evidence is limited on methods to prevent CA-MRSA, the Infectious Diseases Society of America (IDSA) issued recommendations in 2011 for the practical management of recurrent skin and soft tissue infections. The society offers clinical guidelines on decolonization as a strategy to reduce recurrence of MRSA infections. These include a 5–10 day course of intranasal mupirocin which may be used alone or in combination with chlorhexidine or diluted bleach baths.[61] Newer agents such as lysostaphin, an endopeptidase, are being investigated in treating MRSA in animal models.[86] Less conventional antibacterial agents such as tea tree oil (*Melaleuca alternifolia*) have been studied as well. In one small study, tea tree oil was applied in a 4% nasal ointment with a 5% tea tree oil–based body wash and compared with mupirocin nasal ointment with triclosan body wash for MRSA eradication. The tea tree oil regimen was found to be more efficacious, although not significantly so.[87] Newer studies suggest that habituation may occur with tea tree oil and caution that this may decrease efficacy of other topical antibiotics.[88,89] The increasing importance of MRSA infections calls for more work in this area.

SUPERFICIAL WOUNDS

An Australian study of 177 superficial wounds in schoolchildren found infection rates of 8.5% and 12.5% by microbiologic and clinical criteria, respectively.[90] A landmark study on the natural history of superficial wound infection demonstrated a 47% streptococcal colonization rate of minor skin trauma (largely mosquito bites and abrasions) in a control group.[91] This same study showed that TAO containing bacitracin, polysporin, and neomycin decreased this rate to 15% when applied thrice daily.

Topical antibacterial agents also appear to have effects on wound healing in a manner seemingly unrelated to their antimicrobial properties. TAO has been shown to increase the reepithelialization rate of experimentally induced wounds by up to 25%[92] and minimize scarring and dyspigmentation compared with other agents and placebo.[93]

OPERATIVE WOUNDS

Preoperative Prophylaxis

Preoperative disinfection of the skin is widely accepted as the standard of care for decreasing postoperative wound infection.[94] Chlorhexidine and iodophors are generally accepted as among the most effective and widely used agents.[95] One prospective study found that preoperative showering with 4% chlorhexidine gluconate was more effective than povidone-iodine soap in reducing positive intraoperative wound cultures (4% vs 9%, respectively).[96] A more recent study suggested that a 2% chlorhexidine gluconate preparation with 70% isopropyl alcohol was more effective than either of the two constituents alone at reducing microbial counts at different time points.[12]

Postoperative Wound Care

Despite their excellent preoperative performance, disinfectants such as chlorhexidine, NaOCl, and povidone-iodine are generally not helpful in preventing infections in postoperative wounds; moreover, many experimental studies have demonstrated significant cytotoxicity from these agents.[4,97–99] Better suited for this task are the topical antibiotics such as bacitracin, mupirocin, and silver sulfadiazine (SSD), which appear to decrease infection rates and enhance wound healing.[92,100–102] In one large study of 6,000 surgical cases, neomycin-bacitracin-polymyxin spray was found to decrease infection rates.[103] Another trial of the neomycin-bacitracin-polymyxin spray versus no treatment of 851 surgical wounds demonstrated significant reduction in infection in the experimental group.[104]

In a mouse surgical wound model, mupirocin cream showed equal efficacy to the oral penicillin flucloxacillin and greater efficacy than oral erythromycin in reducing bacterial counts. It was also similar in efficacy to oral cephalexin against *S pyogenes* but superior against *S aureus*.[105]

Honey has been studied in a number of clinical settings, including as an agent for wound healing. The hyperosmolarity of honey impedes bacterial growth, whereas factors in honey called inhibines, which include hydrogen peroxide, flavonoids, and phenolic acids, appear to elicit antibacterial effects directly.[106] A systematic review of the data on honey concluded that, with some reservation due to study quality and small numbers, wound healing and infection rates were consistently better in those subjects treated with topical honey compared with several other active agents.[107]

BURNS

The moist, necrotic tissue in a burn patient is an ideal environment for bacterial growth. The large areas of ischemic tissue around the wounds may limit the availability and, thus, the usefulness of systemic antibiotics. Before 1965, the rate of burn wound sepsis was reported to be as high as 60%; this quickly fell to 28% after the widespread use of topical silver nitrate.[108] A 2008 review of wound management in the *New England Journal of Medicine* concluded that the optimal therapy for highly contaminated or infected burns with significant exudate is the application of topical antimicrobial agents and absorbent gauze dressings.[109]

Numerous topical agents and regimens have been proposed and tested, but SSD has long been recognized as the mainstay of topical burn therapy. With broad antimicrobial properties and a relatively small side-effect profile, it continues to be the standard by which other treatments are measured, especially for second- and third-degree burns.[109] Because SSD can cause cytotoxicity and thereby delay healing, newer synthetic dressings that release the silver slowly and reduce cytotoxicity are being developed.

A recent study demonstrates that the addition of 0.2% chlorhexidine digluconate to SSD results in superior antimicrobial effects against all bacteria studied in an in vitro model.[108] SSD has several documented side effects, however rare, including neutropenia, erythema multiforme, crystalluria, and methemoglobinemia.[110] These, in part, continue to drive the search for other agents.

Several studies have demonstrated the efficacy of mupirocin ointment for burn wounds, particularly those that are infected with MRSA. One such study of 45 children with burn wounds who developed MRSA infections despite treatment with SSD with chlorhexidine or povidone-iodine showed complete eradication of MRSA within 4 days of initiating mupirocin therapy.[111]

A large study compared 1053 burn subjects treated with povidone-iodine plus neomycin-framycetin-bacitracin ointment (PVP+N) with 1089 subjects treated with SSD and found that healing times and infection rates were statistically favorable for the PVP+N group.[112]

Honey has been studied as an alternative to SSD in burns. A 1998 study of 50 subjects, 25 of them treated with honey and 25 with SSD-impregnated gauze, showed that 100% of the honey-treated subjects showed evidence of wound healing by day 21 versus only 84% by day 21 in the SSD-treated group, although this was not statistically significant.[113] The study also found similar infection eradication rates in both groups. A systematic review of six studies with honey in burn wound treatment found that wound healing infection rates were consistently better in those subjects treated with topical honey compared with other active agents.[107] Recently, there has been some promising new data on honey. Using a standardized medical-grade honey, it was demonstrated that the bacteria on the arms of 42 healthy adults was reduced by 100-fold versus the placebo group, including multiple antibiotic-resistant strains.[114] The investigators suggest that with a more standardized honey preparation, future studies may show more consistent results and open the door for new possibilities for honey as a topical therapy.

The adverse effects associated with SSD are thought to be associated with the sulfa moiety; several attempts have been made to use silver alone. Silver is thought to exhibit its antibacterial properties by interacting with thiol groups in bacterial proteins, which leads to inactivation and by direct DNA condensation and loss of replication abilities.[115] Earlier studies demonstrated that coating nylon fibers with silver resulted in sustained broad bactericidal effects similar to those of SSD without the potential adverse effects of the sulfa moiety.[116] A modern version of this principle, in the form of a dressing of nanocrystalline silver (Acticoat, Smith & Nephew, London, England) was found nearly equivalent to SSD in terms of antimicrobial effects in an in vitro model.[108]

Despite great advances, burn management continues to be a highly challenging area. The authors follow the developments of some of these newer agents with great interest.

IMPETIGO

Impetigo is a superficial skin infection that can be divided into primary—arising in previously intact skin; and secondary—arising in skin that has had barrier damage, such as dermatitis. Whether primary or secondary, the skin manifestation is classically a superficial erosion and honey-colored crust. *S aureus* and *S pyogenes* are most often the causative agents. A Cochrane systematic review of impetigo[47] and a recent large systematic review[117] highlighted the following points:

- The peak incidence occurs between the ages of 2 and 6 years.
- Topical antibiotics are more effective than placebo.
- There is evidence that topical antibiotics are more effective than some systemic antibiotics for the treatment of impetigo.
- Topical antibiotics are the preferable first-line treatment.

One study compared oral erythromycin to topical mupirocin in 75 subjects who had impetigo. The mupirocin performed similarly on clinical grounds and superiorly on microbiological data.[118] Another more recent study in 159 subjects who had secondarily impetiginized eczema demonstrated that mupirocin cream applied thrice daily was bacteriologically superior to oral cephalexin.[119] Finally, experiments in a hamster impetigo model infected with *S aureus* demonstrated that mupirocin cream was

significantly more effective than mupirocin ointment, not significantly different from neomycin-bacitracin cream, but significantly superior to oral erythromycin and cephalexin.[105]

More recently, retapamulin has been approved for use in impetigo caused by MSSA and *S pyogenes*, as described above.[47]

ULCERS

Preventing bacterial colonization and infection of deeper wounds likely depends on a number of factors, including debridement, active cleansing, and dressing choice. It is therefore difficult to evaluate the role of topical antibacterial agents when divorced from these other factors. A systematic review of topical antimicrobials in chronic wounds in 2001[120] and a more recent Cochrane review of antiseptics and antibiotics used for venous leg ulcers were inconclusive in terms of these agents' ability to promote ulcer healing, although the latter study offered evidence to support the use of cadexomer iodine.[121]

Daily application of gentian violet 0.1% solution and ointment (an antiseptic) was demonstrated to eradicate 18 cases of MRSA-infected ulcers that had failed previous treatment with povidone-iodine and systemic antibiotics.[122] The mechanism of gentian violet is not fully understood, but early studies demonstrated nonspecific protein and cell wall synthesis inhibition, as well as accumulation of cytidine diphosphoribitol and peptidoglycan precursors.[123]

Honey has also been used successfully for clearance of MRSA infection and improved healing in ulcers.[107,124]

Disinfectants are often empirically applied but may be too harsh for routine use in wounds. In vitro studies have demonstrated that antiseptics such as povidone-iodine and chlorhexidine show cytotoxic properties and may therefore delay healing of ulcers.[125]

INTRAVASCULAR CATHETERS

There is a 10%–20% mortality attributed to catheter-related bloodstream infection.[126] Appropriate antiseptic care of intravascular catheters should ideally decrease the incidence of infection and, thus, the risk of sepsis. Impregnation of central venous catheter cuffs with antibacterials is beyond the scope of this article.

A large meta-analysis involving a total of 4143 catheters concluded that chlorhexidine gluconate reduced the risk for catheter-related bloodstream infection by 49% compared with povidone-iodine.[126] The investigators hypothesized that chlorhexidine was more effective due to the fact that blood and serum can lessen the microbicidal effect of povidone-iodine but not chlorhexidine, and that chlorhexidine has both a more potent and a longer residual antimicrobial effect compared with povidone-iodine. A follow-up analysis by the same group calculated that the slightly higher cost of chlorhexidine compared with the decreased morbidity and mortality from its use in this clinical context resulted in a $113 savings per catheter used.[127]

Other topical antibiotics have been used for intravascular catheter care. A study of 709 consecutive subjects with venous catheters treated with neomycin-bacitracin-polymyxin spray or control demonstrated decreased colonization by more virulent potential pathogens such as *E coli*, *Klebsiella*, and *Staphylococcus* when the antibiotic spray was used.[128]

Despite decreasing colonization successfully, a prospective study of 827 catheters treated with neomycin-bacitracin-polymyxin ointment at the insertion of a catheter and every 48 hours thereafter failed to show a difference from placebo in the rate of local infection or catheter-associated sepsis.[129]

SUMMARY

Topical antibacterial agents have an important role in antimicrobial therapy. Antiseptics and antibiotic preparations offer important alternatives and supplements to systemic agents in a variety of clinical scenarios. These agents are highly versatile. Uses include prophylaxis of infection for traumatic and surgical wounds, *S aureus* decolonization, treatment of burns, and treatment of primary and secondary pyodermas. Although topical antibacterials are widely used in clinical practice, ongoing trials continue to elucidate their relative efficacies.

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