Dermatology Practical & Conceptual

Review - Expert Opinion on Antibiotics and Antibiotic Resistance in Dermatology

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Key Message: This is an expert opinion on the abuse of topical antibiotics and proposing alternative solutions like polyhexanide to antibiotics in specific indications, like: small wounds, burns, ulcers and post-traumatic injuries, impetigo, folliculitis, and acne.

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ABSTRACT

Introduction: Antibiotic resistance has become a serious, severe problem worldwide. This issue does not only relate to the use of systemic antibiotics but to topical ones as well, like systemic therapies and local treatment of skin and mucosal infections. Antiseptics, an alternative to the topical treatment with antibiotics of wounds and some inflammatory dermatological conditions, tend to be microbicidal and have a broader spectrum of antimicrobial activity than antibiotics. Among these, polyhexanide (PHMB) allows for the control of the infection while avoiding the development of resistance.

Objectives: Recommendations on the rules of good clinical practice for the management of small wounds, burns and post-traumatic ulcerative wounds, impetigo or folliculitis in the initial stages, and acne.

Methods: Literature review on the principal topical therapies for small wounds, injuries, impetigo, folliculitis, and acne and a proposal of innovative, highly-tolerated treatments.

Results and conclusions: Given the abuse of topical antibiotics in dermatology, for the treatment of small wounds, injuries, localized folliculitis, impetigo, and acne, the use of alternative topical treatments like polyhexanide and Rigenase® is recommended.

Key words: Antibiotic resistance, Antiseptics, Rigenase®, Polyhexanide

Introduction

The development and use of antibiotics since the second half of the 20th century have revolutionized the treatment and prevention of infectious diseases previously considered incurable. However, the extensive and often inappropriate use of these precious molecules has led to an exponential increase in the bacterial resistance phenomenon, a serious issue in the antibiotics field that is jeopardizing the effectiveness of these drugs. Antibiotic resistance is a complex mechanism that heavily impacts the health and social care context: failure to eradicate infections, increased relapses, adverse effects to therapies, healthcare costs, and last but not least, decreased trust in the physician/therapeutical approach. Over 10,000 deaths per year in Italy are attributable to the improper use of these drugs, out of a total of approximately 33,000 in the entire European Union [1]. The ability of bacteria to develop antibiotic resistance represents a natural protection mechanism implemented by microbial agents to survive and reproduce themself in a hostile environment. However, this biological activity is nowadays mainly due to the selective pressure induced by their improper use. This is why the World Health Organization (WHO) reiterates the need for a synergistic network that coordinates the monitoring and sharing of data on antibiotic resistance at a global level [1].

The problem of antibiotic resistance is related to both systemic therapies and local treatment of skin and mucosal infections. Antiseptics, an alternative to the topical treatment of wounds and some inflammatory dermatological conditions, tend to be microbicidal and have a broader spectrum of antimicrobial activity than do antibiotics. Among these, polyhexanide (PHMB) allows for the control of the infection while avoiding the development of resistance [2].

In dermatology, the use of antiseptics such as polyhexanide, associated with innovative molecules that present regenerative properties, such as those found in Rigenase®, can be useful for small wound treatment, burns, post-traumatic and ulcerative wounds, superficial bacterial infections of the skin, and in acne as they do not cause resistance [3]. Polyhexanide has a broad-spectrum antiseptic action, high tolerability, and several applications. It interacts with phospholipids at the bacterial membrane level, resulting in its increased permeability and rupture leading to microorganism death. At the cytoplasmic level, it inhibits microbial metabolism. Its broad spectrum covers gram-positive and gram-negative bacteria, biofilm-producing bacteria, intracellular bacteria (e.g., *Chlamydia sp.* and *Mycoplasma sp.*), and fungi (*Candida sp.* and *Aspergillus sp.*) [2].

Given the relevance of the problem, a panel of expert dermatologists developed recommendations on the rules of good clinical practice for the management of small wounds, burns and post-traumatic ulcerative wounds, impetigo or folliculitis in the initial stages, and acne.

Management of Small Wounds

The care of minor skin lesions following simple dermatologic surgery treatments, including electrodesiccation, laser therapy, superficial peelings, curettage, cryotherapy, and incisional or shave biopsies, is a frequent issue. Although the risk is low, the most common complications of such procedures are post-surgical infections, which may hamper optimal tissue repair, cause poor cosmetic outcome, and, rarely, lead to systemic infection [4]. The first objective of wound dressing must be to support tissue repair and avoid superinfection by maintaining asepsis. Scientific evidence points towards the exclusive use of antiseptic medications to achieve the objective of promoting wound healing without risk of bacterial resistance related to the indiscriminate use of antibiotics [5]. The ideal antiseptic should be a wide-spectrum antimicrobial with a fast and persistent effect and a negligible risk of irritation or allergy [5]. The most effective and widely used antiseptics with these features according to the most recent European guidelines include octenidine (OCT), polyhexanide (PHMB), povidone-iodine (PVP-I), sodium hypochlorite (NaOCl) and nanosilver-based compounds [6]. OCT and nanosilver compounds have shown promising results in hard-to-heal wounds [7,8].

Povidone iodine has a broad spectrum of antimicrobial coverage lasting for up to two hours and has been shown to have superior efficacy to chlorhexidine as an antiseptic agent in hand washing [9]. However, it must be left to act longer before the skin procedure is effective. As its abuse can cause thyroid alterations, it should be avoided in subjects with hyperthyroidism or being treated with radioiodine; its use is also contraindicated in patients with Dühring disease [7,5].

Chlorhexidine is less active than povidone iodine, even though it has a more rapid and persistent antiseptic action, lasting for up to six hours. Although generally safe, it can sometimes cause keratitis and ototoxicity even following minimal exposure, and for this reason its use on the face and scalp is contraindicated [9,2].

Polyhexanide is a synthetic peptide polymer with antiseptic properties that is widely used, especially in dentistry and urogynecology. It has a broad antimicrobial spectrum, and it has been shown to have greater antibacterial activity than silver sulfadiazine against *Staphyloccocus aureus* and *Klebsiella pneumoniae* and is equal to silver sulfadiazine against *Escherichia coli* and *Pseudomonas aeruginosa* [10]. Furthermore, its efficacy is comparable to that of povidone iodine against *K. pneumoniae* and *S. aureus* + *K. pneumoniae*. In vitro studies have shown a rapid onset of action (within 30') when used at a concentration of 0.1% [2].

Structurally similar to antimicrobial peptides, its antiseptic action is mainly related to a non-specific electrostatic interaction with cell walls; this guarantees its effectiveness without any risk of bacterial resistance and with high skin tolerability [10]. However, its use, considered safe in subjects of all ages [11], is not recommended in the first trimester of pregnancy [2].

Polyhexanide is available as creams, gauzes, and spray solutions intended to be applied on the skin either for the medication of acute skin lesions (such as those secondary to dermatological procedures) or for the treatment of chronic ones (such as burns or pressure sores). Active ingredients promoting wound healing, such as *Triticum vulgare* extract, are included in their formulation [12]. The extract from *Triticum vulgare* promotes tissue repair by increasing chemotaxis, proliferation, and maturation of fibroblasts and keratinocytes, and it also has moisturizing and antioxidant properties. A study that compared two cream formulations containing silver sulfadiazine + hyaluronic acid (which also promotes tissue regeneration) and polyhexanide + *Triticum vulgare* extract, respectively, showed the usefulness of both formulations in the treatment of superficial lesions and burns, but a greater effectiveness of the latter in promoting tissue repair [12].

In conclusion, the use of topical and/or systemic antibiotic therapy in the management of small wounds must be strictly limited to specific circumstances only, such as healing by second intention and dermatologic surgery interventions carried out near the nasal mucosa or on the lower limbs in subjects with diabetes or poor hygienic/sanitary conditions. For all other circumstances, the use of antiseptic-based medical aids enriched with active anti-inflammatory and immunomodulatory agents capable of improving the healing of small wounds not only by fighting infections but also by effectively promoting tissue repair is recommended

Management of Burns, Ulcers and Post-Traumatic Injuries

The dermatologist's outpatient activity in vulnology involves skin/deep wounds of various nature, which can be globally divided into "spontaneous" wounds and "induced/iatrogenic" wounds. It is the task of the dermatologist/vulnologist to take into account the patient's clinical history and wound appearance, along with conducting additional instrumental investigations, to recognize the specific etiology and then classify the wound as vascular, neurotrophic, metabolic, due to deficiency, infectious, inflammatory (vasculitic/from connectivopathy), neoplastic, iatrogenic, traumatic, or as a result of chemical agents/physical agents [13]. From a temporal point of view, wounds can be divided into "acute" (any loss of substance affecting the epidermis, the dermis ± the subcutaneous tissue, with rapid onset after an acute often external injury/agent) or "chronic," that is, any wound which persists for more than 42 days and/or tends to recur frequently and is typically characterized by tendency towards poor spontaneous healing and does not proceed through an orderly and timely repair process. The ulceration process can involve the epidermis, dermis, hypodermis, tendons, muscle fascia, muscle tissue, and the underlying ligament, bone, and/or cartilaginous structures. The restoration of the physiological healing repair cycle (i.e., coagulation > inflammation > proliferation > remodeling) starts from proper wound bed preparation, which relies on cleansing, antiseptic disinfection strategies, and removal of local contamination by microbiological agents [14].

To date, topical antibiotic therapy is often used both in the debridement and dressing phases, especially on ulcerative wounds for preventive purposes, on non-infected lesions, and as self-medication. However, it is notable that antiseptic agents tend to be microbicidal and have a broader spectrum of antimicrobial activity than antibiotics, while antibiotics often fail to pass the biofilm structure into the wound bed. In fact, the problem of topical antibiotic resistance has emerged progressively in recent decades, in parallel with oral antibiotic resistance [16,17,18]. Thus, we will briefly discuss here the management of burns from physical/chemical agents, post-traumatic wounds, and vascular/inflammatory ulcers, with a specific focus on the current recommendations concerning disinfection strategy, topical antibiotic therapy, and systemic antibiotic therapy.

With regards to burns, dermatologists manage mostly minor burns (i.e., patients with a burned body surface area of less than 10%-15% or grade I-II burns (with possible areas of III in a hospital setting), while major burns are addressed at burn centers. While systemic antibiotic therapy is recommended for major burns, for minor burns in the early stages (0-48 hours), the administration of topical or systemic antibiotics for prophylactic purposes is not recommended [19,20,21]. Therefore, in cases of bacterial contamination of the area (initially *S. aureus* and/or *Streptococcus pyogenes*, subsequently *P. aeruginosa*/*K. pneumoniae*/*C. albicans*), with feverish manifestations, lesional/perilesional inflammation/suppuration, and/or positive swab, covering/targeted systemic antibiotic therapy is recommended in the event of an available susceptibility test, while topical antibiotic therapy (cream) varies depending on the extent of the exudate. For grade III burns, the difficulty of antibiotic diffusion into necrotic tissues must be kept in mind. In intermediate situations such as burns on the second day without obvious signs of infection, topical dressings with both re-epithelializing and antimicrobial/antiseptic covering activities (not antibiotic-based), such as those based on Rigenase® and polyhexanide, are indicated [21,22,23].

For post-traumatic wounds (lacerations, contusions, etc.), antibiotic therapy is usually needed at a systemic level, both for prophylactic purposes in the early stages, depending on the injurious agent, wound conditions, and the patient's comorbidities. At the topical level, the loss of dermis/hypodermis generally requires non-adhesive antiseptic dressings aimed at preparing the lesional base for the reconstructive phase. In specific situations, such as trauma on a road surface or generated by blunt iron/metal agents, animal/human bites, cutting wounds, or in the presence of risk factors of the patient, such as diabetes, immunosuppression, atopic dermatitis, or iatrogenic Cushing, it is advisable to apply local antibiotic therapy in the first days after the trauma in order to prevent colonization of the wound by agents such as Staphylococcus aureus or *S. pyogenes* [25,26,27].

Regarding chronic ulcerative wounds that are vascular or inflammatory, topical antibiotic therapy is not recommended unless there are signs of perilesional epidermal-dermal infection (i.e., erysipelas) or if lesional infection appears generally in distal edema [28,29]. The wound with a fibrinous base is largely colonized by microbes organized in a thick biofilm, which also prevents the correct diffusion of both topical and systemic antibiotics. The use of antibiotic powders (i.e., antibiotics for systemic use) or lotions/creams on ulcers is also not recommended due to the possibility of inducing contact or allergic dermatitis [20,30,31]. In the debridement/preparation phase of the wound bed or following a contamination, non-adhesive dressings with both fibrinolytic and antiseptic effects, such as hydrogel based on Rigenase® and polyhexanide, are applied.

Finally, the improper use of topical antibiotic therapy on wounds of various types in the dermatological field, for example, in combination with corticosteroids or antifungals for "empirical coverage"/do-it-yourself use, in the prevention of possible infection even in continuous wounds not at risk or in body areas subjected to chronic maceration/erosion, in sites of intertrigo, in sites of uncomplicated insect bites, in grade I burns, or in in ulcers with thick/organized biofilm where the agent does not penetrate the lesional base, is therefore not recommended outside of the particular indications/conditions mentioned above and in general is dependent on a careful evaluation of the cost/benefit in the specific case [15,16,17].

Management of Superficial Bacterial Skin Infections: Impetigo and Folliculitis

Impetigo

Impetigo is a highly infectious and extremely itchy bacterial skin infection (generally an infection caused by *S. aureus* and, less frequently, by *S. pyogenes*) that commonly affects children under age 10 years [32]. The infection can manifest with variable clinical pictures depending on the location and depth of the infection. Generally, impetigo is presented as red patches and crusts, but it can also appear as blisters. The clinical manifestation of classic impetigo is characterized initially by involvement of face and perinasal area, followed by extension of crusted lesions due to self-inoculation and by the significant itching induced by the infection itself with a myeliceric appearance that exudes on an erythematous base [33]. Often, the infection originates in the nasal cavities and then spreads to other areas of the body or can be the result of inoculation of the infection from the environment onto damaged/grazed skin [34]. The therapy must be chosen in consideration of the extent of the infection in several skin areas and, even though local antibiotic therapy is preferred, it involves a combination of local antibiotic therapy and systemic therapy for up to about 10 days to avoid recurrence and spread in the individual patient and/or to other individuals. The preventive skin swab for microbiological examination accompanied by an antibiogram is ideal to avoid the use of antibiotics, which can led to partial effectiveness and consequentially higher bacteria resistance. The use of topical detergents and antiseptics, such as those based on Rigenase® and polyhexanide, is often useful to avoid relapses. If localized, only a local antibiotic therapy is recommended since it can directly cover the affected area with bandages and after a careful cleansing of the hands and the nails [35].

Furthermore, impetigo may initially remain unrecognized due to less common clinical presentations, such as bullae, which can quickly evolve into erosion. In these cases, the clinical presentation depends on the depth of the infection into the skin. Also in these conditions, therapy has to follow the development of the pathological manifestation [36]. If it is not extensive, rather than immediately resorting to the use of antibiotics, the application of creams containing antiseptics, such as those based on Rigenase® and polyhexanide, is recommended to avoid relapses.

Finally, impetigo quite frequently presents the complication of preexisting inflammatory processes such as eczema, and more rarely, psoriasis. This is the phenomenon of impetiginization characterized by a skin infection produced by bacterial inoculation due to the itching predetermined by the inflammatory process. The therapy, in this case, requires the use of a combination of antibiotics and local steroids to treat both the infection and the underlying inflammatory process.

Folliculitis

Folliculitis is an infection of the hair follicles that is generally itchy and associated with pain. It represents a very common condition and can involve localized sites (face, limbs). The etiology of folliculitis is often unclear, but sweating, trauma, friction, and occlusion of the skin are known to potentiate

the infection. The pathogen can be bacterial, fungal, and more rarely, viral. Bacterial etiology accounts for more than 80% of cases. Bacterial folliculitis is usually caused by *S. aureus*, but occasionally *P. aeruginosa* or other bacteria (most commonly *Enterobacter* when there is involvement of the genital, perianal, or crural areas) [36].

Areas such as the beard are often affected, due to shaving, which can determine a path of bacterial inoculation on a traumatic basis. The treatment of folliculitis, in this case, is generally based on topical antibiotics (fusidic acid, mupirocin, etc.). Only when folliculitis extends to multiple sites in a noncontiguous area is it treated with systemic therapies, such as penicillins. If, as in our scenario, a response to therapy does not occur within 6–10 days, a skin swab is recommended to search for bacteria and *Candida* and consequentially to avoid neglecting folliculitis caused by methicillin-resistant *S. aureus* or gram-negative bacteria. Thus, it is possible to proceed with targeted therapy (antibiotics for local or systemic use). In clinical practice, while waiting for the susceptibility test, one can resort to the use of creams based on Rigenase® and polyhexanide, with antiseptics that can solve the problem.

For follicular and pustular manifestations, the possibility of amicrobial pustulosis must also be considered as in cases of localized or diffuse pustular psoriasis, acne, rosacea, decalvans folliculitis of the scalp, or in the case of follicular inflammatory processes during therapy such as in patients receiving anti-EGFR therapy. For appropriate treatment, anti-inflammatory therapies with the association of topical creams such as those based on Rigenase® and polyhexanide is preferred instead of local or systemic antibiotic therapy.

Management of Acne with Topical and Oral Antibiotics

Antibiotics have been used in acne therapy since the mid-1950s. Originally, the main objective of the therapy was the reduction of the load of *Propionibacterium acnes* (as it was called then) because acne was believed to be "caused" by this bacterium. The inhibition of bacterial lipase synthesis and release, with consequent reduction in the quantity of free fatty acids with a pro-inflammatory action, was considered the main mechanism of action of antibiotics in acne. Indeed, several studies demonstrated a strong correlation between reduction in *Cutibacterium acnes* load and clinical improvement in patients treated with topical and/or systemic antibiotics. It was subsequently demonstrated that some antibiotics, such as tetracyclines and macrolides, also have an important anti-inflammatory action, mainly due to the inhibition of the chemotaxis of neutrophils, modulation of the classical and alternative complement pathways, and the inhibition of the expression of pro-inflammatory cytokines.

The problem of bacterial resistance emerged when it was understood that the latter clinically corresponds to a more or less significant worsening of acne [37]. Another typical clinical marker of resistance is gram-negative bacteria folliculitis. These bacteria, by autoinoculation, are transported from the anal-perianal region to the skin of the face. Almost all patients with gram-negative folliculitis have previously been treated for long periods with topical antibiotics, especially clindamycin and erythromycin, and/or oral antibiotics, especially erythromycin. The bacteria most frequently involved are *Enterobacter sp., Escherichia coli*, *K. pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa*. When we talk about bacterial resistance in acne, we are not only referring to *C. acnes*, but also to other bacteria, such as *Staphylococcus epidermidis* and *S. aureus*, both due to their direct contact with the antibiotic used and for the acquisition of genetic material from *C. acnes* [38]. Apart from primary resistance, a physiological and natural event, it has been demonstrated that secondary resistance is, above all, although not exclusively, iatrogenic due to:

1. The use of old antibiotics
2. Daily dosages that are too low
3. Duration of therapy that is too short
4. Duration of therapy that is too long
5. Application of the antibiotic only on acne lesions and not on the entire skin of the face, shoulders, chest, and back
6. Poor penetration of the antibiotic at the level of the pilosebaceous follicle: the use of topical gentamicin, especially by general practitioners, makes no sense from this point of view
7. Insufficient counseling
8. Poor adherence and compliance of the patient

The mechanisms that cause resistance have been studied mainly for systemic antibiotics but can also be applied to topical antibiotics [39,40].

For tetracyclines, the following have been observed:

1. Reduced penetration of the antibiotic, due to "permeabilization" of the cell wall or membrane
2. Accelerated and increased elimination of the drug
3. Enzymatic inactivation

For macrolides, the following have been observed:

1. Accelerated and increased elimination
2. Ribosomal "protection" by methylase synthesis
3. Hydrolysis by esterase
4. Chromosomal mutations that alter the 50S ribosomal subunit

Bacterial resistance was mainly caused by oral antibiotic misuse: for example, the optimal starting dosage and the optimal duration of therapy of erythromycin was never understood. As for topical antibiotics, the problem of cross-resistance is also relevant: cross-resistance affects over 50% of patients using clindamycin and erythromycin. It therefore makes no sense to prescribe erythromycin to a patient who does not respond to clindamycin, and vice versa. Limiting the development of resistance is possible. The 2009 the Global Alliance suggested: a) limiting the use of oral antibiotics to moderate and severe acne; b) use topical antibiotics in mild-moderate acne only if combined with benzoyl peroxide and a topical retinoid; c) limit the duration of antibiotics to a maximum of 12 weeks; d) apply benzoyl peroxide for 5–7 days between one course and another of antibiotics; e) avoid using antibiotics, both topical and oral, in monotherapy, both in initial therapy and in maintenance therapy.

In conclusion, if you decide to use topical antibiotics, it would be important to use newer antibiotics (although they do not exist) at full daily doses for adequate periods (no more than three months). Certainly, an innovative therapy could be represented by the use of topical antiseptics such as a combination of Rigenase® and polyhexanide, a new-generation antiseptic that does not cause bacterial resistance [42].

Below are the prescriptive standards recommended by the Agenzia Italiana del Farmaco (AIFA) relating to antibiotic therapy for acne:

- Avoid antibiotics, both topical and systemic, in monotherapy
- Combine the antimicrobial with a topical retinoid, also combine benzoyl peroxide
- Use antibiotics for a duration not exceeding three months
- Avoid the combined use of topical and systemic antibiotics
- Evaluate the clinical progress after 6–8 weeks of therapy
- In case of lack of clinical response, stop the antibiotic and change the therapy
- Consider as maintenance therapy a topical retinoid and possibly associate benzoyl peroxide, avoiding antibiotics

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