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Treatment Strategies: A Systematic Review of The Advancements of Topical Antibiotics for Impetigo

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ABSTRACT

Impetigo, a highly contagious bacterial skin infection primarily affecting children, poses significant management challenges due to the increasing prevalence of antibiotic resistance, particularly mupirocin and fusidic acid. This study aims to analyze the effectiveness and safety of the new topical antibiotic ozenoxacin in the management of impetigo. This systematic review adheres to PRISMA 2020 guidelines and includes studies published between 2014 and 2024, utilizing databases such as PubMed, Embase, and Cochrane Library to identify relevant research. The findings demonstrate that ozenoxacin offers superior clinical outcomes compared to traditional agents, with significantly higher rates of microbiological success and good tolerability among patients. Additionally, the rising resistance rates to mupirocin and fusidic acid underscore the urgent need for alternative treatment strategies. These results highlight the importance of adopting evidence-based management techniques for impetigo, emphasizing the necessity for ongoing research to optimize treatment options and improve patient outcomes. By integrating newer therapies like ozenoxacin into clinical practice, healthcare providers can enhance the quality of care for individuals affected by this common yet challenging infection.

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Introduction

Impetigo is a highly contagious bacterial skin infection that primarily affects children between 2 to 5 years of age, although individuals of all age groups can be susceptible (Galindo & Hebert, 2021). Globally, over 162 million children are afflicted with impetigo at any given moment. The condition is predominantly caused by Staphylococcus aureus and Streptococcus pyogenes (group A beta-hemolytic), with less frequent involvement of anaerobic bacteria (D'Cunha et al., 2018). Although pruritic lesions can spread the infection to other body regions

when scratched, impetigo lesions are usually found on the face, neck, and hands. Two clinical subtypes of impetigo are recognized: nonbullous (impetigo contagiosa) and bullous impetigo (Hebert & Gold, 2019). Nonbullous impetigo, accounting for approximately 70% of cases, typically presents with maculopapular lesions that progress to thin-walled vesicles, followed by erosions and characteristic golden-yellow crusting. This form is commonly treated in pediatric primary care. Bullous impetigo, caused by toxin-producing strains of S. aureus, manifests as large, fragile bullae and erosions, often affecting intertriginous areas. Both forms are highly transmissible, especially in crowded environments with suboptimal hygiene, with peak incidence in warmer months (D'Cunha et al., 2018; Hebert & Gold, 2019).

In nearly every case of impetigo, topical antibiotic therapy is the preferred course of treatment; nevertheless, antibiotic resistance, primarily to methicillin, has rapidly increased in recent years. Prompt treatment is essential to mitigate the discomfort, cosmetic concerns, and potential complications associated with impetigo (Vila et al., 2019). Management options include topical and systemic antibiotics. Topical antibiotics are preferred for localized cases due to their ability to deliver high antimicrobial concentrations directly to the infection site with minimal systemic toxicity (Gatto et al., 2023; Gorges et al., 2021). However, rising antibiotic resistance, particularly to agents like mupirocin and fusidic acid, has become a significant concern. Systemic antibiotics are generally reserved for widespread or severe infections (Oranje et al., 2007; Stevens et al., 2014).

Despite the availability of various treatment modalities, the growing threat of antibiotic resistance and limitations of existing therapies underscore the need for systematic, evidence-based guidance on the optimal management of impetigo. Previous efforts, such as reviews by Galindo et al. and Schachner et al., have contributed valuable insights, yet gaps remain in the comparative effectiveness and safety of current treatment options (Galindo & Hebert, 2021; Schachner et al., 2020). This systematic review addresses these gaps by evaluating existing evidence to identify the most effective and practical approaches for managing impetigo across diverse populations.

Impetigo is a highly contagious bacterial skin infection that primarily affects children aged 2 to 5 years, though it can occur in individuals of all ages. Its prevalence is alarming, with over 162 million children worldwide suffering from this condition at any given moment. The infection is mainly caused by Staphylococcus aureus and Streptococcus pyogenes, with occasional involvement of anaerobic bacteria. The two clinical subtypes of impetigo, nonbullous and bullous, present distinct characteristics and management challenges, emphasizing the need for effective treatment strategies.

Nonbullous impetigo accounts for approximately 70% of cases and typically manifests as maculopapular lesions that progress to vesicles and characteristic golden-yellow crusting. This form is commonly treated in pediatric primary care settings. In contrast, bullous impetigo, caused by toxin-producing strains of Staphylococcus aureus, presents as large, fragile bullae and erosions, often affecting intertriginous areas. The highly transmissible nature of both forms of impetigo, particularly in crowded environments with poor hygiene, underscores the urgency of effective management.

Topical antibiotics are the first-line treatment for localized impetigo, delivering high antimicrobial concentrations directly to the infection site with minimal systemic toxicity. However, the rise of antibiotic resistance, particularly to mupirocin and fusidic acid, has become a significant concern. This increasing resistance complicates treatment options and highlights the need for ongoing research into alternative therapies.

Prompt treatment is essential to alleviate the discomfort, cosmetic concerns, and potential complications associated with impetigo. Effective management addresses the immediate health needs of affected individuals and contributes to public health efforts to control the spread of

infection within communities. Educating caregivers and healthcare providers about hygiene practices and early intervention cannot be overstated.

Recent advancements in research have introduced new topical antibiotics, such as Oz enoxacin, which have demonstrated promising efficacy and safety profiles compared to traditional agents. Clinical trials have shown that Oz enoxacin offers rapid bacterial clearance and clinical resolution, particularly for pediatric cases. This novel agent's low systemic absorption minimizes adverse effects, making it a suitable option for young patients.

Despite these advancements, significant gaps exist in the literature regarding the' comparative effectiveness and safety of newer treatments. This systematic review addresses these gaps by evaluating the current evidence surrounding topical antibiotics for impetigo, focusing on their efficacy, safety, and resistance trends. By synthesizing recent studies, this review seeks to provide clearer guidance on optimal management strategies for impetigo, ultimately improving patient outcomes and enhancing the quality of care.

Impetigo is a highly contagious bacterial skin infection that predominantly affects children aged 2 to 5, yet it can occur in individuals of all ages. The increasing prevalence of antibiotic resistance, particularly to commonly used topical agents like mupirocin and fusidic acid, complicates treatment strategies and necessitates the exploration of alternative therapies. Effective management is essential to alleviate discomfort, prevent complications, and address the cosmetic concerns associated with this infection.

The rising rates of antibiotic resistance pose significant challenges in treating impetigo, as traditional therapies become less effective. This situation is exacerbated by the high incidence of impetigo in children, who are particularly vulnerable to complications if infections are not managed promptly and effectively. Furthermore, the impact of impetigo on quality of life, especially in pediatric populations, underscores the need for timely and efficient treatment strategies to mitigate both physical and psychological burdens. In addition, public health efforts must focus on educating caregivers and healthcare providers about hygiene practices and the importance of early intervention. As antibiotic resistance continues to grow, it is crucial to identify and implement evidence-based practices that ensure effective treatment and prevent the spread of infection within communities.

Several studies have highlighted the effectiveness of topical antibiotics in treating impetigo, with mupirocin being the traditional first-line treatment. However, the emergence of resistance to mupirocin has prompted researchers to investigate newer alternatives. Ozenoxacin, a novel topical antibiotic, has shown promising results in clinical trials, demonstrating superior efficacy and safety compared to traditional agents. Research by Rosen et al. (2018) and Torrelo et al. (2020) supports the potential of ozenoxacin as a first-line treatment option, particularly in pediatric patients. Despite the positive findings regarding newer treatments, gaps remain in understanding the comparative effectiveness of these agents across diverse populations and settings. Previous reviews have not fully addressed the nuances of treatment efficacy, safety, and resistance trends, especially in regions with varying resistance patterns. Comprehensive studies are needed to establish guidelines for impetigo management that consider the evolving landscape of antibiotic resistance. Moreover, existing literature often focuses primarily on pediatric populations, limiting insights into treatment strategies for adults and individuals with comorbidities. Research that encompasses a broader demographic scope is essential for optimizing impetigo management in diverse patient populations.

The current literature lacks comprehensive head-to-head comparisons of newer antibiotics like ozenoxacin with established mupirocin and fusidic acid treatments. Additionally, there is insufficient data on the long-term outcomes and resistance patterns associated with these treatments, particularly in various geographical regions where resistance rates may differ significantly. This systematic review aims to fill these gaps by evaluating the effectiveness and safety of emerging topical antibiotics, particularly ozenoxacin, compared to

traditional treatments. By synthesizing data from recent studies, this review seeks to provide a clearer understanding of the optimal management strategies for impetigo in the context of rising antibiotic resistance.

This study aims to systematically review and analyze the advancements in topical antibiotics for impetigo treatment, focusing on their efficacy, safety, and resistance trends. This review will identify the most effective treatment options for various patient populations and contribute to evidence-based clinical guidelines. The findings of this research will provide valuable insights for healthcare professionals, enabling them to make informed decisions regarding impetigo management. By identifying effective treatment strategies and addressing the challenges posed by antibiotic resistance, this study aims to improve patient outcomes and enhance the overall quality of care for individuals affected by impetigo.

Research Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, consistency, and reproducibility. The protocol is designed to systematically review and evaluate the effectiveness of treatment strategies for impetigo, focusing on antibiotic therapies and their outcomes. This review will include studies published between 2014 and 2024 that investigate the treatment of impetigo, particularly focusing on antibiotic therapies (topical and systemic) and alternative management strategies. Eligible studies must involve human participants diagnosed with impetigo and evaluate the treatments' effectiveness, safety, or resistance trends. The review will consider clinical trials, cohort studies, case-control studies, and observational studies providing data on treatment effectiveness, antibiotic resistance patterns, patient outcomes, and adverse effects. Exclusion criteria include review articles, expert opinions, conference abstracts, non-peer-reviewed articles, animal studies, in vitro experiments, or studies lacking a detailed methodology relevant to impetigo management. Studies must be published in English.

A comprehensive search will be conducted using electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, and ScienceDirect. Search terms will focus on impetigo treatment and antibiotic resistance. Primary search terms will include "Impetigo," "Staphylococcus aureus," "Streptococcus pyogenes," "Topical Antibiotics," "Systemic Antibiotics," and "Antibiotic Resistance." Secondary terms such as "Bullous Impetigo," "Nonbullous Impetigo," "Mupirocin," "Fusidic Acid," and "MRSA" will also be used. Boolean operators (AND, OR) will enhance search coverage.

Titles and abstracts will be screened to identify studies relevant to impetigo treatment. Full-text articles meeting inclusion criteria will be reviewed, and data extraction will focus on study characteristics, participant demographics, types of interventions (e.g., mupirocin, fusidic acid, systemic antibiotics), antibiotic resistance patterns, patient outcomes, and reported adverse effects. Studies not meeting the inclusion criteria will be excluded.

Two independent reviewers will assess the methodological quality of included studies, considering factors such as study design, sample size, control of confounding variables, and reliability of outcome measures. Discrepancies will be resolved through discussion or consultation with a third reviewer. Studies with robust methodological quality will be included in the final synthesis. A qualitative analysis will summarize the findings on impetigo treatment, focusing on the effectiveness of topical and systemic antibiotics, antibiotic resistance trends, and patient outcomes. If data homogeneity permits, a meta-analysis may be performed to compare the effectiveness of different treatments. Subgroup analyses will explore patient age, impetigo type (bullous vs. nonbullous), geographical region, and resistance trends. The risk of bias for each included study was assessed using the JBI Critical Appraisal Tools.

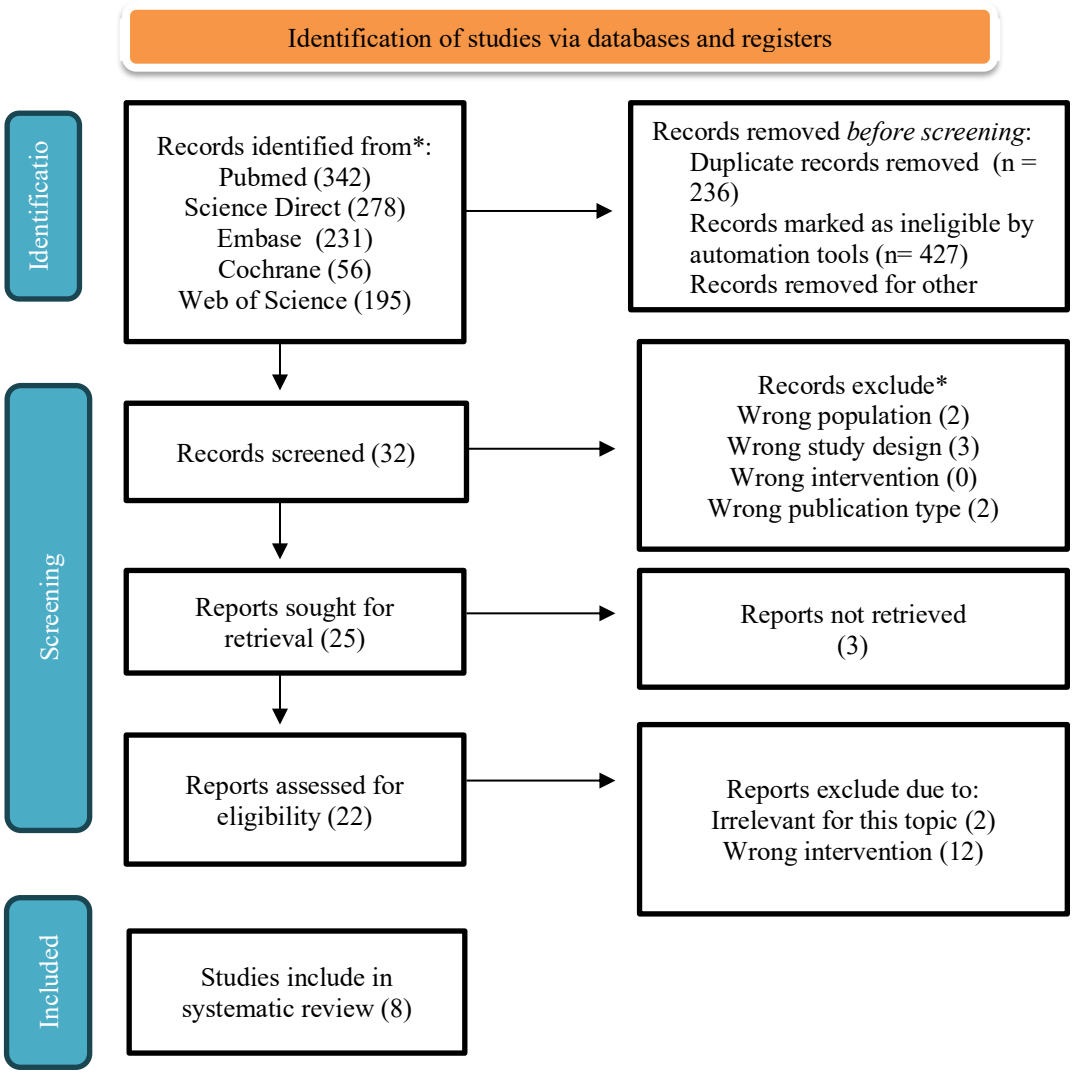

Figure 1. PRISMA Flowchart for Study Selection

Results and Discussion

Our research team first gathered publications from reputable sources such as Science Direct, PubMed, Cochrane, Web of Science, and Embase. After a thorough three-level screening procedure, only nine papers were determined to be directly relevant to our ongoing systematic evaluation. These sections were then picked for additional research and a close reading of the entire manuscript. The material evaluated for this analysis is compiled in Table 2 for ease of viewing.

Overall, topical antibiotics demonstrated significantly higher cure rates compared to placebo (risk ratio [RR] 2.24; 95% confidence interval [CI] 1.61–3.13). The analysis found no significant difference in efficacy between the two primary topical antibiotics, mupirocin and fusidic acid (Koning et al., 2012). Rosen et al. (2018) investigated ozenoxacin in 411 patients and found superior clinical success compared to placebo after five days of therapy (54.4% vs. 37.9%, p = 0.001). Microbiological success was also significantly higher for ozenoxacin after two days of treatment (87.2% vs. 63.9%, p = 0.002). Ozenoxacin was well-tolerated, with only eight out of 206 patients reporting adverse events, of which only one was potentially treatment-related and none were serious (Rosen et al., 2018).

In a study by Gropper et al. (2014), the efficacy and safety of ozenoxacin (a novel non-fluorinated quinolone cream) 1% were compared with placebo for impetigo treatment.

Conducted as a multicenter, randomized, double-blind trial, patients received ozenoxacin cream or placebo twice daily for five days, with a third group receiving retapamulin 1% ointment as an active comparator. Results showed ozenoxacin outperformed placebo in clinical success rates (34.8% vs. 19.2%, p = 0.003) and achieved microbiological success in 70.8% of cases by days 3–4, compared to 38.2% with placebo. By days 6–7, success rates were 79.2% for ozenoxacin and 56.6% for placebo. Furthermore, ozenoxacin achieved faster microbiological clearance than retapamulin, confirming its efficacy and safety in treating impetigo (Gropper et al., 2014).

Between Nov 26, 2009, and Nov 20, 2012, 508 patients were randomly assigned to receive benzathine benzylpenicillin (n=165 [156 analyzed]), twice-daily co-trimoxazole for 3 days (n=175 [173 analyzed]), or once-daily co-trimoxazole for 5 days (n=168 [161 analyzed]). Treatment was successful in 133 (85%) children who received benzathine benzylpenicillin and 283 (85%) who received pooled co-trimoxazole (absolute difference 0·5%; 95% CI –6·2 to 7·3), showing non-inferiority of co-trimoxazole (10% margin). Results for twice-daily co-trimoxazole for 3 days and once-daily co-trimoxazole for 5 days were similar. Adverse events occurred in 54 participants, 49 (90%) of whom received benzathine benzylpenicillin (Bowen et al., 2014).

Similarly, Torrelo et al. (2020) analyzed data from 529 patients with non-bullous impetigo treated with ozenoxacin (n = 239), vehicle (n = 201), and retapamulin (n = 89). Clinical success rates after five days of treatment (days 6–7) and microbiological success rates after 3–4 days and at the end of therapy were significantly higher for ozenoxacin than vehicle ($p < 0.0001$). These findings validate ozenoxacin 1% cream as an effective and safe treatment option for non-bullous impetigo in children aged six months to <18 years (Torrelo et al., 2020).

In 8.4% of the cases (256/3051 cases), ozenoxacin was prescribed. The most prescribed topical antimicrobials (74%) were in the class of other topical antibiotics (ATC: D06AX*), followed by antibiotics in association with a corticosteroid (23%, ATC: D07C*). The distribution remains similar after the approval of ozanexozacin since the latter is part of the other topical antimicrobial class (Supplementary Materials Table S3). In the period before ozenoxacin was available on the market, fusidic acid was prescribed in 37.8% of the cases, followed by muciprocin (18%), antibiotics in association with betamethasone (17.2%), and gentamicin (13.1%); in the period after, the most prescribed was muciprocin (26%), followed by fusidic acid (20.8%) and ozenoxacin (20.3%) (Barbieri et al., 2023).

Clinical cure, defined as ≥80% cured lesions (fully recovered lesions, visually determined by investigators), was achieved by 57.1% and 50.0% of FMX-102 1% and 4% subjects, respectively, at the end of treatment (visit 3). Clinical success, defined as the absence of lesions, or the drying or improvement of treated lesions (decrease in size of affected area, lesion number, or both), was demonstrated in 81.3% and 78.6% of FMX-102 1% and 4% subjects, respectively, following 3 days of treatment (visit 2), in 92.3% and 100% of the respective subjects at the end of treatment, and 100% in both groups at follow-up (visit 4). Bacteriologic success rates at the end of treatment, defined as complete pathogen eradication, were 85% and 74% in the FMX-102 1% and 4% groups, respectively. The bacteriologic success rate for MRSA infections was 100% (11/11), with no recurrences. Both FMX-102 1% and 4% were considered well tolerated and safe (Chamny et al., 2016).

The majority of patients had SITL (70.4% [188/267] and 66.4% [91/137] in the retapamulin and linezolid groups, respectively; intent-to-treat clinical population). Clinical success rate at follow-up was significantly lower in the retapamulin versus the linezolid group (63.9% [39/61] vs 90.6% [29/32], respectively; difference in success rate -26.7%; 95% CI, -45.7 to -7.7) (Tanus et al., 2014).

Impetigo peaked in summer. Most patients and children experienced a single episode (93%), and 25% had eczema as a comorbidity. Topical antibiotics (primarily fusidic acid) were

the most prescribed initial treatments (85%), followed by oral antibiotics (14%). Topical antibiotics were progressively used less over subsequent treatments, while oral antibiotic use increased. As the most common first-line treatment, topical fusidic acid seemed satisfactory, as only 12% of initial treatments with this drug received further therapy. Repeat treatments generally occurred within 7 days (Loadsman et al., 2019).

Two participants received SWP (n=1) and mupirocin (n=1). Both commenced oral antibiotics following failure of topical treatment. Recruitment barriers included reduced presentation of impetigo due to COVID-19, pre-treatment with existing at-home medications and moderate/severe infection. Childcare centers and pharmacies were identified as alternative venues to improve the recruitment rate.

Table 2. The literature included in this study

Author	Origin	Method	Sample Size	Result
Rosen et al. (2018)**.**	US	Randomized double-blind, vehicle-controlled clinical trial.	411 patients, 2 months or older with impetigo, were enrolled at centers in 6 countries from June 2, 2014, through May 30, 2015.	Ozenoxacin cream was applied twice daily for 5 days, with clinical and microbiological assessments conducted at baseline, day 3, day 6, and days 10-13. Clinical efficacy was measured using the Skin Infection Rating Scale (SIRS), which graded the affected areas based on five symptoms: blistering, exudate and/or pus, crusting, erythema and/or inflammation, and itching and/or pain, with scores ranging from 0 (absent) to 3 (severe). Clinical success was defined as a score of 0 for blistering, exudate, and/or pus, crusting, and itching and/or pain, and no greater than 1 (mild) for erythema and/or inflammation, indicating that no additional antimicrobial therapy was necessary. Microbiological samples were collected from the affected areas at all visits, provided culturable material was present. The study found that ozenoxacin cream was superior to placebo in clinical success (54.4% vs. 37.9%) and microbiological eradication (87.2% vs. 63.9%) at key time points. Early positive responses were observed, with a higher therapeutic success rate in the ozenoxacin group (57.6%) compared to the placebo (34.5%). Ozenoxacin demonstrated good tolerability, with low rates of adverse events and no serious events related to the study drug. This is consistent with previous studies showing negligible systemic absorption of ozenoxacin. The study concluded that ozenoxacin is an effective and well-tolerated treatment for impetigo.

Bowen et al. (2014)**.**	Israel	Randomized, controlled, non-inferiority trial.	663 children were eligible for randomization.	Between Nov 26, 2009, and Nov 20, 2012, 508 patients were randomly assigned to receive benzathine benzylpenicillin (n=165 [156 analyzed]), twice-daily co-trimoxazole for 3 days (n=175 [173 analyzed]), or once-daily co-trimoxazole for 5 days (n=168 [161 analyzed]). Treatment was successful in 133 (85%) children who received benzathine benzylpenicillin and 283 (85%) who received pooled co-trimoxazole (absolute difference 0·5%; 95% CI –6·2 to 7·3), showing non-inferiority of co-trimoxazole (10% margin). Results for twice-daily co-trimoxazole for 3 days and once-daily co-trimoxazole for 5 days were similar. Adverse events occurred in 54 participants, 49 (90%) of whom received benzathine benzylpenicillin.
Torrelo et al., (2020)**.**	Spain	Randomized, controlled trial.	The combined population comprised 529 patients with non-bullous impetigo treated with ozenoxacin (n = 239), vehicle (n = 201), or retapamulin as an internal validation control (n = 89).	Studies were well matched for the extent and severity of impetigo and the therapeutic schedule (twice daily application for 5 days). The clinical success rate after 5 days' treatment (day 6-7, end of therapy) and microbiological success rates after 3-4 days' treatment and at the end of therapy were significantly higher with ozenoxacin than with vehicle ($p < 0.0001$ for all comparisons). Clinical and bacterial eradication rates were higher with ozenoxacin than with vehicle in each age group. No safety concerns were identified with ozenoxacin. One (0.3%) of 327 plasma samples exceeded the lower limit of quantification for ozenoxacin, but the low concentration indicated negligible systemic absorption.

Gropper et al., (2014)**.**	The study was performed in 27 centers in 5 countries (Germany, Romania, South Africa, Ukraine, and the USA).	In a randomized, double-blind, multicenter study, patients received oz of enoxacin cream or placebo cream twice daily for 5 days (a third group received retapamulin 1% ointment as a control).	The ITT clinical population comprised 465 patients randomized to treatment with ozenoxacin (155), placebo (156), or retapamulin (154), and 455 of these completed the study.	Ozenoxacin was superior to placebo (success rate 34.8 vs 19.2%; p = 0.003). Microbiological success was 70.8% for ozenoxacin and 38.2% for placebo after 3–4 days and 79.2% versus 56.6% after 6–7 days. Ozenoxacin produced more rapid microbiological clearance than retapamulin. All treatments were well tolerated.
Barbieri et al., (2023)**.**	Italy	Retrospective analysis.	A total of 3051 cases were identified: most children (N = 2813) had only one impetigo, with around 4% having two or more cases.	In 8.4% of the cases (256/3051 cases), ozenoxacin was prescribed. The most prescribed topical antimicrobials (74%) were in the class of other topical antibiotics (ATC: D06AX*), followed by antibiotics in association with a corticosteroid (23%, ATC: D07C*). The distribution remains similar after the approval of ozanexozacin since the latter is part of the other topical antimicrobial class (Supplementary Materials Table S3). In the period before ozenoxacin was available on the market, fusidic acid was prescribed in 37.8% of the cases, followed by muciprocin (18%), antibiotics in association with betamethasone (17.2%), and gentamicin (13.1%); in the period after, the most prescribed was muciprocin (26%), followed by fusidic acid (20.8%) and ozenoxacin (20.3%)

Chamny et al., (2016)**.**	US	randomized, parallel-group, double-blind, comparative clinical trial,	32 subjects aged ≥2 years with a clinical diagnosis of pure impetigo, impetigo contagiosa, or uncomplicated blistering impetigo were randomized to treatment with FMX-102 1% or 4%, twice daily for 7 days.	Clinical cure, defined as ≥80% cured lesions (fully recovered lesions, visually determined by investigators), was achieved by 57.1% and 50.0% of FMX-102 1% and 4% subjects, respectively, at the end of treatment (visit 3). Clinical success, defined as the absence of lesions, or the drying or improvement of treated lesions (decrease in size of affected area, lesion number, or both), was demonstrated in 81.3% and 78.6% of FMX-102 1% and 4% subjects, respectively, following 3 days of treatment (visit 2), in 92.3% and 100% of the respective subjects at the end of treatment, and 100% in both groups at follow-up (visit 4). Bacteriologic success rates at the end of treatment, defined as complete pathogen eradication, were 85% and 74% in the FMX-102 1% and 4% groups, respectively. The bacteriologic success rate for MRSA infections was 100% (11/11), with no recurrences. Both FMX-102 1% and 4% were considered well tolerated and safe.
Tanus et al. (2014)**.**	US	A randomized, double-blind, double-dummy, multicenter, comparative study	A total of 410 patients were enrolled in the study. Of these, 270 patients were randomized to retapamulin, and 140 patients were randomized to linezolid; 6 patients, 3 in each treatment group, were randomized but did not receive treatment.	The majority of patients had SITL (70.4% [188/267] and 66.4% [91/137] in the retapamulin and linezolid groups, respectively; intent-to-treat clinical population). Clinical success rate at follow-up was significantly lower in the retapamulin versus the linezolid group (63.9% [39/61] vs 90.6% [29/32], respectively; difference in success rate -26.7%; 95% CI, -45.7 to -7.7).

Loadsman et al., (2019)**.**	Netherlands	A retrospective, observational study.	A total of 1761 impetigo episodes were managed, with an incidence rate of 13.6 per 1000 person-years.	Impetigo peaked in summer. Most patients and children experienced a single episode (93%), and 25% had eczema as a comorbidity. Topical antibiotics (primarily fusidic acid) were the most prescribed initial treatments (85%), followed by oral antibiotics (14%). Topical antibiotics were progressively used less over subsequent treatments, while oral antibiotic use increased. As the most common first-line treatment, topical fusidic acid seemed satisfactory, as only 12% of initial treatments with this drug received further therapy. Repeat treatments generally occurred within 7 days.
Gorges et al., (2021)**.**	Australia	The study was designed in keeping with the SPIRIT statement and in accordance with the CONSORT statement for pilot RCTs	Twenty-three people were assessed for eligibility, of which 21 were excluded, most commonly due to having more than 3 lesions (n = 11) or previous treatment within the 48 h preceding presentation to the GP (n = 5).	Two participants received SWP (n=1) and mupirocin (n=1). Both commenced oral antibiotics following the failure of topical treatment. Recruitment barriers included reduced presentation of impetigo due to COVID-19, pre-treatment with existing at-home medications, and moderate/severe infection. Childcare centers and pharmacies were identified as alternative venues to improve recruitment rates.

Discussion

Recent advancements in impetigo management have significantly improved therapeutic approaches, balancing efficacy, safety, and accessibility across diverse patient populations. Ozenoxacin, a novel topical antibiotic, has emerged as a particularly effective option (Gropper et al., 2014). Clinical studies, such as those by Rosen et al. (2018) and Torrelo et al. (2020), demonstrated ozenoxacin's rapid bacterial eradication and clinical resolution, particularly in pediatric cases. This quinolone agent has proven effective against Staphylococcus aureus and Streptococcus pyogenes, including strains resistant to older antibiotics. Its low systemic absorption minimizes adverse effects, making it especially suitable for young children and those with sensitivities to other treatments (Rosen et al., 2018; Torrelo et al., 2020).

While topical therapies are effective for localized impetigo, systemic antibiotics remain crucial for extensive or complicated cases. Oral agents such as co-trimoxazole have been

validated in studies by Bowen et al. (2014) as effective alternatives to injectable treatments, particularly in resource-limited settings. These findings are vital for regions where infrastructure limits refrigeration or injectable medications access. Systemic therapies, however, require careful consideration of their safety profiles, especially in vulnerable groups such as neonates, immunocompromised individuals, and pregnant patients (Bowen et al., 2014).

The rise of antibiotic resistance continues to pose challenges in impetigo treatment. Fusidic acid, once a mainstay therapy, has shown increasing resistance rates in certain regions. The introduction of ozenoxacin offers a promising solution due to its novel mechanism of action, which reduces resistance risk compared to traditional agents like mupirocin and fusidic acid. Studies like Barbieri et al. (2023) suggest shifts in prescribing patterns favoring ozenoxacin for localized infections, reflecting growing clinical confidence in its efficacy and safety (Barbieri et al., 2023).

The COVID-19 pandemic significantly disrupted healthcare delivery and research in dermatology, including impetigo care. Reduced patient presentations, delays in clinical trials, and logistical barriers highlighted the need for adaptive healthcare strategies. Gorges et al. (2021) noted an increase in telemedicine and community-based interventions to ensure continuity of care, particularly in underserved areas. These innovations underscore the importance of flexibility in addressing public health challenges (Gorges et al., 2021; Williamson et al., 2017).

In clinical practice, personalized treatment plans are essential. For patients with localized impetigo, topical therapies like ozenoxacin are often the first-line treatment due to their targeted action and favorable safety profile. In contrast, systemic antibiotics are reserved for more severe cases, ensuring effective management while minimizing the risk of resistance. The use of oral co-trimoxazole in low-resource settings exemplifies the importance of cost-effective, accessible solutions that do not compromise care quality (Bowen et al., 2014; Koning et al., 2012; Wren et al., 2018).

Ongoing research is crucial to optimize impetigo management strategies. Head-to-head comparisons of newer treatments like ozenoxacin should be made against established options such as mupirocin and fusidic acid to refine clinical guidelines. The findings of this study emphasize the importance of implementing targeted preventive interventions. Impetigo may be reduced by promoting hygiene through educational campaigns focusing on modifiable practices, especially among high-risk demographic groups. This integrated approach will help address disparities in treatment outcomes and resistance patterns, ultimately improving patient care worldwide (Chamny et al., 2016; Tanus et al., 2014).

A systematic review on impetigo management, particularly focusing on advancements such as ozenoxacin, encounters several notable limitations. A key challenge lies in the heterogeneity of studies. Research often varies in design, population characteristics, disease severity, and outcome measures. This variability complicates direct comparisons across studies and limits the ability to perform comprehensive meta-analyses. Moreover, the availability of high-quality data is limited; many studies are open-label or non-randomized, involving small sample sizes that may introduce biases and diminish the reliability of conclusions. For example, there is a lack of robust head-to-head trials comparing newer treatments like ozenoxacin to standard options such as mupirocin or fusidic acid.

Another significant limitation is the regional variability in antibiotic resistance patterns. Fusidic acid resistance, for instance, is notably higher in some geographical areas, while it remains effective in others. This variability challenges the generalizability of the review's findings, as treatment efficacy can differ based on local resistance profiles. Additionally, most studies tend to focus on pediatric populations, given the higher prevalence of impetigo in children. This focus limits the applicability of findings to adult populations, those with

underlying comorbidities, or immunocompromised patients who may require alternative management strategies.

Topical Antibiotics

Mupirocin is widely regarded as the first-line treatment for localized impetigo; mupirocin is effective against Staphylococcus aureus (including MRSA) and Streptococcus pyogenes. Applied twice daily (bid) for 5 days to treat both bullous and non-bullous impetigo, mupirocin disrupts bacterial protein synthesis by inhibiting isoleucyl-tRNA synthetase. It is highly effective against Staphylococcus aureus and Streptococcus pyogenes but less active against Group D streptococci. Its minimal systemic absorption makes it particularly safe for children and those with mild infections. Topical mupirocin is typically the first-line therapy for localized impetigo, with oral antibiotics reserved for extensive lesions or treatment failure. Options for oral therapy include dicloxacillin, amoxicillin/clavulanate, and cephalexin (D'Cunha et al., 2018; Dallo et al., 2023; Pereira, 2014).

Retapamulin is a semi-synthetic substance developed from the edible mushroom Clitopilus scyphoides. Its antibacterial activity is mediated by specific binding to bacterial ribosomes, which inhibits protein synthesis. It is efficient against S. aureus and S. pyogenes. A pleuromutilin antibiotic, retapamulin, is applied twice daily and offers an alternative for mupirocin-resistant cases. Its unique action on bacterial protein synthesis, coupled with a low risk of cross-resistance, enhances its utility. Retapamulin's effectiveness is comparable to mupirocin, with rapid symptom resolution reported in clinical studies (Pereira, 2014).

In 1962, Godtfredsen et al. isolated fusidic acid from a Fusidium coccineum culture. Fusidic acid inhibits bacterial protein synthesis by disrupting elongation factor G during its translocation to the ribosome, which is involved in peptide elongation via a GTPase. Fusidic acid has demonstrated antibacterial efficacy against gram-positive bacteria, including S. aureus and S. pyogenes. Fusidic acid is a skin antibiotic available in cream or ointment form. It is mainly used in countries outside the U.S., Europe, Australia, and some parts of Asia.1

According to the 2012 Cochrane review, fusidic acid and mupirocin were equally effective in reducing infection severity and recovery time. However, concerns about antibiotic resistance have grown. Topical antibiotics remain preferred for uncomplicated, localized impetigo due to their higher efficacy compared to oral antibiotics. Nevertheless, increasing resistance to agents like mupirocin and fusidic acid has highlighted the need for alternative treatments. Retapamulin, a pleuromutilin antibiotic with bacteriostatic activity, has demonstrated efficacy comparable to fusidic acid and mupirocin, with minimal resistance concerns (Oranje et al., 2007).

Ozenoxacin, a new non-fluorinated quinolone, has strong bacteriostatic and bactericidal activity against Gram-positive pathogens, including MRSA and methicillin-resistant S. epidermidis in adult and pediatric patients aged 2 months and older, applied topically over the affected area two times a day for five days. Ozenoxacin inhibits the enzymes DNA gyrase and topoisomerase IV, which are involved in DNA synthesis in bacteria. This prevents bacterial DNA replication. Its superior efficacy and safety profile, coupled with low systemic absorption and resistance potential, make it a promising alternative for impetigo management.27 Despite its benefits, gaps remain in determining the optimal topical treatment for impetigo. Practitioners must weigh therapy duration against resistance patterns, emphasizing the importance of local surveillance data.28 In conclusion, while impetigo is largely manageable with topical therapies, the rise of antibiotic-resistant pathogens necessitates vigilant prescribing practices and the development of novel antibacterial agents.

Topical antibiotics are the treatment of choice for most cases of impetigo. Systemic antimicrobial agents are indicated when there is involvement of deeper structures (subcutaneous tissue, muscle fascia), fever, lymphadenopathy, pharyngitis, infections near the oral cavity, infections on the scalp and/or numerous lesions. The first-generation cephalosporins, such as

cephalexin and cefadroxil, may be used, since no differences between them were found in a meta-analysis (Pereira, 2014).

Conclusion

This systematic review highlights the evolving landscape of impetigo management, particularly emphasizing the role of newer treatments like ozenoxacin. Given its broad-spectrum antibacterial activity, minimal resistance concerns, and favorable safety profile, current evidence supports ozenoxacin as a promising alternative to standard therapies such as mupirocin and fusidic acid. However, traditional treatments remain effective in many regions, especially in areas with low resistance rates. In conclusion, while progress in impetigo management is evident, there is a pressing need for more robust, long-term, and geographically diverse research to optimize treatment strategies. Addressing these gaps will ensure that advancements like ozenoxacin can be integrated into global treatment guidelines, improving outcomes for diverse patient populations.

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