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Impetigo Update: New Challenges in the Era of Methicillin Resistance

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Impetigo is a bacterial infection of the superficial epidermis most commonly seen in infants and children. It is clinically characterized by crusted erosions or ulcers that may arise as a primary infection in which bacterial invasion occurs through minor breaks in the cutaneous surface or a secondary infection of a preexisting dermatosis or infestation. Impetigo occurs in 2 forms: bullous and nonbullous. Staphylococcus aureus *currently is the most common overall cause of impetigo, but* Streptococcus pyogenes *remains an important cause in developing nations. Community-acquired methicillin-resistant* S aureus *(CA-MRSA) poses a challenge because of its enhanced virulence and increasing prevalence in children. For limited uncomplicated impetigo, either topical mupirocin or fusidic acid is as effective if not more effective than systemic antibiotics. For extensive or complicated impetigo, systemic antibiotics may be warranted, but β-lactam antibiotics should be avoided if methicillin-resistant* S aureus *(MRSA) is suspected.*

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Impetigo is a bacterial infection of the superficial epidermis usually occurring in children. It was first described by Fox[1] in 1864 as "circular, umbilicated quasi-bullous spots which increase centrifugally, and become covered by yellow flat crusts which cover over superficial ulceration." Impetigo is the most common skin infection in children with an annual incidence in the United Kingdom of 2.8% for children up to 4 years of age and 1.6% for 5 to 15 years of age.[2]

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Impetigo can be classified as a primary infection in which bacterial invasion occurs through minor breaks in the cutaneous surface or a secondary infection of a preexisting dermatosis or infestation. Likewise, impetigo can be clinically classified as bullous and nonbullous. In the last 2 decades, *Staphylococcus aureus* has eclipsed *Streptococcus pyogenes* as being the most common cause of nonbullous impetigo. *Streptococcus pyogenes*, however, may predominate in warm and humid climates. Bullous impetigo is exclusively caused by *S aureus*.[3]

Isolates of *S aureus* resistant to β-lactam antibiotics are referred to as methicillin-resistant *Staphylococcus aureus* (MRSA). Since being recognized in the early 1960s, the prevalence of MRSA in hospitals has steadily increased. In the late 1990s, MRSA infections started to originate in the community and became known as community-acquired MRSA (CA-MRSA), which is partially differentiated from hospital-acquired MRSA by most strains producing a neutrophil-destroying exotoxin known as Panton-Valentine leukocidin (P-VL).[4-6] This cytotoxin, produced from the genetic material of a bacteriophage infecting *S aureus*, initially was discovered in 1894 because of its ability to lyse leukocytes. It was later linked to soft-tissue infections in 1932.[7] As such, colonization with CA-MRSA is much more inclined to progress to clinical infection than methicillin-sensitive *S aureus* colonization.[8] Most cases involve skin and soft-tissue infections (SSTIs), with lung involvement including necrotizing pneumonia representing a relatively rare and distinct phenomenon.[8,9]

Methicillin resistance is conferred by small DNA cassettes that can be easily transferred by CA-MRSA. Acquiring CA-MRSA is most likely to occur in areas of close contact such as households and day care centers.[4] The prevalence of CA-MRSA has dramatically increased and is now the most common organism isolated in SSTIs in urban emergency

departments.[10] Not limited to adults, one study isolated P-VL$^+$ *S aureus* strains in 81 of 96 (84%) staphyloccocal SSTIs in children.[11] Further evidence of an alarming upward trend comes from Driscoll Children's Hospital in Corpus Christi, Texas, where infections increased from 9 in 1999 to 459 in 2003.[12]

The incidence of either CA-MRSA or hospital-acquired MRSA isolated from impetigo historically has been low. In a Japanese study, either type of MRSA was isolated in less than 20% of cases of impetigo between 1994 and 2000, which is lower than the average rate of MRSA isolation in other SSTIs. The incidence of MRSA in impetigo, however, was relatively high compared to prior accounts.[12] While P-VL genes tend to be expressed by *S aureus* isolates from furuncles and abscesses, bullous and nonbullous impetigo are more commonly associated with exfoliative toxins.[13]

Clinical Features

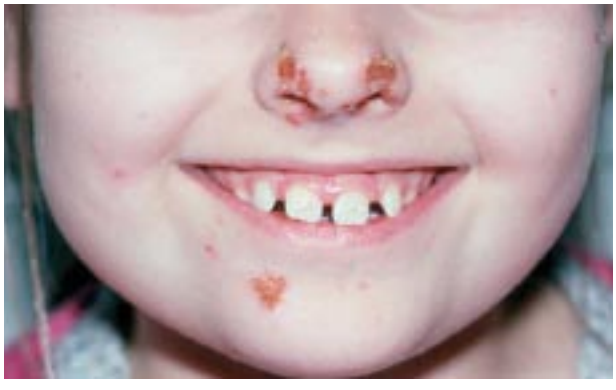
Bullous impetigo most commonly affects neonates, hence the occasionally used and inadvisably employed name *pemphigus neonatorum*. It is characterized by rapidly enlarging vesicles that evolve to flaccid bullae over grossly normal skin. Meanwhile, the encased fluid progresses from being clear yellow to turbid and darkish yellow. Within 24 to 48 hours, the pustules rupture, resulting in thin, light brown to golden yellow crusts and a typical collarette of scale at the periphery of the erosion (Figure).[14,15] Bullous impetigo appears to be less contagious than nonbullous impetigo and usually is sporadic in presentation.[16] Typical areas of occurrence include the trunk and extremities, as well as intertriginous zones such as the diaper area, neck folds, and axillae. The differential diagnosis of bullous impetigo is listed in Table 1.[14,17-19]

Nonbullous impetigo, otherwise known as impetigo contagiosa, typically affects preschool-aged children and has been known to occur in epidemics.[20] It may begin as vesicles or pustules that quickly rupture to form thick yellow crusts that can exceed 2 cm in diameter. Peripheral erythema, local lymphadenopathy, and pruritus may or may not be present. Spread to contiguous areas usually occurs through autoinoculation. Typically affected areas are parts of the body that are exposed to the environment such as the face and extremities.[14,15] The differential diagnosis of nonbullous impetigo is listed in Table 2.[14,21-24]

Table 1.

Differential Diagnosis of Bullous Impetigo

Bullous erythema multiforme
Bullous pemphigoid
Bullous scabies
Contact dermatitis
Dermatitis herpetiformis
Necrotizing fasciitis
Pemphigus vulgaris
Thermal burns



Child with bullous impetigo.

Common impetigo refers to secondary impetiginization of conditions that disrupt the integrity of the epidermis, including insect bites, abrasions, varicella, dermatitis, tinea capitis, pediculosis, and scabies. In addition, common impetigo can complicate systemic diseases such as diabetes mellitus and AIDS.[14,25] The clinical presentation resembles nonbullous impetigo.[14,15] Both atopic dermatitis and cutaneous T-cell lymphoma have a helper T cell type 2 (T_H2) cytokine profile and appear to be associated with decreased antimicrobial peptides, perhaps predisposing patients to bacterial colonization and infection.[26,27]

Although there are typical histologic findings, a clinical judgment usually is sufficient to make a diagnosis. If the diagnosis is in doubt or if impetigo is refractory to treatment, a biopsy may be warranted. Under the microscope, vesicopustules arise in the upper epidermis, either above, within, or below the granular layer. In nonbullous impetigo, numerous neutrophils are seen within the vesicopustule, along with occasional acantholytic cells and gram-positive cocci in clusters or chains. Under the vesicopustule, the malpighian stratum is spongiotic with migrating neutrophils sometimes evident. Bullous

Table 2.

Differential Diagnosis of Nonbullous Impetigo

Atopic dermatitis
Contact dermatitis
Dermatophytosis
Discoid lupus erythematosus
Herpes simplex virus
Herpes zoster (shingles)
Pediculosis
Scabies
Varicella (chickenpox)

impetigo shows few, if any, inflammatory cells within the bulla cavity.[28]

Complications

The occurrence of invasive infection (ie, cellulitis, lymphangitis, necrotizing fasciitis, sepsis) has substantially decreased since antibiotics have been in widespread use.[17,18] Likewise, the incidence of toxin-mediated staphylococcal scalded skin syndrome has dramatically decreased but remains a common and serious disease in infants and children.[29] When considering staphylococcal infections of facial regions drained by the cavernous sinus, it is important to recognize cavernous sinus thrombosis, which is an uncommon but potentially lethal complication.[30]

Another serious complication of *S pyogenes* impetigo is acute poststreptococcal glomerulonephritis, which can occur in up to 5% of patients. Appropriate antibiotic treatment is believed to have no effect on the likelihood of developing this complication. In children, acute poststreptococcal glomerulonephritis normally resolves without sequelae; in adults, the effects can be more long-term.[14] Streptococcal skin infections currently are not thought to be associated with the development of acute rheumatic fever; however, this concept has been called into question.[31,32]

Treatment

Impetigo usually is a self-limiting infection with spontaneous resolution expected. However, placebo arms of controlled trials have shown variability in resolution rates ranging from 8% to 42% after 7 to 10 days.[33,34] Treatment is initiated to avoid complications, expedite resolution, and prevent recurrence and spread to other people.

Methicillin-resistant *S aureus* has become increasingly common in children. Despite the enhanced virulence and rapid progression of MRSA strains, uncomplicated infections can still be treated with removal of crusts, good hygiene, and topical antibiotics.[35] The use of disinfecting agents such as chlorhexidine or povidone-iodine has no role as a sole or supplementary treatment.[3]

In general, children are more compliant with topical rather than oral treatment, and fewer systemic side effects occur.[36] Mupirocin and fusidic acid, the latter available in Canada and elsewhere except the United States, are the only topical antibiotics shown to be more effective than placebo. Based on a Cochrane review and meta-analysis, treatment with either mupirocin or fusidic acid for one week is as effective if not more effective than systemic antibiotics for localized uncomplicated impetigo.[3] Other topical agents such as bacitracin, polymyxin B, neomycin, and gentamicin tend to be less beneficial.[2,3]

Mupirocin and fusidic acid generally are effective in treating impetigo caused by MRSA.[37,38] The emergence of fusidic acid–resistant *S aureus*, including MRSA, has threatened the utility of this antibiotic. In the United Kingdom, *S aureus* resistance to fusidic acid has increased from 8.1% in 1995 to 17.3% in 2001, which correlates directly with a 2-fold increase in fusidic acid prescriptions during the same time interval.[39,40] Similarly, low-level and high-level resistance to mupirocin has been identified in isolates of MRSA. The latter predicts clinical failure and may be increasing in prevalence.[4]

The recent introduction of topical retapamulin has provided clinicians with another topical treatment option, especially if treatment with mupirocin fails.[8] As the first member of the newly developed pleuromutilin class of antibiotics, retapamulin employs a unique mechanism to interrupt bacterial protein synthesis. More specifically, retapamulin selectively binds to a novel site on the 50S ribosomal subunit, subsequently blocking peptidyltransferase and P site interactions bringing the elongation phase of protein synthesis to a halt.[41]

Retapamulin has demonstrated good in vitro activity against various streptococcal and staphylococcal isolates, including erythromycin-resistant *S pyogenes* as well as fusidic acid–resistant or mupirocin-resistant *S aureus* and MRSA (inclusive of P-VL$^+$strains).[41] Despite in vitro efficacy against MRSA, retapamulin has shown reduced activity against MRSA in secondarily infected traumatic lesions. As a result, retapamulin is

approved for impetigo due to *S aureus* (excluding MRSA) or *S pyogenes* in patients aged 9 months or older.[41]

Retapamulin has demonstrated low potential for development of resistance in both single-step and multi-step passage testing.[42,43] Reduced susceptibility to retapamulin may develop from mutations in the retapamulin ribosomal binding site or a nonspecific efflux mechanism.[44] In a randomized, double-blind, placebo-controlled trial (N=213), retapamulin ointment 1% applied twice daily was superior to placebo after 5 days of treatment of impetigo (85.6% vs 52.1% success rate).[45]

Systemic antibiotics may be required to treat extensive impetigo. Before starting an oral regimen for impetigo, culture and sensitivity studies should be obtained to detect MRSA and other antibiotic-resistant organisms. Empiric antibiotic choice should be guided by the prevalence of MRSA in the community. Although there is no specific threshold that mandates empiric MRSA coverage, some experts recommend an arbitrary prevalence of more than 10% to 15%.[46,47]

When MRSA is not suspected, treatment with an anti-staphylococcal penicillin or cephalosporin is reasonable for first-line therapy.[46] When MRSA is suspected, either due to high community prevalence or positive culture and sensitivity, β-lactams should be avoided.[35] The optimal antibiotic regimen, however, remains unclear. Results of susceptibility testing and clinical experience support the use of clindamycin, tetracyclines, and trimethoprim-sulfamethoxazole, but their efficacy in SSTIs due to MRSA awaits further study or comparison in clinical trials. Fluoroquinolones should be avoided because of the increased risk for arthropathy in children and rapid induction of resistance.[4] Interestingly, prior use of a fluoroquinolone has been shown to be an independent risk factor for persistent MRSA colonization, which may be due to the increased expression of *S aureus* adherence factors and overexpression of fibronectins-binding protein in the presence of fluoroquinolones.[48,49]

Disadvantages of using clindamycin are *Clostridium difficile* colitis and inducible resistance. The latter refers to MRSA isolates that appear erythromycin resistant and clindamycin susceptible by routine susceptibility testing but exhibit in vivo resistance to clindamycin resulting in treatment failure. In these instances, use of the specialized laboratory D-zone disk diffusion test is warranted to detect inducible clindamycin resistance.[4,46] Trimethoprim-sulfamethoxazole has been a popular choice, reportedly comprising more than half the antibiotic regimens active against CA-MRSA prescribed in the emergency department.[50] Rarely the use of trimethoprim-sulfamethoxazole can be associated with life-threatening adverse events such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Screening for MRSA colonization on hospital admission is increasingly being mandated to reduce hospital-acquired MRSA infections. Rapid diagnosis of MRSA carriage has become possible through detection of the *mecA* gene using multiplex polymerase chain reaction.[51] While the topic is still controversial, studies have shown that rapid MRSA screening on hospital admission does not significantly reduce MRSA transmission and infection.[51,52]

Efforts to eliminate *S aureus* colonization have been employed in healthcare settings and more recently in the community to prevent autoinfection among colonized patients and control MRSA outbreaks. Among these measures have been various combinations of topical and systemic antibiotics and antiseptic body washes. The most extensive research in MRSA decolonization has been conducted with mupirocin, which is applied to the anterior nares 2 to 3 times daily for 5 days.[49] In addition, current evidence now expands the reservoir domain of MRSA to also include the perineum, groin, and axillae.[53] To improve the likelihood of eradication, bathing or showering with chlorhexidine in combination with the topical application of mupirocin may be recommended. Bleach baths also may be effective based on an in vitro study demonstrating a greater than 3-log decrease in MRSA colony-forming units after 5 minutes in 2.5 L/mL of bleach, which nearly equates to half a cup of bleach in a quarter tub of water.[54] Bleach baths may hold promising value for MRSA decolonization pending further investigation in clinical settings.

In general, the efficacy of decolonization therapy of any kind for preventing *S aureus* infections has not been well-established.[46] It also is unclear if it is preferable to provide a decolonization regimen to all members of a cohort or just those with confirmed colonization. In addition, limitations to decolonization include recolonization, emerging bacterial resistance to mupirocin, and extranasal colonization if using mupirocin alone.[46,55] As such, the Centers for Disease Control and Prevention currently support decolonization regimens for patients with multiple documented recurrences of MRSA infection or ongoing MRSA transmission occurring in a well-defined closely-associated cohort. Decolonization, however, should be considered only when standard prevention measures such as hand washing, wound care, and good general hygiene have been unsuccessful at interrupting transmission.[46]

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