Journal of Chemotherapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/yjoc20

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To cite this article: Luisa Galli, Andrea Novelli, Giuseppe Ruggiero, Stefania Stefani & Anna Belloni Fortina (2022) Pediatric impetigo: an expert panel opinion about its main controversies, Journal of Chemotherapy, 34:5, 279-285, DOI: 10.1080/1120009X.2021.1961185

To link to this article: https://doi.org/10.1080/1120009X.2021.1961185

Published online: 18 Aug 2021.

JOURNAL OF CHEMOTHERAPY
2022, VOL. 34, NO. 5, 279–285
https://doi.org/10.1080/1120009X.2021.1961185

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REVIEW

Pediatric impetigo: an expert panel opinion about its main controversies

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ABSTRACT

Bacterial impetigo is one of the most common skin infection in childhood. Uncertainty exists about its management. This article offers practical suggestions, given the existing evidence and experts' opinions, for correctly managing pediatric impetigo in both hospital and ambulatory settings. Italian physicians with an expertise on pediatric impetigo appointed a working group. A preliminary literature search using Pubmed/MEDLINE and Cochrane Library databases has been performed. The most common controversial issues about pediatric impetigo have been identified and then discussed from multidisciplinary perspectives, according to the 'structured controversy' methodology, a technique discovered and designed to get engaged in a controversy and then guide participants to seek consensus. The expert panels identified 10 main controversies about pediatric impetigo. All of them have been discussed from dermatological, pediatric, pharmacological and microbiological points of view reaching consensus. Each controversy has been revised thus giving practical issues for an easy use in clinical practice. Based on clinical experts' opinion, local epidemiology and literature review this article offers practical suggestions for the management of pediatric impetigo trying to reduce uncertainty in this setting of care.

ARTICLE HISTORY
Received 21 June 2021
Accepted 23 July 2021

KEYWORDS
Pediatric skin infections; impetigo; children; antibiotic resistance; ozenoxacin

Introduction

Worldwide bacterial impetigo is one of the most common pediatric skin infection, in particular among children aged 2–5 years [1], with a peak in tropical areas and low-income settings [2]. Poor hygiene, high humidity, maceration, skin lesions with disruption of the epidermis barrier (e.g., scabies, atopic dermatitis, insect bites), comorbidities and adverse reactions (rash, itch) associated with drugs administration are well-established risk factors for impetigo. Impetigo presents in bullous or non-bullous forms. Non-bullous impetigo accounts for 70% of cases and is caused by *Staphylococcus aureus* and *Streptococcus pyogenes,* which is still the dominant pathogen in tropical areas, while in temperate regions such as USA and Europe *S. aureus* has become the most prevalent aetiological pathogen, with a rising role of community acquired methicillin-resistant *S. aureus* (CA-MRSA) [3]. It is characterized by vesicles progressing to pustules and then to yellow crusts. Bullous impetigo is caused by *S. aureus*, even capable to produce the extracellular exfoliatins A and B [3], and presents with clear or purulent, fluid-filled blisters and shallow erosions. The diagnosis is mainly clinical. Prompt identification of its common or atypical presentations is necessary to differentiate impetigo from other skin conditions with similar presentation including herpes simplex, scabies, and eczema for non-bullous impetigo, or burns, Stevens-Johnson syndrome, and other bullous diseases (e.g., bullous pemphigoid) for the bullous form. Topical treatment (e.g., fusidic acid, mupirocin, ozenoxacin) is recommended in patients with limited extension (<2% of total body surface area) of the disease, while systemic antibiotics (e.g., first-line oral treatment with isoxazolyl penicillins such as flucloxacillin or a first-generation cephalosporin such as cephalexin or cefadroxil or amoxacillin/clavulanic acid) should be recommended in cases with extensive/

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Table 1. The list of the main controversies about pediatric impetigo.

1.	Impetigo caused by methicillin-resistant *Staphylococcus aureus* (MRSA) may be treated only with systemic antibiotic therapy
2.	The association between topical and oral antibiotics represents the adequate treatment of impetigo
3.	Readmission to the community life may occur only after a complete disappearance of cutaneous lesions, in order to reduce the risk of transmission
4.	Ozenoxacin has a potent antimicrobial activity against staphylococci and streptococci, as well as a rapid bactericidal activity and a low risk of antibiotic resistances
5.	The efficacy of topical antibiotics is lower than that of the vast majority of oral antibiotics used for localized impetigo
6.	In order to evaluate recovery, bacteriological results of skin swabs are crucial
7.	The topical antibiotic treatment presents the disadvantage of limited absorption and the risk of developing sensitization
8.	The topical antibiotic treatment is strongly recommended only for children affected by localized non-bullous impetigo
9.	Oral antibiotic treatment presents the disadvantage of major risk of systemic side effects (e.g., gastrointestinal side effects) and development of antibiotic resistances
10.	Topical disinfectants represent the ideal strategy for the treatment of impetigo

multiple lesions, relapses and/or a systemic involvement, poor response to topical treatment as well as in children <1 year of age. An adequate coverage with clindamycin or trimethoprim-sulfamethoxazole should be considered when MRSA is confirmed or suspected [4]. In 13–52% of patients, impetigo spontaneously resolves within 7–10 days without scarring [5,6]. Occasionally, patients will present a systemic involvement with fever and lymphadenopathy; rare complications include cellulitis, osteomyelitis, septic arthritis, pneumonia, sepsis, and acute glomerulonephritis [1]. Complicated impetigo is increasing due to the emergence of MRSA colonization which varies between 0.5 and 15.1% of pediatric population according to the local area. Patients with impetigo often receive inappropriate management, due to misdiagnosis, under- or over-estimation of the disease severity, failure to recognize patient's risk factors, and misuse of diagnostic tools. MRSA colonization and antimicrobial-resistant pathogens increase the challenge of treating pediatric impetigo. As a consequence, a better knowledge about its adequate management is desirable. The present paper aims at providing a practical guide on the best practice for appropriately managing pediatric impetigo, with particular emphasis on its main controversies.

Materials and methods

After a preliminary virtual meeting held in July 2020, an expert Italian panel including clinicians from several areas of expertise (pediatrics, infectious diseases, dermatology, pharmacology and microbiology) identified the main controversies about pediatric impetigo. A virtual first round on the 10 main controversies identified by the panel collected the pros and contras arguments on each item. All of them have been discussed from multidisciplinary points of view reaching consensus, according to the 'structured controversy' methodology, during a final virtual meeting held in November 2020. Participants decided to draft an expert opinion paper about the main controversies of pediatric impetigo, according to their independent suggestions and clinical experiences, as well as to evidence-based practices and literature review. A preliminary literature search using Pubmed/MEDLINE and Cochrane Library databases has been performed. Articles pertaining to the topic of interest published until November 2020 have been identified. English language restriction was applied. The paper aims at reaching consensus on the main controversies of pediatric impetigo in order to try to improve its management thus reducing inappropriate antibiotics use and so, antibiotic resistances. Total agreement among participants was needed in order to reached consensus.

Results

The expert opinion panel identified the main controversies about pediatric impetigo, listed in Table 1. Experts' final consensus is reported for each controversy.

Impetigo caused by methicillin-resistant Staphylococcus aureus (MRSA) may be treated only with systemic antibiotic therapy

When MRSA aetiology is suspected or confirmed, systemic antibiotic therapy is necessary in cases of recurrent impetigo (two or more relapses), widespread/multiple lesions (>2% of total body surface area), bullous impetigo, complications (e.g., cellulitis), poor response to topical treatment, nasal colonization, availability of drugs not registered by age group, congenital or acquired immunodeficiency or other comorbidities (e.g., tumors) as well as in newborns and infants. As a matter of fact, panel's opinion was that age <1 year of age does not represent an absolute criterion for the use of systemic antibiotics, however impetigo in infants younger than 2 months could be associated with a colonization by a maternal strain and mother-child pair decolonization should be considered. Conditions which can be treated without using systemic antibiotic therapy are the following: impetigo with a limited extension (small number of lesions confined to a single anatomical area not exceeding 2% of total body surface area), first episode

or first relapse of impetigo (in particular in cases with localized impetigo previously treated with an antibiotic which was inactive against MRSA (e.g., gentamicin), availability of a topical treatment effective against MRSA, poor handling and systemic side-effect profile of oral antibiotics [7].

The association between topical and oral antibiotics represents the correct treatment of impetigo

Oral antibiotics are indicated in addition to a topical treatment in cases with widespread or recurrent impetigo, independently from the bullous or non-bullous form. On the contrary, the proper management of complicated impetigo requires a systemic antibiotic treatment (topical treatment is not necessary in these subjects). Treatment of suppurative complications, such as abscesses, requires incision and drainage of the lesions, before starting topical antibiotics. Dermatologists suggest to disrupt the bottom of the blister/s, which favour topic antibiotic penetration. The panel recommend to monitor patients' and caregivers' compliance when a combined topic and oral antibiotic treatment is prescribed [7]. Readmission to the community life may occur only after a complete disappearance of cutaneous lesions, in order to reduce the risk of transmission. Impetigo is a contagious infection and schools are advised to exclude affected children until they have received at least 24/48 h of an appropriate antimicrobial therapy and after clinical improvement, thus respecting adequate hygienic conditions (because poor hygiene may increase the risk of transmission) as well as recommendation about not occlusive medication of cutaneous lesions. Good hygiene measures help prevent spread of impetigo to other areas of the body and to other people. According to the clinical practice, if lesions are placed on specific sites (such as the face or other exposes areas), patients should be kept at home and excluded from school and daycare centers (including gym and swimming pool) until their significant clinical improvement [8,9]. Because of its communicable nature, the social effects of impetigo can be serious, including loss of school and work days.

Ozenoxacin has a potent antimicrobial activity against staphylococci and streptococci, as well as a rapid bactericidal activity and a low risk of antibiotic resistances

According to a recent consensus from our scientific societies, topical antibiotics for impetigo treatment are mupirocin, fusidic acid, and retapamulin [7]. Mupirocin, a crotonic acid derivative extracted from *Pseudomonas fluorescens*, has a wide spectrum of activity against Gram-positive and some Gram-negative pathogens, inhibiting the bacterial protein synthesis by reversibly binding to isoleucyl-tRNA synthetase. Against *S. aureus,* at concentrations around the MIC the drug is bacteriostatic, being bactericidal at higher levels [10]. In recent years, the emergence of mupirocin resistance is largely increasing among *Staphylococcus* spp, especially in countries routinely applying MRSA decolonization, and the emergence of resistance appears to be more common when the drug is unrestrictedly used [11,12]. Fusidic acid is a tetracyclic triterpenoid antibiotic derived from the fungus *Fusidium coccineum*, structurally related to cephalosporin P1, it inhibits the bacterial protein synthesis at the translation phase and it is active *in vitro* against several Gram-positive bacteria and few Gram-negative strains (*Neisseria* and *Moraxella* species and some *Bacteroides fragilis* group). However the compound is largely bacteriostatic and primarily effective against staphylococci since even the MICs for S. pyogenes are generally higher [11]. This antibiotic comes in a variety of formulations for oral, intravenous and topical use, though for impetigo is indicated only as topical treatment [3]. In staphylococci, there are many molecular mechanisms that mediate resistance to fusidic acid, both chromosomal and acquired. At the chromosomal level, resistance is most commonly associated with mutations in *fusA*, while there are several acquired genes that confer resistance, such as *fusB, fusC*, *fusD* and *fusF* [11]. In recent years, the resistance to this antibiotic has risen significantly. One of the major clinical source of fusidic acid resistance is heterologous expression of the FusB family of proteins. To date, several studies have identified potential associations between the use of topical fusidic acid and the emergence of resistance in staphylococci, both at patient and population level [11]. Moreover, it has been recently suggested that in *S. aureus* the acquired resistance to fusidic acid or mupirocin may play a role in co-selecting for broader antibiotic resistance [13]. Finally, retapamulin, a tricyclic semisynthetic derivative belonging to the pleuromutilin class, inhibits protein synthesis by binding to domain V of the 50S ribosomal subunit thus inhibiting translation, and it is active against *S. aureus* and *S. pyogenes*. Resistance in *S. aureus* has been associated either with mutations in the *rplC* gene, which encodes ribosomal protein L3, or with mutations in the 23S. There are also efflux pumps, and in addition,

acquired resistance can a be observed by the *cfr* (chloramphenicol-florfenicol resistance)-encoded methyltransferase [11]. Limited data are available on the prevalence of resistance to retapamulin among clinical isolates of *S. aureus* and *S. pyogenes*, though this antibiotic is not approved by the US Food and Drug Administration and the European Medicines Agency for treatment of MRSA impetigo. Therefore, new molecules for an effective topical treatment of impetigo, particularly when MRSA aetiology is suspected, were needed. Ozenoxacin, a novel non-fluorinated quinolone, has been recently approved for the topical treatment of impetigo. In May 2019, ozenoxacin 1% cream has been approved in Europe for topical treatment of non-bullous impetigo in patients aged 6 months and older [14]. In USA and Canada ozenoxacin is indicated for topical treatment of both non-bullous and bullous impetigo in patients aged 2 months or more [15]. *In vitro* studies have shown that ozenoxacin has potent antimicrobial activity against staphylococci and streptococci and also a broad range of activity against MRSA, as well as mupirocin-, and ciprofloxacin-resistant strains of *S. aureus* [16]. Its dual inhibitory activity against the bacterial DNA gyrase and topoisomerase IV, protects it from development of resistances [17]. According to real-life evidences, ozenoxacin leads to a rapid remission of cutaneous lesions within few days. Microbiological success rates with ozenoxacin ranged from 81.8 to 100% after 3–4 days of treatment, and from 90.5 to 100% after 5 days [14]. In susceptibility studies, ozenoxacin was shown to be bactericidal also against MRSA [16]. Being a novel drug, the main limitation of ozenoxacin is the lack of clinical trials as well as the lack of data at long-term.

The efficacy of topical antibiotics is lower than that of the vast majority of oral antibiotics used for localized impetigo

Localized impetigo is indicated when small number of lesions (no more than 4–5) confined to a single anatomical area not exceeding 2% of total body surface area. In such conditions, an appropriate use of topical antibiotics provides benefits. Delivering a high dose of drug directly to infected areas can overcome bacterial resistances with minimal dermal absorption thus avoiding potential systemic side effects associated with oral therapy. Moreover, topical treatment may be more handling (for the caregiver) than oral therapy. Nevertheless, against local treatment are sensitization and the difficult application on areas which are frequently wash or at risk for accidental removal [18].

In order to evaluate recovery, bacteriological results of skin swabs are crucial

According to the clinical practice, the diagnosis of impetigo is based on its clinical appearance, rather than on bacteriological results. Moreover, skin swabs do not reliably differentiate between infection and colonization. As a consequence, cultures on skin swabs are not necessary for the diagnosis nor to evaluate impetigo healing.

The topical antibiotic treatment presents the disadvantage of limited absorption and the risk of sensitization developing contact dermatitis

Topical therapies are a key component in the management of mild-to-moderate skin infections. In such cases, topical antibiotics may be preferable to systemic treatment, since they maximize the effective dose of the drug in the targeted area while minimizing the systemic absorption and so, the systemic side effects [19]. This is consistent with the fact that impetigo is an infection limited to the epidermis not affecting deeper tissues, in uncomplicated cases. The risk of sensitization is high with several molecules such as neomycin and gentamicin. In particular, sensitization with neomycin occurs in 1–6% of the general population [20]. Also mupirocin may lead to sensitization thus leading to drug withholding. Although the risk of sensitization is less known with novel molecules, phase I studies on ozenoxacin showed little tendency for single or repeated doses of ozenoxacin to cause irritation, sensitization, phototoxicity or photoallergy [21].

The topical antibiotic treatment is strongly recommended only for children affected by localized non-bullous impetigo

According to the consensus by Galli et al.[7] topical antibiotic treatment is indicated for limited non-bullous impetigo (<2% of total body surface area) for 5–7 days (or until complete resolution). The association with topical steroids should be avoided.

Oral antibiotic treatment presents the disadvantage of major risk of systemic side effects (e.g., gastrointestinal side effects) and antibiotic resistances

Clinical practice guidelines recommend the use of oral antibiotics for treatment of cases with numerous or extensive lesions or systemic infection, as well as for those who are not responding to topical therapy. Oral treatment is usually well tolerated, and the side effects reported are usually limited to the gastrointestinal tract or to skin rash [18]. However, the global spread of antibiotic resistances has negatively affected treatment outcomes of patients with impetigo, a condition where treatment is often started empirically. Resistances are often associated with prolonged use of antibacterial therapy. In particular, there is growing evidence of resistances against penicillin, erythromycin, cloxacillin, clindamycin and cephalexin [1,22].

Topical disinfectants represent the ideal strategy for the treatment of impetigo

Currently, topical disinfectants do not represent a valid treatment for impetigo, although they could be used in addition to the standard therapy for prevention of recurrence [7]. Sodium hypochlorite baths (10 mL of sodium hypochlorite in a liter of water) have been used effectively to decrease bacterial carriage in populations with recurrent infections, such as those that manifest in patients with atopic dermatitis [23]. Dilute bleach baths may help alleviate local skin infections. 0.025% sodium hypochlorite was found to be bactericidal against Gram-positive and Gram-negative bacteria [24] and may help prevent the spread of *S. aureus* within families. Fisher and Colleagues found that after 5 min in a bath of sodium hypochlorite it was most effective at killing multiple community-acquired MRSA strains [25], being useful for MRSA decolonization. On the contrary, according with the Centers for Disease Control and Prevention (CDC), chlorhexidine is not recommended for patients younger than 18 years because of its risk of skin irritation and hypersensitivity reactions, due to a significant impairment of the epidermic barrier. Allergic contact dermatitis to chlorhexidine has been well known since the first publication by Calnan in 1962 [26]. Being a problem of great concern, the Food and Drug Administration (FDA) has issued an alert concerning hypersensitivity reactions to chlorhexidine-impregnated medical devices. Povidone-iodine is a preferable option (expert for neonates) being less aggressive to the stratum corneum than chlorhexidine [27].

Conclusions

Treatment of pediatric impetigo is characterized by several areas of uncertainty which could be call controversies. Mapping of controversies is an useful tool able to analyze decision making, by means of a collective investigation conducted by groups of experts. The goal of mapping controversies of pediatric impetigo is twofold: it helps clinicians in its challenging management and it enables them to detect pros and cons on the basis of both scientific evidence and clinical practice, thus trying to improve diagnostic and therapeutic tools of impetigo in children. Treatment should be individualized according to several factors including the extension of the disease, patient's age/immunological performance status/comorbidities, as well as antibiotic sensitization and resistances. The first-line oral treatment is represented by flucloxacillin or a first-generation cephalosporin such as cephalexin, while amoxicillin/clavulanic acid should be considered as the second-line therapy considering its broad-spectrum activity. When a MRSA etiology is suspected/confirmed, the antimicrobial agents available are clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX). Topical molecules are classified in bacteriostatic and bactericidal. A rapid bactericidal activity, like that of ozenoxacin, may have a critical role in reducing the transmission of impetigo. Topical disinfectants could be used in addition to the standard therapy for prevention of recurrence. Finally, good hygiene measures should be recommended to prevent spreading to other areas of the body and to other people. To conclude, given the emerging issues related to antimicrobial resistances, the present paper aims at gaining insights into the management of impetigo identifying among its treatment options which ones appear to be satisfactory with respect to effectiveness, symptom duration and prevention of recurrence, thus trying to overcome its pivotal controversies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work received an unconditional support by Angelini Pharma, that provided funding for the organization of the expert meetings.

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