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Do Antimicrobial Resistance Patterns Matter? An Algorithm for the Treatment of Patients With Impetigo

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ABSTRACT

Background: Impetigo is a highly contagious bacterial skin infection commonly occurring in young children, but adults may also be affected. The superficial skin infection is mainly caused by *Staphylococcus aureus (S. aureus)* and less frequently by *Streptococcus pyogenes (S. pyogenes)*. Antimicrobial resistance has become a worldwide concern and needs to be addressed when selecting treatment for impetigo patients. An evidence-based impetigo treatment algorithm was developed to address the treatment of impetigo for pediatric and adult populations.

Methods: An international panel of pediatric dermatologists, dermatologists, pediatricians, and pediatric infectious disease specialists employed a modified Delphi technique to develop the impetigo treatment algorithm. Treatment recommendations were evidence-based, taking into account antimicrobial stewardship and the increasing resistance to oral and topical antibiotics.

Results: The algorithm includes education and prevention of impetigo, diagnosis and classification, treatment measures, and follow-up and distinguishes between localized and widespread or epidemic outbreaks of impetigo. The panel adopted the definition of localized impetigo of fewer than ten lesions and smaller than 36 cm^2 area affected in patients of two months and up with no compromised immune status. Resistance to oral and topical antibiotics prescribed for the treatment of impetigo such as mupirocin, retapamulin, fusidic acid, have been widely reported.

Conclusions: When prescribing antibiotics, it is essential to know the local trends in antibiotic resistance. Ozenoxacin cream 1% is highly effective against *S. pyogenes* and *S. aureus*, including methycyllin-susceptible and resistant strains (MRSA), and may be a suitable option for localized impetigo.

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INTRODUCTION

Impetigo is a highly contagious bacterial skin infection, caused mainly by *Staphylococcus aureus (S. aureus)*, and less frequently by *Streptococcus pyogenes (S. pyogenes)* or both organisms.[1,2] In developing countries, group A *S. pyogenes* is a common cause of non-bullous impetigo. Impetigo occurs typically in children aged 2 to 5 years but may affect younger and older children as well as adults.[1,2] The worldwide prevalence of impetigo was estimated to be more than 140 million cases in 2010.[3,4] The global median childhood prevalence is estimated to be 12.3% with a peak in tropical, low-income settings.[4] In general practices in Western Europe, impetigo is the most common superficial skin infection in young

children.[3,4] Moreover, impetiginized dermatitis is a frequent disorder also seen in the pediatric dermatologist office.

Non-bullous impetigo accounts for 70% of cases and usually resolves without complications.[5] Bullous impetigo lesions are typically large, transparent superficial flaccid blisters. The risk of complications requiring hospital admittance is higher than for non-bullous impetigo.[5,6] The cost of hospitalizations related to *S. aureus* skin infections, including severe impetigo, is estimated at $5 billion annually in the US.[7] Approximately 6.9 million topical and 8.2 million oral antibiotic prescriptions annually are dispensed for dermatologic conditions in the US.[8,9]

Bacterial resistance is reported to many antibiotics prescribed for the treatment of impetigo, including mupirocin, retapamulin, and fusidic acid.[10-15]

Another more recent therapeutic option is Ozenoxacin cream 1%, which has been developed for the first-line treatment of impetigo in patients from two months and up in the U.S. and Canada and six months in E.U. countries. This bactericidal topical non-fluorinated quinolone has been studied in seventeen clinical trials to date but has not yet been incorporated in published practice guidelines for impetigo treatment.[10] Ozenoxacin has been shown to be highly effective against *S. pyogenes and S. aureus*, including methicillin-susceptible and resistant strains (MRSA).[42,43] Additionally, preliminary data show ozenoxacin's capacity to eradicate biofilm-forming MRSA at therapeutic concentrations. Unpublished research on 700 *S. aureus* and *S. pyogenes* strains derived from wound infections showed that ozenoxacin is also active against, mupirocin-, fusidic acid-, macrolide-, clindamycin-, and fluoroquinolone-resistant *S. aureus* and against clarithromycin-, clindamycin, and fusidic acid-resistant *Streptococcus pyogenes* strains.

Although there are guidelines on the skin and soft tissue infection treatment, currently, an algorithm that specifically addresses the treatment of impetigo is lacking.[5,10] An evidence-based impetigo treatment algorithm was developed to fill this gap.

Scope

An international panel of pediatric dermatologists, dermatologists, pediatricians, and pediatric infectious disease specialists developed an evidence-based impetigo treatment algorithm for pediatric and adult populations. The algorithm supports healthcare providers to optimize clinical outcomes for their patients with impetigo. The treatment of other forms of soft tissue infections is beyond the scope of this work.

METHODS

Preliminary Considerations

In February 2020, an international expert panel was convened for a meeting to develop an impetigo treatment algorithm for both pediatric and adult populations. For this purpose, the best available evidence, coupled with the panel opinion, was used. The process used for this project was following a modified Delphi technique, which is used to gain judgment on complex matters or achieve consensus among experts.[16,17] The classical Delphi technique can be successfully modified for the development of medical algorithms.[16,17]

Literature Review

Before the expert panel meeting, a systematic literature review selected present clinical guidelines, algorithms, and evidence-based recommendations describing current practice for impetigo treatment. Literature was selected for clinical relevance, addressing aspects of impetigo management, including clinical efficacy and safety of the treatment, antimicrobial resistance, costs, quality of life effects, and handling and tolerance of the treatment regimens. The systematic review included research studies, clinical guidelines, consensus papers, and reviews published in the English language from 2014 to February 2020.
For the literature search, the following terms were used: *Impetigo; bullous impetigo; non-bullous impetigo; impetigo pathogenesis and diagnosis; topical and systemic impetigo treatment; adjunctive impetigo treatment; adherence; concordance; efficacy; safety; tolerability; antimicrobial and antibiotic resistance.*

Exclusion criteria were: No original data (unless a review article was deemed relevant), not dealing with the clinical management of impetigo, and publication language other than English. The searches yielded a total of 43 papers detected after the exclusion of duplicates (Figure 1).

The Role of the Panel

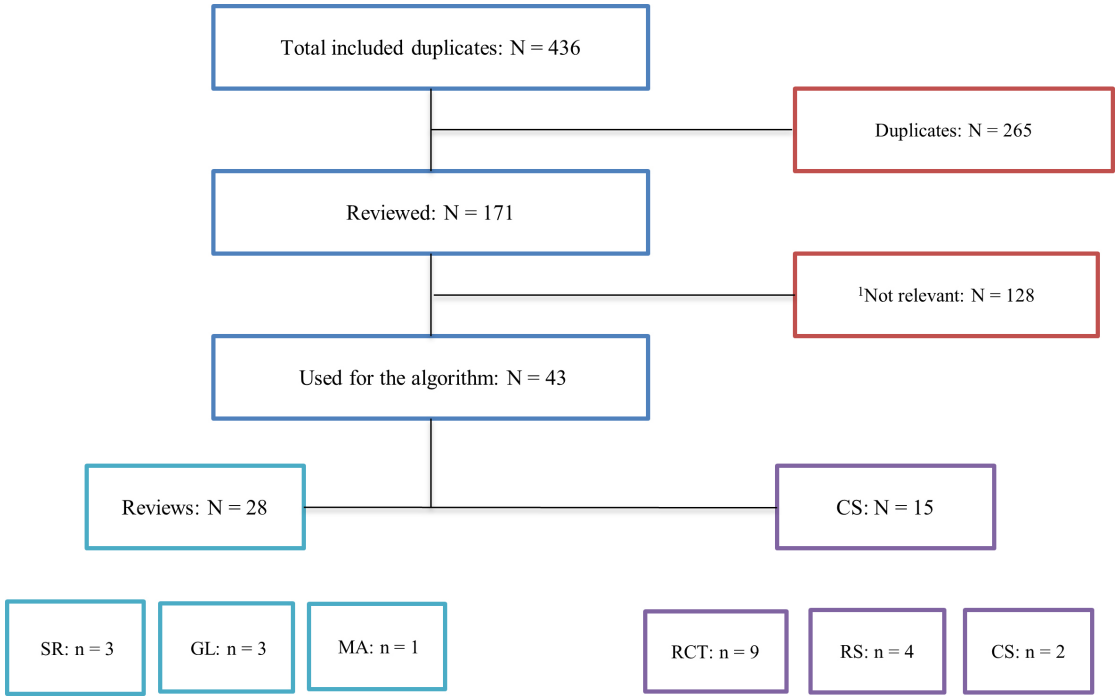
The panel, consisting of nine members, discussed the proposed design of an algorithm for the prevention, treatment, and maintenance approach for impetigo, developed based on the selected literature from the conducted searches. After presentations on current issues in impetigo diagnosis, treatment, antibiotic resistance, and modified Delphi method, summaries of the literature searches, and the proposed algorithm, the panel worked in small groups, offering their algorithm, editing, and revising it at length. The panel then reconvened into a plenary group to define the algorithm. Reviewing and finetuning, as well as developing and reviewing the manuscript, took place online.

RESULTS

The Algorithm

An algorithm is a precise, unambiguous, logical step-by-step method used to solve a problem.[18] The function of an algorithm in this context is to standardize and support medical decision making, such as standardizing the selection and use of treatment regimens, thereby improving adherence to evidence-based

FIGURE 1. Not relevant: Other subject, poor quality, small number, case studies, in-vitro or in-vivo studies, animal studies.



Clinical studies (CS); Randomized controlled trials (RCT); Retrospective studies (RS); Cross-sectional studies (CS); Systematic reviews (SR); Guidelines (GL); Meta-analysis (MA)

guidelines. Well-designed algorithms have inputs and outputs, are precise, and have uniquely defined steps. The algorithm stops after a finite number of instructions.[18] For the development of the impetigo treatment algorithm, the unpublished mnemonic RECUR (Reliable, Efficient, Clear instructions, Understandable, Remember easily) was used.

The algorithm has the following steps: Education and prevention of impetigo, diagnosis and classification, treatment measures, and follow-up (Figure 2A and Figure 2B).

Education and Prevention of Impetigo

Education on risk factors for impetigo development is an important part of the total approach. These risk factors are a warm, humid climate, poverty, crowding, poor hygiene, and underlying scabies.[1] Impetigo may be spread in children through pets, in schools, daycare centers, or crowded housing areas; for adults, sources include infected children and self-inoculation from nasal or perineal carriage.[1] Carriage of group A *Streptococcus* (GAS; *S. pyogenes*) and *S. aureus* predisposes to subsequent impetigo.[4]

Diagnosis and Classification

Non-bullous impetigo frequently presents on the face around the nose and mouth with erythematous pustules or vesicles changing to superficial erosions with a characteristic "honey-colored" crust.[1,5] Lesions can also occur elsewhere on the body and are usually smaller than 2 cm and not or minimally painful. Frequently impetigo occurs without remarkable erythema or constitutional symptoms, although regional adenopathy may be present.[1,5]

Bullous impetigo is caused by strains of *S. aureus* that produce toxin A which induces a loss of cell adhesion in superficial epidermal layers by targeting protein desmoglein-1.[5,6]

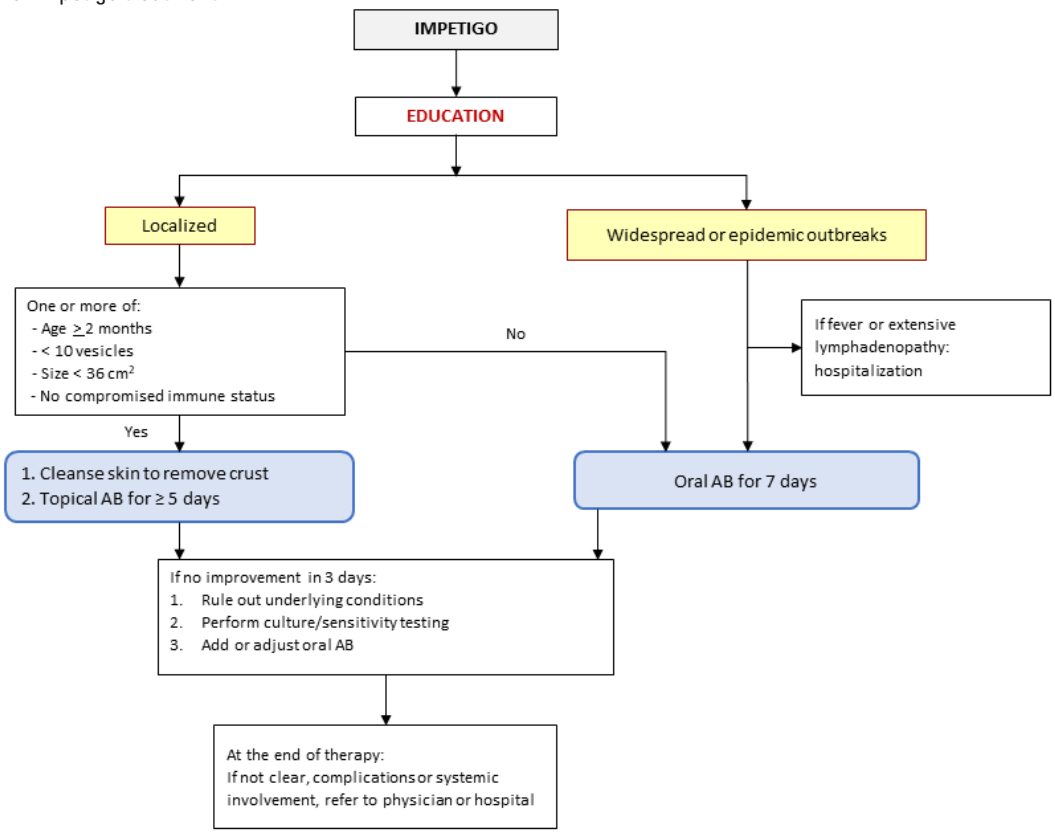
Bullous impetigo lesions are usually large, transparent superficial bullae before rupturing, leaving round erosions that become crusted. Bullous impetigo frequently occurs in intertriginous areas and the trunk.[6]

Impetigo is either a primary (direct bacterial invasion of an intact skin) or secondary infection of pre-existing skin disease or traumatized skin (atopic dermatitis, scabies, cuts, abrasions, insect bites, and chickenpox). Secondary impetigo is also called impetiginization.

There is an ongoing discussion regarding the definition of localized impetigo, which varies from five to ten lesions and an affected area smaller than 50 cm^2 up to 100 cm^2.[10]

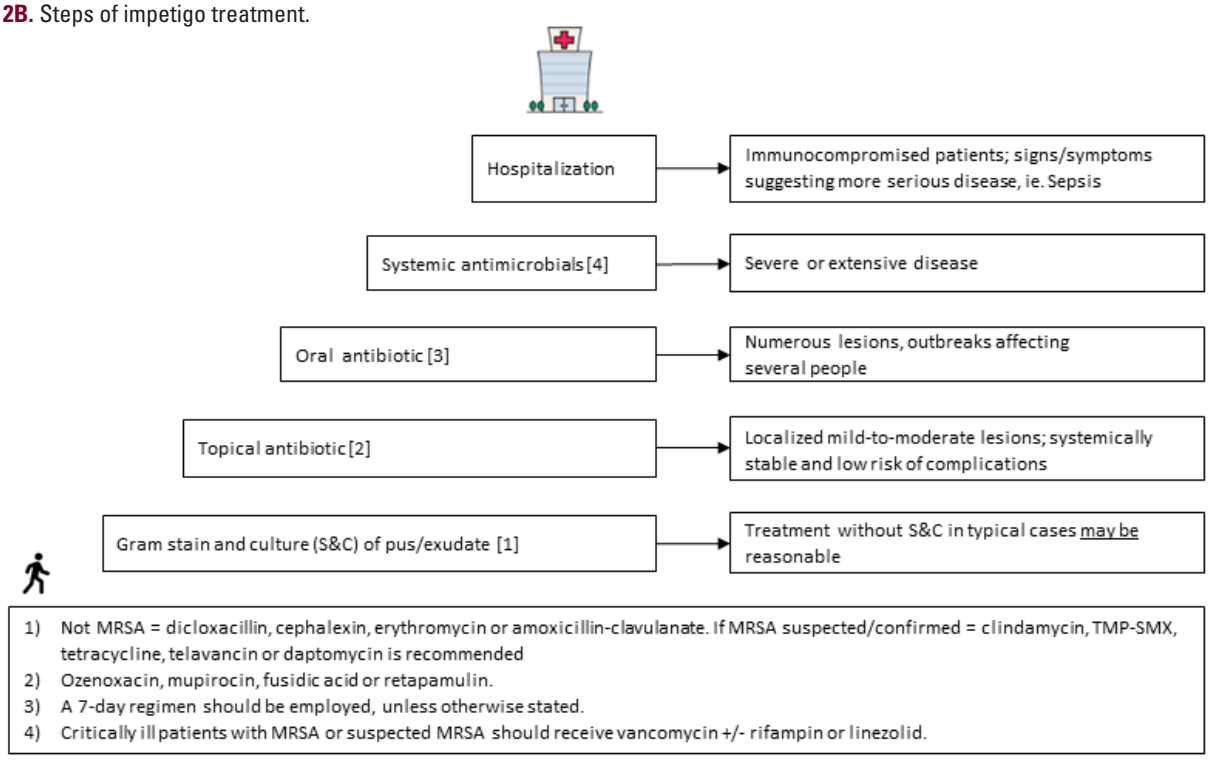
Clinical trials of ozenoxacin, retapamulin, and mupirocin defined

FIGURE 2A. Algorithm for impetigo treatment.



Antibiotics (A.B.)

FIGURE 2B. Steps of impetigo treatment.



Sensitivity and culture (S & C), Methicillin-resistant *Staphylococcus aureus* (MRSA), Trimethoprim/sulfamethoxazole (TMP/SMX)
[10]*Courtesy of Prof Schachner and Eran Gwillun, MD*

TABLE 1.

Topical Antibiotics for Impetigo[10]

Order	Name of Drug	Indication	Antimicrobial Activity*	Dosing Regimen
1	Ozenoxacin 1% cream	2 months of age and older*	Gram-positive bacteria, especially *S. aureus*, including MRSA, or *S. pyogenes*. Efficacy against mupirocin-resistant *S. aureus* (MRSA), fusidic acid resistant *S. aureus*, quinolone-resistant *S. aureus* and clindamiycin-resistant *S. aureus*.	BID/ 5 days
2	Mupirocin 2% ointment, 1% ointment for children aged 2 months to 16 years	2 months of age and older	Effective against gram-positive bacteria, especially *S. aureus* including MRSA and *Streptococci*.	TID/ 7-10 days
3	Retapamulin 1% ointment	Impetigo in patients 9 months of age and older	Active against *S. aureus* (methicillin susceptible isolates only) and *S. pyogenes*.	BID/ 5 days
4	Fusidic acid	No age limitation stated in the PI.	Active against *S. aureus, Streptococcus spp.* and *Corynebacterium minutissimum*.	TID/7-10days

*in EU countries, 6 months of age and older

localized impetigo as fewer than ten lesions and an affected area smaller than 36 cm^2. The panel adopted this description of localized impetigo. Apart from the clinical presentation, underlying conditions such as a compromised immune status should be considered when defining treatment.[10,19,46,47]

Differential Diagnosis

For nonbullous impetigo, the differential diagnosis includes contact dermatitis, eczema herpeticum, herpes simplex, scabies, pemphigus foliaceous, and tinea infection. The presence of the characteristic golden crust should raise suspicion for impetigo.[5] The bullous form should be distinguished from other blistering skin conditions such as acute contact dermatitis, bullous drug eruptions, burns, bullous insect bite reactions, varicella, and subcorneal pustular dermatosis, Stevens-Johnson syndrome, and other bullous diseases (ie, bullous pemphigoid).[10,20]

Impetigo is a clinical diagnosis, although Gram stain and culture of the skin lesions are useful for identifying causative pathogens. Culture and sensitivity testing allow clinicians to detect antimicrobial susceptibilities and support prescription of the most appropriate antibiotic treatment. This approach is especially important when MRSA infection is being considered, though empiric coverage for MRSA may be instituted if clinical suspicion is high.[10]

Although complications of non-bullous impetigo are rare, local and systemic spread of infection can occur that may result in cellulitis, lymphangitis, or septicemia.[5,10] Complications of *S. pyogenes* infection include scarlet fever, guttate psoriasis, and post-streptococcal glomerulonephritis.[5]

Treatment of Impetigo

Typically, impetigo, whether non-bullous or bullous, is self-limiting and is resolved without scarring within two to three weeks.[5,10] Reasons for the treatment of impetigo include preventing the spread of infection, hastening the resolution of discomfort, and improving cosmetic appearance.[10] Bullous and non-bullous impetigo can be treated with either topical or oral therapy. Topical therapy is used for patients with limited skin involvement, whereas oral treatment is recommended for patients with extensive impetigo involvement.[5,10]

In healthcare settings, contact precautions to avoid the spread of impetigo are indicated until 24 hours after the start of appropriate antibiotic therapy.

The algorithm for treatment decision is depicted in Figure 2A, and the steps in the treatment of impetigo are shown in Figure 2B.[10] When a patient presents with impetigo, a Gram stain and culture of pus or exudate may be performed.[10] In localized cases defined as fewer than ten lesions and smaller than 36 cm^2 area affected, in those that are systemically stable and with a low risk of complications, topical ozenoxacin cream 1%, topical mupirocin 2% ointment,[5] fusidic acid 2% cream or retapamulin 1% ointment are recommended (Table 1).[5,10] Cleanse the skin and remove the crusts before the application of the topical treatment.[10]

During the panel discussions, the use of a topical antibiotic rotation regime, for instance, was mentioned in the case of recurrent infection. In the USA, the topical regime may comprise a rotation of mupirocin and ozenoxacin cream 1%, and in Europe, a rotation of mupirocin, ozenoxacin, and fusidic acid may be used.

According to the panel, systemic antibiotic treatment for impetigo patients may differ between the USA and Europe. In the

TABLE 2.

Systemic Antibiotics For Impetigo: The Suggested Dosages Should be Confirmed by the Clinical Specialists	
Systemic Antibiotics for Impetigo (Extensive Infection)[10]	
Not MRSA infection	MRSA Infection
Dicloxacillin 4 times daily PO for 1 week	Vancomycin IV +/- Rifampin BID for 10 days
Cephalexin 4 times daily PO for 1 week (weight-based dosing)	Clindamycin 3 times daily PO for 7 days
Erythromycin 4 times daily PO for 1 week (3rd line, based on sensitivity/allergy)	Trimethoprim-sulfamethoxazole PO BID for 7 days
Amoxicillin/Clavulanate PO BID for 7 days	Doxycycline BID PO for 7 to >12 days Telavancin, Linezolid, Daptomycin (3rd line, based on sensitivity/allergy)
Cefadroxil PO BID for 10 days	

Medication dosages are weight and age based.[10] Oral (PO); Two times daily (BID).

USA, for non-MRSA impetigo cases, dicloxacillin or cephalexin, and for MRSA cases, after culture and sensitivity testing, trimethoprim-sulfamethoxazole is mainly used. In Europe, for non-MRSA cases, amoxicillin-clavulanate, clindamycin, or flucloxacillin may be prescribed, and for those with MRSA, mainly clindamycin or vancomycin are recommended.

Oral antibiotics, for seven days, are recommended in widespread or severe bullous impetigo or when the outbreak of impetigo affects several people.[5,10] Oral antibiotics are also applicable if the patient has a fever or extensive lymphadenopathy, in which case hospitalization is indicated.[10] In those impetigo cases with no MRSA involvement, dicloxacillin, cephalexin, erythromycin, or amoxicillin-clavulanate can be prescribed, and for MRSA suspected or confirmed cases, clindamycin, TMP-SMX, tetracycline, telavancin, or daptomycin is recommended (Table 2).[10]

If the skin has not cleared after the treatment, underlying conditions should be ruled out, and another culture and sensitivity test should be performed.[10] In patients who received oral antibiotics, the type of antibiotic should be adjusted. If the skin has not been cleared or exacerbated after three days, hospitalization is to be considered.

DISCUSSION

Antimicrobial resistance has become a worldwide concern. In 2015 the WHO launched the Global Action Plan on Antimicrobial resistances (GAP on AMR), specifically the One Health program, to fight antimicrobial resistance at the human, veterinary and environmental levels. It is being implemented by many countries in the world with specific country-based programs.[21]

The strategic objectives of the GAP are 1. Improve awareness and understanding of infections and bacterial mechanisms of action and resistance; 2. Strengthen knowledge on AMR through surveillance and research; 3. Reduce the incidence of infection (preventive measures); 4. Optimize the use of antimicrobial medicines: antibiotic stewardship programs, and 5. Ensure sustainable investment for R&D and implementation of control measures.[21]

To comply with the strategic objectives of the GAP[21] the panel discussed trends of antibiotic resistance related to impetigo treatment and agreed that when prescribing antibiotics, it is essential to know the local trends in antibiotic resistance. The panel recognized that doctors need education in antibiotic stewardship principles as, for some of them, it is an unknown field. For the newest treatment of impetigo with topical ozenoxacin, the panel insisted on short-term use (5 days, twice a day) for localized cases of impetigo.

Antibiotic Resistance and Choosing a Treatment

Antimicrobial resistance is a major threat to public health in the world, and resistance to mupirocin and fusidic acid is increasing worldwide.[11-15,22-30] Resistance rate varies from country to country, center to center, as it is linked to resistant bacteria and mechanisms of resistance. Due to increasing concerns about emerging resistance to commonly used antibiotics for impetigo, treatment decisions should consider resistance patterns of *S. aureus*.[22-28] MRSA has been shown to cause impetigo.[11]

Retrospective observational data collected from skin culture isolates annually between 2005 and 2011 from the University of Miami Hospital outpatient dermatology clinic showed 387 *S. aureus* isolates and that MRSA increased by 17.0% during the last three years.[28]

Updates in 2016 on trends in *S. aureus* resistance in the USA demonstrated that resistance to clindamycin is up by seventeen percent and that there is a changing susceptibility of *S. aureus* in a pediatric population with an increase of 40% in resistance of isolates to Oxacillin.[31]

Resistance to Mupirocin

Topical mupirocin is used widely to treat skin and soft tissue infections and eradicate MRSA's nasal carriage. The increase in resistance to mupirocin is related to the widespread use of

MRSA carrier decolonization.[14] The proportion of resistance of the community-acquired MRSA (Ca-MRSA) is also increasing. In the USA, mupirocin resistance as high as 30% has been reported in children with SSTIs.[14] A retrospective study looked at 358 *S. aureus* isolates from 249 children in an outpatient setting in New York City between May 2012 and September 2013.[14] The study demonstrated that 19.3% of patients had mupirocin-resistant *S. aureus* isolates at the time of their first culture and that 22.1% of patients with *S. aureus* infection had a mupirocin-resistant isolate at some time during the study period. Of all *S. aureus* isolates collected during the study period, 31.3% were resistant to mupirocin.[14] The study further revealed that prior mupirocin usage was strongly correlated (P<0.001) with mupirocin resistance. Of the MRSA isolates, 67.7% stemmed from atopic patients, from which 68% were mupirocin resistant versus 28% resistance in non-atopic patients.[14]

In Greece, the emergence of a new community-associated methicillin-susceptible *Staphylococcus aureus* (MSSA) clone has led to an alarming increase in the resistance rate to mupirocin, with a 7-fold increase in 3 years, being 4.2% in 2013 and 37.7% in 2016. For the same clone, an increase in resistance to fusidic acid from 26.8% to 51.9% has been reported.[15]

The prevalence of mupirocin resistance in different countries varied; in South Korea, the overall percentage of MSSA and MRSA resistance to mupirocin was 13.6%, in the USA, 1.2 % in the community, 12.2% in nursing homes, 11%, and in the UK 0.8%, respectively.[32] In countries where a restriction on OTC use of topical antibiotics has been implemented, the percentages of mupirocin resistance decreased, for instance, New Zeeland from 28% (2006) to 11% (2014) and Australia from 18% to 0.3% in the same period.[32]

Resistance to Retapamulin

Retapamulin is a derivative of pleuromutilin, a component of a mushroom called *Clitopilus scyphoides*, which selectively binds the 50S bacterial ribosomal subunit and inhibits protein synthesis.[33] Despite that in the prescribing information of retapamulin 1% ointment, the product is indicated for methicillin-susceptible *S. aureus* only, in the USA (2013), out of 155 MRSA isolates, only 2.6% were resistant to retapamulin.[33] However, in 2014, decreased susceptibilities to retapamulin, mupirocin, and chlorhexidine among *Staphylococcus aureus* isolates, causing skin and soft tissue infections in otherwise healthy children, were reported.[34] Of 200 *S. aureus* isolates from pediatric patients in Houston, TX from otherwise healthy children with *S. aureus* SSTI, such as impetigo, furunculosis, abscess, pustulosis, and cellulitis, 9.5% of isolates were resistant to retapamulin, and 9.8% resistance to mupirocin was observed.[34]

Resistance to Fusidic Acid

In the E.U., some impetigo outbreaks due to fusidic acid-resistant clones of *S. aureus* have been reported. Compared to other topical antibiotic agents, fusidic acid retains its high concentration at deeper layers of the skin. Resistance to fusidic acid has been reported in various countries. In Taiwan, the resistance of MRSA isolates to fusidic acid increased from 3.2% in 2002 to 18.1% in 2012.[35]

In 2017, 32.1% of MRSA isolates were shown to be resistant to fusidic acid in Egypt,[36] and in 2018 a Danish study of atopic dermatitis patients showed resistance of *S. aureus* colonization to fusidic acid as high as 41.0%.[13] Further studies within Sweden demonstrated that in 2010, 33% of *S. aureus* isolates were resistant to fusidic acid in impetigo and 12% in secondarily infected A.D.[14] In a case-control study conducted in the U.K., fusidic acid resistance was shown to be significantly associated with A.D., and bacterial isolates showed three acquired resistance genes: *fusA, fusB, and fusC*2.[32]

Topical Hydrogen Peroxide

A rationale for the use of topical hydrogen peroxide is to limit the usage of antibiotics. A 2012 Cochrane review showed no superiority of fusidic acid but a lack of evidence for antiseptic use in impetigo.[37] However, the UK-based National Institute for Health and Care Excellence (NICE) guidelines suggest it is a valid option in some instances.[38]

Ozenoxacin

Before the introduction of ozenoxacin in December 2017, the last approved topical antibiotic for impetigo was retapamulin (April 2007).[10,39] Ozenoxacin (Xepi in the U.S. and Ozanex or Dubine in other countries) is a non-fluorinated quinolone antibiotic that is active on susceptible and resistant strains of *S. aureus* and *S. pyogenes*, causal agents of the majority of SSTIs.[40-43] Ozenoxacin cream 1% was developed for the first-line treatment of impetigo in patients aged two months and older and has been studied in seventeen clinical trials up to date.[19,40,44-47] Fifteen studies in phase 1 and 2 have been conducted, and two pivotal phase 3 studies in both adult and pediatric patients with impetigo have been completed.[44-46] In these studies, twice daily ozenoxacin treatment for five days demonstrated superior clinical and bacteriologic outcomes versus matching vehicle control.[19,44-47]

The high activity on MRSA and other resistant strains is an important point that favors ozenoxacin.[10,40-47] Since its introduction, there is no data on bacterial resistance.[10,39,42,43]

Antibiotic resistance in *S. aureus* poses a rapidly increasing global problem.[48] Antimicrobial stewardship is critical to optimize patient outcomes and to prevent the development of resistance.[10]

LIMITATIONS

Due to COVID-19, the review process of the algorithm and the manuscript was conducted online. The international panel was

able to adapt to the current situation and finalized the review process in good order.

CONCLUSION

An evidence-based impetigo treatment algorithm was developed to address the treatment of impetigo for pediatric and adult populations. When recommending treatment, antimicrobial resistance must be taken into account when selecting effective treatment for impetigo patients.

The presented algorithm for impetigo treatment, including a newer safe and effective topical antibiotic as a first-line treatment, could be an essential step in antimicrobial stewardship.

DISCLOSURES

All authors contributed to the development of the algorithm and the review of the manuscript and agree with its content.

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