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THE MOST FREQUENTLY USED TOPICAL ANTIBACTERIAL AGENTS IN THE DERMATOLOGY PRACTICE

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SUMMARY

Topical antibacterial agents are being widely used for the treatment and prevention of superficial skin infections. The most frequent problems with many of the topical agents are the rapidly development of resistant mutant strains of microorganisms and the possibility of appearance of irritant and allergic contact dermatitis. This article emphasizes on their spectrum of activity, ressistance patterns, contact sensitivity potential and clinical uses.

Key words: antibiotics, antiseptics, topical agents, dermatology

The beginning and the development of any infectious process or infection disease depends on three groups of factors - features of the microorganism, characteristics and the status of the microorganism and the environment.

The pathogen and the virulent abilities of the microorganisms depend on their possibilities to adhere, to colonize, to invade and to reproduce in the infected organism; to secrete toxins and enzymes; to protect itself against the natural resistance and to overcome or withstand the constant pressure of the host immunity defenses the of the microorganism.

The adherence is the process or condition of adhering to the cells of the microorganism. The adhesion possibility of many bacterial species is prerequisite for their colonization.

The colonization is the establishment of the pathogen at the appropriate portal of entry /for example the urogenital tract, the digestive tract, the respiratory tract and the conjunctiva/. The colonization is marked with location, development and reproduction of the infectious agent over and in the host tissues. Once the so called "critical colonization" is reached the infectious process is transformed into infectious disease with its typical or not so typical symptoms caused by the pathogen damage process on the different organism's, cell or molecule levels. The prevention of the development of the critical colonization is crucial for the progress of the infectious process and in the terms of the dermatology for the faster granulation and epitelization of the tissue and the prevention of superinfection.

The application of the topical antimicrobial agents aims the prevention of this critical colonization. In the dermatology practice the choice of a topical agent depends on the microorganism isolated, its susceptibility features and its ability to become resistant as well as the possibility of sensitization of the microorganism. Drugs as Neomycin, Bacitracin or lanolin-containing may increase the inflammation and are considered to cause sensitization. The topical aminoglycosides for example gentamicin increase the risc of development of drug resistance. On Table 1 are shown some of the most frequently used in the clinical practice topical antibacterial agents.

The topical antibacterial drugs are being used for the treatment and the prevention of wide spectrum bacterial dermatologic infections and in other branches of our medicine. These agents may substitute the use of systemic antibiotics in the case of mild or moderate skin bacterial infection but their long time or unreasonable application is not harmless. For example emergence of drug resistant mutant strains of microorganisms or development of irritant or allergic contact dermatitis are frequent. That is the reason why the debate for the usage of topical antibacterial instead their systemic analogs is still a question of interest. The analysis of the data in the literature reveals the need of elucidation of the advantages or disadvantages of the different topical antimicrobial agents, including the more and more frequently used compounds like fusidic acid, mupirocin, octenisept that show low levels of acquired resistance or development of allergic reactions.

Mupirocin - one of the main metabolites of *Pseudomonas fluorescens* that shows strong antibacterial activity against coagulase negative and coagulase positive staphylococci including MRSA strains. This antibacterial agent with its wide specturum of activity against *Streptococci, Peptostreptococci, Clostridium spp., Haemophilus influenzae, Neisseria spp., E. coli, K. pneumoniae, Proteus spp.,* and *Enterobacter spp.,* is unique among the topical skin drugs (8,17). Mupirocin's disadvantage is its low ef-

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fectiveness in the presence of serum or exudates because 95% of the drug is protein bound. In the clinical practice it is used for the treatment of impetigo, folliculitis, impetiginized eczema, burns, lacerations. Intranasal Mupirocin is effective for the elimination and prolonged suppression of staphylococcal carriage including MRSA strains (17). The prolonged intranasal usage have shown decrease of the rate of recurrent skin infections in immunocompetent patients. The drug has very low incidence of skin sensitization and cross-reactivity (14). Its widespread use is the reason for the more and more frequently found resistance among MRAS strains.

Table 1. Some of the most frequently used in the dermatological practice topical antibacterial agents.

Drug	Spectrum of activity	Comments
Mupirocin /Bactroban/	Gram /+/	Suitable for MRSA
Fusidic acid	*Staphylococcus; Streptococcus*	Contains lanolin and may lead to sensitization
Neomycin sulphate	Gram /-/; *Pseudomonas*	May lead to sensitization. May be toxic if spread over large areas
Gentamicin	Gram /-/; Pseudomonas	May be toxic if spread over large areas
Bacitracin	Gram /+/	May lead to sensitization
Polymyxin-B	Gram /-/	Rarely may lead to sensitization
Framycetin	Gram /+/; Gram /-/	Frequently may lead to sensitization
Erythromycin	Gram /+/ cocci	The frequent use of the drug leads to resistance
Clindamycin	Gram /+/ aerobes/anaerobes; Gram /-/ anaerobes	
Povidone-iodine	Gram /+/; Gram /-/	Resistant toward S. aureus. Rarely may lead to sensitization

Sodium fusidate is derivate of fusidic acid and is isolated from the fungus *Fusidium coccineus*. Its steroid-like structure is responsible for the ability of penetration in damaged structures even in the presence of different kind of exudates. Other feature of the drug is its low or missing cross resistance and sensitization with other topical antibacterials (5). Its spectrum assume Gram positive bacteria such as *S. aureus, S. epidermidis, Nocardia asteroids, Clostridium spp.* and MRSA (15). There are dada that announce activity against *Neisseria spp., Bacteroides fragilis, Mycobacterium tuberculosis* and *Mycobacterium leprae*. The drug with its 2% cream variant may be used as mono therapeutic agent in case of staphylococcal cutaneous infection or in combination with topical steroids in the atopic dermatitis. It must be stressed that the frequency of contact sensitivity to the fusidic acid is low. Low is the bacterial resistance toward the drug nevertheless yet there are fusidic acid resistant *S. aureus* strains (12).

Neomycin is an aminogycoside antibiotic isolated from *Streptomyces fradiae*. The drug shows effectiveness against Gram positive and Gram negative microorganisms including *S. aureus, S. pyogenes, E. coli, H. influenzae, Klebsiella and Proteus*. In combination with Polymyxin-B or Bacitracin the antibacterial is used for the prevention of infections in abrasions, burns or superficial skin infections (11). The incidence of contact sensitization to neomycin depends on the frequency of its usage. The allergic contact dermatitis develops between 0,9 - 11% (14) and patients with hypostatic eczema, leg ulcerations or post-operative wounds are prone to neomycin sensitivity. It is not rare the cross sensitivity and resistance with other aminoglycosides. For this reason it is better to use neomycin in combination with Bacitracin or Polymyxin-B (3).

Framycetin is another aminoglycoside, mixture of Neomycin-B, Neomycin-C and neamine. It has wide activity spectrum - both Gram negative and Gram positive microorganisms including *S. aureus, S. pyogenes, E. coli, H. influenzae, Klebsiella spp.* and *Proteus spp.* (1). The drug is considered to be the third most frequent sensitizer after Nitrofurazone and Neomycin (4). From the other side the cross sensitivity among Framycetin and Neomycin is quite common.

The aminoglycoside Gentamicin is derivate of *Micromonospora purpurea*. It is effective against *S. aureus* and Gram negative microorganisms like *E. coli, Proteus spp.* and *P. aeruginosa* (8). The drug shows relatively low sensitizing abilities in comparison with Neomycin but strong cross reactivity between the two (4). Its frequent use as topical agent have let to the development of high levels of easy resistance (19).

Bacitracin, produced by *Bacillus subtilis* and *Bacillus licheniformis*, is one of the most frequently applied antibiotics in the microbiology practice. Its spectrum *S. aureus, S. pneumoniae, Neisseria spp., H. influenzae*, and other Gram positive microorganisms (9). It demonstrates minimal activity against Gram negative organisms and is not active against *P. aeruginosa, Nocardia, Enterobacteriaceae* and *Cryptococcus.* Its sensitizing ability depends on many factors and varies widely (14,20).

Polymyxin-B is cyclic decapeptide isolated form *Bacillus polymyxa*. It is effective against Gram negative microorganisms like P. *mirabilis, P. aeruginosa, S. marcescens*, predominantly used in combination with other topical agents (8). Its contact sensitivity is lesser as compared with Neomycin and Bacitracin (14).

Octenisept is a colorless water-soluble disinfectant with wide spectrum of activity that stimulates the physiological process of recovery of damaged skin structures. It could be used for a long time, nevertheless resistance occurs rarely. In the composition of Octenisept does not enter toxic sub-

stances and the visual control of the damaged skin wound is easy. This antibacterial product affects Gram positive staphylococci, including MRSA, streptococci, enterococci, *Neisseria spp., E. coli, P. aeruginosa, Proteus spp., Klebsiella spp., Mycobacterium spp., fungi* and *vira*. Its activity in the presence of blood, blood products or proteins remains unchanged (16).

Erythromycin is a macrolide agent isolated from *Streptomyces erythraeus*. It is used in the therapy of infections caused by Gram positive cocci, *Corynebacterium diphtheriae, H. influenzae, L. pneumophila, Chlamydia spp.* (8). Its topical use is restricted to the treatment of acne vulgaris, erythrasma and pitted keratolysis (6). Erythromycin shows weak sensitizer activity. Because of its wide usage in the practice the resistance increases rapidly. *Propionibacterium acnes* may become resistant in patients with acne. The prevalence of coagulase negative staphylococci ranges between 87-99,8%.

Clindamycin is a derivate of Lincomycin, isolated by *Streptomyces spp.* Its activity spectrum includes most of the aerobic Gram positive cocci, the anaerobic Gram negative and positive bacteria even *Propionibacterium acnes*. Although it has been used effectively in erythrasma, folliculitis, rosacea and Fox-Fordyce disease nowadays its use is restricted to acne vulgaris (2). Rare are the cases with contact allergies caused by its usage (18). A few data exist of Clindamycin resistant *P. acnes*.

Silver sulfadiazine is a synthetic product which acts through slow release of silver into the damaged tissues. Its spectrum includes Gram positive and Gram negative microorganisms, MRSA, *P. aeruginosa* and anaerobes (8). Available as 1% cream it is used for burnt skin and its emollient effect keeps eschar soft. Studies show that Silver sulfadiazine is very appropriate for superficial cutaneous infections. Few are the contact sensitivity reactions and only in burn patients (7).

Metronidazole is a synthetic nitroimidazole. Applied as 0,75% or 1% cream or gel it is effective against the anaerobes including *Bacteroides fragilis, Fusobacterium, Clostridium, Peptococcus, Trichomonas vaginalis*. The drug may be used in case of rosacea, acne vulgaris or skin ulcerations (8). Few are the registered cases with developed contact sensitivity.

Povidone-iodine is may be the most commonly used iodofor in the practice - a combination of surfactant and iodine. It is active against Gram positive and Gram negative bacteria. Its 5% and 10% concentration variants are used as anticeptics before different types of operations and for skin wounds (10). Contact dermatitis toward the drug is rare however prolonged exposure may lead to irritant contact dermatitis, tissue necrosis or systemic adverse effects. Is spite of the good *in vitro* effectiveness against *S. aureus,* the *in vivo* test are negative so the drug could not be used for this purpose.

Topical antimicrobial agents like tetracyclines, chloramphenicol, gentian violet are discard form the practice. Other substances such as cetrimid, chlorhexidine or triclosan are mostly used for anticeptic treatment of the skin surfaces.

The data form the literature show us that the topical antibacterials are used alone or in combination with other products in the cases of mild to moderate infections affecting small or superficial areas of the skin (13). They provide prevention and good control of restricted cutaneous infections. While selecting a topical antibacterial agent for a particular infection it is important to take in mind the spectrum of activity, the resistance of the isolated bacteria and the contact sensitivity potential. The aim is to obtain maximum efficacy and minimum adverse effects.

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