Review

Emerging Treatment Strategies for Impetigo in Endemic and Nonendemic Settings: A Systematic Review

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ABSTRACT

Purpose: Impetigo affects approximately 162 million children worldwide at any given time. Lack of consensus on the most effective treatment strategy for impetigo and increasing antibiotic resistance continue to drive research into newer and alternative treatment options. We conducted a systematic review to assess the effectiveness of new treatments for impetigo in endemic and nonendemic settings.

Methods: We searched PubMed, MEDLINE, CINAHL, Web of Science, and Embase via Scopus for studies that explored treatments for bullous, nonbullous, primary, and secondary impetigo published between August 1, 2011, and February 29, 2020. We also searched online trial registries and hand-searched the reference lists of the included studies. We used the revised Cochrane risk of bias (version 2.0) tool for randomized trials and the National Heart, Lung, and Blood Institute for nonrandomized uncontrolled studies to assess the risk of bias.

Findings: We included 10 studies that involved 6651 participants and reported on 9 treatments in the final analysis. Most clinical trials targeted nonbullous impetigo or did not specify this. The risk of bias varied among the studies. In nonendemic settings, ozenoxacin 1% cream appeared to have the strongest evidence base compared with retapamulin and a new minocycline formulation. In endemic settings, oral co-trimoxazole and benzathine benzylpenicillin G injection were equally effective in the treatment of severe impetigo. Mass drug administration intervention emerged as a promising public health strategy to reduce the prevalence of impetigo in endemic settings.

Implications: This review highlights the limited research into new drugs used for the treatment of impetigo in endemic and nonendemic settings. Limited recent evidence supports the use of topical ozenoxacin or retapamulin for impetigo treatment in nonendemic settings, whereas systemic antibiotics and the mass drug administration strategy have evidence for use in endemic settings. Given the troubling increase in resistance to existing treatments, there is a clear need to ensure the judicious use of antibiotics and to develop new treatments and alternative strategies; this is particularly important in endemic settings. PROSPERO identifier: CRD42020173042. (*Clin Ther.* 2021;43:986–

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INTRODUCTION

Impetigo is a highly contagious, superficial bacterial skin infection that most commonly occurs in children 2 to 5 years of age typically because of damage to the cutaneous barrier.[1,2] It is classified as a primary infection with direct bacterial invasion or a secondary infection (eg, in association with scabies or eczema).[3–5] Impetigo clinically presents as a bullous or nonbullous type.[4] Nonbullous impetigo is the most common form of impetigo and is caused by *Staphylococcus aureus* in 80% of cases and group A β-hemolytic *Streptococcus* alone or in combination with *S aureus* in the remainder.[1,4] Bullous impetigo is almost exclusively caused by *S aureus*.[1,6]

An estimate of 162 million children globally experience impetigo at any given time.[7] There is a disproportionately high prevalence reported in Indigenous Australian children.[7] Almost half of the Aboriginal children (45%) in the northern regions of Australia have impetigo at any time, equaling approximately 16,000 children.[7] An estimated approximately two-thirds of these children are treated for impetigo before their first birthday.[8] The risk factors for impetigo include young age, crowding, close contact, and warm humid conditions.[9] When left untreated, impetigo can lead to severe skin, soft tissue and bone infections, and sepsis, which contribute to a 5% to 10% case fatality rate.[10] Impetigo also leads to serious sequelae, including glomerulonephritis and potentially acute rheumatic fever and rheumatic heart disease.[10]

Management strategies of impetigo vary, depending on whether the condition is localized or widespread across the body, the resistance patterns to causative agents, and the guidelines in place. Bullous or nonbullous impetigo with a limited number of lesions is typically treated with topical antibiotics, such as mupirocin or retapamulin.[11] When impetigo is associated with numerous lesions, as in remote communities where impetigo is considered endemic, oral (such as dicloxacillin, cephalexin, and trimethoprim-sulfamethoxazole) or intramuscular (benzathine penicillin G) antibiotics are recommended.[10–12]

The rapid emergence and spread of antibiotic-resistant bacteria, including methicillin-resistant *S aureus* (MRSA), pose serious threats to public health.[13,14] The increase in antimicrobial resistance to topical mupirocin and fusidic acid[1,15–18] has had adverse consequences for individuals and communities, necessitating the development of newer treatment alternatives or strategies to promote the judicious use of existing drugs. There are a variety of treatments for impetigo with varying level of evidence, which range from topical and oral treatment antibiotics to disinfectants and herbal therapies.[6,19] The previous major systematic review on impetigo treatments was published in 2012 by Koning et al[19] and included studies published until 2011. The review concluded that topical mupirocin and fusidic acid are equally or more effective than oral treatment and highlighted the lack of evidence to support disinfection for impetigo management.[19] Another focused review published in 2019 explored treatment strategies for commonly encountered infectious skin conditions, including impetigo in endemic settings, and covered a broad range of interventions, including complementary or alternative therapies, hand washing and hygiene practices, and other public health interventions.[20] In recent years, newer treatments have emerged, and an updated review of existing treatments and strategies could better inform clinical practice and future research. Therefore, this systematic review aims to examine the most recent evidence (since 2011) related to newer treatment options and strategies to reduce the burden of impetigo in endemic and nonendemic settings.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered in PROSPERO (CRD42020173042).

Search Strategy

We searched PubMed, MEDLINE via EBSCOhost, CINAHL via EBSCOhost, Web of Science, and Embase via Scopus for studies published between August 1, 2011, and February 29, 2020. The search duration was restricted to this period because of the review published in 2012. Keywords used in the search included *impetigo* OR *skin sores* OR *school sores* OR *pyoderma* AND

treatment OR *drug therapy* OR *staphylococc** OR *streptococc** and *skin and infection**. A detailed search strategy is available in the Appendix.

ELIGIBILITY SCREENING AND STUDY SELECTION

This systematic review included randomized controlled trials (RCTs), prospective studies, and pre-post interventional studies that assessed the effect of drugs on bullous or nonbullous impetigo or the prevalence of impetigo after intervention. Mass drug administration (MDA) studies that evaluated impetigo as an outcome were also included. Studies targeting participants of any age in primary or secondary care settings were included. Case reports or studies that did not report the clinical success rate, conference or dissertation abstracts without full texts, and other *in vitro* and *in vivo* studies were excluded. The articles identified based on the key word search were exported to Covidence[21] for study screening. Two reviewers (G.G. and W.T.) independently screened the articles using titles, abstracts, and full texts to identify studies that met the inclusion criteria. Whenever inconsistencies arose between the reviewers, a consensus was sought through the involvement of a third reviewer (J.T.).

Data Extraction and Synthesis

Study characteristics, such as setting, design, and participant demographic details, were extracted. Population included authors, journal, study year, location, setting, study aims, and demographic characteristics. Intervention included treatment agent, intervention type, frequency, dose, duration, and any cointervention. Outcomes included clinical cure (or improvement of impetigo reported 7–14 days after treatment), impetigo prevalence before and after MDA, and secondary outcomes and results (including microbiologic responses, adverse effects, and user satisfaction). Study design included participants (studies targeting individuals with a diagnosis of bullous or nonbullous impetigo, identified by a health care professional), inclusion and exclusion criteria, sample size, comparison groups, and randomization. The data extracted were presented using a textual narrative synthesis in a tabular format (Table I). Meta-analysis was not performed because of the heterogeneity of studies.

Quality Appraisal

The Cochrane risk of bias (version 2.0) assessment tool[22] was applied for RCTs. Two reviewers independently completed the assessment, with disagreements resolved via discussion. The risk of bias for non-RCTs was assessed using a tool by the National Heart, Lung, and Blood Institute.[23]

RESULTS

The search resulted in a total of 4757 titles. After removal of duplicates and studies not relevant to our objectives, 47 studies were assessed for eligibility, and 10 were included in the final data synthesis (Figure 1).[12,24–32]

Characteristics of the Included Studies

Overall, 10 studies (7 targeted and 3 community MDA interventions) were included in this review[12,24–32] (Table I).

Studies in Nonendemic Settings

The clinical studies comprised 4 RCTs[25,26,28,29] that evaluated the efficacy and tolerability of ≥1 drugs and 2 non-RCTs.[24,27] The clinical studies were conducted in the United States, Israel, and Spain, and 2 studies[26,28] targeted a multinational cohort, including the United States, Russia, South Africa, Germany, Romania, Spain, and Ukraine.

Studies in Endemic Settings

Four studies were conducted in endemic settings. Of these, 1 clinical study was conducted in Australia,[12] and 3 MDA interventions were conducted in Fiji[32] and the Solomon Islands.[30,31] Since the last systemic review on impetigo treatments in 2012, the Australian study[12] is the only non-MDA RCT (open-label, randomized, controlled, noninferiority trial) published in an endemic setting that compared oral administration of short-course cotrimoxazole with intramuscular benzathine benzylpenicillin. The other 3 were MDA studies, including 2 randomized interventions[30,32] and 1 pre-post interventional study.[31] The MDA studies, other than the one by Marks et al,[30] were designed to assess the impact of MDA measures on scabies as the primary outcome, and impetigo was only examined as a secondary outcome; none assessed impetigo alone.

A clinical diagnosis of impetigo was made in all the studies included in this systematic review. Laboratory

Table I. Characteristics of included studies.

Study	Study Setting and Country of Study	No. of Patients/Mean (SD) Age, y	Study Design	Inclusion Criteria	Diagnosis Method	Type of Impetigo and/or Causative Organism	Intervention Description, Including Treatment Frequency		Key Outcomes	Results	AdverseEvents	User Satisfaction/ Preferences/ Attitudes	Treatment Adherence	Strengths and Limitations
							Test	Comparator						
Studies from nonendemic settings														
Bohaty et al,[22] 2014	Outpatient dermatology clinic in the United States	38/ 18.5 (25.7)	Prospective, nonrandomized, uncontrolled center trial	People aged 9 months to 98 years with impetigo, folliculitis, or minor soft tissue infection	Patients received an initial clinical and microbiological evaluation at the clinic during the baseline visit	• *Staphylococcus aureus*: 26 (72.2%); • MRSA: 7 (19.4%); MSSA: 19 (52.8%); • *Streptococcus pyogenes;* 2 (5.5%); other occus species: 1 (2.8%); coagulase-negative *Staphylococcus;* 7 (19.4%); no pathogen: 2 patients	Retapamulin ointment 1% twice daily for 5 days	Not applicable	• Primary outcome: clinical response success/failure at follow-up in the efficacy population with MRSA; secondary outcomes: microbiologic responses in patients were culture positive for any species of bacteria; comparison of wound size from baseline to follow-up; comparison of signs and symptoms from baseline to follow-up; and the tolerability of treatment	• 5 of 7 Patients had clinical success and 2 of 7 had clinical improvement at 7 day; 5 of 7 had presumed microbiological eradication, whereas 2 of 7 had presumed microbiological improvements; wound size decreased significantly by 71.3% at follow-up; overall success rates were favorable for clinical, microbiologic, and therapeutic responses, with values of 66%, 97%, and 69%, respectively	• 10.5% (4/38 patients) experienced mild and moderate AEs	Not reported	Not reported	• Wide range of age and ethnicities included in the study; safety profile appears favorable given the low number of adverse events; small sample size and uneven age distribution; no placebo comparator included

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Table I. (*continued*)

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Chamny et al,[24] 2016	3 Outpatient clinics in Israel	32/ 5.2	Randomized, parallel-group, double-blind, comparative clinical trial	Healthy people aged ≥2 years with a clinical diagnosis of 2–7 lesions of pure impetigo, impetigo contagiosa, or uncomplicated blistering impetigo	Clinical diagnosis	• *S. aureus*: 21 (65.6%); *S pyogenes*: 13 (40.6%); MRSA: 11 (34.4%); other: 5 (15.6%); nonbullous impetigo (75%)	Minocycline 1% foam twice daily for 7 days	Minocycline 4% foam twice daily for 7 days	• Primary outcome: clinical cure at the end of treatment, defined as having a minimum of 80% cured lesions; secondary outcome: clinical cure at follow-up and clinical success at each study visit; bacteriologic success; individual efficacy parameters; clinical assessment of impetigo-related signs and symptoms	Clinical cure was achieved by 57.1% and 50.0% in the 1% and 4% minocycline groups, respectively, at the end of treatment; clinical success occurred in 81.3% and 78.6% of 1% and 4% groups, respectively, following 3 days of treatment in 92.3% and 100% of the respective patients at the end of treatment and in 100% in both groups at follow-up	• Adverse events occurred in 6 patients treated: 2 in the 1% group and 4 in the 4% group	>90% Reported treatment satisfaction with the 1% minocycline	High treatment adherence rate of 85.5% for 1% minocycline and 75% for 4% minocycline	• Strengths: randomized nature of study, high adherence to treatment; multicenter recruitment; limitations: only children included in the study; small sample

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Gropper et al,[25] 2014	27 Outpatient clinics in 5 countries	464/ 16.1 (16.66)	Phase III, randomized, double-blind, multicenter study	Patients aged ≥2 years with bullous or nonbullous impetigo, a total SIRS score of at least 8 and a total affected area of 1–100 cm^2 with surrounding erythema not exceeding 2 cm from the edge of the affected area	Through swabbing and gram staining, pathogens were identified based on bacterial cultures in a Laboratory.	• Bullous impetigo: 96 (20.7%); nonbullous impetigo: 368 (79.3%); *S aureus*: 285 (61.4%); *S pyogenes:* 214 (46.1%)	Twice daily 1% ozenoxacin cream for 5 days	Twice daily placebo Cream for 5 days OR Twice daily retapamulin 1% ointment for 5 days	• Primary outcome: clinical response (success or failure) in the intention-to-treat clinical population at the end of therapy (visit 3; days 6–7); secondary outcome: clinical response at days 2 (days 3–4) and 4 (days 10–13); microbiological response according to the baseline susceptibility profile at visits 2, 3 and 4; microbiological response at visit 4	Ozenoxacin was superior to placebo (success rates of 34.8% vs 19.2%; P = 0.003). at the end of therapy; retapamulin was also significantly superior to placebo (37.7% vs 19.2%; $P < 0.001$); microbiological success was 70.8% for ozenoxacin and 38.2% for placebo after 3–4 days and 79.2% vs 56.6% after 6–7 days; ozenoxacin produced more rapid microbiological clearance than retapamulin	• Adverse events occurred in 35 patients; nasopharyngitis (n = 4 in ozenoxacin group; n = 4 in retapamulin group); rhinitis (n = 3 in retapamulin group); application site pain and irritation (n = 2 in retapamulin group)	Not reported	Treatment adherence was 99.6% in ozenoxacin vs 97.9% in placebo and 100.5% in retapamulin	• Strengths: strong randomization process performed by an independent statistician using an interactive web response system; multicentered trial; placebo controlled

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Gropper et al,[26] s2014	Spain	46	Phase I, open-label study	People aged 2 months to 65 years with nonbullous or bullous impetigo; SIRS score of at least 8; a total affected area of ≤100 cm^2 with surrounding erythema not extending >2 cm from the edge of any affected area	Clinical diagnosis	• Bullous Impetigo – 2 (4.30%) • Non-Bullous Impetigo – 43 (93.5 %)	Single 0.5-g dose of ozenoxacin 1% cream on day 1 followed by twice-daily application for 4 days (every 12 h) and a final single dose on day 6	Not applicable	• Primary outcome: systemic absorption of ozenoxacin 1% cream after repeated topical applications in patients with impetigo; secondary outcome: assess the clinical response, as well as tolerability) of ozenoxacin 1% cream	• Decrease in the mean skin lesion surface area was observed from visit 1 through to visit 6 in all 4 patient groups treated with ozenoxacin 1% cream; 22 of 45 patients (48.9%) were assessed as cured after 5 days; all other patients (23 of 45 patients) had a clinical improvement	• 25 Mild (n = 22) or moderate (n = 3) adverse events were reported in 21 of 46 patients	Not reported	Treatment adherence: 93.5% with ozenoxacin	• Limitation: lack of placebo/comparative treatment; small sample size

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Rosen et al,[27] 2018	36 Outpatient clinics in 6 countries	412/ 18.6 (18.3)	Randomized clinical trial, multicenter, double-blind, vehicle-controlled, parallel group, Phase III study	People aged ≥2 months with impetigo, a total SIRS score of ≥3; the total affected area at baseline measured from 2 to 100 cm^2, and for patients >12 years of age, the total area could not exceed 2% of the body surface area	Clinical diagnosis	• S. Aureus – 223 (54.3%) • S. Pyogenes- 39 (9.46%) • Other Pathogens – 147 (35.9%)	Twice daily 1% ozenoxacin cream	Twice daily placebo cream	• Primary outcome: clinical response at the end of therapy in the intention-to-treat clinical population; secondary outcome: clinical response at visit 3, or clinical; bacteriologic response at visits 2 and 3; therapeutic response (combined clinical and microbiological response) at visit 3	• Ozenoxacin had superior clinical success compared with placebo, which was evident after 5 days of therapy (112 of 206 [54.4%] vs 78 of 206 [37.9%]; $P = .001$); ozenoxacin also had superior microbiological success compared with placebo after 2 days of therapy (109 of 125 [87.2%] vs 76 of 119 [63.9%]; $P = .002$)	• Adverse events in 15 of 411 patients: 8 in the ozenoxacin group and 7 in the placebo group; rosacea and seborrheic dermatitis in ozenoxacin group; dermatitis and skin tightness in placebo group	Nor reported		• Strength: central randomization via an interactive web response system was used to allocate patients to treatment groups, stratified by age subset, to ensure a 1:1 distribution and avoid selection bias; limitations: small number of children with bullous impetigo included; data in children <6 mo of age are also limited

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Tanus et al,[28] 2014	Patients recruited from 36 study centers in the United States	410	Randomized, double-blind, double-dummy, multicenter, comparative study	Patients ≥2 months of age with impetigo (bullous or nonbullous) suitable for treatment with a topical antibiotic and not requiring surgical intervention; a total SIRS score of ≥8	Clinical diagnosis and bacteriologic culture testing	• Bullous Impetigo – 51 (12.4%) • Non-Bullous Impetigo – 74 (18%) • S. Aureus – 216 patients. • S. Pyogenes – 31 (10.5%) • Other Streptococcus Species – 8 (2.7%) • Other Gram -Positive Pathogens – 3 (1%) • Other Gram-negative pathogens – 38 (12.8%)	1% Retapamulin ointment twice daily, at 10- to 12-h intervals, for 5 days. OR linezolid dosed 2 or 3 times daily, depending on patient age, for 10 days	Placebo ointment or oral placebo	• Primary outcome: clinical response (success/failure) at follow-up in patients with MRSA at baseline (per-protocol population); secondary outcome: clinical and microbiologic response and outcome at follow-up and end of therapy; therapeutic response at follow-up	• Clinical success rate at follow-up was significantly lower in the retapamulin vs the linezolid group (63.9% [39/61] vs 90.6% [29/32]; difference in success rate (26.7%; 95% CI, 45.7–7.7)	• Adverse events were recorded for 26.2% (70/267) of patients in the retapamulin group and 30.7% (42/137) of patients in the linezolid group; serious adverse events were reported for 8.6% of patients with a reported adverse effect in the retapamulin group (2 cellulitis, 1 patient each with abscess) • 7.1% of patients with adverse events in the linezolid group (1 patient each with hypoglycemia, hyponatremia, and hypersensitivity)	Treatment preference: 63.9% (188/294) preferred the topical medication versus the oral medication, whereas 17.3% (51/294) had no preference	• Strengths: randomization was center based, stratified by age and performed via automated telephone system; block size remained confidential; study was blinded until after all patients had received a clinical evaluation at visit 5; multicenter study; limitations: retapamulin and linezolid had different routes of administration and different treatment durations (5 vs 10 days), which may have biased the study in favor of linezolid treatment; the definition of clinical success may not represent clinical practice, and the study was not powered to show statistical outcomes between treatment groups; 15.4% and 14.6% of patients in the retapamulin and linezolid groups, respectively, had exposure to anti-infective medications, such as cotrimoxazole

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Studies from endemic settings (including MDAs)														
Bowen et al,[23] 2014	Remote community setting In Australia	508	Open-label, controlled, randomized trial	Indigenous Australian children aged 3 months to 13 years with impetigo	A manual screening in schools by trained nurses; other participants were referred from community health care clinic or recruited by door-to-door visits of households	• Non-bullous impetigo (100%)	Cotrimoxazole twice daily for 3 days (4 mg/kg plus 20 mg/kg per dose) OR once-daily cotrimoxazole for 5 days (8 mg/kg plus 40 mg/kg per dose)	Benzathine benzylpenicillin intramuscular injection	• Primary outcome: treatment success at day 7 according to digital image scoring; secondary outcomes: treatment success at day 2 according to digital images; clinical success at days 2 and 7 according to clinical assessment by nurses; resolution of sores from the whole body at day 7; detection of *S aureus* or *S pyogenes* on days 0, 2, and 7; antibiotic susceptibility of *S aureus* and *S pyogenes*; nasal carriage of *S aureus* on days 0 and 7	Treatment was successful in 133 children (85%) who received benzathine benzylpenicillin and 283 (85%) who received pooled cotrimoxazole (absolute difference 0.5%; 95% CI, −6.2% to 7.3%), showing noninferiority of cotrimoxazole within a 10% margin; results for secondary outcomes were not different for a 3-day twice-daily and a 5-day once-daily cotrimoxazole regimens vs benzathine benzylpenicillin (86%; absolute difference, 0.1%; 95% CI, −6.5% to 6.5%)	• Adverse events occurred in 54 participants; 49 (91%) were from benzathine benzylpenicillin, whereas the remaining 5 were from cotrimoxazole group	Not reported	Excellent treatment adherence with directly observed oral antibiotics (>95%)	• Strengths: randomized, controlled design; low attrition; high adherence; similar baseline characteristics between treatment groups; multicenter recruitment; and an objective, blinded outcome assessment; limitations: research nurses and participants were unmasked to treatment allocation and no long-term follow-up was done to assess for complications

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Marks et al,[29] 2018 (MDA intervention)	Remote community setting in the Solomon Islands	1291/25	Community, randomized, open-label study	Not Applicable	Clinical diagnosis; impetigo lesion swabs were collected at baseline and 3 and 12 months to detect antimicrobial resistance; swabs were streaked onto horse blood agar	• *S aureus*: 80%; *S pyogenes:* 56%	Single-dose oral azithromycin MDA, 30 mg/kg, maximum 2 g with ivermectin, single dose. 200 g/kg.	Ivermectin single dose, 200 g/kg	• Primary outcome: prevalence of impetigo at baseline and 12 months; secondary outcome: macrolide resistance in each study arm at base line, 3 mo, and 12 mo	• At 12 mo, prevalence of impetigo decreased from 10.1% to 2.5% in the ivermectin-only group and from 12.1% 3.3% in the combined treatment group; at 3 mo, 53% of the *S aureus* strains were macrolide resistant in the combined treatment arm, but no resistant strains were detected at 12 mo; no macrolide resistance was detected among streptococci in either arm at any of the 3 time points	• Not reported	Not reporter	Not reported	• Limitations: sample size too small to draw firm conclusions; swabs were not taken from every individual or from every lesion on an individual; study was not blinded; diagnosis of impetigo was made on clinical grounds alone by a single experienced physician

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Romani et al,[30] 2019 (MDA intervention)	Remote community setting in the Solomon Islands	Baseline: 1399; 12 months: 1261	Prospective, single-arm, before and after, community intervention study	Not Applicable	Clinical diagnosis by study coordinator and nurses	• Not reported	Single dose of 20 mg/kg of azithromycin MDA with 2 doses of oral ivermectin, 200 g/kg 7–14 days apart	Not applicable	• Primary outcome: the prevalence of scabies and impetigo in the 10 randomly selected villages at 12 mo compared with 10 different randomly selected villages at baseline; secondary outcome: comparison of the number of all-cause outpatient attendances at government clinics before and after MDA	• At baseline, 1399 (84.2%) of 1662 people living in the first 10 villages had their skin examined, of whom 347 (24.8%) had impetigo; at 12 mo after MDA, 1261 (77.6%) of 1625 people had their skin examined, of whom 81 (6.4%) had impetigo (relative reduction, 74%; 95% CI, 63.4%–84.7%); when comparing the 3-month period before MDA with the 3 mo after, a substantial decrease in outpatient attendance was observed (55.8%; 95% CI, 54.8%–56.7%)	• Not reported	Not reported	Not reported	• Strength: to allow for estimates of prevalence to be generalized across population; 10 different villages were assessed at 12 mo after MDA; limitations: given this is a nonrandomized pragmatic before-and-after design in a large-scale setting, it is difficult to rule out the contribution of other factors

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							Test	Comparator						
Romani et al,[31] 2015 (MDA intervention)	Remote community setting in Fiji	Baseline: 2051; 12 months: 1782	Prospective, before and after, community intervention study	Not applicable	Clinical diagnosis by nurse	• Not Reported.	MDA of 1 dose of permethrin cream followed by a second dose 7–14 days apart if scabies observed at baseline OR MDA of oral ivermectin, 200 g/kg	Standard care group: 1 dose of topical permethrin to affected people and their contacts with a second dose after 14 days if symptoms persisted	• Primary outcome: prevalence of scabies and impetigo from baseline to 12 mo	• Prevalence of impetigo significantly reduced in the ivermectin group: 24.6% to 8.0% (relative reduction, 67%; 95% CI, 52%–83%); prevalence in the standard care group: declined from 21.4% to 14.6% (relative reduction, 32%; 95% CI, 14%–50%); the prevalence decreased from 24.6% to 11.4% in the permethrin group (relative reduction, 54%; 95% CI, 35%– 73%)	• Adverse events were mild and were reported more frequently in the ivermectin group than in the permethrin group (15.6% vs 6.8%)	Not reported	Not reported	• Limitations: as an MDA, relied on clinical diagnosis (I believe in all cases by a single examiner)

MDA = mass drug administration; MRSA = methicillin-resistant *Staphylococcus aureus;* MSSA = methicillin-susceptible *Staphylococcus aureus*; SIRS = skin infection rating scale.

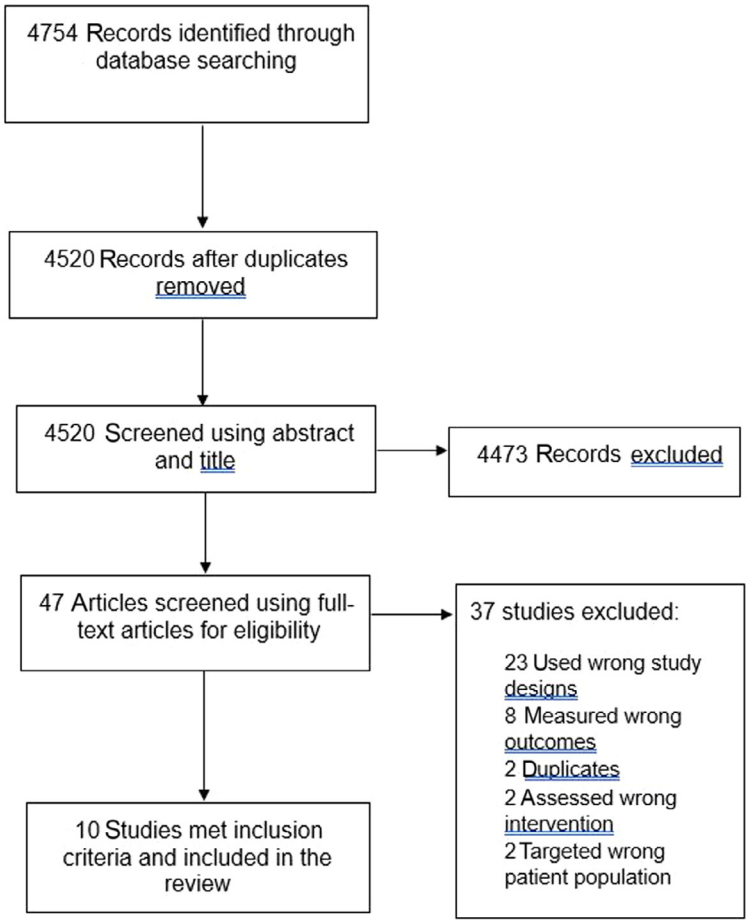

Figure 1. The Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

testing, such as a bacterial culture, was included in 6 studies to determine the causative agent of impetigo.[24–26,28–30]

Efficacy and Tolerability of Interventions

Studies from Nonendemic Settings

Topical Ozenoxacin. Three clinical studies evaluated the efficacy and tolerability of 1% topical ozenoxacin.[26–28] Of these, 2 RCTs[26,28] that involved 723 participants provided suitable data for pooled analysis, revealing superior efficacy of ozenoxacin over placebo (relative risk = 1.52; 95% CI, 1.25–1.85) when applied twice daily for 5 days.

The first study by Gropper et al[26] recruited 464 individuals predominantly with nonbullous impetigo (79%) from 27 outpatient clinics in 5 countries. Ozenoxacin was superior to placebo in terms of clinical efficacy (defined based on changes in skin infection rating scale [SIRS] scores at day 6–7) after 5 days of application (35% vs 19.2%; $P = 0.003$). The active control (topical retapamulin) in this study had slightly greater clinical efficacy than ozenoxacin (38%). The microbiological success (ie, absence of the pathogen after 6–7 days) was 79% in the ozenoxacin group compared with 57% for placebo ($P < 0.0001$). Retapamulin, despite being effective in microbiological clearance, was significantly slower in terms of this effect than ozenoxacin (60% vs 75% for retapamulin vs. ozenoxacin after 3–4 days; $P = 0.0087$). Treatment adherence was high in all groups. A total of 35 patients reported adverse effects, such as nasopharyngitis, rhinitis, and application site pain and irritation, with most of the adverse effects reported by those treated with retapamulin.

The second study involving ozenoxacin (n = 412) targeted patients with *S aureus* infection (54%) and was also a multinational study conducted across 6 countries.[28] After 5 days of twice-daily treatment, there was a higher clinical success (cure of impetigo) among those treated with ozenoxacin compared with placebo (54% vs 38%; $P = 0.001$). Minor adverse events were reported in 4% of people taking ozenoxacin as opposed to 3% in the placebo group, including rosacea and seborrheic dermatitis in the ozenoxacin group and dermatitis and skin tightness in the placebo group.

The third study on ozenoxacin was a Phase I open-label trial that primarily aimed to establish the bioavailability and tolerability of the drug in 46 individuals.[27] Overall, 94% of the individuals had nonbullous impetigo and were treated with a single 0.5-g dose of 1% ozenoxacin cream on the first day, twice-daily application for 4 days, and a single dose on day 6. On follow-up, nearly half (49%) of participants were clinically cured from impetigo (based on a reduction in the SIRS score from baseline), with 51% of the individuals demonstrating clinical improvement. Overall, 22 mild adverse events were reported in 46% of participants, and there were 3 moderate adverse events: anemia, tympanic membrane perforation, and superficial thrombophlebitis.

Retapamulin. The first study on retapamulin was a double-blind, comparative RCT that compared 1% retapamulin applied twice daily for 5 days with oral linezolid (10 mg/kg for children aged <5 years and 600 mg/kg for those aged >12 years) dosed 2 to 3 times daily for 10 days.[29] It included 410 patients with impetigo as well as patients with secondarily infected wounds and lacerations. Clinical success (defined as cure from impetigo caused by MRSA [ie, based on microbiological testing] or clinical improvement) was significantly higher in the linezolid group (84.2% vs 57%), with a −27% difference in success rate (95% CI, −46.0% to −8.7%). Frequency of adverse events were comparable for the 2 groups (31% and 27%, respectively). Treatment acceptability was higher for retapamulin, with 64% reporting a preference of the topical application over oral linezolid.

The second retapamulin study was a prospective, single-center non-RCT of 35 patients that evaluated the efficacy of retapamulin[24] for treatment of impetigo, including impetigo caused by MRSA (n = 7). After treatment with retapamulin twice daily for 5 days, 5 of 7 patients had clinical success, whereas 2 of 7 had clinical improvement at day 7. The wound size of impetigo lesions had also decreased significantly by a mean of 71% at follow-up. Retapamulin was found to have a favorable safety profile, with only 11% of the patients having mild-to-moderate adverse events, such as burning sensation at the application site, cough, furuncle, or upper respiratory tract infection, with no serious adverse effects reported.

Minocycline. A study conducted in outpatient clinics in Israel compared the efficacy of 1% minocycline foam twice daily for 7 days with the 4% minocycline foam formulation.[25] In this RCT, the main causative agent for impetigo was also *S aureus,* with 75% of patients diagnosed with nonbullous impetigo. Clinical cure was achieved in 57% and 50% of people treated with the 1% and 4% minocycline formulations, respectively. The minocycline foam was rated to have moderate-to-excellent satisfaction and usability in 90% of the study participants. The relatively high treatment adherence further emphasized this, with 86% and 75% of participants reporting adherence to the 1% and 4% treatments, respectively.

Studies From Endemic Settings

The first study was an open-label RCT[12] that compared the efficacy of 2 different doses and durations of oral cotrimoxazole (4 mg/kg plus 20 mg/kg per dose given twice daily for 3 days and 8 mg/kg plus 40 mg/kg per dose given for 5 days) with benzathine benzylpenicillin injection. The study was conducted among 508 Indigenous Australian children with severe impetigo and a mean (SD) age of 7 (4.6-9.7) years. Treatment success (defined as healing or improvement of sores based on digital imaging) was 85% for all 3 treatment regimens on day 7. The absolute difference between the benzylpenicillin and the pooled cotrimoxazole group combining both the 3- and 5-day regimens was 0.5% (95% CI, −6.2% to 7.3%), indicating noninferiority of cotrimoxazole. However, a significant difference was found in the number of adverse events reported: –31% in the benzathine benzylpenicillin (mostly injection site pain) and 2% in the combined cotrimoxazole groups. High treatment adherence (>95%) was reported with oral cotrimoxazole. No differences were found in outcomes between the 3- and 5-day cotrimoxazole regimens.

The other studies in endemic settings were MDA interventions in remote community settings.[30–32] The study by Marks et al[30] conducted in Solomon Islands compared single-dose ivermectin (200 g/kg) with a combination of single-dose ivermectin (200 g/kg) and azithromycin (30 mg/kg) in reducing impetigo. The baseline impetigo prevalence was 10.1% and 12.1% in the ivermectin-only and combination treatment groups, respectively. There was no difference in outcome; after 12 months, there was a 75% and 73% relative reduction in impetigo prevalence from baseline, respectively. Another MDA study conducted in the Solomon Islands was a pre-post intervention study that evaluated the tolerability and feasibility of large-scale administration of azithromycin and ivermectin in reducing impetigo prevalence.[31] The whole province was given single-dose azithromycin (20 mg/kg) and 2 doses of ivermectin (200 g/kg) administered 7 to 14 days apart. The study concluded that the coadministration of these drugs led to a 16% absolute reduction in impetigo prevalence and a 74% relative reduction from baseline (24.8%) to 12 months (6.4%) after treatment. There was also a significant reduction in the outpatient clinic presentations for skin sores, abscesses, and boils, when the period 3 months before the MDA was compared with the period 3 months after (51%; 95% CI, 49%-53%).

The third MDA study was conducted in Fiji to compare the impact of an ivermectin-based MDA (given at 200 g/kg) with a guideline-recommended dose of permethrin and a standard care group (involved 1 dose of permethrin to affected people and their contacts with a second dose after 14 days if symptoms persisted).[32] This trial found that the prevalence of impetigo decreased in all 3 treatment groups, with the highest relative reduction observed in the ivermectin group (67%; 95% CI, 52%-83%). Adverse events were more common in the ivermectin than permethrin group (16% vs 7%) and included itchy skin, headache, abdominal pain, joint pain, and dizziness.

Risk of Bias Assessment

The risk of bias varied among the studies and across different domains (Figures 2 and 3). Two clinical trials targeting ozenoxacin 1% cream,[26,28] a trial involving retapamulin,[29] and an ivermectin-based MDA trial[32] had a low risk of bias in the overall assessment as well as in individual domains. The lack of description of the participation rate and an inadequate sample size and/or power description were among the deficiencies identified from the nonrandomized studies.[24,27] Finally, the RCTs on ozenoxacin were industry funded, and the investigators declared affiliations as employees or consultants of the sponsor company.

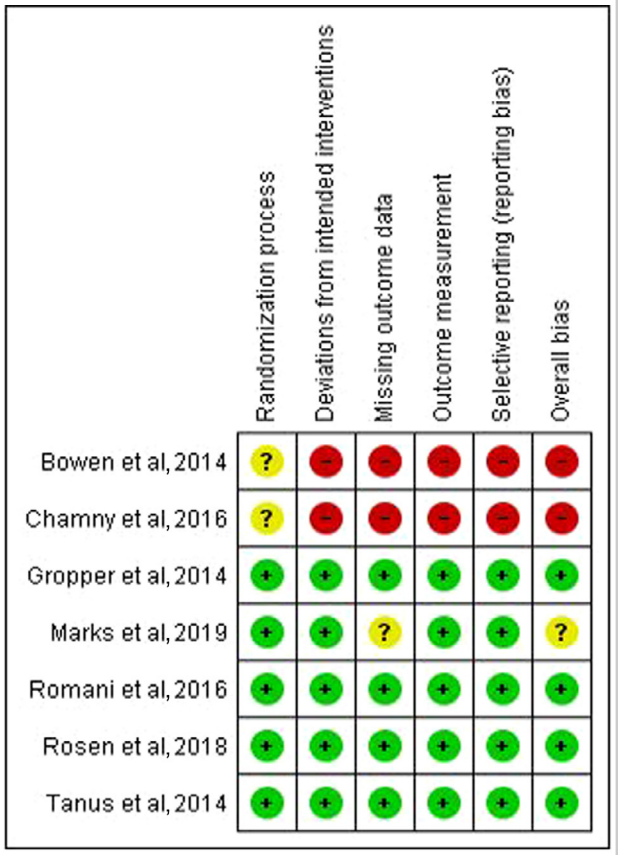

Figure 2. Methodological quality summary.

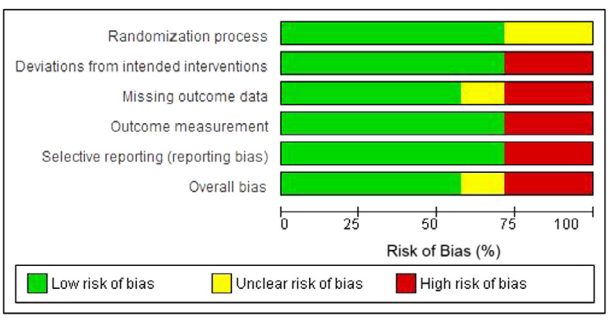

Figure 3. Methodological quality graph, as percentages across all included studies.

DISCUSSION

This study presents an updated review of treatment strategies for impetigo in endemic and nonendemic settings. Although the number of publications on impetigo treatments from the past 10 years is limited, a few treatment alternatives have emerged. In nonendemic settings, topical drugs, such as ozenoxacin, retapamulin, and a new minocycline formulation, have been investigated through RCTs and other clinical studies. Of these, ozenoxacin 1% cream has the strongest evidence base to date, as demonstrated by 2 multinational trials.[26,28] This new nonfluorinated quinolone antibiotic has superior efficacy without significant tolerability concerns when compared with placebo. It possesses potent bacteriostatic and bactericidal properties against gram-positive pathogens such as *S. aureus* and *Streptococcus pyogenes*,[33,34] although the reported clinical success rates are lower than those for retapamulin or sodium fusidate.[29,35,36] This finding could be related to the more stringent criteria used to define clinical success in the ozenoxacin studies.[26,28] Nevertheless, in light of this evidence, the US Food and Drug Administration approved ozenoxacin for use in 2017 for treatment of impetigo in adults and children aged ≥2 months.[37]

Another topical agent investigated in nonendemic clinical settings during the past 10 years is retapamulin, a new topical antibiotic from the pleuromutilin class.[38] It may have similar efficacy with ozenoxacin.[26,28] Retapamulin was approved for use in 2007 for the treatment of impetigo in adults and children from the age of ≥9 months by the US Food and Drug Administration.[39] One RCT[29] comparing 1% retapamulin ointment with oral linezolid found that the clinical success observed with retapamulin was similar to that reported in previous studies[35,36] but that linezolid was superior. A non-RCT clinical study also demonstrated high clinical efficacy of the 1% retapamulin ointment in patients with MRSA.[24] In addition, its tolerability profile has been established in a postmarketing surveillance study.[40] Overall, the evidence supports the use of the drug for the management of impetigo and other uncomplicated bacterial skin infections.[41,42]

Although the burden of impetigo is enormous in endemic settings, the only clinical trial that explored the treatment of impetigo in endemic areas was conducted in 2009 to 2012, targeting Australian Aboriginal children with nonbullous impetigo living in the Northern Territory.[12] The results indicated that oral cotrimoxazole (for 3 or 5 days) was not inferior to benzathine benzylpenicillin injection in treating severe impetigo. Benzathine benzylpenicillin is not recommended in most endemic and nonendemic settings where MRSA is uncommon as first-line treatment of impetigo; rather oral cloxacillin (or equivalent) or cephalexin is the usual recommendation.[11] Nonetheless, this was an important finding in the Australian context given oral treatments have better uptake than injectable forms of treatments. The limited treatment options in this setting indicate the need to ensure the judicial use of existing antibiotics and to find sustainable alternative treatment strategies to tackle the enormous burden of skin infections in these settings.

We evaluated community-based MDA as a strategy to reduce the prevalence of impetigo in endemic settings. We found 3 ivermectin-based MDA interventions that targeted scabies and had an associated benefit in reducing the occurrence of impetigo,[30–32] suggesting that managing causes that underlie impetigo, such as scabies, may be effective in preventing impetigo in such settings. The addition of azithromycin to an ivermectin-based MDA had no apparent benefit in further reducing impetigo, emphasizing the fact that the reduction in impetigo was largely related to the decrease in scabies.[30] On the contrary, there was an increase in macrolide-resistant *S aureus* strains after adding azithromycin to the MDA. This increase is important in view of induction in resistant strains after azithromycin was administered as a regimen for trachoma MDA[43] and highlights the need to carefully assess the use of antibiotics in such programs.

On the basis of the Australian New Zealand Clinical Trials Registry, only 2 registered trials are currently examining the effect of topical antibiotics and antiseptics for the treatment of impetigo. One is a pilot RCT comparing topical hydrogen peroxide or soft white paraffin ointment with mupirocin ointment in the Australian general practice setting (awaiting ethics approval, ACTRN12619001366145p), and the other is an RCT in New Zealand assessing the efficacy of topical fusidic acid and hydrogen peroxide for mild impetigo in school children (ACTRN1261000356460), which is close to completion. Given the size of the burden of impetigo, we believe there is a need for more trials, especially in endemic settings.

Implications for Practice

Considering the significant burden of skin infections, such as impetigo, and the increase in antibiotic resistance, treatment choices are limited, especially in people with impetigo caused by MRSA. Ozenoxacin is highly effective against methicillin-susceptible *S aureus*, MRSA, and *S pyogenes*.[44] Furthermore, it has a superior resistance profile when compared with quinolone antibiotics because of its ability to simultaneously inhibit bacterial DNA gyrase and intravenous topoisomerase, whereas most quinolones bind with only 1 of the 2.[45] It is also relatively less affected by the efflux pumps that some bacteria use for resistance.[45] Overall, ozenoxacin appears to be a promising treatment alternative, although further clinical studies are needed to establish its efficacy and safety across different settings. Retapamulin is recommended by the Infectious Diseases Society of America for treatment of bullous and nonbullous impetigo[11]; however, the emergence of resistant bacterial strains (eg, *S aureus*)[41,46,47] raises potential concerns for long-term clinical usefulness, particularly for impetigo caused by MRSA. The cost associated[6,48] with newly introduced treatments, such as ozenoxacin and retapamulin, as opposed to off-patent products, such as mupirocin and fusidic acid, is too high to be afforded by the most vulnerable communities in resource-limited settings. Their use has been therefore limited to settings such as North America and Europe.

In addition to oral cotrimoxazole or benzathine penicillin G injection, MDA has emerged as an effective treatment strategy for community-based impetigo management campaigns in endemic settings. Ivermectin-based MDA, targeting scabies, had a positive spillover effect on impetigo. In addition, recent works further found the benefit of MDA in reducing the prevalence of impetigo even at 24[49] and 36 months[50] after the intervention, highlighting the long-term relevance of MDA interventions. Nevertheless, additional works are warranted to understand the sustainability of periodic administration, potential antibiotic resistance, and applicability in other endemic contexts outside the Pacific. Finally, the National Institute for Health and Care Excellence (United Kingdom) recommends the use of topical antiseptic (1% hydrogen peroxide) as a first-line option, especially for localized, nonbullous impetigo,[51] although this recommendation is based on low-quality evidence that indicated no significant difference between fusidic acid and hydrogen peroxide.[19,51] A Phase IV trial of the efficacy of topical hydrogen peroxide cream for mild impetigo in school children is currently under way in New Zealand, and the results of this trial are likely to provide additional insight into using topical antiseptics for impetigo treatment.[52] The National Healthy Skin Guidelines (Australia) also recommend washing hands with soap for the prevention of impetigo in resource-limited settings,[53] although this too was based on evidence from 1 RCT published in 2005.[54]

Limitations

The inclusion of a small number of studies with significant heterogeneity precluded a quantitative analysis of the studies. Because of the limited pool of high-quality studies, it was not possible to make treatment recommendations toward clinical guidelines using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. The limited pool of studies is mainly attributed to the lack of development of new drugs for impetigo. Some of the included studies also had small sample sizes.

CONCLUSION

This review identifies a limited evidence base supporting the use of topical ozenoxacin or retapamulin for impetigo treatment in nonendemic settings, whereas systemic antibiotics and the MDA strategy have evidence for use in endemic settings. The rapid emergence of resistant bacteria across the world is endangering the clinical efficacy of antibiotics and highlights the need for judicious use of existing antimicrobials and the development of newer agents. Although the emergence of drugs such as ozenoxacin for impetigo treatment in nonendemic settings is a positive development, the findings are indicative of the clear need for research into finding tolerable and effective alternative treatments. Although further validation is needed, MDA trials targeting scabies maybe useful in reducing impetigo burden in endemic settings during a longer period. Substantial morbidity from impetigo and the resultant sequelae in endemic settings highlight the clear need for less expensive, widely available, and acceptable alternative agents and treatment strategies. In sum, our review calls for well-designed RCTs, including MDA interventions, for the treatment of impetigo in endemic settings.

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study. Garima Gahlawat, Wubshet Tesfaye, Mary Bushell, Solomon Abrha, and Jackson Thomas contributed to the study design. Garima Gahlawat, Wubshet Tesfaye, Mary Bushell, Gregory M. Peterson, Solomon Abrha, and Jackson Thomas participated in literature searches, data acquisition, evidence synthesis and interpretation of findings. Garima Gahlawat, Wubshet Tesfaye, and Solomon Abrha were involved in critical appraisal of the studies. Garima Gahlwat, Wubshet Tesfaye, Mary Bushell and Jackson Thomas drafted the initial manuscript. Garima Gahlawat, Wubshet Tesfaye, Mary Bushell, Solomon Abrha, Gregory M. Peterson, Cynthia Mathew, Mahipal Sinnollareddy, Indira Samarawickrema, Tom Calma, Aileen Y. Chang, Daniel Engelman, Andrew Steer, and Jackson Thomas were involved in critical revision of the work for intellectual content and validation. Wubshet Tesfaye, Mary Bushell, and Jackson Thomas were involved in supervision of the work. All authors reviewed and approved the final manuscript.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2021.04.013.

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