REVIEW ARTICLE

Topical antibiotics in dermatology: An update

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ABSTRACT

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 offers several advantages, 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. Resistance to topical antibiotics is of growing concern to dermatologists. In this review, we have discussed various topical antibiotics currently available to us, their uses in different dermatological conditions. Also discussed are the precautions to be followed, so as to minimize the emergence of drug resistance.

INTRODUCTION

Topical antibiotics are commonly prescribed by dermatologists in clinical practice for a variety of potential uses, which are the following: (i) infectious, including localized cutaneous bacterial infections, (ii) crusted (secondarily impetiginized) eczematous dermatoses, (iii) staphylococcal nasal carriage, and (iv) for non-infectious dermatoses, such as acne vulgaris. Other clinical dermatologic uses include: (v) application postoperatively to surgical wound sites for prophylaxis against infection, and (vi) for chronic wounds such as leg ulcers, sometimes based on culture and sensitivity results.

DEFINITION

1. A substance produced by or derived from certain fungi, bacteria, and other organisms, that can destroy or inhibit the growth of other microorganisms.

2. Antibiotics may be informally defined as the sub-group of anti-infective agents that are derived from bacterial sources and are used to treat bacterial infections. Other classes of drugs, most notably the sulfonamides, may be effective antibacterials. Similarly, some antibiotics may have secondary uses, such as the use of demeclocycline (Declomycin, a tetracycline derivative) to treat the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion. Other antibiotics may be useful in treating protozoal infections.

CLASSIFICATIONS

Although there are several classification schemes for antibiotics, based on bacterial spectrum (broad versus narrow) or route of administration

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(injectable versus oral versus topical), or type of activity (bactericidal vs. bacteriostatic), the most useful is based on chemical structure. Antibiotics within a structural class will generally show similar patterns of effectiveness, toxicity, and allergic potential.

Penicillins

The penicillin is the oldest class of antibiotics, they share a common chemical structure with the cephalosporins. The two groups are classed as the beta-lactam antibiotics, and are generally bacteriocidal. The penicillin can be further subdivided. The natural pencillin is based on the original penicillin G structure; penicillinase-resistant penicillin, notably methicillin and oxacillin, are active even in the presence of the bacterial enzyme that inactivates most natural penicillin. Aminopenicillin such as ampicillin and amoxicillin have an extended spectrum of action compared with the natural penicillin; extended spectrum penicillin is effective against a wider range of bacteria. These generally include coverage for *Pseudomonas aeruginosa* and may provide the penicillin in combination with a penicillinase inhibitor.

Cephalosporins

Cephalosporins and the closely related cephamycins and carbapenems, like the penicillin, contain a beta-lactam chemical structure. Consequently, there are patterns of cross-resistance and cross-allergenicity among the drugs in these classes. The "cepha" drugs are among the most diverse classes of antibiotics, and are themselves sub grouped into 1st, 2nd and 3rd generations. Each generation has a broader spectrum of activity than the one before. In addition, cefoxitin, a cephamycin, is highly active against anaerobic bacteria, which offers utility in treatment of abdominal infections. The 3rd generation drugs, cefotaxime, ceftizoxime, ceftriaxone and others, cross the blood-brain barrier and may be used to treat meningitis and encephalitis. Cephalosporin's are the usually preferred agents for surgical prophylaxis.

Fluroquinolones

The fluroquinolones are synthetic antibacterial agents, and not derived from bacteria. They are included here because they can be readily interchanged with traditional antibiotics. At earlier times, related class of antibacterial agents, the quinolones, were not well absorbed, and could be used only to treat urinary tract infections. The fluroquinolones, which are based on the older group, are broad-spectrum bacteriocidal drugs that are chemically unrelated to the penicillins or the cephaloprosins. They are well distributed into bone tissue, and so well absorbed that in general they are as effective by the oral route as by intravenous infusion.

Tetracyclines

Tetracyclines got their name because they share a chemical structure that has four rings. They are derived from a species of Streptomyces bacteria. These are broad-spectrum bacteriostatic agents effective against a wide variety of microorganisms, including rickettsia and amoebic parasites.

Macrolides

The macrolide antibiotics are derived from Streptomyces bacteria, they all have a macrocyclic lactone chemical structure. Erythromycin, the prototype of this class, has a spectrum and use similar to penicillin. Newer members of the

group, azithromycin and clarithyromycin, are particularly useful for their high level of lung penetration. Clarithromycin has been widely used to treat *Helicobacter pylori* infections, the cause of stomach ulcers.

Others

Other classes of antibiotics include the aminoglycosides, which are particularly useful for their effectiveness in treating *Pseudomonas aeruginosa* infections; the lincosamindes, clindamycin and lincomycin, which are highly active against anaerobic pathogens. There are other, individual drugs which may have utility in specific infections.

Topical antibiotics are medicines applied to the skin to kill bacteria. The skin is readily accessible and topical agents can be applied at high concentration, achieving effective levels locally with little systemic toxicity. The high local levels of antibiotic that can be achieved with topical formulations can help kill bacteria in bacterial biofilms.

PURPOSE

Topical antibiotics help prevent infections caused by bacteria that get into minor cuts, scrapes, and burns. Treating minor wounds with antibiotics allows quicker healing. If the wounds are left untreated, the bacteria will multiply, causing pain, redness, swelling, itching, and oozing. Untreated infections can eventually spread and become much more serious. Different kinds of topical antibiotics kill different kinds of bacteria. Many antibiotic first-aid products contain combinations of antibiotics to make them effective against a broad range of bacteria.

When treating a wound, it is not enough to simply apply a topical antibiotic. The wound must first be cleaned with soap and water and patted dry. After the antibiotic is applied, the wound should be covered with a dressing, such as a bandage or a protective gel or spray. For many years, it was thought that wounds heal best when exposed to the air. But now most experts say it is best to keep wounds clean and moist while they heal. The covering should still allow some air to reach the wound, however.

DESCRIPTION

Some topical antibiotics are available without a prescription and are sold in many forms, including creams, ointments, powders, and sprays. Some widely used topical antibiotics are bacitracin, neomycin, mupirocin, and polymyxin B. Among the products that contain one or more of these ingredients are Bactroban (a prescription item), Neosporin, Polysporin, and Triple Antibiotic Ointment or Cream.

RECOMMENDED DOSAGE

It depends on the type of topical antibiotic being used. In general, they should be applied within four hours after injury.

PRECAUTIONS

Many public health experts are concerned about antibiotic resistance, a problem that can develop when antibiotics are overused. Over time, bacteria develop new defenses against antibiotics that once were effective against them. Because, bacteria reproduce so quickly, these defenses can be rapidly passed on through generations of bacteria until almost all are immune to the effects of a particular antibiotic. The process happens faster

than new antibiotics can be developed. To help control the problem, many experts advise people to use topical antibiotics only for short periods, that is, until the wound heals, and only as directed. For the topical antibiotic to work best, it should be used only to prevent infection in a fresh wound, not to treat an infection that has already started. Wounds that are not fresh may need the attention of a physician to prevent complications such as blood poisoning.

Topical antibiotics are meant to be used only on the skin and only for only a few days at a time. Do not use topical antibiotics on large areas of skin or on open wounds. These products should not be used to treat diaper rash in infants or incontinence rash in adults.

Only minor cuts, scrapes, and burns should be treated with topical antibiotics. Certain kinds of injuries may need medical care and should not be self-treated with topical antibiotics. These include:

- large wounds
- deep cuts
- cuts that continue bleeding
- cuts that may need stitches
- burns any larger than a few inches in diameter
- scrapes imbedded with particles that won't wash away
- animal bites
- deep puncture wounds
- eye injuries

Although topical antibiotics control infections caused by bacteria, they may allow fungal infections to develop. The use of other medicines to treat the fungal infections may be necessary. Some people may be allergic to one or more ingredients in a topical antibiotic product. No harmful or abnormal effects have been reported in babies whose mothers used topical antibiotics while pregnant or nursing. However, pregnant women generally are advised not to use any drugs during the first 3 months after conception.

SIDE EFFECTS

The most common minor side effects are itching or burning. These problems usually do not require medical treatment unless they do not go away or they interfere with normal activities. Other reported side effects are as follows:

- rash
- swelling of the lips and face
- sweating
- tightness or discomfort in the chest
- breathing problems
- fainting or dizziness
- low blood pressure
- nausea
- diarrhea
- hearing loss or ringing in the ears

Other rare side effects may occur.

INTERACTIONS

Using certain topical antibiotics at the same time as hydrocortisone (a topical corticosteroid used to treat inflammation) may hide signs of infection or allergic reaction.

COMMON TOPICAL ANTIBIOTICS USED IN DERMATOLOGY

Bacitracin

A complex of cyclic peptide antibiotics produced

by the Tracy-I strain of *Bacillus subtilis*. The commercial preparation is a mixture of at least nine bacitracins with bacitracin A as the major constituent. It is used topically to treat open infections such as infected eczema and infected dermal ulcers, and as a prophylaxis in operative wounds.[1] Bacitracin binds to C55-isoprenyl pyrophosphate, a biphosphate lipid transport molecule that carries the building blocks of the peptidoglycan bacterial cell wall.[2] The binding interferes with the enzymatic dephosphorylation of the C55-isoprenyl pyrophosphate and prevents peptidoglycan synthesis, thereby inhibiting bacterial cell growth.

Mupirocin

A natural crotonic acid derivative extracted from a strain of *Pseudomonas fluorescens*. It has shown excellent activity against gram-positive staphylococci and streptococci. It inhibits bacterial protein synthesis by specific reversible binding to bacterial isoleucyl tRNA synthase.[3] It has excellent activity against gram-positive staphylococci and streptococci. It is used primarily for the treatment of primary and secondary skin disorders, nasal infections, and wound healing.

Dapsone

A sulfone synthesized in 1908 was initially used as an antileprosy agent.[4] It is well 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 approved for the treatment of mild-to-moderate acne.[5] 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.[6] Despite these negative findings, it is possible that other uses for topical dapsone will be uncovered as it becomes more widely available.

Retapamulin

It belongs to a class of the naturally occurring pleuromutilin produced by *Pleurotus mutilus*, an edible mushroom. The pleuromutilin class has a unique mode of action, which involves inhibition of bacterial protein synthesis by binding to the prokaryotic ribosome. Retapamulin selectively inhibits bacterial protein synthesis through an interaction at a binding site on the 50S subunit of the bacterial ribosome that differs from that of other antibiotics.[7] Retapamulin is predominantly bacteriostatic against *Staphylococcus aureus* and *Streptococcus pyogenes*. It is used primarily for the treatment of primary skin infections, and secondarily infected lesions.[8]

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*.[9] Its mechanism of action is to inhibit protein synthesis by binding with ribosomal RNA, causing misreading of the bacterial genetic

code.[9] With the exception of *P. aeruginosa*, it is bactericidal against most gram negative bacteria; however, it lacks activity against anaerobes.[10] It is active against some gram-positive bacteria, including staphylococci, but is not effective against streptococci.[10] 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. [9,10]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.[10] 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*.[10]

Erythromycin

Topical erythromycin is used most frequently in the treatment of acne vulgaris; 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.[12] 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. 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%. Erythromycin 2% ointment was therefore deemed to be a worthy substitute for other topical antibiotics.

Gentamicin

It belongs to the aminoglycoside group of antibiotics. It is a product of a strain of *Micromonospora purpurea*.[13] The mechanism of action of gentamicin appears to be inhibition of protein synthesis and messenger ribonucleic acid translation. It has a similar "spectrum" to related antibiotics such as neomycin and kanamycin, but a rather greater activity than these against some species of bacteria. Almost all enterobacteria are sensitive to it, including species of Aerobacter, Escherichia, Klebsiella, Salmonella, Shigella, Proteus (three species fully sensitive, but P. vulgaris less so), and Pseudomonas.[14] A high degree of activity against *Ps. aeruginosa* is an outstanding property: Among Gram positive organisms the most sensitive are staphylococci. Streptococci (except *S. faecalis*) and pneumococci are also moderately sensitive, but much less so than to many other antibiotics. It is bactericidal in concentrations little greater than those inhibiting growth. The application of a cream or ointment

containing 0.1% gentamicin has been successful in the treatment of burns, bedsores, impetigo and other pyogenic skin infections, and of nasal carriers of staphylococci.[15] The principal indication for gentamicin is infection caused by *Ps. aeruginosa*, against which it is the most potent antibiotic known. Its activity against staphylococci, even when they are resistant to neomycin and kanamycin, is also important.

Polymyxin

Polymyxins are decapeptides that are isolated from Bacillus polymyxa.[16] 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. [9,16] 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.[16] 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.

Indolmycin

Topical indolmycin demonstrates good antistaphylococcal activity and seems promising for treating MRSA strains resistant to fusidic acid and mupirocin.[17] The agent is bacteriostatic but shows good in vitro activity against MSSA, MRSA, and vancomycin-intermediate S aureus (VISA), including strains resistant to mupirocin and fusidic acid.[17] Some indolmycin-resistant strains have emerged, with high-level resistance most commonly associated with an H43N mutation in tryptophanyl-tRNA synthetase, the target enzyme of indolmycin.[18]

Nadifloxacin

Nadifloxacin is a potent, broad-spectrum, quinolone agent approved for topical use in acne vulgaris and skin infections in Japan. Quinolones are bactericidal drugs that inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, two enzymes absent in eukaryotic cells, thereby stopping DNA replication and transcription. [19] A European 12-week study comparing the clinical and bacteriological efficacy of nadifloxacin 1% cream with erythromycin 2% cream has demonstrated that nadifloxacin was as efficacious and safe as erythromycin and that the number of nadifloxacin-resistant microorganisms was extremely low during the treatment period.

Rifalazil

Rifalazil and other benzoxazinorifamycins are modified rifamycins that contain a distinct planar benzoxazine ring.[20] Rifalazil shows high tissue penetration and achieves high intracellular levels.

Drugs within this family are promising as topical agents, but resistance has been a significant problem with rifampin, and the potential for development of resistance to topical forms deserves careful scrutiny.

Fusidic Acid

Fusidic acid belongs to the fusidanes, which have molecular structures similar to corticosteroids without the steroid-like effects.[21] It is derived from the fungus *Fusidium coccineum* that works by interfering with bacterial protein synthesis, by preventing the translocation of the elongation factor G (EF-G) from the ribosome. It is able to achieve a high penetration and concentration at the site of infection, and is highly effective against S. aureus. Many guidelines suggest fusidic acid as first line in the treatment of superficial skin infections and infected eczema, as the main bacterial culprit is S. aureus.[22] Topical fusidic acid and mupirocin appear to be equally effective in cases of primary cutaneous infections.[23] Both ointments appear to be effective against Gram-positive, Gram-negative or a combination of these organisms. The only adverse effect was that of greasiness, which was higher in the mupirocin group. Randomized trials have demonstrated the existence of resistance to topical fucidin and oral fusidic acid.[24] Recent studies from Yorkshire and Bristol have further highlighted this concern over growing fucidin resistance. The West Yorkshire study found that 50% of fusidic acid-resistant strains were from dermatology patients exposed to topical fucidin in the 6 months prior to the study.[25] The Bristol study found a doubling of fusidic acid resistance in methicillin-susceptible S. aureus over a 4-year period.[26] There may be prolonged use of topical fucidin in people with atopic eczema. It is true that 90% of atopic eczema sufferers are colonized by S. aureus; however, the risk of atopic children developing MRSA infection in the future remains a growing and real concern. The resistance level to fucidin is low at present, most likely due to its unique molecular structure and therefore is less likely to share resistance mechanisms with other antibiotics. Prolonged treatment with fucidin ointment should be avoided, even in the community setting.[27] Short-term use of fusidic acid, over a 2-week period, has not been found to increase resistance.[28]

Newer Compounds

New antibiotics are being studied, including new topical macrolides. BAL19403, which belongs to a new family of macrolide antibiotics, shows excellent in vitro activity against propionibacteria, including erythromycin- and clindamycin-resistant propionibacteria.[29]

Combination Topical Antibiotics

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*.[30] However, the combination does not provide adequate coverage against *Serratia marcescens*. 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.

GENERAL INFORMATION

As a general rule in topical medication, to use the cream, gel, lotions or ointments, the patient is instructed to follow these steps:

- Wash the affected skin with saline or water and a mild soap and pat dry with a soft towel. Be careful to remove previous topical drugs or cosmetics
- Apply a thin layer of the topical medication to the affected skin. The "fingertip unit" can be considered as the golden standard.
- Gently and thoroughly massage the topical medication onto the skin.
- The recommended dosage depends on the type of topical antibiotic. In general, topical antibiotics should not be applied often than three times a day.
- After the antibiotic is applied, the area should be covered with a dressing, such as a bandage.
- Hands should be washed with soap and water after handling the medication.
- All topical medication may cause side effects. Although side effects are usually local (itching, burning, stinging, tingling), systemic reaction can occur.
- Using certain topical antibiotics combined with a topical corticosteroid may hide signs of infection or allergic reaction. Certain compounds of two or more topical antibiotics may complicate the diagnosis of an accidental contact/systemic reaction. Do not use these products unless told to do so by a doctor.
- Treat carrier sites. In impetigo, a frequent source of infection comes from mucosal surfaces, especially from nasal ones. In this case, special antibiotic ointment should be applied to the nostrils three times daily for 7 days.
- As general measures during the infectious stage, (i.e., while the impetigo is oozing or crusted), it should be remembered to avoid close contact with others, to use separate towels and flannels and to change and launder clothes and linen daily.
- Affected children must stay away from school until crusts have dried out.

ACNE

Oral and topical antibiotics are often the most important part of an acne treatment regimen. They are especially effective in treating inflammatory acne.[31,32] Numerous controlled trials have assessed the efficacy of topical erythromycin, clindamycin, and tetracycline in treating facial acne, usually characterized as moderately severe. Some studies have defined this as the presence of at least ten to 12 inflammatory lesions (papules and pustules) and, sometimes, fewer than 60 to 70. Certain trials have excluded patients with more than three to six nodulocystic lesions. All investigators have used as their outcome criteria a reduction in the number of lesions and a global assessment of improvement during the eight to 12 weeks of twice-daily application of the trial medications.[33] Topical erythromycin and clindamycin are equal, but not superior to tretinoin and benzoyl peroxide, two other topical acne treatments. A 5% benzoyl peroxide gel is equivalent to 1.5% erythromycin in overall effectiveness, but benzoyl peroxide is better for non inflammatory lesions.[34] Three percent erythromycin gel and benzoyl peroxide

5% gel are equally efficacious and better than the vehicle, but a combined erythromycin-benzoyl peroxide gel is better than either component alone.[35] The combination of clindamycin and tretinoin, however, confers no advantage over the individual agents.

The topical antibiotics are also equal, but not superior, to oral tetracycline. The response to topical antibiotics is more impressive for inflammatory lesions (papules and pustules) than for comedones, nodules, and cysts, but these non inflammatory lesions benefited some as well. In general, improvement is evident early, often within two weeks. In some studies the maximum effect had occurred at six or eight weeks, but in others a steady diminution of lesions continued throughout 12 weeks. No trial extended its observations beyond this point, but the practical clinical conclusion is that, in a patient who has shown initial benefit, the clinician should not assume that a maximal response has occurred until at least 12 weeks of treatment have elapsed. In these studies, adverse effects have been uncommon. Local reactions, such as dryness, scaling, soreness, and itching occur in a small number of patients, usually from the vehicle rather than the antibiotic, and, uncommonly, require discontinuing the therapy. Allergic contact dermatitis is rare, as are systemic reactions. The effect of topical antibiotics on the antimicrobial susceptibility of skin organisms, an important concern, has received relatively little attention. Since oral and parenteral erythromycin, tetracycline, and clindamycin are prescribed for systemic infections, widespread topical use of these agents could, theoretically, encourage the emergence of antibiotic-resistant organisms and thereby compromise the effectiveness of these medications in treating serious disorders. Furthermore, antibiotics may be efficacious in acne by diminishing the number or impairing the metabolism of P acnes; the effect may be to decrease this organism's conversion of sebum to free fatty acids, which cause inflammation in the pilosebaceous unit. The development of antibiotic resistance in *P acnes*, therefore, might diminish the efficacy of topical antibiotics in treating acne. In one study of topical erythromycin given for four weeks, the percentage of patients with erythromycin-resistant micrococci increased from 3% before therapy to 60% afterward, but *P acnes* remained susceptible.[36] Similarly, in a trial of clindamycin given for eight weeks, no resistant *P acnes* emerged; resistant staphylococci, however, became more common during therapy but decreased after the medication was discontinued.[37] Investigators in another study isolated clindamycin-resistant *P acnes* in 24% of patients who had received topical clindamycin for two to 24 months and erythromycin-resistant *P acnes* in 19% of patients treated with topical erythromycin for eight weeks. These organisms were also resistant to clindamycin. Within one to two months after topical therapy ended, however, susceptible *P acnes* replaced the resistant bacteria.[38] In summary, topical erythromycin, clindamycin, and meclocycline are safe and effective for treating moderately severe facial acne. About 70% of patients have a good to excellent outcome when treated for eight to 12 weeks, with papules and pustules responding better than comedones, nodules, or cysts. While clearly more effective than their vehicles, these agents are equal, but not superior to, oral tetracycline or topical treatment with benzoyl peroxide or tretinoin, which are better for comedones. Since the frequency of

adverse effects with these agents is approximately equivalent, the choice among them will usually depend on other factors such as cost, convenience, and personal preference.

ROSACEA

Topical metronidazole is significantly superior to its vehicle when used as a 0.75% gel[39] or as a 1% cream[40] in treating rosacea. It reduces papules, pustules, and erythema, but not telangiectasias. In a double-blind trial for nine weeks half of each patient's face was treated with metronidazole, the other half with the vehicle. Metronidazole produced a reduction of 65% in papules and pustules, compared with 15% for the vehicle.[39] The side treated with metronidazole showed improvement in 78% of patients compared to 3% for the side treated with the vehicle. In a two-month trial of 1% metronidazole cream, about 65% of treated patients had a good or excellent clinical response compared with about 20% of those receiving the placebo.[40] Metronidazole 1% cream is about equivalent to oral tetracycline, 500 mg daily, when given for two months.[41] The rapidity of improvement and the number of patients completely free of papules and pustules may be higher with tetracycline, [40] but the frequency and speed of relapse after the agents are discontinued may be lower with metronidazole. [42] Controlled clinical trials have not evaluated other topical antibiotics, but one uncontrolled study of 2% topical erythromycin given twice daily to 15 patients for eight weeks demonstrated a good to excellent response in 87% and suggested that once daily or thrice weekly application would prevent relapse after the initial course was completed.[43] How these agents work in rosacea is unclear, but inhibition of anaerobic bacteria may be important, since metronidazole has little effect on aerobic organisms.

HIDRADENITIS SUPPURATIVA

When given for three months to patients with axillary and/or perineal hidradenitis suppurativa, topical clindamycin caused a significant reduction in abscesses, inflammatory nodules, and pustules, when compared with the vehicle.[44] The duration of disease varied between one and ten years (mean, 5.5 years) in this study, which did not evaluate the bacteriology of the lesions. In another study[45] a total of 46 patients with stage 1 or 2 hidradenitis suppurativa were treated in a double-blind, double dummy controlled trial. All patients received a minimum of 3 months of therapy with systemic as well as topical treatment, that is, active systemic plus topical placebo, or systemic placebo plus active topical. Active systemic treatment consisted of tetracycline 1 g daily, and active topical treatment consisted of 1% clindamycin phosphate. No significant difference was found between the two types of treatment.

IMPETIGO

A Cochrane systematic review of impetigo[46] and a recent large systematic review[47] 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. [48] 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.[49] 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.[50] More recently, retapamulin has been approved for use in impetigo caused by MSSA and S pyogenes, as described above. [46]

INFECTED ECZEMA

Eczematous skin, particularly in atopic dermatitis, often harbors *S aureus*, without causing clinically obvious infection. The density of organisms is greater in exudative lesions than in erythematous or lichenified ones. [51,52] Treatment of the eczema with topical corticosteroids markedly diminishes the number of staphylococci, although these medications have no intrinsic antibacterial activity. [52] Presumably, the reduction in cutaneous inflammation creates a less hospitable environment for the organism. At times, however, frank staphylococcal infection complicates eczema, with the development of cellulitis, fever, lymphangitis, or pustules.[53] Several trials have examined whether the combination of topical antimicrobial and corticosteroid produces better results than corticosteroids alone. In a study of impetiginized eczema, topical gentamicin was less effective than betamethasone valerate, and the combination was no better than the steroid by itself.[54] In a group of infected or potentially infected eczema, betamethasone valerate alone was equivalent to its combination with fusidic acid, an antimicrobial with good activity against staphylococci.[55] In a small study, fluocinolone and neomycin were better than the steroid alone, and hydrocortisone plus polymyxin B, neomycin, and gramicidin was superior to the topical antibiotics alone.[56] In several trials of infected eczema, mupirocin was more effective than its vehicle, but the combination of it and topical corticosteroids was not superior to the steroids alone.39 In one trial of patients who had no overt secondary infection, however, mupirocin plus topical corticosteroids was better than steroids alone.[57] Two trials investigated the use of systemic antibiotics in atopic eczema. When patients received topical corticosteroids, flucloxacillin produced no additional benefit.[58] When patients received no topical corticosteroids, those treated with cephalexin experienced better results than controls, because the antibiotic resulted in a mild clinical improvement.[59] A reasonable conclusion from these various investigations is that topical or systemic antistaphylococcal agents provide, at best, minor clinical benefit in patients who receive no topical corticosteroids, but proper therapy of atopic eczema must include medications that reduce inflammation, such as corticosteroids. When patients appropriately receive topical corticosteroids, adding topical or systemic antimicrobial therapy is, at most, minimally helpful, and may encourage the emergence of drug-resistant organisms and increase medical care costs. Recognizing the presence of infection in atopic eczema may seem perplexing when erythema, weeping, and crusting occur, but these studies indicate that such features alone do

not justify antimicrobial therapy. Antibiotics in atopic eczema are clearly warranted only in the presence of unambiguous signs of infection (eg, fever, pustules, cellulitis,lymphangitis).[53] Such manifestations obviously represent "infected eczema," but some investigators believe that a population of *S aureus* greater than $10^6/cm^2$, even without signs of suppuration, represents secondary infection, because eczema seems to worsen with such a density of organisms.[51] The issue of infected eczema is further confounded by the difficulty of distinguishing between S aureus as a colonizing organism and as a pathogen in a weeping, crusted eczematous lesion. The lack of a clinically reliable and universally acceptable definition of "infected eczema" has hampered the studies of the efficacy of topical antibiotics in this setting. The difficulties are apparent in the most elaborate investigation of treating "infected eczema" with topical antibiotics, corticosteroids alone, or the combination. Another double-blind trial of these two treatments, however, yielded different results.[60] The combination of steroid and antibiotic produced excellent responses in 70% of subjects compared with 30% in those receiving fluocinolone alone. In a second phase of this investigation, 25 patients received polymyxin B-neomycin-gramicidin on half of the body, the same cream plus 0.5% hydrocortisone on the other half. The steroid-antibiotic combination produced excellent results in 12%, good in 64%; the antibiotic cream alone, while markedly reducing the density of *S aureus*, had no excellent results and only good in 12%.

SUPERFICIAL WOUNDS

The common use of topical antibiotics for treating skin infections following minor trauma, such as scratches, cuts, abrasions, insect bites, and simple surgical procedures, received little controlled evaluation until the advent of mupirocin. The double-blind trials of this agent against its vehicle nearly uniformly demonstrate significantly superior bacteriologic results with the antibiotic.[61-65] An Australian study of 177 superficial wounds in schoolchildren found infection rates of 8.5% and 12.5% by microbiologic and clinical criteria, respectively.[66] 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.[67] This same study showed that topical antibacterial agents containing bacitracin, polysporin, and neomycin decreased this rate to 15% when applied thrice daily. Topical antibacterial agents(TAO) 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%[68] and minimize scarring and dyspigmentation compared with other agents and placebo.[69]

OPERATIVE WOUNDS

Although clinicians commonly recommend the prophylactic application of a topical antibiotic preparation to the site of a dermatologic surgical procedure performed in an outpatient setting (i.e., biopsy, excision, suture repair site), there is no definitive evidence to show that this practice is of clinical benefit.[70] The most common antibiotic agents included in recommended topical preparations are bacitracin and neomycin. Based on four series inclusive of approximately 6000 dermatologic procedures, the reported rate

of postoperative wound infection was 1.3%. [71-74] When one considers the low postoperative infection rate reported after office-based dermatologic procedures, and the prevalence of neomycin-induced (11%) and bacitracin-induced (8%) allergic contact dermatitis, it becomes apparent that routine prophylactic use of a topical antibiotic at the site of basic dermatologic procedures performed in the office setting (i.e., biopsy, shave, saucerization, excision, suture repair line) may not be rational or optimal.[75]

On the other hand there are many studies with topical antibiotics such as bacitracin, mupirocin, and silver sulfadiazine (SSD), which have shown to decrease infection rates and enhance wound healing.[76-79] In one large study of 6,000 surgical cases, neomycin-bacitracin-polymyxin spray was found to decrease infection rates.[80] Another trial of the neomycin-bacitracin-polymyxin spray versus no treatment of 851 surgical wounds demonstrated significant reduction in infection in the experimental group. [81] 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*. [82]

NASAL CARRIAGE OF S. AUREUS

Staphylococcus aureus is present in the anterior nares of about 20% to 40% of normal adults. Eliminating this bacterium from the nose may help reduce the frequency of attacks in patients suffering from recurrent staphylococcal pyoderma and may help terminate the spread of organisms in nosocomial staphylococcal epidemics.

A multitude of studies have evaluated the potential benefits and success rates of eradicating *S. aureus* colonization of the anterior nares.[83,84] Overall, studies utilizing topical therapy alone, or in combination with oral antibiotic therapy, demonstrate variable success rates, with recolonization over time commonly noted. The latter observation is especially true in subjects who have a predilection for persistent or intermittent carriage.[83] In the United States, utilizing a large population-based assessment, the estimated prevalence of *S. aureus* and MRSA nasal colonization was reported to be 32.4 and 0.8%, respectively.[85] The perineum also exhibits a high rate of *S. aureus* colonization, and similar to the nares, demonstrates high organism density and a greater tendency for more consistent carriage over time.[86] Mupirocin has been the most common topical agent recommended for decolonization of nasal staphylococcal carriage, although eradication rates vary.[83,84] Importantly, the success rate after a single attempt at decolonization of the nares has been reported to be lower than most clinicians may appreciate, at least in some studies.[84] In one double-blind, placebo-controlled study, a five-day course of topical mupirocin was successful in eradicating MRSA from the anterior nares in 25% of treated subjects. The addition of skin washing with chlorhexidine cleanser in one of the study arms did not enhance the eradication rate.[87] Several other regimens have been studied using combinations of topical antibiotic/antimicrobial and oral antibiotic agents for eradication of nasal *S. aureus* colonization with varied results, which are reviewed elsewhere. [83-84, 88-89]

OTHER SKIN DISORDERS

Uncontrolled observations support the use of

topical antibiotics in certain other skin disorders in which the pathogenesis apparently involves microorganisms. Erythrasma, probably caused by *Corynebacterium minutissimum*, seems to respond to topical clindamycin,[90] although the imidazole antifungals like miconazole, Whitfield's ointment, [91] and other forms of topical therapy are also effective. A case of gram-negative bacillary superinfection of acne cleared with topical gentamicin. [92] Perioral dermatitis, perhaps a form of acne, subsided in 80% of cases treated with topical tetracycline.[93] Pitted keratolysis, caused by either a corynebacterium[94] or *Micrococcus sedentarius*,[95] has responded to treatment with topical tetracycline, clindamycin, and erythromycin, and to several other agents as well, including clotrimazole, miconazole, glutaraldehyde, and formaldehyde. Trichomycosis, a corynebacterial infection of hair in the axillary or pubic areas, has been controlled with topical clindamycin,[96] although shaving the hair is the usual form of treatment.

CONCLUSION

Topical antibiotics are widely used in dermatology for a variety of indications. Some of the prevalent uses are supported by reasonable amount of scientific evidence, whereas others are based on anecdotal support, clinical judgment, or habit based on recycled dogma that is not supported scientific data. Topical antibiotic change the inherent microbiologic environment of skin, and on prolonged use, can also alter the bacteriology of the anterior nares and oropharynx. This might lead to emergence of resistant pathogens. These microbiologic changes induced by topical antibiotic use warrant consideration by clinicians, and support the concept that antibiotics are to be used judiciously. There is no perfect topical antibiotic agent, and as such, both researchers and clinicians must remain vigilant to detect resistance patterns, and to establish optimal treatment regimens.

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