Evaluating Ozenoxacin in Pediatric Patients: An update

Reviewed by:
Dr. Diganta Barman
DCH, MD (Pediatrics)
Assistant Professor of Pediatrics, Gauhati Medical College, Guwahati, Assam
Consultant Child Specialist, Guwahati

Briefly understanding impetigo

Impetigo is a common bacterial infection of the skin that affects superficial layers of the epidermis. It is common in young children, and in fact is considered the most common bacterial skin infection in the pediatric age group. Skin lesions in impetigo appear primarily as itchy erythematous plaques, often with yellow crusts. These lesions are mainly located on the face, neck and hands (Figure 1). The infection is deemed highly contagious. It is further classified into two broad groups, non-bullous and bullous impetigo. Non-bullous impetigo initially presents with vesicles or pustules mainly on the face or extremities, which coalesce and eventually rupture with purulent exudate and formation of classical honey-colored crusts. Bullous impetigo presents as fragile, thin roofed flaccid bullae. Composed initially of clear fluid which later turns dark, these bullae upon rupture lead to an erythematous base with a rim of scale.[1,2]

Figure 1:Clinical presentation of impetigo[1,2]

Impetigo are primarily caused by Gram-positive bacteria. Nonbullous impetigo are overwhelmingly due to *Staphylococcus aureus* which account for about 80% of these cases; in 10% cases group A beta-hemolytic Streptococci (GABHS) are accountable while in the remaining cases a mix of *S. aureus* and GABHS are the underlying cause of these infections. Bullous impetigo is almost always caused by *S. aureus*.[1] Choice of therapy in impetigo is dependent on various factors including site and severity of lesions, and presence or absence of systemic features.[3] Most children with impetigo are treated with application of topical antibiotics, either used alone or in combination with systemic therapies (usually oral medications).[1] There are several advantages of employing topical antibiotics as the front-line treatment of impetigo in children. Owing to their minimal absorption in the blood stream, topical antibiotics are largely devoid of serious systemic adverse effects. Moreover, they can deliver high drug concentrations within the therapeutically acceptable range locally at the site of infection, thereby improving outcomes and overcoming mutational resistance among the causative pathogens.[2]

Concerns with rising antibacterial resistance

The last few years have been witness to a growing threat from emerging resistant bacterial strains that have jeopardized treatment outcomes to many commonly used topical antimicrobials. Topical drugs like fusidic acid, mupirocin, and retapamulin were used as treatment options for impetigo, however efficacy of some of these drugs lately appears to have been compromised due to the emergence

and spread of these resistant strains. Growing resistance against topical mupirocin has been reported since the last decade. Similarly, now resistance to topical fusidic acid is also known in several parts of the world.[2,4] These reports necessitate rethink of the treatment strategy for impetigo in children and consideration of novel treatment options which have a broad coverage against both sensitive and multi-drug resistant bacterial population.

Ozenoxacin in children

Ozenoxacin is a non-fluorinated topical antibiotic, a quinolone, which has been widely used for the treatment of impetigo in children and adults. It has dual inhibitory activity against two key bacterial replication enzymes, DNA gyrase and topoisomerase IV. This dual inhibitory activity of ozenoxacin against bacterial replication reduces resistance development. It has a broad spectrum of activity against both drug-sensitive and -resistant Staphylococcal and Streptococcal strains, including methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. epidermidis* (MRSE), *S. pyogenes*, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus* (Box 1). This broad bactericidal activity of ozenoxacin, particularly against drug-resistant bacteria; along with its reported efficacy and safety allows pediatricians and dermatologists to use it with confidence as an empirical therapy for localized impetigo in the pediatric age group. Another feature worth noting is the absence of a fluorine atom in the structure of ozenoxacin, as a result of which it offers a more favorable safety profile compared to fluorinated quinolones (particularly lack of quinolone-induced chondrotoxicity).[3]

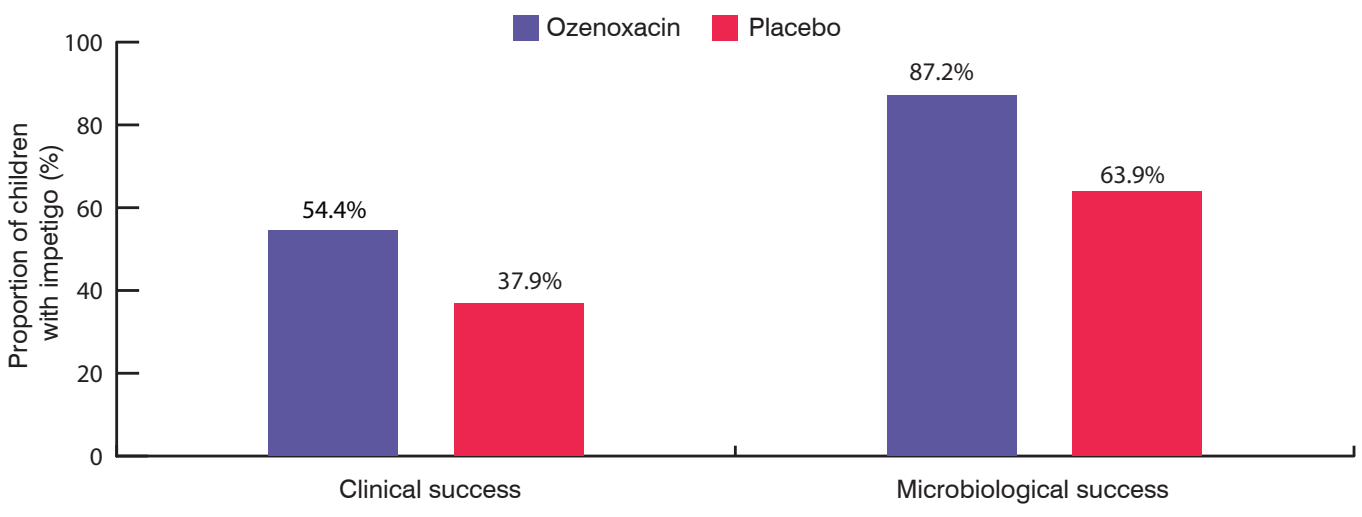
Box 1: Antibacterial coverage of ozenoxacin[3]

- Methicillin-resistant *S. aureus* (MRSA)
- Methicillin-sensitive *S. aureus* (MSSA)
- Methicillin-resistant *S. epidermidis* (MRSE)
- *S. pyogenes*
- Drug-resistant strains (mupirocin-, and ciprofloxacin-resistant strains of *S. aureus*)

Ozenoxacin – Evidence of efficacy and safety in children

Topical ozenoxacin 1% cream applied twice-daily for 5 days has shown effectiveness in treating impetigo in children. Rosen et al[2] included patients of impetigo, 2 months or older recruited from centres across 6 countries in their vehicle-controlled study and treated them with topically applied ozenoxacin 1% cream vs placebo. Results of the study showed superiority of ozenoxacin compared to placebo in clinical success after 5 days of treatment (54.4% vs 37.9%) and in microbiological success (bacterial eradication) after 2 days of treatment (87.2% vs 63.9%); Figure 2. Additionally, ozenoxacin was effective against drug-resistant strains including in all patients with mupirocin-resistant *S. aureus* and all patients with MRSA. Overall, ozenoxacin was well-tolerated without serious adverse effects.[2]

Figure 2: Proportion of children with impetigo showing clinical and microbiological success after treatment with topical ozenoxacin vs. placebo[2]



Advantages of topical ozenoxacin

- Ozenoxacin is a newer topical antibiotic with faster clinical efficacy, favorable microbiological profile and safety
- Ozenoxacin is indicated in Gram positive superficial skin infections caused by *Staphylococcus aureus* or *Streptococcus pyogenes* in adult and pediatric patients 2 months of age and older
- The MIC90 concentration of ozenoxacin against *S. aureus* (both MSSA and MRSA) and *Strep pyogenes* is shown to be lower compared to mupirocin, fusidic acid and retapamulin
- Ozenoxacin is applied in a convenient twice-daily doses for 5 days compared to mupirocin and fusidic acid that are applied in thrice-daily doses, often for 7-14 days
- Ozenoxacin has an excellent dermal tolerability

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. 8. Clinical Review Report: Ozenoxacin 1% Cream (Ozanex): (Ferrer Internacional, S.A.): Indication: The topical treatment of impetigo in patients aged two months and older [Internet]. Ottawa (ON): *Canadian Agency for Drugs and Technologies in Health*; 2018 Oct. Table 2, Key Characteristics of Ozenoxacin, Fusidic Acid, and Mupirocin. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539433/table/cl2.tab1/ 9. Torrelo A, Grimalt R, Masramon X, *et al.* Ozenoxacin, a New Effective and Safe Topical Treatment for Impetigo in Children and Adolescents. *Dermatology*. 2020;236(3):199-207.

Another study[4] that analysed pooled data from previous ozenoxacin clinical trials (one phase I and two phase III clinical trials that included children from 6 months to <18 years) also confirmed treatment benefits of this antimicrobial. In this pooled pediatric population with nonbullous impetigo, ozenoxacin 1% cream was shown to be both effective and safe. These children were treated with either of ozenoxacin, vehicle or retapamulin as internal validation control. Patients treated with ozenoxacin achieved higher clinical success rates compared to the vehicle in all pediatric age groups. Clinical success rates for ozenoxacin vs vehicle in 0.5–<2 years group were 100% vs 57.1%; in 2–<6 years group were 88% vs 71.4%; in 6–<12 years group were 91.5% vs 77.4%; and in 12–<18 years were 93.3% vs 79.5%, respectively. In retapamulin group, clinical success rates for 2–<6 years, 6–<12 years, and 12–<18 years were 93.5%, 71.1% and 76.9%, respectively.

Additionally, in this pooled analysis ozenoxacin-treated patients also showed higher microbiological success at visits 2 (3/4 day of treatment) and 3 (after 5 completed days of treatment) compared to the vehicle. At visit 2, microbiological success with ozenoxacin vs vehicle in 0.5–<2 years group were 100% vs 60%; in 2–<6 years group were 81.8% vs 55.3%; in 6–<12 years group were 87.7% vs 59.8%; and in 12–<18 years group were 81.8% vs 42.3%, respectively. Similarly at visit 3, the respective microbiological success with ozenoxacin vs vehicle in 0.5–<2 years group were 100% vs 60%; in 2–<6 years group were 92.2% vs 70.3%; in 6–<12 years group were 97.2% vs 73.8%; and in 12–<18 years group were 90.5% vs 64%, respectively. In retapamulin group, microbiological success rates at visit 2 in 2–<6 years, 6–<12 years, and in 12–<18 years were 60%, 50% and 46.2%, respectively. At visit 3, these rates for retapamulin in 2–<6 years, 6–<12 years, and 12–<18 years groups were 87.1%, 82.2%, and 84.6%, respectively. This data analysis therefore confirmed a place for ozenoxacin in the treatment armamentarium of pediatric impetigo, with significantly superior clinical and microbiological success rates compared to the vehicle.[4]

> **OZENOXACIN WAS EFFECTIVE AGAINST DRUG-RESISTANT STRAINS INCLUDING IN ALL PATIENTS WITH MUPIROCIN-RESISTANT S. AUREUS AND ALL PATIENTS WITH MRSA**

Conclusion

Impetigo is a commonly reported bacterial skin infection in children. These children present with skin lesions including erythematous plaques with yellow crusts, primarily on the face, neck and hands. Ozenoxacin 1% cream is a topical antimicrobial that has been successfully used in children above 2 months for the treatment of impetigo. It offers potent bactericidal activity against a wide range of sensitive and resistant bacterial strains. A 5 days treatment regimen in children shows high clinical and microbiological success rates with no major safety concerns.

References

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3. Davino G, D'Alvano T, Esposito S. The Use of Ozenoxacin in Pediatric Patients: Clinical Evidence, Efficacy and Safety. *Front Pharmacol.* 2020;11:559708.
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