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IMPETIGO: Addressing Treatment Challenges and Burden of Disease

Introduction

Impetigo, a very common bacterial skin infection, is a moving target. Over the past few decades there has been a shift in the associated bacteriology and resistance patterns, making the choice of best treatment more difficult without the benefit of culture and sensitivity guidance.¹ Evidence that *Staphylococcus aureus* (*S. aureus*) strains and streptococcal species are developing resistance to typical first-line topical treatments is mounting.²⁻⁴ Emergence of Mupirocin resistance has been reported in several recent studies.⁵ Methicillin-resistant *S. aureus* (MRSA) is also a growing concern in the community setting. Oral penicillin and macrolides are no longer viable treatment options and resistance is emerging against clindamycin, cephalexin, and linezolid, leading to the potential for more expensive and intensive therapies.^{2,6,7}

While often described as “self limiting,” treatment of impetigo is generally advised as this disorder is highly contagious, often requiring isolation from school, work, or social activities. A multitude of blistering skin disorders complicate the differential diagnosis with no good immediate diagnostic tests.⁷ Additional concerns over disease progression to more serious problems put primary caregivers on a precarious tipping point, balancing the need for a quick and effective treatment with good antibiotic stewardship. Current treatments include a new topical antibiotic, ozenoxacin (Xepi), retapamulin (Altabax), and the old topical treatments such as mupirocin and fusidic acid (not available in the United States), which are still widely used as first-line therapies. This, coupled with a recent study highlighting the need for improved proficiency in impetigo recognition, warrants a refresher to ensure diagnosis and empiric treatment of the infection is well understood by those on the front lines.^{7,8}

Review of Impetigo

Impetigo affects the epidermal skin layer with either nonbullous or bullous presentation. Approximately 70% of all impetigo cases present as the nonbullous form, which largely affects preschool and school-aged children (ages 2-6 years), though all ages can experience this contagious infection. Impetigo is predominantly caused by *S. aureus* or *Streptococcus pyogenes* (*S. pyogenes*), sometimes referred to as group A beta-hemolytic streptococcus (GABHS).^{9,10} Risk of infection increases in populations where hygiene is poor, or where there is inadequate access to housing, health care, and other resources. Primary infection occurs in intact skin. Secondary infection occurs following excoriation of scabies or insect bites, and/or in the presence of comorbid conditions such as atopic dermatitis (eczema) and diabetes. Nonbullous impetigo is characterized by the presence of small pustules that form a yellow-gold crust located around the nose and mouth as well as on extremities; it is usually not associated with systemic symptoms such as fever.^{6,7,9} *S. aureus* has become more prominent as the causative agent in the nonbullous form, though in more tropical locations and indigenous peoples *S. pyogenes* is still of concern.^{7,11} The bullous form is exclusively caused by *S. aureus*, which produces toxins that cause larger superficial bullae filled with yellow fluid. These occur on the trunk and intertriginous skin of extremities, mostly in diapered regions of children younger than 2 years of age.^{6,7,9}

Globally, impetigo has been estimated to affect over 100 million people at any one time and ranks within the top 50 burden-inducing disease states.^{3,12} In the United States, approximately 3 million cases occur annually.¹³ Heat, humidity, and prior skin trauma are predisposing factors, and as such there can be seasonal variation favoring

warmer weather and exposure to insect bites.^{3,7} Incidence rates have been noted to vary over the course of several years, and children with atopic dermatitis are at greater risk for infection.³ Placing a dollar value on the overall burden is difficult as costs of treatment constitute only a portion of the total encumbrance. Lesions in either form are highly contagious and require that the affected individual be kept from school or work. Families are impacted when parents must care for infected children, or when cross-contamination results in the need to treat more than 1 individual.^{3,6} Though less severe cases will self resolve after 4 weeks, treatment is recommended to hasten recovery time or prevent progression to more severe disease and spread to others. Poststreptococcal glomerulonephritis and rheumatic heart disease have become less common with the shift toward *S. aureus* as the causative pathogen, though glomerulonephritis can occur in up to 5% of nonbullous cases in areas where impetigo is highly prevalent.^{6,7,10} Antibiotic treatment has not been proven to reduce the incidence of glomerulonephritis.^{7,9}

Despite the pressure to treat impetigo, clinicians may also feel sanctioned to limit antibiotic use in the face of growing microbial resistance.^{3,6,7} Antonov et al reported that 31.3% of all *S. aureus* isolates collected from children seen in a predominantly outpatient setting in New York City were resistant to mupirocin, and that prior mupirocin use was strongly correlated.¹⁴ McNeil et al documented that up to 10% of in vitro *S. aureus* isolates from healthy, community-based children in the Houston area displayed resistance to topical antibiotics, including MRSA. MRSA accounted for over 60% of isolates from children with chronic conditions like eczema. In those with recurrent infection, 14.7% of isolates were mupirocin-resistant and included cross-resistance with clindamycin, while 9.5% showed resistance to retapamulin, including some that were cross-resistant to linezolid and daptomycin, augmenting concern that topical treatments may impart resistance to systemic antibiotics.^{2,4} If *S. pyogenes* is considered a likely pathogen, known resistance of streptococcus to macrolides and mupirocin factor into the decision to treat.⁷ *S. aureus* resistance rates to fusidic acid, widely used

outside of the United States, vary greatly among studies and demonstrate the importance of knowing local resistance patterns.³ Overall resistance rates to the commonly prescribed topical antibiotics are reportedly as high as 81%.¹⁵ As resistance is known to increase health costs due to hospitalization and the need for more expensive and intensive treatment, this is considered a major threat to public health.⁶

Proper diagnosis adds to the difficulty of treatment choice, with both family/caregivers and medical personnel potentially attributing skin blisters to other causes. Nonbullous impetigo may be mistaken as atopic dermatitis, contact dermatitis, scabies, herpes simplex, or varicella zoster virus, and not be prescribed the appropriate treatment. The bullous form may be misinterpreted as insect bites, tinea corporis, eczema, contact dermatitis, or a drug eruption.^{7,8,16} A 2015 survey of pediatricians at Johns Hopkins University found that only 31.9% were able to correctly diagnose bullous impetigo, and though most chose mupirocin as first-line therapy for localized infections, 31.3% chose bacitracin, which is not recommended in either form of impetigo as a first- or second-line treatment.⁸ While skin swabs may not be helpful in determining empiric treatment, cultures should be obtained if MRSA is suspected, and serologic tests can help determine poststreptococcal glomerulonephritis or herpes simplex virus (HSV).^{7,9,10,17} Differentiation between impetigo and herpes gladiatorum is of particular importance with athletes of close-contact sports to ensure early effective treatment and to avoid transmission.^{17,18} Of note, many of the diagnoses listed above may be primary disease states with impetigo as a secondary superinfection, and follow-up studies for immune-based skin diseases may be needed in refractory cases.^{9,17,18}

Treatment

Given the high potential for exposure in daycare and preschool settings, the best line of defense is to incorporate good hygiene measures into the daily lives of children. Proper hand-washing techniques are important and should be conducted frequently throughout the day. Should there be an outbreak, avoiding contact with lesions, regular bathing with soap and water, washing linens and

clothing in hot water (60°C/140°F), and keeping fingernails short can help mitigate the spread of bacteria.^{7,9,19} Natural remedies, such as tea tree oil and Manuka honey have been used with anecdotal success, but are not well studied and may not satisfy daycare requirements.^{6,7}

Access to readily available disinfectants and over-the-counter (OTC) topical antibiotics may entice individuals or families to self treat. Topical antiseptics are not well studied as comparator agents, and there is little evidence to support routine use for primary therapy over topical antibiotics.^{6,7,10} While certain alcohol-based hand cleansers,^{*} hydrogen peroxide, povidone-iodine, and chlorhexidine solutions are not shown to cause resistance and may therefore be used concomitantly, there is still the need to consider their overall environmental impact, and the Dutch College of General Practitioner's guidelines recommend they be avoided.^{3,4,10} Bacitracin is available in combination with polymixin B and/or neomycin OTC in the United States, and while this OTC product appears to have good laboratory data to support its effectiveness against Gram-positive bacteria, it has not stood the test of clinical applicability and is feared to not effectively eradicate bacteria.^{1,10} Additionally, it is implicated in severe contact allergic reactions in people both with and without preexisting conditions.⁴

Most recent reviews indicate that there is no significant data to recommend one topical antibiotic over another, or to recommend oral therapy over topical, and there remains variations across countries on therapy standards.^{3,7} The topical antibiotics mupirocin, fusidic acid, or retapamulin have been recommended as initial treatment choices for smaller bullae or localized nonbullous lesions.⁹ One trial in nonbullous impetigo compared retapamulin to fusidic acid, but no significant difference was found.¹ The most common problems associated with topical agents are application site reaction (irritation), and difficulty in application to certain areas, such as eyelids, mouth, or inaccessible areas.^{7,10} Advantages of topical agents over systemic include delivery of higher concentrations to the infection site for a potentially more rapid onset, greater patient compliance, and avoidance of systemic side effects.⁴ Topicals can be used for

^{*}Those agents that contained triclosan did show bacterial resistance over time.

TABLE. Review of topical antibiotics used in impetigo¹⁹⁻²³

Drug Name, Generic (US Trade Name/Year of FDA approval)	Dose	Indication/Antibacterial Activity	Common Adverse Events/Issues
Ozenoxacin (Xepi™) December 2017	1% cream BID for 5 days; NTE coverage of 100cm ² in adults, and 2% of total body surface in pediatrics aged 2-12 years	- The topical treatment of impetigo due to <i>S. aureus</i> or <i>S. pyogenes</i> in adult and pediatric patients 2 months of age and older. - Inhibits bacterial DNA replication enzymes, DNA gyrase A, and topoisomerase IV. - Bactericidal. - Activity against MRSA. - No contraindications.	- Rosacea and seborrheic dermatitis - Safety in patients younger than 2 months has not been established. - Limited total application
Retapamulin (Altabax®) April 2007	1% ointment BID for 5 days; NTE coverage of 100 cm ² in adults, and 2% of total body surface in pediatrics	- For use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo (up to 100 cm² in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) due to <i>S. aureus</i> (methicillin-susceptible isolates only) or <i>S. pyogenes</i>. - Inhibits peptidyl transfer, blocks P-site interactions, and prevents the normal formation of active 50S ribosomal subunits. - Bacteriostatic.	- Application site irritation - Safety in patients younger than 9 months has not been established. - Limited total application
Mupirocin (Bactroban®) December 1987 <i>Generic available</i>	2% cream or ointment (w/PEG),* TID for up to 10 days	- Topical treatment of impetigo due to susceptible isolates of <i>S. aureus</i> and <i>S. pyogenes</i>. - RNA synthetase inhibitor. - Bacteriostatic at MIC.	- Eye irritation - Local irritation - Risk of PEG absorption
Fusidic Acid/Sodium Fusidate Not approved in the United States	2% cream/ 2% ointment TID-QID	- For use in the treatment of primary and secondary skin infections caused by sensitive strains of <i>S. aureus</i>, <i>Streptococcus</i> spp, and <i>Corynebacterium minutissimum</i>. Infections may include: impetigo contagiosa, erythrasma, and secondary skin infections such as infected wounds and infected burns. - Interferes with amino acid transfer from aminoacyl-tRNA to protein on the ribosomes. - Bacteriostatic or bactericidal depending on inoculum size.	- Application site pain and mild irritation - More frequent application, though TID adequate when dressing applied

Abbreviations: BID, 2 times daily; DNA, deoxyribonucleic acid; IV, intravenous; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NTE, not to exceed; P-site, peptidyl; PEG, polyethylene glycol; QID, 4 times daily; RNA, ribonucleic acid; S, Svedberg unit; spp, species; TID, 3 times daily.

*non-PEG nasal formulation available

5 to 14 days, however a retrospective study of Dutch primary care found that, on average, practitioners prescribed a second antibiotic after just 7 days, indicating that more studies are needed to determine the appropriate length of time in evaluating the effectiveness of first-line therapy.³ Mupirocin has been the most common initial choice in the United States, while fusidic acid may be a front-runner in other countries; retapamulin is usually reserved as an alternative when mupirocin or fusidic

acid resistance is suspected, however it is not approved for MRSA.^{16,7} The **table** summarizes important prescribing information for the topical agents.

With concerns over emerging resistance to the above topical agents, a new antibiotic with a differing mechanism of action, even compared to others within its quinolone class, has been added to the arsenal. Ozenoxacin is a nonfluorinated quinolone for impetigo treatment in patients 2 months of age and older.¹⁹ In vitro studies found

that 4 hours after a single application, ozenoxacin achieved bactericidal activity (killed the bacteria) at very low concentrations, with favorable activity against MRSA and quinolone-resistant strains of *S. aureus*, compared to the 24 hours it took for mupirocin, retapamulin, and fusidic acid to reach bacteriostatic activity (only inhibits the growth of bacteria). Because of its dual-target mechanism of action and rapid bactericidal activity, ozenoxacin has shown very low probability to induce sponta-

neous bacterial resistance. In two phase 3 clinical trials, ozenoxacin demonstrated superior clinical success rates over vehicle after 5 days of twice-daily treatment (pooled analysis 88.5% vs 78.2%, respectively [$P<.0001$]).²⁴ Ozenoxacin demonstrated negligible systemic absorption, and only 1 patient out of 362 assessed for safety in phase 3 trials reported worsening preexistent rosacea and seborrheic dermatitis.¹⁹ It is thought defluorination has contributed to the lack of photoreactivity and skin sensitization found with ozenoxacin, and that *S. aureus* efflux mechanisms do not impact its ability to reach high intracellular concentrations more rapidly than other quinolones.¹⁵

Oral antibiotics should be reserved for use on severe wide-spread impetigo, when resistance patterns to topical treatments is known, or when topical treatments have failed.⁶ Only penicillins that are immune to beta-lactamase, such as dicloxacillin or amoxicillin/clavulanate, should be considered for *S. pyogenes* and methicillin-sensitive *S. aureus* (MSSA). No single generation of cephalosporins has proven more effective over another, but cephalexin is widely used. Clindamycin, the tetracy-

cline class, and quinolones that cover Gram-positive organisms are best if MRSA is suspected.^{7,10} Trimethoprim/sulfamethoxazole treats MSSA and MRSA, but is ineffective against *S. pyogenes*.⁷ Oral antibiotics have generally more egregious side effect profiles than topicals, like diarrhea, anaphylaxis, photosensitivity, arthropathies/tendonopathies, or pseudomembranous colitis; additionally, they either need carefully calculated dosing, or should be avoided in children altogether (tetracyclines, fluoroquinolones).¹⁷ As these often are taken for 7 or more days, compliance and storage difficulties may be an issue.^{6,7}

Conclusion

In addressing skin infections, it is important that general practitioners and pediatricians, as well as extension caregivers such as physician assistants and nurse practitioners, become well acquainted with the proper differential diagnosis of impetigo and the local microbiology resistance patterns.^{4,6,8} Early treatment is recommended given the contagious nature of impetigo and the need to prevent escalation to more costly care. Topical antibiotics are the best initial choice for good antibiotic stewardship

and in considering the role of patient compliance and preference.^{1,4,6} As such, patients should be instructed to wash away crusted skin gently with soap and water prior to topical application. Also important is that the patient not return to daycare, school, sports, or work until the lesions have cleared or antibiotics have been consistently used for 24 hours.^{9,10,13,25} Patients should additionally be instructed on proper storage and to discard unused medications (both topical and oral) after therapy is complete.

Systemic therapy should be reserved for extensive disease and second-line therapy.¹⁷ While oral antibiotics are frequently used after perceived topical treatment failure, the release of the novel topical quinolone approved for impetigo, ozenoxacin, may prompt comparative studies and a review of practice guidelines within the next few years.¹³ Overall, prescribers need to weigh the quickest onset of action (to ensure the patient can return to work or school), tolerability, compliance, and the shortest duration of therapy coupled with pathogen-targeted treatment to ensure success while minimizing the risk of resistance.

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