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Mupirocin, fusidic acid and bacitracin: activity, action and clinical uses of three topical antibiotics

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Abstract Antibiotics applied to the skin must be formulated in a base that is nonirritant and nontoxic. They may have a narrow or fairly wide spectrum of activity but should produce no local reaction or sensitization; the commensal flora should not be affected unduly. Three antibiotics that have been used topically in humans and animals are fusidic acid, mupirocin and bacitracin, all of which have a narrow antibacterial spectrum. When applied to intact skin, fusidic acid penetrates more rapidly than other antibiotics. Clinically, the frequency of staphylococcal resistance to it and to mupirocin has remained low. Fusidic acid and mupirocin have been recommended for the treatment of acute staphylococcal skin lesions. However, the use of topical antibiotics for the treatment of chronic or recurring dermatitis and surgical or infected wounds may be inappropriate because of possible development of resistance and sensitization. Topical use of bacitracin may produce treatment failure and sensitization.

Keywords: acne, bacitracin, cat, dog, fusidic acid, mupirocin, pyoderma, topical antibiotics.

INTRODUCTION

Antibiotics have been widely used systemically for many years for the treatment of bacterial and fungal infections in humans and animals.[1–3] Preparations for such purposes include oral products, e.g. tablets, capsules, suspensions, mixtures and parenteral formulations. Other antibiotic products are also available for topical application to the skin, ear and eyes but are less widely employed than those for systemic administration.[4–7] There are, moreover, some disadvantages in using antibiotics topically and these will be discussed later. Nevertheless, when employed judiciously, antibiotics for topical application do have certain benefits, e.g. avoiding an effect on gut flora that can occur with enteral antibiotics.

Only a limited number of antibiotics are used topically. *The Veterinary Formulary*,[8] for example, in a section on anti-infective skin preparations, considers topical antibacterial and antifungal skin preparations and preparations for minor skin conditions. In the former category are included (a) topical antibacterial preparations of chlortetracycline, oxytetracycline, fusidic acid and sulfanilamide (sulphanilamide) with other antibiotics listed for systemic therapy of more serious skin infections in various types of animals, e.g. dogs, cats, horses, cattle; (b) topical antifungal skin preparations, for instance, enoconazole and ketoconazole, although a shampoo containing chlorhexidine (a bisbiguanide[9,10]) and miconazole is often used.[8] Preparations for minor skin infections and abrasions, and to prevent infection after surgery or when dehorning, include various antiseptic preparations based on quaternary ammonium compounds such as benzalkonium chloride and cetrimide, phenolics (e.g. chloroxylenol, fentichlor, chlorocresol), halogens (iodophors, chloramine-T), alcohols (phenoxyethanol) and organic acids (salicylic acid).[8] These may be applied topically in various forms ranging, as appropriate, from creams or ointments to dusting powders. They are not considered further in this presentation, but additional information about their spectrum of activity can be obtained by consulting an appropriate reference work.[11]

This paper will concentrate on three topical antibacterial antibiotics.

COMMON CURRENT USE

For effective and proper use, topically applied antibiotics should be formulated in a nonirritant, nontoxic base and should produce no local reaction or sensitization. The spectrum of activity may be narrow or fairly wide, but the commensal skin flora should not be unduly affected. The antibiotic should be able to permeate superficial skin and not be inactivated by tissues fluids or proteins.[12–15] In an excellent review of topical antibiotics, Hirschmann[16] has pointed out that they provide safe and effective treatment in certain human conditions, such as acne, rosacae and eradication of the nasal carriage of

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S. aureus, as well as in impetigo of limited extent. Hirschmann[16] points out also that topical antibiotics used in treating pyodermas in humans must be effective against *S. aureus* and Group A streptococci, the most important pathogens. Neomycin, active against staphylococci but less so against streptococci, may be combined with bacitracin (considered below). Neomycin is also effective against gram-negative bacteria, except *Pseudomonas (Ps.) aeruginosa* and polymyxin B (effective against this organism) has sometimes been used in combination with neomycin and bacitracin. Gentamicin, unlike neomycin, has important systemic uses and its topical usage is restricted, whereas mupirocin is only employed topically.

Possible adverse effects of topically applied antibiotics are (i) allergic reactions, which are usually low, although contact allergy is most paramount with neomycin,[16] and (ii) the possible development of resistant bacteria. Contact sensitivity occurs more frequently when medications are applied to chronically inflamed skin.[17] Antibiotic resistance develops more frequently when topical and systemic drugs are used concurrently and are pharmacologically related. Noble[18–21] has shown that the transmission of plasmids conferring antibiotic resistance can occur on human skin and that the value of an important antibiotic, such as gentamicin, may be greatly reduced if it is widely used topically. Kucers *et al.*[3] do not recommend the topical use in humans of fusidic acid because they state that it encourages the emergence of resistant nosocomial strains thereby compromising its value for the treatment of systemic infections due to methicillin-resistant staphylococci. French and Phillips[22] point out that topical antibiotics are particularly likely to select for resistance and emergence, e.g. of gentamicin-resistant *Ps. aeruginosa* following heavy topical use in burns, and of fusidic acid-and mupirocin-resistant *S. aureus* after heavy dermatological use. Hospital patients and staff may thus become colonized with resistant bacteria which can be disseminated both within hospitals and into communities.

Primary skin infections in animals are commonly caused by bacteria of the genera *Staphylococcus, Streptococcus* and *Proteus*, together with *Escherichia coli* and *Dermatophilus congolensis*.[8] The main pathogen of canine skin is *Staphylococcus intermedius*.[23] This is often isolated from the skin, haircoat and mucosae of healthy dogs, but may be a resident of the mucosae rather than of canine skin.[24–27] Elimination of mucosal populations of *S. intermedius* has been proposed as being important in the successful treatment of recurrent staphylococcal infections in dogs.[28] It is likely that strains of this organism differ in virulence.[29]

S. intermedius is also associated with ear and ocular infections[30,31] and topical treatment with appropriate antibiotics may again be necessary. Systemic therapy for canine pyodermas may also be advocated; this is outside the scope of the present manuscript but has been well considered elsewhere.[27,31]

Topical antibiotics are useful in the treatment of superficial pyoderma because high concentrations, well above levels obtained by systemic therapy, can be achieved locally. The efficacy of topical antibiotics depends on the site of infection, the ability of the antibiotic to penetrate the skin, the extent of inactivation by organic debris, the development of resistance in bacteria at the site of infection and the development of contact sensitivity to the preparation. In dogs and cats, obstacles to effective topical antibiotic therapy include the presence of a thick hair coat (limiting access to lesions), reluctance by the owner to apply ointments and the infrequency of isolated lesions.

Whether the choice to use topical antibiotics is appropriate is determined by several factors. These include the positive and negative long-term changes in bacterial populations on the skin, the effect of topical therapy on the usefulness – or loss of usefulness – of concurrent systemic therapy and the ability to adequately control focal bacterial populations as well as generalized pathogenic bacterial carriage.

As mentioned earlier, *Staphylococcus intermedius* is the most frequent coagulase-positive staphylococcus isolated from canine skin, and is also the most common staphylococcus isolated from feline skin.[23,32,33] It is the main pathogen in canine pyoderma.[31,34–36] Multiple studies have attempted to characterize the carriage of *S. intermedius* on normal canine skin and on the skin of dogs with atopy and pyoderma. *S. intermedius* is considered a transient colonizer of the canine skin and hair coat, but is a resident member of the microflora of the nares, oral cavity and anal mucosa with reported carriage rates between 40 and 82.9% in healthy dogs.[37–41] The organism is found in greater numbers on the distal hair shaft compared with the proximal hair shaft and within the follicles compared with the skin, and this is similar to findings in humans.[38] Hair type has also been shown to influence bacterial recovery rates, perhaps indirectly by altering the cutaneous microclimate.[38,42] Thus it has been proposed that there are two distinct resident populations of *S. intermedius* on canine skin: a population that resides within the hair follicle and causes only transient surface and proximal hair shaft colonization, and a population in mucocutaneous regions that can contaminate the distal hair.[42] This concept may explain why treatment of focal pyoderma, without regard to resident populations, may fail because of redistribution of pathogenic bacteria from normal carriage sites.

Significantly increased bacterial counts have been reported on the lesional skin of dogs and humans with atopic dermatitis, as well as on anal and nasal surfaces in dogs with pyoderma, but the number of bacteria recovered from nonlesional skin is identical in normal and allergic dogs.[37,43,44] In addition, one study reported no significant difference in recovery of *S. intermedius* between normal dogs and clinically

controlled atopic dogs.[39] Thus, factors other than bacterial virulence must be associated with the development of pyoderma. The action of topical antibiotics on pyoderma may involve not only the reduction of bacterial counts on lesional skin but may also decrease the amount of pro-inflammatory free fatty acids produced by bacteria, resulting in decreased epidermal inflammation.[45]

The zoonotic potential of canine bacterial carriage has been highlighted in several recent articles. In one report, canine and human isolates of *Propionibacterium acnes* were indistinguishable.[46] *P. acnes* is a normal part of the canine microflora but is considered a significant factor in the pathogenesis of acne vulgaris in humans. A second report demonstrated the same results for strains of *S. intermedius* in dogs and their owners, illustrating that the dog and human may be reservoirs for cross-contamination with this organism.[47] Transmission of *S. intermedius* through bite wounds has been documented, as has the transfer of antibiotic resistance between *S. intermedius* and *S. aureus* on the skin of dogs.[48,49] There has been no direct evidence, however, to suggest that the veterinary use of topical antibiotics affects the susceptibility of human pathogens.

The high carriage rate of *S. intermedius* on canine skin does not necessarily result in pyoderma; healthy skin appears to be relatively resistant to infection by this organism. Multiple factors are required to diminish epidermal defence mechanisms by altering the normal resident flora, thereby permitting colonization by pathogenic bacteria from resident population sites. These factors include alterations in the microclimate of the skin resulting from hypersensitivity, keratinization defects, and metabolic abnormality (including endocrinopathy), as well as changes in the normal flora of the skin. Increased skin temperature and humidity (as seen with inflammation and in intertriginous zones) facilitate the colonization by and the virulence of pathogenic staphylococci. One virulence factor for staphylococci is slime production, which indicates its ability to adhere.[50] Staphylococci are poorly able to colonize unbroken epithelium. Breaks in the epidermis reveal fibronectin receptors, permitting adherence and colonization. Deposits of fibrinogen on bacterial surfaces may reduce phagocytosis by neutrophils.[40] Future topical treatments for pyoderma may include compounds that competitively block the ability of pathogenic staphylococci to adhere to the skin.[51,52] The epidermis defends against colonization by adherent pathogenic staphylococci with its intrinsic barrier function and with normal epidermal turnover which promotes the shedding of pathogenic bacteria, and the re-establishment of the resident flora. *S. aureus* has been observed to migrate between keratinocytes, as well as to enter the skin through the follicles.[51] If it can be assumed that *S. intermedius* shares this propensity for migration, the relative paucity of intercellular lipids and the lack of a sebaceous follicular plug in the canine vs. human epidermis may explain the relative increase in the occurrence of superficial pyoderma in the dog.

Localized changes in the epidermis, especially from increased epidermal proliferation induced by inflammation and possibly by excoriation, causes enhanced expression of receptors for staphylococcal adhesins and the exposure of extracellular matrix proteins.[39] The rates for adherence to extracellular matrix proteins were shown to be significantly higher in strains of *S. intermedius* isolated from lesions of canine pyoderma compared with nonlesional sites.[29] Indeed, rRNA gene restriction patterns from strains of *S. intermedius* isolated from healthy dogs and those with pyoderma or otitis externa suggest the presence of distinct subpopulations with different virulence in dogs.[53] Therefore, when considering the appropriateness of topical antibiotic therapy for canine and feline pyoderma, the following factors should be addressed: the antibiotic should be safe, it should specifically target *S. intermedius*, it should achieve bactericidal concentrations locally to eliminate bacteria for a prolonged period and it should interact with resident bacterial populations in such a way as to discourage both the development of antibiotic resistance and the recolonization by pathogenic bacteria.

Three antibiotics in common topical use are fusidic acid and its sodium salt, sodium fusidate (fusidate sodium), mupirocin and bacitracin. These will be discussed in the following sections.

PHARMACOLOGY AND PHARMACEUTICS

Fusidic acid

Fusidic acid (Fig. 1) is an antimicrobial steroidal substance originally produced by the growth of certain strains of *Fusideum coccineum*.[54] It is used therapeutically as such and in the form of its sodium and diethanolamine salts.[55] The acid and salts have a

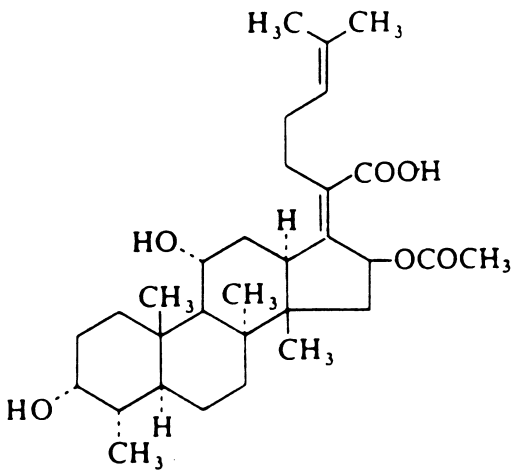

Figure 1. Chemical structure of fusidic acid.

narrow antibacterial spectrum; the most susceptible organisms are staphylococci (penicillin-sensitive and resistant) with streptococci and enterococci being less susceptible and, apart from *Branhamella* and *Moraxella*, gram-negative bacteria are generally highly resistant (Table 1).[56–62] Fusidic acid and its salts are bacteriostatic rather than bactericidal, with low concentrations inhibiting the growth of *S. aureus*. Minimum inhibitory concentrations (MICs) against staphylococci are around 0.05 μg mL^{-1}, the actual MIC depending on the inoculum size used.[56,57] Resistance in staphylococci to fusidic acid develops readily *in vitro*[58] but combination with an antistaphylococcal penicillin may prevent the emergence of resistant mutants.[3] The clinical relevance of resistance to fusidic acid is considered below.

Fusidic acid and fusidates inhibit protein synthesis in susceptible bacteria. This action differs from other protein synthesis inhibitors such as the tetracyclines, macrolides or chloramphenicol in that binding to the ribosomes *per se* does not occur; instead, fusidic acid inhibits a factor involved in translocation of polypeptide units and elongation.[63] The macrolides also inhibit translocation but at a different point.[64] Gram-negative bacteria such as *E. coli* are intrinsically resistant to fusidic acid and its salts by virtue of an outer membrane that acts as a permeability barrier limiting uptake and intracellular penetration of the antibiotic. However, protein synthesis in *E. coli* spheroplasts (cell envelope-modified forms) and in cell-free systems from *E. coli* is inhibited by the drug.[65,66]

Several mechanisms of resistance of bacteria to fusidic acid have been described. Impermeability as an example of intrinsic resistance was alluded to above. In staphylococci, chromosomal mutation *in vitro* to resistance to fusidate is a well-known phenomenon.[67] In this acquired resistance mechanism, a modified G factor with a decreased affinity for the antibiotic is responsible.[68] Acquired, plasmid-mediated resistance to fusidic acid in *S. aureus* appears to involve a decreased uptake of the antibiotic across the cytoplasmic membrane, although the exact mechanism has not been elucidated. Plasmid-mediated acquired resistance in the *Enterobacteriaceae* has also been described and again the mechanism is unknown but, strangely, appears to be associated with a gene encoding a chloramphenicol acetyltransferase (CAT).[69]

Table 1. Minimum inhibitory concentrations (MICs) of fusidic acid

Organism	MIC (μg mL^{-1}) of fusidic acid*
S. aureus	0.03–0.25
S. aureus (oxacillin-resistant)	0.03–0.25
S. epidermidis	0.03–0.25
S. intermedius	0.03
Most anaerobes and microaerophiles	0.5–1 (MIC_{90} values)
Bacteroides fragilis	0.5–16
Streptococcus pyogenes	4–8
Enterococci	1–4
Gram-negative bacilli	> 100

*Concentration of fusidic acid (or salt) necessary to inhibit the majority of strains.
Data obtained from M. Pott (personal communication) for *S. intermedius* and from references 56–62 for other (human) isolates.

However, in the clinical context, staphylococcal resistance to fusidic acid and its salts does not appear to be a problem[61,70–75] and a recent survey has shown that less than 2% of human staphylococcal isolates are, in fact, resistant to these drugs.[76] Thus, resistance development does not appear to be a major problem. Furthermore, fusidic acid has a unique mode of action, described above, and cross-resistance to structurally dissimilar antibiotics with different actions would not be expected to occur.

As pointed out by Reeves,[77] several preparations of fusidic acid have been used in antibacterial chemotherapy since 1962. Fusidic acid in the hemihydrate form is used in the oral suspension dosage form, as the sodium salts for slow intravenous administration and orally as tablets, all for human use. Fusidic acid is lipophilic in nature and thus has the ability to penetrate tissue, including necrotic tissue and bone. An ointment, cream and gel of fusidic acid/sodium salt with or without hydrocortisone acetate, and an intertulle sterile gauze dressing of sodium fusidate are available, again for human use. Preparations of fusidic acid with betamethasone are marketed for human and animal use, e.g. for the treatment of surface pyoderma in the dog such as acute moist dermatitis and skin fold dermatitis.[78] The rationale for such a combination (see below also) is the high activity of fusidic acid against *S. intermedius*, which is the major organism associated with pyoderma in the dog, coupled with the potent antipruritic and anti-inflammatory properties of betamethasone valerate.[55] Ophthalmic preparations of fusidic acid are also available for use in animals and humans. An aqueous sterile release viscous eye-drop formulation ensures a prolonged contact with the conjunctival sac and is indicated for the topical treatment of bacterial conjunctivitis where the infecting organism is known to be susceptible to fusidic acid; in canine conjunctivitis *S. intermedius* is a common isolate and *Staphylococcus* spp. have been isolated from cases of feline conjunctivitis. The antibiotic penetrates well into the cornea and anterior chamber of the eye in humans and animals.[78] The ophthalmic preparation is a particularly interesting formulation;[79] its viscous nature means that it can be rapidly and easily administered to the eye where it rapidly disperses. Its sustained release results in persistence in the lachrymal fluid. For otitis externa in the dog and cat, combination therapy is necessary to eradicate associated micro-organisms and ear-drops are available that contain diethanolamine fusidate, framycetin (to enhance the antibacterial spectrum), nystatin as an antifungal agent and prednisolone.

When given orally (in humans), sodium fusidate is better absorbed from the gastrointestinal tract than is

fusidic acid.[77] However, the antibiotic is poorly absorbed in animals. When applied to the intact skin, fusidic acid penetrates more rapidly than other antibiotics.[80–82] The amounts of fusidic acid and betamethasone 17-valerate, applied in a carbomer gel, absorbed percutaneously from canine skin over a 24-h period have been calculated as being 1.3% and 10%, respectively, of the applied dose, levels similar to those following application to human tissue.[80,82] Both compounds show rapid penetration through canine epidermis. The carbomer gel is a formulation that is readily miscible with exudate, adheres to wet lesions and achieves a high level of success clinically without the need for systemic therapy.

Fusidic acid preparations are not available in the United States but are widely employed in the United Kingdom, as well as many other countries. Clinical efficacy will be considered later in this review.

Mupirocin

Mupirocin (pseudomonic acid, Fig. 2a) is produced from *Pseudomonas fluorescens* and is chemically unrelated to any other antibiotic,[12,83–86] It consists of a short fatty acid side-chain linked to a larger molecule (monic acid) that mimics the amino acid isoleucine (Fig. 2b). As described below, these aspects are relevant to its mechanism of action.[87–91]

Mupirocin shows activity mainly against Gram-positive bacteria (Table 2). Staphylococci, including MRSA strains,[91] and streptococci are sensitive to low mupirocin concentrations (MICs 0.01–0.5 μg/mL), whereas enterococci are comparatively resistant. *Haemophilus influenzae* and *Neisseria* spp. are sensitive but most gram-negative bacteria are highly resistant, with MICs of mupirocin > 100 μg mL^{-1}.[83,84] Fungi are likewise insusceptible, although eradication of human perineal candida infection has been reported.[92]

Mupirocin is bacteriostatic, rather than bactericidal,[93,94] although the high concentrations applied to the skin may be bactericidal.[55] It acts by competitively inhibiting isoleucyl tRNA synthetase, thereby preventing incorporation of the amino acid isoleucine (which it resembles chemically: Fig. 2a,b) into growing polypeptide chains during polypeptide synthesis.[87–89] Mupirocin is a selective inhibitor of protein synthesis,[87–89] as a consequence of the depletion of cellular levels of isoleucyl tRNA.

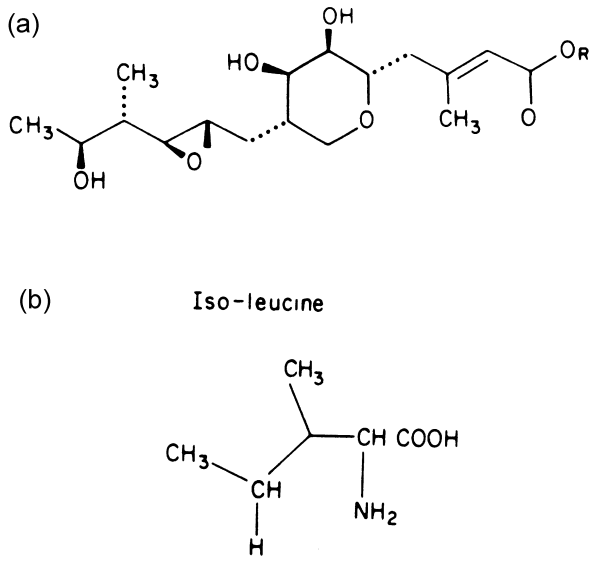

Figure 2. Chemical structures of (a) mupirocin (b) isoleucine.

Table 2. Minimum inhibitory concentrations (MICs) of mupirocin

Organism	MIC (μg mL^{-1}) of mupirocin*
S. aureus	0.015–0.12
S. aureus (moderately resistant)	2–16
S. aureus (highly resistant)	> 512
Strep. pneumoniae	0.12
Strep. pyogenes	0.12
Strep.agalactiae	0.5
Enterococci	32–64
Haemophilus influenzae	0.12
Neisseria meningitidis	0.05
Neisseria gonorrhoeae	0.05
Gram-negative bacilli	> 100

*Concentration necessary to inhibit the majority of strains.

Bacterial resistance to mupirocin may be intrinsic or acquired. Intrinsic insusceptibility is found in many gram-negative bacteria such as *E. coli* where the outer membrane acts as a permeability barrier to limit intracellular penetration of the antibiotic.[95] This has been clearly demonstrated in studies with outer membrane mutants and wild-type strains, the former – but not the latter – showing a high degree of mupirocin sensitivity.[96] In *S. aureus* naturally resistant strains appear to occur comparatively rarely[76] but resistance can emerge especially during long-term therapy.[97–104] Such strains may show a moderate (so-called) or high level of mupirocin resistance (Table 2). The mechanisms of such resistance have been evaluated as follows:

(i) high-level mupirocin resistance is plasmid-mediated, the transferable mupirocin resistance gene being responsible for producing a different isoleucyl tRNA synthetase from that present on the *S. aureus* chromosome.[105–113] This second, plasmid-encoded enzyme may compete more strongly for the active site in the acylation process than the chromosomally encoded enzyme and thus will require higher mupirocin concentrations to reduce its activity;

(ii) moderately resistant strains can be trained to give a stable, high-level resistance to mupirocin. This trained resistance cannot, however, be transferred to mupirocin-sensitive recipients and such resistance is chromosomally mediated rather than being located on a plasmid.[113]

Mupirocin is unsuitable for systemic administration. Following intravenous injection, it is rapidly eliminated by hydrolysis by nonspecific esterases of the ester link to produce monic acid; its elimination half-life is less than 30 min.[114] Topical administration (mupirocin 2% ointment in a polyethylene glycol)

results in less than 0.24% of the antibiotic being absorbed across intact normal human skin.[115] This ointment is used in humans for the treatment of bacterial skin infections such as impetigo, folliculitis and furunculosis. It is not suitable for intranasal use or for application to burns.[116] Boon *et al.*,[117] however, have described the efficacy of topical mupirocin against an experimental *S. aureus* surgical wound infection.

A nasal ointment containing 2% w/w mupirocin in a white soft paraffin base is used for the nasal eradication of staphylococci, including MRSA,[118–120] nasal carriage being expected to clear within 5–7 days of treatment. As pointed out earlier, resistance (including high-level plasmid-mediated transferable resistance) may arise during long-term treatment and difficulty may be experienced in controlling outbreaks of epidemic MRSA (EMRSA) strains that are also resistant to mupirocin (referred to as MuMRSA strains).[121]

Mupirocin preparations are not used in veterinary practice in the U.K. but are widely employed in the United States. Clinical efficacy based on experiences in the USA will be considered later in this review.

Bacitracin

Bacitracin (Fig. 3) consists of one or more of the antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis*. It is active at low concentrations (Table 3) against gram-positive bacteria, including staphylococci and streptococci, and some gram-negative cocci but gram-negative bacilli are highly resistant.[122]

Early studies on its mechanism of antibacterial action produced conflicting results. Siewert and

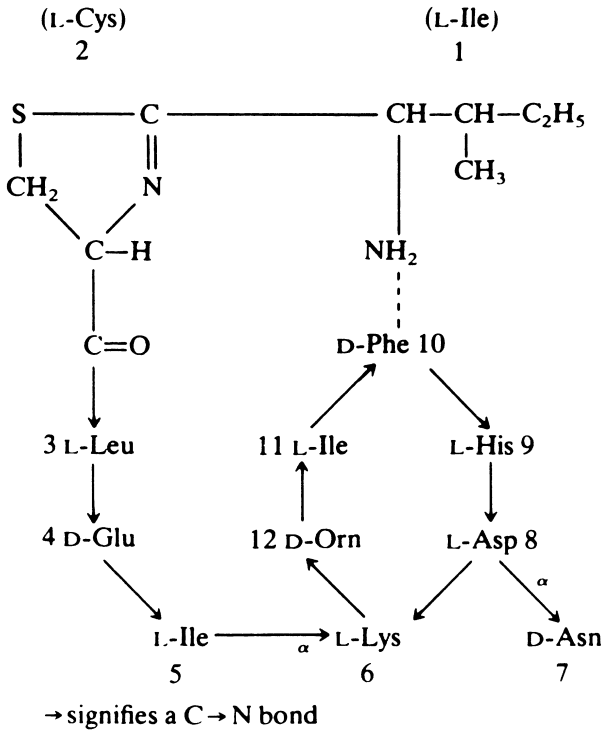

Figure 3. Chemical structure of bacitracin.

Table 3. Minimum inhibitory concentrations of bacitracin

Organism(s)	MIC ($\mu g\,mL^{-1}$) of bacitracin*
S. aureus	4
Strep. pyogenes	0.16
Neisseria gonorrhoeae	0.12
Haemophilus influenzae	12
Ps. aeruginosa	> 100
Enterobacteriaceae	> 100
Gram-positive bacilli	4

*Concentrations necessary to inhibit the majority of strains.

Strominger[123] reported that bacitracin inhibited the biosynthesis of bacterial cell walls, whereas others have shown that its activity requires the presence of a divalent cation,[124,125] with effects of membrane permeability of bacterial protoplasts also being described.[126,127] The primary effect, however, involves an inhibition of peptidoglycan synthesis,[123] the stages of which are now well documented. Bacitracin inhibits the enzymatic dephosphorylation of a C55-isoprenyl pyrophosphate,[128] which is responsible for the transfer of peptidoglycan building units across the cytoplasmic membrane, i.e. an intermediate stage in peptidoglycan synthesis. Bacitracin complexes with the substrate, the membrane-bound undecaprenyl (C55-isoprenyl) lipid carrier molecule that remains after the N-acetylglucosamine-N-acetylmuramyl pentapeptide unit has been transferred to the nascent peptidoglycan chain. This binding[123] prevents the enzymatic dephosphorylation of the carrier lipid to its monophosphate form, which is used for another round of synthesis and transfer of the disaccharide pentapeptide unit.

Thus, bacitracin inhibits the following reaction:

$$C_{55} - \text{isoprenyl pyrophosphate} \longrightarrow C_{55} - \text{isoprenyl phosphate} + Pi$$

Resistance to bacitracin in staphylococci[71] has been described. However, bacitracin has been shown to be bactericidal to MRSA strains[93] and to most strains of organisms isolated from patients with conjunctivitis and blepharitis.[70] Gram-negative bacteria are intrinsically resistant to bacitracin, presumably as a consequence of their outer membrane permeability barrier.[64] Acquired resistance to bacitracin is rare.[3] In the laboratory, bacitracin-resistant mutants of *S. aureus* have been isolated but this resistance is rapidly lost when the cells are cultured in antibiotic-free media, i.e. on removal of the selective pressure.[64] The mutations thus appear to revert at high frequency, which probably accounts for the failure to develop bacitracin resistance clinically.

Bacitracin is considered too toxic for systemic use and is thus used in human medicine as a topical agent, often in conjunction with an antibiotic such as polymyxin B which has activity against predominantly gram-negative bacteria.

Although shown to be useful as a topical agent in veterinary medicine,[122] bacitracin is not used in the

UK for this purpose nowadays. Perhaps its use in, for example, the treatment of otitis externa needs to be re-evaluated, although it would have to be combined with another appropriate antibiotic (or antibiotics) for this purpose. Certainly, in the United States, ophthalmic ointments containing bacitracin, neomycin and polymyxin B ointment have been shown to eradicate organisms from the (human) skin surface and from the underlying stratum corneum and to prevent repopulation of the stratum corneum by coagulase-negative bacteria; it was considered to be more efficacious than chlorhexidine, povidone-iodine or mupirocin where repopulation occurred.[129] The sensitizing powers of bacitracin have been emphasized.[130]

EFFICACY OF TOPICAL ANTIBIOTICS

The use of topical antibiotics in veterinary dermatology has focused on the treatment of four syndromes: acute moist dermatitis, skin fold dermatitis, interdigital furunculosis, and acne in dogs and cats. The pathogenesis and clinical signs of these diseases are beyond the scope of this paper. There is a paucity of original reports on the use of topical antibiotics in animals. However, it is one author's opinion (AW) that sufficient similarities exist in human and animal staphylococcal infection to permit correlation between results of human studies and potential applicability for animals. Literature regarding the treatment of comparable syndromes in human dermatology (acne, impetigo and pyoderma) was reviewed in order to present relevant data in this discussion. Unless otherwise specified, reports in this article are based on the results of studies in humans. As mentioned previously, multiple reports have documented the efficacy of mupirocin and fusidic acid against coagulase-positive staphylococci. An excellent review of the use of fusidic acid for skin infection was recently published.[75]

Fusidic acid

Studies of the percutaneous absorption of fusidic acid in canine skin reveal that therapeutic levels are present in the epidermis within a few hours of application and can be maintained with twice daily dosing. Absorption through human skin is enhanced by the use of salicylic acid, an ingredient in the keratolytic shampoos frequently used when treating pyoderma. This enhancement is most likely a result of disruption of the stratum corneum by salicylic acid; fusidic acid penetrates intact skin poorly.[82]

Clinical studies in humans have compared the use of fusidic acid vs. placebo (vehicle) ointment and fusidic acid alone vs. oral antibiotics. Fusidic acid was shown to be more effective than its vehicle.[75] Fusidic acid cream was more effective than hydrogen peroxide cream (82% vs. 72%) in curing impetigo.[131] Studies have documented faster healing time in patients using fusidic acid alone vs. oral antibiotics.[75,132,133] In one study, healing time for all patients using fusidic acid was significantly faster (7.1 days vs. 9.7 days) than for patients receiving oral antibiotics (clindamycin, flucloxacillin, or erythromycin). Deep infection (described as abscess or boil) and paronychia also responded significantly more quickly to topical than to systemic antibiotic therapy.[133] Similarly, patients with nasal furunculosis that were treated with nasal fusidic acid ointment had significantly fewer relapses over a one year period than did patients treated with oral antibiotics.[134]

Studies in humans demonstrate that 2% fusidic acid with 1% hydrocortisone or 0.1% betamethasone is more effective than the steroid alone and significantly more effective than 2% fusidic acid cream alone for the treatment of atopic dermatitis.[135,136] These results are similar to a recent study demonstrating that a neomycin and prednisolone emulsion was more effective than neomycin alone, prednisolone alone or vehicle in healing canine acute moist dermatitis lesions.[137]

Illustrating the theory that mucosal carriage of staphylococci serves as a significant reservoir for infection in the dog, a study was conducted in which cutaneous and mucosal carriage of *S. intermedius* was measured before and after application of fusidic acid to mucosal surfaces.[30] In this study, 1% fusidic acid eye drops were instilled into each eye and each nostril, and a small amount applied to the vulva and anus of dogs twice daily for seven days. Samples for culture were collected from the mucosa as well as nontreated areas of skin (axillae, groin, dorsal midline) prior to treatment and then two days to three weeks after the treatment period. Significantly lower numbers of staphylococci were isolated from both treated mucosal sites and nontreated skin sites two days post-treatment as compared to controls. Populations of bacteria remained significantly depressed in mucosal samples for three weeks, and in skin samples for one week, after treatment. The researchers concluded that the effect of mucosal treatment on populations of staphylococci on the skin demonstrates the importance of the mucosae as reservoirs for this organism, further suggesting that control of mucosal bacterial populations may assist in the control of recurrent pyoderma in the dog. It may be equally as important to ascertain the effect of topical antibiotic treatment of focal pyoderma lesions on mucosal and nasal bacterial carriage rates as well.

Mupirocin

Mupirocin ointment has been documented in humans to be more effective than its vehicle base for the treatment of patients with primary bacterial skin infections (80–90% vs. 25–85%, respectively).[12] Several reports, however, have noted a poorer clinical response when mupirocin is used to treat infected wounds.[12] Equal efficacy has been reported in multiple studies comparing mupirocin ointment and fusidic acid ointment for the treatment of superficial

skin infection.[138–143] One study reported an 86% satisfactory response for both ointments.[139] Two studies reported mupirocin as superior to fusidic acid.[141,143] An additional report demonstrated 100% clinical success in the treatment of superficial bacterial skin infection.[144] Ointments were generally applied two to three times daily for 6–8 days.

Colonization with *S. aureus* increases significantly in human patients treated with isotretinoin for acne, resulting in an increased incidence of bacterial folliculitis.[145] The effect of intranasal mupirocin ointment was evaluated for its ability to reduce staphylococcal folliculitis in isotretinoin-treated patients. During therapy there was an overall increase in isolation of *S. aureus* in both treatment and control groups, but the increase was significantly smaller in mupirocin-treated patients. However, there was no reduction in the incidence of *S. aureus* folliculitis in the treated group. Therefore, concurrent treatment of acne patients with nasal mupirocin cannot be recommended. The effect of nasal mupirocin to reduce the folliculitis seen in canine and feline acne, with or without concurrent use of isotretinoin, has not been documented.

Impetigo is a contagious disorder in children caused primarily by *S. aureus* or beta-haemolytic streptococci. The nonbullous form accounts for 70% of cases and is associated with skin that has been traumatized as a result of pruritus. Pustules and crusted plaques on the face and extremities commonly develop; similar lesions of secondary pyoderma may be seen in allergic dogs. The bullous form of impetigo is always caused by *S. aureus,* and develops on intact skin as flaccid bullae that rupture to reveal inflammatory collarettes.[51] Although not identical, bullous impetigo may have similarities to pustular dermatitis in puppies as well as to inflammatory pyoderma in adult dogs. Several studies have demonstrated the efficacy of mupirocin ointment in treating lesions of impetigo in children as compared with oral antibiotics.[146–148] This is due in part to the development of erythromycin-resistant *S. aureus* strains in children. Similar studies have not been reported in dogs.

The prevalence of *S. aureus* carriage in humans is reported as 20–25%, with 70–90% of humans being transient carriers.[149,150] *S. aureus* nasal carriage and subsequent nosocomial infection has been well established; *S. aureus* nasal carriers have a two- to 10-fold increased risk of developing surgical site or catheter infections from endogenous nasal flora. Mupirocin ointment has been shown to be 97% effective in reducing *S. aureus* nasal carriage.[150,151] Because of the established link between the density of nasal staphylococci and the risk of subsequent staphylococcal skin infection, many studies have attempted to prevent recurrent infections by reducing nasal bacterial carriage. The main drawback of therapies other than mupirocin has been the rapid recolonization that occurs when treatment is discontinued.[152] Studies have indicated that nasal carriage can be eliminated in 57% of patients for more than 14 weeks by 5 days of nasal mupirocin.[153,154] Nasal mupirocin has been investigated for the prevention of recurrent staphylococcal skin infection in humans because of this prolonged effect on bacterial populations.[149] Treated patients applied nasal mupirocin ointment for five days every month for one year. A significant reduction in positive nasal cultures and skin infections was noted in the treated patients compared to placebo-treated controls. The researchers concluded that long-term therapy with mupirocin ointment reduces the risk of skin infection in staphylococcal carriers. Similar long-term studies are needed to determine if nasal mupirocin therapy will reduce the recurrence of pyoderma in the dog. Unfortunately, many factors are likely to result in a less than optimal effect of nasal mupirocin in the treatment of canine pyoderma. These factors include the probability of irregular and insufficient coverage by topical ointments due to the larger surface area of the canine nasopharynx and the likely contamination of treated areas from oral or anal bacterial reservoirs due to inherent canine social behaviour.

Mupirocin ointment has been recommended for the treatment of recurrent interdigital abscesses, callus pyoderma and acne in dogs.[155] Recommendations are anecdotal; there are no published studies of mupirocin efficacy for the treatment of dermatoses in dogs in the English literature. The efficacy of mupirocin ointment has been reported for the cat.[156] Feline acne has been described as a keratinization disorder that is frequently complicated by secondary bacterial infection. In an open, prospective study, mupirocin was applied twice daily for three weeks as the sole treatment in 25 cats with acne. Fifteen cats were reported as having an excellent response; there was good response in nine cats. One cat was withdrawn from the study due to topical irritation.

Bacitracin

Bacitracin is most often encountered in over-the-counter preparations containing neomycin sulphate and polymyxin B (triple antibiotic ointment). There are few recent reports demonstrating its efficacy. A study comparing the efficacy of several antiseptic solutions, mupirocin, and triple antibiotic ointment in eradicating bacteria from skin surface in humans, demonstrated the ability of all the compounds to sterilize the skin surface.[129] Mupirocin and triple antibiotic ointment also eradicated bacteria within the deeper stratum corneum. Interestingly, resident flora repopulated the skin within 24 h of treatment cessation for all compounds except triple antibiotic ointment. Studies were not pursued to identify if one antibiotic within this ointment was responsible for delayed repopulation or if effects of the antibiotics were additive or synergistic. Bacitracin may suppress rather than eliminate *S. aureus* colonization.[157] One study determined that bacitracin alone was no more

effective at reducing post-surgical infection than white petrolatum.[158] In a recent study comparing the efficacy of oral cephalexin, topical mupirocin and topical bacitracin in children with impetigo, a good response was seen with either topical mupirocin or oral cephalexin, but most patients treated with bacitracin alone did not respond, leading the authors to conclude that bacitracin use is no longer appropriate.[159]

Resistance to topical antibiotics

The development of multiple drug resistant staphylococci is of great concern in human medicine. The appearance of methicillin-resistant strains of *S. aureus* (MRSA) is particularly worrisome as MRSA strains are usually resistant to the actions of beta-lactam antibiotics. Resistance to fluoroquinolones is also being reported. As mentioned earlier in this paper, the transfer of antibiotic resistance between *S. intermedius* and *S. aureus* on the skin of dogs has been documented, as has the presence of identical strains of staphylococci on dogs and their owners.[47,49] The transfer of bacterial resistance by contact between humans has been described.[160] Thus, there is justified concern about the development of antibiotic resistance in staphylococci in veterinary patients and the potential for spread of this resistance to human pathogenic staphylococci (and vice versa), although there is no documentation yet of such conference.

Bacterial resistance to both fusidic acid and mupirocin has been reported. Fortunately, the frequency of resistance has remained low. A comprehensive review of staphylococcal resistance to fusidic acid found resistance in between 1 and 2% of isolates.[61] Resistance was acquired more often when fusidic acid was used to treat chronic infections. A recent study of *S. intermedius* isolates from canine pyoderma obtained during three successive periods (1986–7, 1992–3 and 1995–6) demonstrated that resistance to fusidic acid has not been acquired. Indeed, sensitivity to fusidic acid increased from 92 to 99% of isolates, confirming previous studies.[161]

The dynamics of mupirocin resistance have been extensively reviewed.[104] Resistance develops most frequently when mupirocin is used over a prolonged period and over large areas of skin. Mupirocin resistance in coagulase-negative staphylococci increased to 42% of isolates in a neonatal intensive care unit after five years of prophylactic application to central venous catheter sites.[162] One year after discontinuing routine mupirocin use, resistance had dropped to 13%. The authors of this and other studies concluded that mupirocin use should be reserved for short-term treatment of acute infections and as prophylactic perioperative therapy for documented *S. aureus* carriers.[104,153] These conclusions cast doubt on the appropriateness of the repeated application of either fusidic acid or mupirocin to nasal or anogenital mucosae as a method to reduce recurrent canine pyoderma. Such chronic use might encourage the development of antibiotic resistant staphylococci.

ADVERSE REACTIONS TO TOPICAL ANTIBIOTICS

Topical antibiotics have a distinct advantage over systemic therapy in limiting the body's exposure to the drug to focal areas where it can be removed by washing should an adverse reaction occur. Any substance has the potential to induce an irritant or hypersensitivity reaction topically; adverse reactions to topical antibiotics have been ascribed to both the active ingredient and the vehicle. There have been multiple reports of sensitization to topical corticosteroids. One evaluation of several commonly prescribed topical ointments revealed a very low risk of clinically significant irritation or sensitization.[163] Cutaneous disorders can enhance the development of irritation or sensitivity. For example, humans with atopic dermatitis are known to be easily inflamed by mild irritants but resistant to topical sensitization.[163] Irritation reactions in these patients are often incorrectly labelled as allergic. Neomycin has been frequently, and perhaps improperly, incriminated as a topical sensitizer. One review of neomycin use in children reported an extremely low amount of contact allergy (0.09%) compared with a much higher incidence of contact irritation (0.9%).[164] Researchers concluded that adverse reactions occurred most often in patients treated multiple times with topical antibiotics for chronic dermatoses. Studies that report the incidence of irritation and allergic reactions to common topical ointments in dogs and cats are lacking.

Irritation and sensitization reactions to fusidic acid are extremely rare. Human cases of allergic contact dermatitis to fusidic acid have been reported.[165] Multiple reports have indicated superior patient acceptance over other ointments, including mupirocin. Side-effects of oral fusidic acid, including gastrointestinal upset, skin rashes, impaired liver function and immune-mediated thrombocytopenia, are particularly unlikely to occur in dogs from topical application because of the relative lack of systemic absorption and the rapid metabolism of the drug.[30,166]

Mupirocin has little potential for causing systemic toxicity or sensitization.[17] Most reported reactions have been due to the polyethylene glycol base when applied to the nares.[12] There has been a single human report recently of contact allergic dermatitis to mupirocin, as documented by patch testing.[167] When 814 patients were evaluated for side-effects in one study, only local irritation (evidenced as pain, stinging, pruritus or skin rash) was reported in 3% of patients with mupirocin and in 5% of patients treated with the polyethylene glycol base; there was no systemic toxicity.[168] These results confirmed previous studies. Nasal irritation from mupirocin ointment has been effectively reduced by reformulation into a lanolin base.[17] In the previously discussed report on the use of mupirocin ointment to treat feline acne, one patient was removed from the study

due to irritation.[156] Irritation to mupirocin is rare in one author's (AW) clinical practice.

The incidence of allergic reaction to topical bacitracin is controversial; true sensitization as documented by patch testing has been described in up to 13% of human patients.[130] There has also been debate on the relative propensity of bacitracin compared with zinc bacitracin to produce sensitivity; zinc bacitracin has been reported to be less of a sensitizer by some researchers while being reported as a strong sensitizer (inducing anaphylaxis) by others. One review of anaphylactic reactions to topical medications reported that of six cases, four were caused by bacitracin, one was caused by neomycin and one was caused by nitrogen mustard.[169] Five of the six cases had manifested mild reactions to the medications during prior treatments. Several other cases of anaphylaxis following bacitracin application have also been reported.[130] There have been recent concerns regarding a possible increase in the rate of contact sensitivity, particularly to bacitracin, in patients treated with topical antibiotics following laser surgery. It has been suggested that Langherhans' cells may be stimulated by laser tissue damage, thus encouraging the development of sensitization.[170] The use of CO_2 lasers in veterinary medicine is increasing. It may be prudent for veterinarians to dispense topical antibiotics other than bacitracin ointment following laser procedures. One report suggests that in humans, bacitracin is a frequent sensitizer, causes delayed contact dermatitis, urticarial reactions or anaphylactic shock, is histamine-releasing when injected intradermally and often co-reacts with neomycin.[130] Therefore, the use of bacitracin in the treatment of ulcerated and chronic canine dermatoses is not recommended.

CONCLUSIONS

Multiple reports have documented the efficacy of topical antibiotics to reduce bacterial counts and to encourage rapid healing of superficial skin infections. A more rapid response is noted when topical antibiotic compounds include corticosteroids. Both fusidic acid and mupirocin have been demonstrated to be equally effective at resolving bacterial skin lesions in humans and animals with minimal irritation. A poorer response has been associated with the treatment of infected or surgical wounds. In countries where both mupirocin and fusidic acid are available, fusidic acid use is more cost effective.[171] Fusidic acid is not available in the United States. Treatment with bacitracin is no longer recommended due to increasing reports of treatment failures and sensitization.

The efficacy of topical antibiotics is not solely due to their ability to achieve bactericidal concentrations locally. Factors that must also be considered include the effect of topical antibiotics on populations of skin bacteria distant from the treatment site, the development of antibiotic resistance (and potential for transmission of this resistance to nontreated individuals) and the increased risk of sensitization from the treatment of chronically inflamed skin. The overall number of pathogenic bacteria is increased in humans and dogs with pyoderma and atopy. However, when clinical signs of atopy are controlled, bacterial counts return to normal. Therefore treating identified underlying causes of pyoderma is paramount and preferable to chronic symptomatic relief of secondary infections. Bacterial carriage rates are decreased when mupirocin or fusidic acid is applied to mucosal surfaces, although effects are temporary. A reduction in the recurrence of folliculitis in humans by this therapy has been documented; studies in animals should be forthcoming. Unfortunately, several researchers have indicated that the incidence of resistance to these antibiotics and the potential for sensitization increases with chronic use in humans. These findings would seem to severely limit the usefulness of protocols aimed at reducing staphylococcal carriage rates for prophylactic control of human and canine recurrent pyoderma.

In summary, fusidic acid and mupirocin are recommended for the treatment of acute staphylococcal skin lesions. The use of topical antibiotics for the treatment of chronic or recurring dermatitis and surgical or infected wounds may not be appropriate as this therapy encourages the development of resistance and sensitization. Current areas of interest in the control of canine pyoderma include the altering of staphylococcal carriage rates to allow colonization by less virulent strains of *S. intermedius* or colonization by antagonists to pathogenic *S. intermedius*.[172] Although documented development of resistance remains low, the potential problems associated with the use of fusidic acid or mupirocin for the prophylactic control of pyoderma make the usefulness of this therapy controversial. Further research into trends in development of resistance to topical antibiotics in canine staphylococcal populations is needed.

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Résumé Les antibiotiques appliqués sur la peau doivent être formulés dans un excipient qui n'est ni irritant ni toxique. Ils peuvent présenter un spectre d'action étroit ou assez large, mais ne doivent pas provoquer de réaction locale ou de sensibilisation; la flore commensale ne doit pas être affectée trop longtemps. Les trois antibiotiques utilisés par voie locale chez l'homme et chez l'animal sont l'acide fucidique, la mupirocine et la bacitracine, qui possèdent tous un spectre antibactérien étroit. Après application sur la peau, l'acide fucidique pénètre plus rapidement que les autres antibiotiques. Les observations cliniques ont montré que la fréquence d'apparition de résistances pour l'acide fucidique et la mupirocine est resté faible. L'acide fucidique et la

mupirocine ont été proposés pour traiter les lésions staphylococciques aigües. Cependant, l'utilisation d'antibiotiques topiques n'est pas indiquée pour le traitement d'affections chroniques ou récidivantes, ou pour le traitement des plaies chirugicales ou infectées, à cause du développement possible de résistances et de sensibilisation. L'utilisation topique de la bacitracine peut provoquer des échecs thérapeutiques et des sensibilisations. [Werner A.H., Russel A.D. Mupirocin, fusidic acid and bacitracin: activity, action and clinical uses of three topical antibiotics. (Mupirocine, acide fusidique et bacitracine: activité, mode d'action et intérêt clinique de trois antibiotiques topiques.) *Veterinary Dermatology* 1999; **10**: 225–240.]

Zusammenfassung Antibiotika, die direkt auf die Haut aufgebracht werden, müssen in einer nicht irritierenden und nicht toxischen Grundlage produziert werden. Sie können ein enges oder weitreichendes Wirkungsspektrum haben, sollten aber keine Lokalreaktion oder Allergie hervorrufen, die normale Hautflora sollte nicht über Gebühr betroffen sein. Drei bei Mensch und Tier verwendete lokale Antibiotika sind Fusidinsäure, Mupirocin und Bacitracin, all mit einem engen antibakteriellen Wirkungsspektrum. Auf intakte Haut aufgebracht penetriert Fusidinsäure schneller als andere Antibiotika. Klinisch sind Resistenzen gegen dieses Medikament und gegen Mupirocin immer noch selten. Fusidinsäure und Mupirocin wurden zur Behandlung von akuten, durch Staphylokokken hervorgerufene Hautläsionen empfohlen. Allerdings könnte die Verwendung von lokalen Antibiotika zur Behandlung von chronischen oder rezidivierenden Hauterkrankungen und operativen oder infizierten Wunden wegen der möglichen Resistenz-und Allergieentwicklung ungeeignet sein. Lokale Anwendung von Bacitracin kann unwirksam sein und Sensibiliserung hervorrufen. [Werner A.H., Russel A.D. Mupirocin, fusidic acid and bacitracin: activity, action and clinical uses of three topical antibiotics. (Mupirocin, Fusidinsäure und Bacitracin: Wirksamkeit, Wirkungsart und klinische Verwendung von drei lokalen Antibiotika.) *Veterinary Dermatology* 1999; **10**: 225–240.]

Resumen Los antibióticos aplicados a la piel deben ser formulados partiendo de la base de no ser irritantes ni tóxicos. Pueden tener un aspectro de acción estrecho o bastante amplio pero no deben causar reacciones ni sensibilidades locales; la flora comensal no debería verse afectada innecesariamente. Tres antibióticos que han sido utilizados tópicamente en humanos y animales son el ácido fusídico, la mupirocina y la bacitracina, todos con un estrecho aspectro antibacteriano. Cuando se aplican a piel intacta, el ácido fucsídico penetra más rapidamente que otros antibióticos. Clínicamente, la frecuencia de la resistencia estafilocócica a éste y a la muporicina se mantuvo bajo. El ácido fucsídico y la mupirocina se han recomendado para el tratamiento de la slesiones cutáneas estafilocócicas agudas. Sin embargo, el uso de antibióticos tópicos para el tratamiento de las dermatitis crónicas o recurrentes y de heridas quirúrjicas infectadas puede no estar indicado debido al posible desarrollo de resistencias y sensibilidades. El uso tópico de bacitracina puede fallar en el tratamiento y producir sensibilización. [Werner A.H., Russel A.D. Mupirocin, fusidic acid and bacitracin: activity, action and clinical uses of three topical antibiotics. (Mupirocina, ácido fusídico y bacitracina: actividad, acción y usos clínicos de tres antibióticos tópicos.) *Veterinary Dermatology* 1999; **10**: 225–240.]