Ozenoxacin for Impetigo in Children and Adolescents: A New Effective and Safe Topical Treatment Approach

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Impetigo in children and adolescents: Overview

Impetigo, a common infection of the superficial layers of the epidermis is characterized by presence of erythematous plaques with a yellow crust and is associated with itching and pain. It is highly contagious and most commonly caused by gram-positive bacteria.[1]

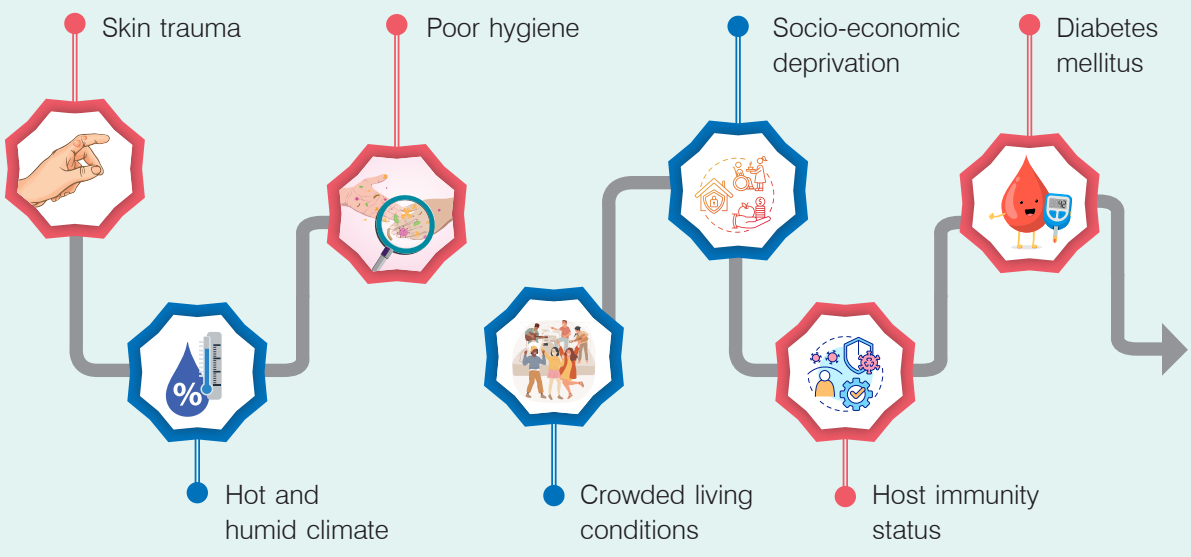
It is basically a disease of children residing in hot and humid climates. It typically affects the face but can occur in any part of the body that has abrasion, laceration, insect bite or trauma.[1]

Etiology

The main types of impetigo are non-bullous (80% of cases) and bullous (20% of cases). *Staphylococcus aureus* and group A beta-haemolytic Streptococcus are the associated causative agents for non-bullous type. Non-bullous impetigo is characterized by maculo-papular lesions and thin-walled vesicles that rupture, leaving superficial erosions covered by honey-colored crusts, involving both healthy and damaged skin.[1,2]

Toxin-producing *S. aureus* is the associated causative agent for bullous impetigo, which is characterized by large,

Figure 1: Risk factors for impetigo development[2,3]



fragile vesicles and flaccid bullae on an erythematous base, evolving into erosions with a thin, varnish-like crust. It is commonly seen in intertriginous areas of the trunk and extremities.[1,2]

Epidemiology

According to the data available, it accounts for approximately 10% of skin complaints in the pediatric population. It affects both males and females aged 2-5 years. It reaches its peak in summer and fall. In infants, bullous impetigo is more common, with children less than 2 years accounting for 90% of cases of bullous impetigo.[1]

Risk factors

Skin trauma, hot and humid climate, poor hygiene, crowded living conditions, socio-economic deprivation, host immunity status and playing close-contact sports, diabetes mellitus or other medical comorbidities are the factors associated with an increased risk of impetigo development (Figure 1). With impetigo being a highly contagious disease, it poses a significant concern for children going to school or day care centres as the likelihood of transmission increased at such places.[2,3]

Pathophysiology

Classified as primary or secondary impetigo, in primary impetigo a direct bacterial invasion affects the normal skin. In secondary impetigo, infection occurs at a previous skin wound site.

Any alteration/breakdown of skin barrier gives entry of GABHS and *S. aureus* to fibronectin receptors that require fibronectin for colonization. Factors such as trauma, cuts, insect bites, surgery, atopic dermatitis, burns, and varicella are associated with skin breakdown. Once a lesion is present, self-inoculation to other sites is very common.[1]

Management of impetigo

Treatment of impetigo depends on the extent and site of the lesions and the presence of systemic symptoms. According to the clinical practice guidelines available, use of topical antibacterial agents has been recommended for small localized areas of lesions and oral antibiotics for the treatment of multiple/extensive lesions not responding to topical therapy.[2,3] Advantages with topical antibiotics include local application to the area where needed, minimizing antibiotic resistance and avoiding gastrointestinal and other systemic adverse effects.[4]

When prescribing antibiotics for impetigo, an ideal treatment should fulfill all the qualities like being effective, inexpensive, have limited adverse effects and should not promote bacterial resistance.[4]

> **IMPETIGO ACCOUNTS FOR APPROXIMATELY 10% OF SKIN COMPLAINTS IN THE PEDIATRIC POPULATION**

However, an increase in multidrug resistance pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), mupirocin-resistant *Staphylococcus aureus* or quinolone-resistant *Staphylococcus aureus*, has laid the focus on developing new antibiotics against such agents.[2]

Ozenoxacin in impetigo

Ozenoxacin is a novel non-fluorinated quinolone with potent antimicrobial activity against staphylococci and streptococci, key pathogens involved in impetigo. It has a broad range of activity against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus*.[2,3,5]

Ozenoxacin possess dual inhibitory activity against bacterial replication enzymes DNA gyrase and topoisomerase IV. This dual inhibitory activity protects it from development of resistance. Furthermore, it is the absence of a fluorine atom in the molecular structure of ozenoxacin that is associated with its good safety and tolerability profile and it thus lacks quinolone induced chondrotoxicity and phototoxicity.[5]

Topical ozenoxacin is negligibly absorbed and exhibits excellent dermal tolerability. It is the minimal dermal absorption and capability of ozenoxacin to reach high concentrations in the upper layers of the epidermidis, which supports its use in impetigo avoiding the emergence of bacterial resistance in presence of a good safety profile.[2]

Ozenoxacin has been approved as an effective and well-tolerated topical treatment of impetigo due to *S. aureus* or *S. pyogenes* in pediatric patients aged 2 months or older.[6]

Clinical evidences

Study 1

A multicenter, randomized, placebo controlled, parallel, blinded, superiority clinical study[7] was done to evaluate and compare efficacy and safety of ozenoxacin cream with placebo and retapamulin ointment in patients with a clinical diagnosis of non-bullous or bullous impetigo. It included 465 patients who were randomized in a 1:1:1 ratio to receive ozenoxacin 1% cream, placebo cream or retapamulin 1% ointment applied twice daily to all impetigo affected areas for 5 days. Findings of the study were:

- Superiority of ozenoxacin with respect to clinical success rate was evident at the end of therapy as compared to placebo group (34.8% vs. 19.2%; Figure 2)

Figure 2: Effect of ozenoxacin on treatment outcomes as compared to placebo in patients with impetigo[7]

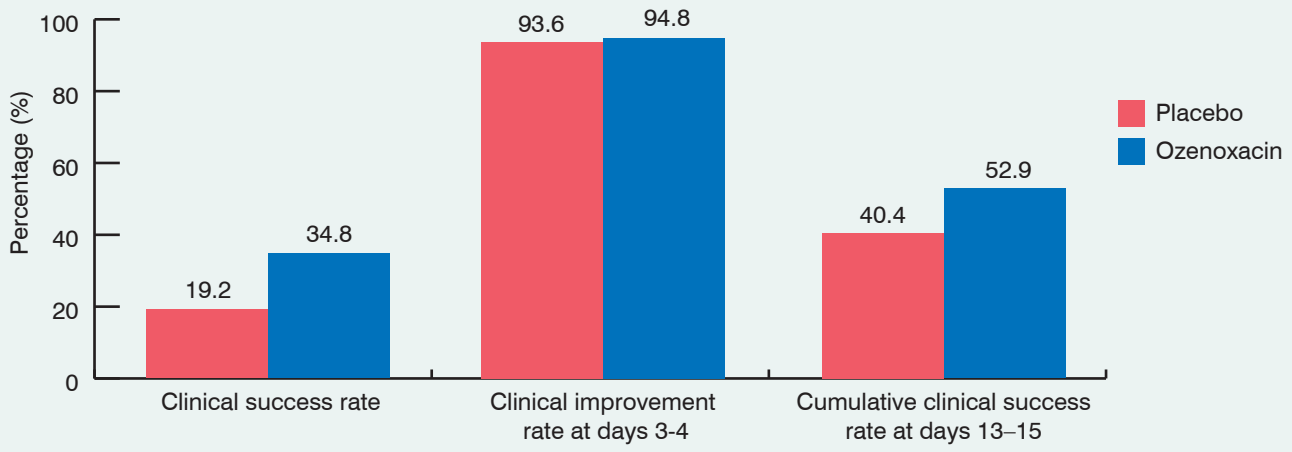
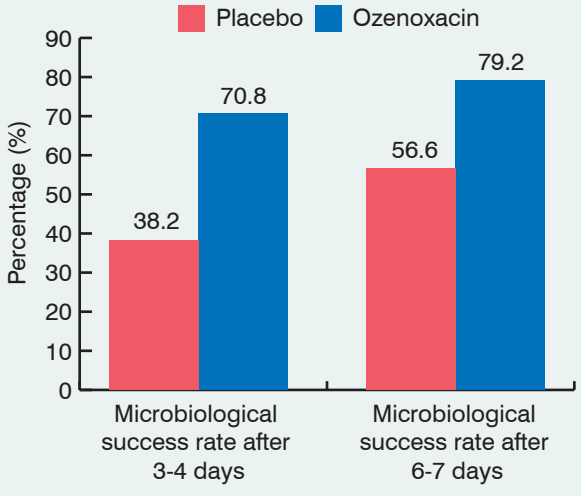


Figure 3: Effect of ozenoxacin on microbiological success rate as compared to placebo in patients with impetigo[7]



- Clinical improvement rate on days 3–4 was similarly high in the ozenoxacin (94.8%) and placebo (93.6%) groups, however, cumulative clinical success rate at days 13–15 was significantly superior for ozenoxacin versus placebo (52.9 vs 40.4%; Figure 2)
- Clinically relevant improvement was seen with ozenoxacin as evident from 81.7% decrease from baseline in the total skin infection rating scale (SIRS) score as compared to 71.6% decrease from baseline in the SIRS score in the placebo group
- Microbiological success rate was 70.8% in the ozenoxacin group and 38.2% in the placebo group after 3–4 days and 79.2 and 56.6% after 6–7 days (Figure 3)
- As compared to retapamulin, ozenoxacin produced more rapid microbiological clearance (Figure 4)
- All treatments were well-tolerated.

In conclusion, it was inferred that ozenoxacin 1% cream is effective and safe in the treatment of impetigo.

Study 2

A study[6] was done to evaluate the safety and efficacy of ozenoxacin in treatment of impetigo in children aged patients aged ≥2 months to <18 years. It included 644 patients. Findings of the study were:

- Significantly higher clinical success rate at the end of treatment and bacterial eradication rates after 3 to 4 days of treatment and at the end of treatment were noted with ozenoxacin as compared to placebo (Figure 5)

Figure 4: Effect of ozenoxacin on microbiological clearance as compared to retapamulin in patients with impetigo[7]

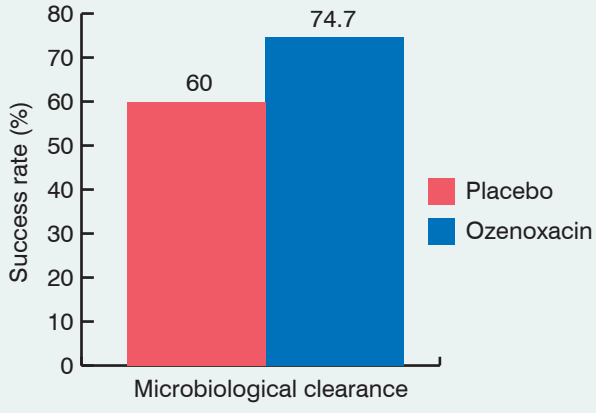
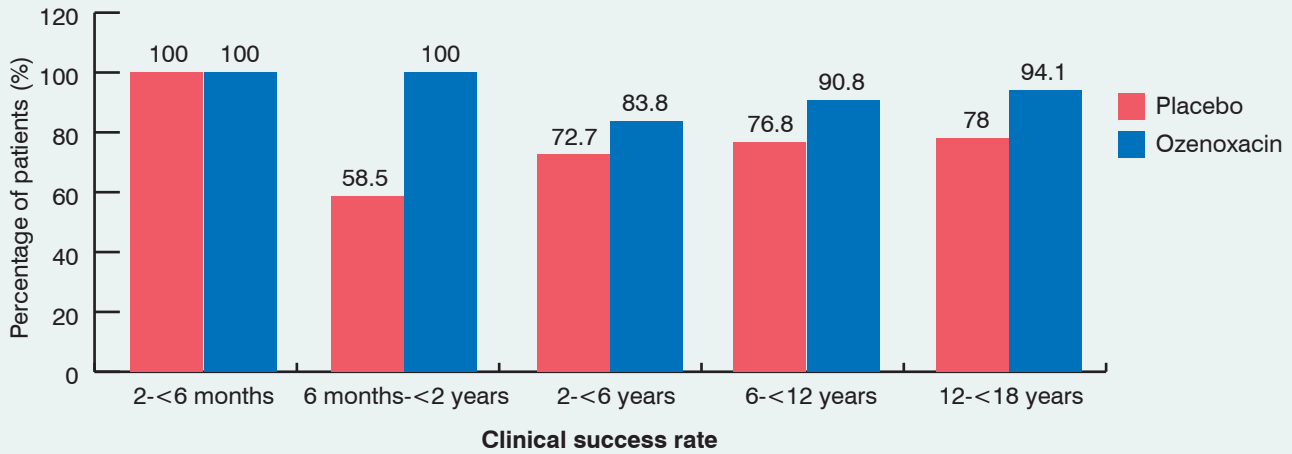


Figure 5: Proportion of patients with impetigo who achieved significant clinical success rate with ozenoxacin as compared to placebo[6]



- Clinical and microbiologic success rates were higher with ozenoxacin than placebo in all age groups
- No safety concerns with ozenoxacin were noted.

In conclusion, ozenoxacin 1% cream is an effective and safe treatment for impetigo in pediatric patients aged 2 months to <18 years.

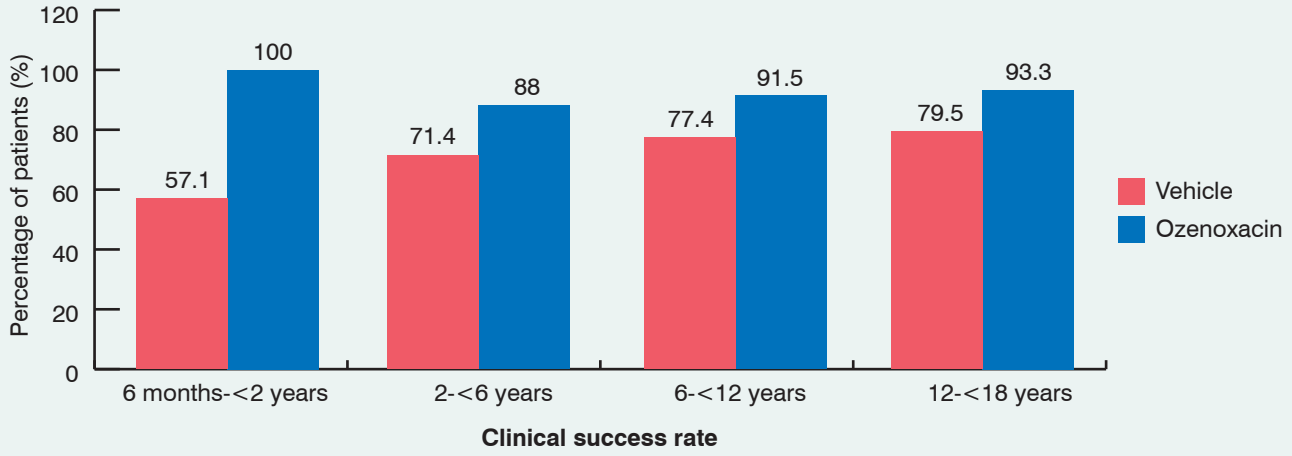
Study 3

In a study[3] done in 529 pediatric patients with non-bullous impetigo, efficacy of ozenoxacin was reported. It had shown significantly higher clinical success rate with ozenoxacin as compared to vehicle (Figure 6). Ozenoxacin was associated with significantly higher microbiological success rates in each age group at both visits compared with vehicle. In patient with resistant strains, ozenoxacin was superior to vehicle in terms of microbiological response. Therefore, it was concluded that ozenoxacin 1% cream is an effective treatment option in pediatric patients when administered twice daily for 5 days.

Study 4

In another study[8] done on 411 patients receiving either ozenoxacin or placebo, superior clinical success was noted with ozenoxacin as compared with placebo as evident after 5 days of therapy (54.4% vs. 37.9%; Figure 7). Ozenoxacin was also effective with respect to superior microbiological success as compared with placebo after 2 days of therapy (87.2% vs 63.9%; Figure 7). It was well-tolerated, with only 8 of 206 patients experiencing adverse effects, with only 1 of these potentially related to the study treatment; none

Figure 6: Proportion of patients with impetigo who achieved significant clinical success rate with ozenoxacin as compared to vehicle[3]

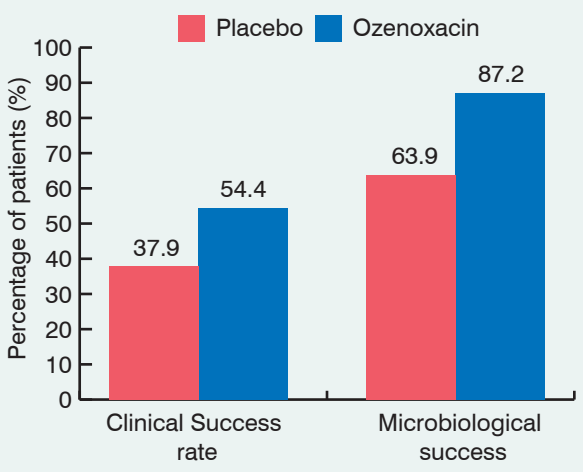


Why Ozenoxacin is emerging as a front-line topical antibiotic for bacterial SSTIs?

- Ozenoxacin appears to be the most potent amongst some of the available topical options like mupirocin, fusidic acid and retapamulin
- Ozenoxacin has shown the lowest MIC90 (mg/L) for methicillin-sensitive S. aureus (MSSA), methicillin-resistant S. aureus (MRSA), and Streptococcus pyogenes
- Ozenoxacin appears to be superior to mupirocin and fusidic acid when placebo based trials of individual topical antibiotics are compared
- Efflux pump is one of the well-noted mechanisms for the development of bacterial resistance; ozenoxacin does not appear to be affected by bacterial efflux pump and hence, may have low rates of anti-bacterial resistance.

Sources: 1. Data on Record. **2.** Vila J, Hebert AA, Torrelo A, et al. Ozenoxacin: a review of preclinical and clinical efficacy. *Expert Rev Anti Infect Ther*. 2019;17(3):159-168. **3.** Canton R, Morrissey I, Vila J, et al. Comparative in vitro antibacterial activity of ozenoxacin against Gram-positive clinical isolates. *Future Microbiol*. 2018;13:3-19. **4.** Rosen T, *et al*. Efficacy and safety of ozenoxacin cream for treatment of adult and pediatric patients with impetigo. a randomized clinical trial. *JAMA Dermatol*. 2018;154:806–813. **5.**. Edge R, *et al*. Topical Antibiotics for Impetigo: A Review of the Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): *Canadian Agency for Drugs and Technologies in Health*; 2017 Feb 21. Summary of Evidence. **6.** Koning S, *et al*. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. BMJ. 2002;324(7331):203-6 **7.**. López Y, Tato M, Gargallo-Viola D, et al. Comparative activity of ozenoxacin and other quinolones in Staphylococcus aureus strains overexpressing the efflux pump-encoding genes mepA and norA. *Int J Antimicrob Agents*. 2020;56(3):106082.

Figure 7: Proportion of patients with impetigo who achieved significant clinical success rate and microbiological success with ozenoxacin as compared to placebo[8]



were serious. In conclusion, topical ozenoxacin is effective and well-tolerated in the treatment of impetigo in patients 2 months and older and represents a novel option for the treatment of impetigo.

Conclusion

Impetigo, a common infection of the superficial layers of the epidermis is characterized by presence of erythematous plaques with a yellow crust and be associated with itching and pain. *Staphylococcus aureus* and group A beta-haemolytic Streptococcus are the associated causative agents for non-bullous type. Toxin-producing *S. aureus* is the associated causative agent for bullous impetigo. Treatment of impetigo depends on the extent and site of the lesions and the presence of systemic symptoms. According to the clinical practice guidelines available, use of topical antibacterial agents has been recommended for small localised areas of lesions and oral antibiotics for the treatment of multiple/extensive lesions not responding to topical therapy. Ozenoxacin has been approved as an effective and well-tolerated topical treatment of impetigo due to *S. aureus* or *S. pyogenes* in pediatric patients aged 2 months or older.

References

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