

# Topical antibiotics in the dermatological clinical practice: Indications, efficacy, and adverse effects

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## Abstract

Topical antibiotic therapy is a central component of patient management for several skin conditions, including acne, hidradenitis suppurativa, rosacea, impetigo or other superinfected dermatitis, and prevention of wound infections. Moreover, particular situations, such as skin diseases of bacterial origin in pregnancy and infants often warrant topical therapy. However, the occurrence of local delayed hypersensitivity reactions and the rising rate of antibiotic resistance are becoming great challenges faced by many dermatologists today. This narrative review provides an overview of the main topical antibiotics used in dermatology, focusing on their clinical role in the most common dermatological indications. For this purpose, a review of MEDLINE and PubMed for pertinent, scientific, and clinical publications until March 2020 was performed. Only articles published in the English language were included.

## KEYWORDS

acne, allergic contact dermatitis, antibiotic resistance, antibiotics, skin, skin infections, *Staphylococcus aureus*

## 1 | BACKGROUND

Topical antibiotics are currently used in many different dermatological conditions; therefore, it is extremely important to have an accurate understanding of how to administer them. Topical antibiotics offer many advantages, as they can deliver higher concentrations of antimicrobials directly in the infected site, reduce the risks for systemic side effects, avoid the use of systemic antibiotics, and allow the administration of molecules that cannot be given systemically. However, their use is limited to superficial lesions because they have a poor penetration of the deepest skin layers.<sup>1</sup>

In addition, many topical antibiotics have been associated with the development of allergic contact dermatitis (ACD); patch testing is mandatory to perform a diagnosis.<sup>2</sup>

What is more, topical antimicrobials are exposed to high resistance risks as they are often stored for some time in patients' homes and then used for inappropriate self-made therapies, even apart from the fact that in this way they undergo contamination.<sup>1</sup>

Resistance to topical antibiotics is, in fact, a challenging threat emerging from years of malpractice during which both clinicians and patients considered topical antimicrobials as less potentially dangerous and consequently more "harmless" than systemic drugs.<sup>1</sup>

Although often considered less threatening than resistance to systemic antibiotics, resistance to topical medications is now making their use extremely difficult. Indeed, increasing resistance is developing against the most common topical antimicrobials, such as mupirocin and fusidic acid, thus leading to the selection of more and more resistant *Staphylococcus aureus* strains.<sup>1,3</sup> Studies conducted in order to better understand the impact of topical antimicrobials use on the development of resistant *S aureus* strains have demonstrated that exposing both MSSA (Methicillin-sensitive *S aureus*) and MRSA (Methicillin-resistant *S aureus*) to fusidic acid and mupirocin resulted not only in the rapid selection of MRSA over MSSA but also to the emergence of MDR (Multi-drug resistant) isolates from the original culture.<sup>3</sup>

**TABLE 1** Topical drugs in the dermatological practice: indications

Skin and soft-tissue infections	Acne vulgaris	Hidradenitis suppurativa	Rosacea	Superinfected atopic eczema
Mupirocin 2%	Erythromycin 2%	Clindamycin 1%	Metronidazole 0.75-1%	Fusidic acid 2%
Retapamulin 1%	Clindamycin 1%		Ivermectin 1%	Mupirocin 2%
Fusidic acid 2%	Benzoyl peroxide 3-10%		Azithromycin 2%	Neomycin 0.1%
Ozenoxacin 1%	Association of benzoyl peroxide 3-5% and clindamycin 1%			
	Association of benzoyl peroxide 3-5% and erythromycin 2-3%			
	Association of clindamycin 1% and tretinoin 0,025%			

Note: Topical antibiotics in the dermatological clinical practice: indications, efficacy, and adverse effects.

For these reasons, it is essential to determine exactly when and how to administer topical antibiotics in clinical practice in order to avoid useless and potentially harmful prescriptions.

In the present article, we review the most common clinical uses of topical antibiotics (Table 1), aiming to clarify the most critical and delicate aspects.

## 2 | THE USE OF TOPICAL ANTIBIOTICS IN CLINICAL PRACTICE

### 2.1 | Topical antibiotics for the treatment of skin and soft-tissue infections

Skin and soft-tissue infections (SSTIs) are one of the most common reasons for patients to seek a medical consultation, especially in the dermatological field. The most common classification of SSTIs divides them into two main groups: non-necrotizing and necrotizing skin infections, depending on their depth and on the nature of the damage they cause to the skin layers. Necrotizing infections normally include pyomyositis, necrotizing fasciitis, clostridial myonecrosis, and Fournier's gangrene, while non-necrotizing infections include impetigo, furunculosis and carbuncles, animal and human bites, and infected pressure ulcers.<sup>4</sup>

However, in 2013, the Food and Drug Administration (FDA) introduced a new entity among the most common SSTIs, now called ABSSSIs, standing for Acute Bacterial Skin and Skin-Structure Infections and including all bacterial infections of the skin with a lesion size area  $\geq 75$  cm<sup>2</sup>. Therefore, according to the FDA classification, ABSSSIs specifically include erysipelas, cellulitis, surgical infections, and cutaneous abscesses.<sup>5</sup>

Nevertheless, despite the extreme variety of skin lesions included in the above classification, topical antibiotics are recommended only in very few specific cases. As a matter of fact, only impetigo, which is a non-necrotizing superficial skin infection, is considered to require topical antimicrobial treatment.<sup>4</sup>

For this disease, either mupirocin or retapamulin, both twice daily for 5 days, are the most commonly recommended topical

antimicrobial agents, but their use in treating impetigo is limited to patients with few skin lesions and a low risk for epidemic outbreaks.<sup>4</sup>

Nevertheless, other administration schemes for local mupirocin have also been described, as it can also be applied on the affected skin three times daily for 7 to 10 days (mupirocin 2% cream) or even three times daily for 7 to 14 days (mupirocin 2% ointment). A re-evaluation of the patient on the third to fifth day must always be scheduled in cases of no clinical response.<sup>6</sup>

Fusidic acid is generally recommended as a second-choice topical antibiotic, although it is in some cases preferred to mupirocin/retapamulin for impetigo, as illustrated in the 2015 UK guidelines, the 2017 Netherlands guidelines, and the 2017 New Zealand guidelines.<sup>7-9</sup> As regards its administration, one of the most common regimens establishes its application on the infected skin three times daily for 7 to 12 days.

However, although international guidelines may seem not to be in agreement upon which topical antibiotic is to be preferred, it is important to underline that topical antimicrobials in impetigo are generally chosen depending on the local bacterial resistance profiles, thus explaining possible different therapeutic choices.<sup>7</sup>

As a matter of fact, no conclusive data are currently available regarding which topical antibiotic works the best for impetigo patients, as several clinical studies demonstrated fusidic acid to be either equivalent or superior to mupirocin and retapamulin.<sup>10,11</sup> Moreover, 57 randomized controlled trials, published together with a whole meta-analysis of 3533 impetigo patients, concluded that mupirocin and fusidic acid are the first-line treatments in impetigo patients.<sup>12,13</sup>

Therefore, despite different antimicrobial molecules being possible treatments for localized impetigo, most guidelines define topical antibiotics as the first choice treatment for localized impetigo, although hydrogen peroxide 1% or povidone-iodine 10% are preferred to topical antibiotics for impetigo with less than three lesions in the 2017 New Zealand guidelines.<sup>7-9</sup>

In cases of recurrent impetigo, only 2% topical intranasal mupirocin is recommended in *S aureus* carrier patients to reduce clinical relapses.<sup>5</sup>

As illustrated earlier, the most commonly used topical antibiotics in impetigo are also those related to the highest resistance rates, thus

underlining the importance of studying and eventually approving new and more sophisticated topical antimicrobials.

In 2017, both in Canada and in the United States, a new topical nonfluorinated quinolone, Ozenoxacin (1% cream), was approved for nonbullous and bullous impetigo in patients aged 2 months and older.<sup>14,15</sup> Later on, in 2019, the same molecule was approved in 12 different European countries for the exclusive treatment of non-bullous impetigo in patients aged 6 months and older.<sup>16</sup>

The molecular features of Ozenoxacin are extremely promising as it lacks the fluorine atom related to the well-known quinolone-induced chondrotoxicity, and also exerts a double inhibition on both bacterial DNA gyrase and topoisomerase IV, thus preventing possible resistances.<sup>16</sup>

In 2020, Torrelo et al published an interesting review, illustrating the results of phase I and phase III Ozenoxacin clinical trials in 529 nonbullous impetigo patients aged from 6 months to 18 years.<sup>17</sup> According to this review, the clinical success, defined as total regression or improvement of skin lesions, of Ozenoxacin after 5 days of treatment was confirmed in all age groups, as compared to vehicle (control).<sup>17</sup> Moreover, microbiological success, defined as the absence of the original pathogens in the bacterial cultures, was also confirmed in all age groups compared to vehicle.<sup>17</sup>

Ozenoxacin was reported to be efficient but also safe, as no adverse effect was considered drug-related, and as only one patient revealed systemic absorption, still at extremely low nontoxic concentrations.<sup>18</sup>

## 2.2 | Topical antibiotics for the treatment of acne vulgaris

Acne is a common, frequent condition that is potentially able to cause intense psychological discomfort, even if not proportional to the actual clinical manifestations of the disease.<sup>19,20</sup> Therefore, the importance of treating acne, even in the mildest forms, relies on the possibility of both reducing clinical manifestations and improving the psychological outcome of the patients.<sup>18,20</sup>

Topical antibiotics have been widely used in clinical practice to treat acne manifestations, which has resulted in selecting resistant *P. acnes* isolates, thus obliging clinicians to experiment with different therapies.<sup>18</sup>

Therefore, it is highly important to establish correctly when and how to use topical antibiotics in acne patients, avoiding useless and potentially dangerous prescriptions.

International guidelines recommend the use of topical antimicrobials mainly in the treatment of mild and moderate acne, including comedonal and localized papulopustular manifestations.<sup>19,21-23</sup>

However, their use as monotherapy is highly discouraged, as it is related to an extremely elevated risk for bacterial resistances.<sup>21,22</sup> Bacterial resistance in acne patients is, in fact, developing into a challenging problem, as discussed by Sardana et al. in 2016.<sup>18</sup> Consequently, the percentage of *Propionibacterium acnes* resistance to topical erythromycin, for instance, reached peaks in the United

Kingdom and in India (94.4% and 98%, respectively), settling at an average of 17.1% in Europe. On the other hand, resistance to clindamycin followed a similar behavior, again achieving peaks in the United Kingdom and in India (90.3% and 90.4%, respectively) and maintaining an average of 15.1% in Europe.<sup>18</sup>

Therefore, the most recommended topical combinations currently include different concentrations of benzoyl peroxide associated with clindamycin or erythromycin, as well as fixed 0.025% tretinoin and 1.2% clindamycin gel formulations.<sup>21,22</sup>

All the major International guidelines strongly recommend the use of benzoyl peroxide together with topical antimicrobials (clindamycin or erythromycin) in most comedonal acne cases, leaving associations of both tretinoin and clindamycin to moderate papulopustular manifestations, with or without concomitant systemic antibiotic therapy.<sup>19,21-23</sup> As for severe acne manifestations, in the end, topical therapies, including antimicrobial medications, are generally discouraged and systemic drugs are commonly preferred.<sup>19,21-23</sup>

What is more, due to the great importance of topical and systemic retinoids in treating acne, specific recommendations for pregnant acne patients have been postulated, in order to avoid teratogenic complications. Not surprisingly, also during pregnancy, topical antimicrobials display a pivotal role in treating acne, once more mainly topical erythromycin and clindamycin.<sup>24</sup> However, only short-term topical antimicrobial treatments have been proved safe in pregnant women, and no conclusive data are currently available for long-term periods.<sup>24</sup>

Ultimately, although no systemic side effects are normally described during acne topical antimicrobial treatments, a few studies reported the possible risks for an alteration of the gastrointestinal microbiota, thus possibly discouraging their use in the presence of pre-diagnosed gastrointestinal disorders.<sup>24,25</sup>

## 2.3 | Topical antibiotics for the treatment of hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a relatively uncommon disorder preferably affecting women in their second and third decade of life.<sup>26</sup> Although its pathogenesis is still unclear, many risk factors have been identified, including genetic predisposition, obesity, smoking habit, and hormonal disorders.<sup>26,27</sup> Moreover, recent studies suggest that HS may be a disorder of the follicular epithelium rather than a disease affecting the sweat glands, opening new, interesting scenarios regarding its etiology.<sup>26,27</sup> However, even if its pathogenic mechanisms are still unknown, it is now certain that HS is an auto-inflammatory disease, and the infective theories have been almost completely abandoned.<sup>26,27</sup> As a matter of fact, superinfection of the most common lesions may occur at any time but only as a secondary process, thus explaining the double role of antimicrobial therapy in HS as both prevention and treatment of any superinfections.<sup>27</sup>

Therefore, topical 1% clindamycin (lotion or solution) is recommended across all guidelines as a first-line treatment for HS. Indeed, since clindamycin is active against anaerobic, streptococcal, and staphylococcal strains, it may both decrease cutaneous

inflammation and inhibit biofilm formation in HS. However, topical clindamycin is recommended only in mild forms of HS (Hurley stage I or initial stage II), mainly characterized by superficial pustules, without deep abscesses.<sup>27</sup>

Finally, as regards the best administration regimen, application twice daily for up to 3 months is most commonly recommended, although many guidelines caution against prolonged use due to the development of bacterial resistance.<sup>27</sup>

## 2.4 | Topical antibiotics for the treatment of rosacea

Rosacea is a common chronic inflammatory disease of the skin, mainly involving the facial area.<sup>28</sup> Although its pathogenesis is still poorly understood, recent studies indicate that different genetic and environmental factors may trigger the onset and aggravation of rosacea, through a profound dysregulation of the innate and adaptive immune system.<sup>28</sup> Moreover, trigger factors also activate various cellular mediators such as keratinocytes, endothelial cells, mast cells, macrophages, and Th1 and Th17 cells, thus inducing the well-known clinical manifestations.<sup>28</sup>

Therefore, since rosacea is not primarily an infectious disease, topical antibiotics are not considered particularly adequate, except for topical metronidazole.<sup>28</sup> As a matter of fact, topical metronidazole is recommended by all the main international guidelines for the treatment of mild to moderate rosacea due to its anti-inflammatory properties.<sup>29-31</sup> There is strong evidence of its efficacy in treating erythematous and papulopustular rosacea, and 1% or 0.75% topical metronidazole gained FDA approval as first-line therapy.<sup>29-31</sup> On the other hand, other topical antibiotics such as topical macrolides are not clearly FDA-approved and generally not recommended by the international guidelines, despite being widely prescribed by some clinicians.<sup>29-31</sup>

However, topical antibiotics, including topical metronidazole, do not have any indications in phymatous and ocular rosacea, even if metronidazole could be indicated for the treatment of the external manifestations of ocular rosacea (eg, blepharitis), as illustrated by the American Acne and Rosacea Association in 2019.<sup>31</sup>

In the end, it is important to limit the use of topical antibiotics in the treatment of rosacea, since infection is not directly implied in its pathogenesis. Only metronidazole is, in fact, indicated in the treatment of rosacea, mainly in its mild forms, as other treatments are preferred for more severe manifestations.<sup>29-31</sup>

## 2.5 | Topical antibiotics for the treatment of other superinfected lesions

Despite their specific uses in the conditions illustrated earlier, topical antibiotics may be required in almost all circumstances, because secondary bacterial infections may occur at any time.

Nevertheless, secondary infections do not occur with the same frequency in all body sites, being more likely to affect bacterial-contamination-prone areas, such as the anogenital zone or the body folds. Moreover, certain lesions are more at risk of developing secondary infections compared to others, since itching lesions, for instance, may be easily contaminated due to the strong urge to scratch them.<sup>32</sup>

Among the most frequently superinfected dermatological conditions, atopic eczema surely warrants closer attention due to its high prevalence in the general population.<sup>32</sup>

### 2.5.1 | Topical antibiotics for the treatment of superinfected atopic eczema

Atopic dermatitis (AD) is an extremely common skin condition preferably affecting children, showing a 20% prevalence among patients younger than 2 years old.<sup>32</sup> Its frequency in the general population explains why among many other dermatological conditions that may undergo superinfections, atopic eczemas deserve more attention.<sup>32</sup>

Actually, there are several reasons why atopic eczema may be at risk for secondary infections, as it is highly itchy and related to a profound alteration of both the cutaneous bacterial flora and the skin lipid barrier.<sup>32,33</sup> Moreover, the characteristic atopic Th2-mediated immune responses are associated to an even higher risk for bacterial infections. Last but not least, *S aureus* is reported to be frequently responsible for skin colonization in atopic patients, also playing a key role in maintaining the inflammation, as its toxins and components may act as superantigens.<sup>33</sup>

It is now well known that the skin microbiome can fluctuate widely in the various states of the disease, as *S aureus* prevalence increases greatly during AD flares-up and decreases after its clinical resolution.<sup>33</sup> Moreover, more than 80% of *S aureus* isolated from patients with AD also secrete superantigens, such as Staphylococcal Enterotoxin B (SEB) and Toxic Shock Syndrome Toxin-1 (TSST-1), correlated with a significant exacerbation of the inflammatory lesions.<sup>33</sup>

Therefore, due to the impressive *S aureus* colonization of the atopic skin and to the strict correlation between the degree of this colonization and the activity of the disease, it goes without saying that atopic eczemas occur on already contaminated skin.

Superinfections of atopic eczemas are, indeed, so common that topical antimicrobial agents are even included as possible therapies in many atopic dermatitis guidelines. The recommended topical antimicrobials are extremely varied, as no specific molecule is to be preferred, as long as its activity against staphylococci and streptococci is preserved.<sup>34</sup>

However, also in atopic dermatitis, it is extremely important to use topical antibiotics only in the presence of clear evidence of secondary infections, in order to avoid bacterial resistances. In 2016, Bessa et al published an interesting study assessing *S aureus* resistance to topical antimicrobials in atopic dermatitis patients and demonstrating high bacterial resistance levels against bacitracin, neomycin, fusidic acid, and mupirocin.<sup>35</sup>

For these reasons, in the end, even if superinfections of atopic eczemas are extremely common, preventive topical antimicrobial therapy is highly discouraged and potentially dangerous due to both the development of bacterial resistances and the risk for local sensitizations.

Moreover, higher rates of positive patch test reactions to bacitracin and neomycin have been demonstrated in the atopic population, including both patients with active lesions and patients with only a positive personal history of atopic dermatitis.<sup>36</sup>

### 3 | TOPICAL ANTIMICROBIAL-INDUCED ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) from topical products is an uncommon but probably underdiagnosed event during the treatment of patients affected by acne vulgaris. ACD, a type IV hypersensitivity reaction, should be suspected when patients complain of worsening of their dermatitis or develop acute pruritic, erythematous-edematous papules, and vesicles at the sites of application of the various products.<sup>37</sup>

The overall prevalence of ACD to topical antibiotics is generally low.<sup>37</sup> The aminoglycosides are recognized as the most common antibiotic molecules responsible for contact sensitization in the general population. Neomycin is an aminoglycoside antibiotic produced by *Streptomyces fradiae*, of which three fractions have been separated, neomycin A, B, and C, even if in therapy only neomycin B is used. Neomycin is a broad-spectrum antibiotic with a bactericidal action against gram-negative and gram-positive bacteria, especially *S aureus*. It is not effective in the treatment of *Pseudomonas aeruginosa* and anaerobic bacteria and is only weakly effective against *Streptococcus*.<sup>38</sup> In European centers, the rates of sensitization range from 1.1 to 3.8%, with a mean rate of 1.9%.<sup>39</sup>

Neomycin frequently shows cross-reactions with other aminoglycoside antibiotics. This phenomenon is inevitable with neomycin, framycetin, and paromomycin, since they are all contained in the same neosaminic group; furthermore, neomycin can present cross-reactions with kanamycin, gentamicin, and tobramycin.<sup>40-42</sup>

The prolonged use on a previously damaged and impaired barrier could easily explain the cases of allergy to topical antimicrobials observed in patients affected by leg ulcers, venous stasis dermatitis, and acne.

Topical drugs containing chloramphenicol and clostridiopeptidase A are frequently used for the treatment of cutaneous ulcers and other necrotic lesions. Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is widely used in eye and skin ointments to treat bacterial infections, and it is a well-known cause of ACD.<sup>43,44</sup> Among acneic patients, clindamycin is one of the most commonly used topical antimicrobials. ACD to clindamycin was reported in 1978,<sup>45</sup> followed by a few other cases.<sup>46-48</sup>

Another topical antibiotic widely employed in acne is erythromycin, a macrolide that is characterized by a high molecular weight and is considered to have a low sensitizing potential. ACD from

erythromycin has only exceptionally been observed, especially when used in diseases other than acne.<sup>49</sup>

### 4 | CONCLUSIONS

Topical antimicrobial agents are widely used in clinical practice, offering excellent treating options for many different diseases. However, despite their unarguable therapeutic effects, emerging bacterial resistances to all the most common topical antimicrobial molecules are making conventional treatments extremely challenging. For this reason, it is becoming more and more important to limit their use to selected cases, as illustrated by the international guidelines, in order to avoid useless and harmful prescriptions while preserving the desired therapeutic effect.

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