Impetigo, Erysipelas and Cellulitis

Dennis L. Stevens, PhD, MD[⊠][1] and Amy E. Bryant, PhD[2]

Created: February 10, 2016.

Introduction

Streptococcus pyogenes (group A *Streptococcus*) is one of the most important bacterial causes of skin and soft tissue infections (SSTIs) worldwide. In addition, no other pathogen causes as many diverse clinical entities as *S. pyogenes*. Specifically, this organism causes infections in the superficial keratin layer (impetigo), the superficial epidermis (erysipelas), the subcutaneous tissue (cellulitis), the fascia (necrotizing fasciitis), or muscle (myositis and myonecrosis). It is also the etiologic agent of scarlet fever and Streptococcal Toxic Shock Syndrome (StrepTSS). Impetigo is a non-life-threatening infection, but can result in post-streptococcal acute glomerulonephritis (AGN). Cellulitis and erysipelas can be mild or moderately severe, while necrotizing fasciitis, myonecrosis and StrepTSS are life-threatening. This chapter focuses on the clinical and epidemiological features of these infections, as well as treatment options, and includes a discussion of bacterial pathogenesis.

Anatomical Relationship of Skin and Skin Structure Infections with *S. pyogenes*

An understanding of the anatomy of the skin layers is crucial for the clinician to establish a correct diagnosis of streptococcal skin and soft tissue infections. Figure 1 illustrates the relationship between different anatomical structures and the types of *S. pyogenes* infections that affect specific layers of the skin and deeper tissues (from (Stevens, 2015)). Note that impetigo involves the outer keratin layer of the skin, which results in crusty lesions, whereas erysipelas affects the superficial epidermis, which results in well-demarcated borders of infection and a brilliant red skin color. Cellulitis occurs in the deeper subcutaneous tissues and has a pinkish hue with less defined edges. Necrotizing fasciitis caused by *S. pyogenes* has been defined by surgeons as an infection that involves the superficial or deep fascia, in association with destruction of tissue. In reality, necrotizing fasciitis in its later stages involves all layers of the skin and muscle as well. Muscle infection by *S. pyogenes* can take on two forms, myositis or myonecrosis. Myositis is not usually associated with necrosis and is most commonly caused by *Staphylococcus aureus*. Myonecrosis due to *S. pyogenes* is an aggressive, often life-threatening infection that can develop in any open wound or by hematogenous seeding of muscle that has been injured by a simple strain or other type of non-penetrating trauma (such as a contusion). The latter infection has been called cryptogenic

Author Affiliations: 1 VA Medical Center, Infectious Diseases Section, Boise, ID; Email: dlsteven@mindspring.com. 2 VA Medical Center, Infectious Diseases Section, Boise, ID; Email: amy.bryant@va.gov.

⊠ Corresponding author.

or spontaneous myonecrosis and is associated with mortality as high as 80%. Note the intimate relationship of blood supply to the muscle layer. As myonecrosis progresses, the blood supply becomes compromised, resulting in the appearance of purple violaceous bullae, hemorrhage into the skin and rapid progression of tissue destruction. See the chapter on invasive *S. pyogenes* infections for further discussion of the pathogenesis of necrotizing fasciitis and myonecrosis.

Figure 2 shows a treatment algorithm prepared for the 2014 Infectious Diseases Society of America Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections (SSTI) (Stevens, et al., 2014). Purulent soft tissue infections are most commonly caused by staphylococcal species, whereas group A streptococcal cellulitis, erysipelas, necrotizing fasciitis, and myonecrosis are non-purulent. Once the clinician has made this distinction, the next decision is to determine whether the patient's signs, symptoms, and laboratory tests indicate mild, moderate, or severe infection. Appropriate diagnostic and therapeutic approaches are then provided for each category.

Streptococcal pyoderma

Pyoderma, impetigo, and impetigo contagiosa are terms used synonymously to describe discrete purulent lesions that are primary infections of the skin and that are extremely prevalent in many parts of the world. In the great majority of cases, pyoderma is caused by β-hemolytic streptococci, *Staphylococcus aureus*, or both.

Epidemiology

The number of existing cases of streptococcal pyoderma in children less than 15 years of age is estimated to be 111 million (Carapetis, Steer, Mulholland, & Weber, 2005). Notably, this figure excludes cases in adults and those in adults and children in developed countries. The incidence of this disease is markedly influenced by several factors, the most important of which appear to be climate and hygiene—both of which parallel global socio-economic inequities between developed countries (northern latitudes, temperate climates) and developing countries (equatorial latitudes, tropical/sub-tropical climates). Thus, the greatest global burden of this infection is found in economically disadvantaged children in tropical or subtropical climates, though it is also prevalent in northern climates during the summer months (Ferrieri, Dajani, Wannamaker, & Chapman, 1972). The peak incidence of impetigo is in children aged 2 to 5 years, but may also occur among older children and adults whose recreational activities or occupation results in cutaneous cuts or abrasions (Adams, 2002; Fehrs, et al., 1987; Wasserzug, et al., 2009). There is no particular gender predilection, and all races appear to be susceptible.

Meticulous prospective studies of streptococcal impetigo have demonstrated that the responsible microorganisms initially colonize the unbroken skin (Ferrieri, Dajani, Wannamaker, & Chapman, 1972), an observation that probably explains the influence of personal hygiene on the incidence of disease. Development of skin colonization with a given streptococcal strain precedes the development of impetiginous lesions by an average interval of 10 days. The mechanism of production of skin lesions is unproven, but it is most likely caused by intradermal inoculation of surface organisms by abrasions, minor trauma, or insect bites. Frequently, there is a transfer of the streptococcal strains from the skin and/or pyoderma lesions to the upper respiratory tract. The interval between colonization of the skin and colonization of the nose and/or throat averages 2 to 3 weeks.

Scabies is also highly prevalent in socially disadvantaged communities, such as indigenous populations and in developing countries. Its association with group A streptococcal pyoderma is well established, and treatment of scabies clearly decreases the prevalence of subsequent bacterial infection. However, such infestations may do more than simply provide a portal of bacterial entry into the skin. A recent molecular study by Mika and colleagues demonstrated that the intestinal compounds excreted from the scabies mite have potent complement-inhibitory functions that promote the growth of group A streptococcus, even in the presence of type-specific antibodies (Mika, et al., 2012). These findings provide the first molecular mechanism to account for the well-recognized association between scabies and streptococcal pyoderma and suggest new targets for intervention.
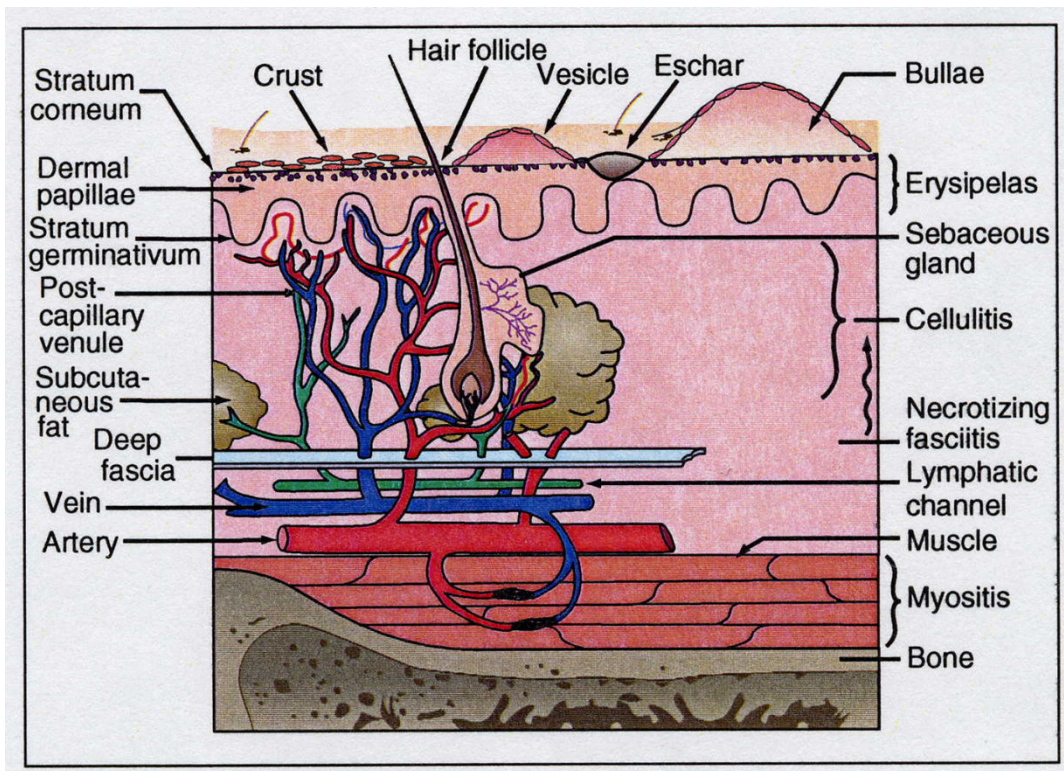
Figure 1. Anatomical relationship between skin and skin structures and different *S. pyogenes* infections. From Harrison's Principals of Internal Medicine, 19th edition, and used with permission (Stevens, 2015).

Bacteriology and Immunology

Streptococci isolated from pyodermal lesions are primarily group A, but occasionally other serogroups are responsible, such as C and G. *S. pyogenes* strains that cause impetigo differ in several respects from those usually associated with tonsillitis and pharyngitis. Skin strains belong to different M serotypes and to different *emm* genotype patterns than the classic throat strains (reviewed in (Bessen, 2009)). For example, among the 3 main *emm* pattern genotypes, (namely, AC, D and E), the *emm* pattern AC group has a strong predilection to cause infection of the throat, and *emm* pattern D strains have a strong tendency to cause impetigo (Bessen, 2009). In contrast, the pattern E strains are designated generalists that readily cause infections at both tissue sites (Anthony, Kaplan, Wannamaker, & Chapman, 1976). Thus, *S. pyogenes* strains can be divided into 3 clinically and ecologically relevant groups, based on their *emm* pattern genotype. Aside from differences in *emm*, throat and skin strains can also be differentiated by other genetic markers (Fiorentino, Beall, Mshar, & Bessen, 1997) and functional traits, including differences in their binding avidity for keratinocytes. Because most skin strains have been identified more recently, they tend to be comprised of the higher numbered M types. The classic skin strain associated with impetigo and post-streptococcal AGN is the M-49 strain, which was isolated in Red Lake, Minnesota.

Clinical manifestations and diagnosis

The lesion of streptococcal pyoderma begins as a papule that rapidly evolves into a vesicle, surrounded by an area of erythema. The vesicular lesions are evanescent and rarely clinically recognized; they give rise to pustules that gradually enlarge and then break down over a period of 4 to 6 days to form characteristic thick crusts. The lesions heal slowly and leave depigmented areas. A deeply ulcerated form of impetigo is known as ecthyma.
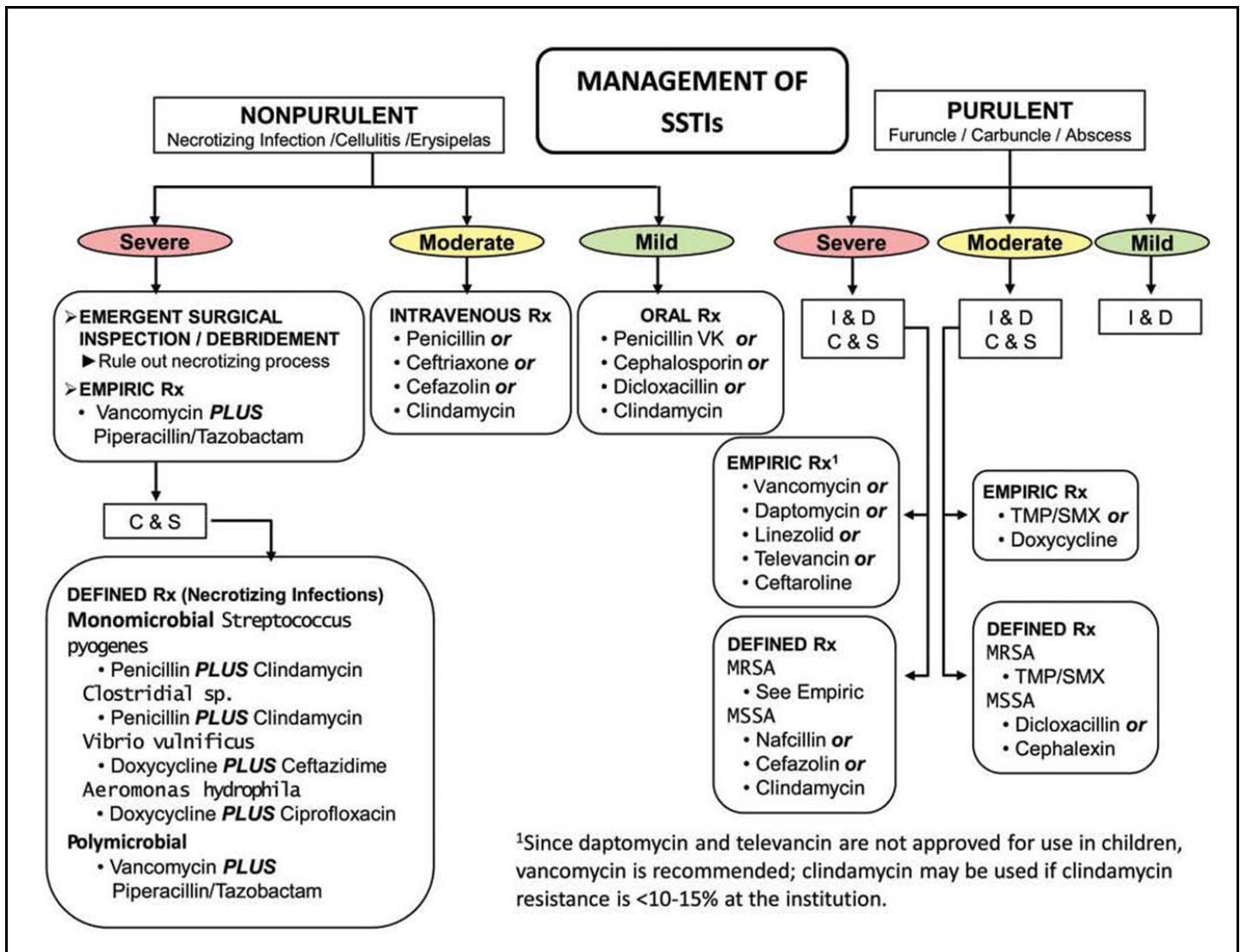
Figure 2. Algorithm for the Management of Skin and Soft Tissue Infections. From Clinical Infectious Diseases, 2014, and used with permission (Stevens, et al., 2014).

Streptococcal impetigo occurs on exposed areas of the body, most frequently on the lower extremities or face. The lesions remain well localized, but frequently appear in multiples. Although regional lymphadenitis may occur, systemic symptoms are not ordinarily present.

In the past, the lesions previously described could be confidently diagnosed as streptococcal. This was the predominant form of impetigo, which could be distinguished from bullous impetigo caused by phage group II *S. aureus*. Although bullous impetigo remains almost exclusively caused by staphylococcus, the bacteriology of non-bullous impetigo has changed (Barnett & Frieden, 1992). *S. aureus*, either alone or in combination with *S. pyogenes*, is now the predominant causative agent (Gonzalez, et al., 1989). Almost all such staphylococci are penicillinase producers. Therefore, treatment with penicillin, which had previously been highly effective against non-bullous impetigo, even when both streptococci and staphylococci were isolated from the lesions, now frequently fails (Demidovich, Wittler, Ruff, Bass, & Browning, 1990).

Assays of anti-streptolysin O (ASO) antibodies are of no value in the diagnosis and management of impetigo, because the ASO response is weak in patients with streptococcal impetigo (Kaplan, Anthony, Chapman, Ayoub, & Wannamaker, 1970; Bisno, Nelson, Waytz, & Brunt, 1973), presumably because the activity of streptolysin O is

inhibited by skin lipids (cholesterol) (Kaplan & Wannamaker, 1976). In contrast, anti–DNase B levels are elevated (Kaplan, Anthony, Chapman, Ayoub, & Wannamaker, 1970; Bisno, Nelson, Waytz, & Brunt, 1973) and thus provide helpful supporting evidence of recent streptococcal infection in patients who are suspected of having post-streptococcal glomerulonephritis.

Treatment and prevention

Because of the current frequency of isolation of *S. aureus* from non-bullous impetigo lesions and concomitant reports of penicillin failures (Demidovich, Wittler, Ruff, Bass, & Browning, 1990; Dagan & Bar-David, 1989; Barton & Friedman, 1987), penicillinase-resistant penicillins or first-generation cephalosporins are preferred (Demidovich, Wittler, Ruff, Bass, & Browning, 1990). Erythromycin has long been a mainstay of pyoderma therapy, but its use is contraindicated in areas in which erythromycin-resistant strains of *S. aureus* or, more recently, *S. pyogenes* are prevalent. Topical therapy with mupirocin is equivalent to oral systemic antimicrobial agents (Barton, Friedman, Sharkey, Schneller, & Swierkosz, 1989; Britton, Fajardo, & Krafte-Jacobs, 1990), and may be used when lesions are limited in number. However, it is expensive, and some strains of staphylococci may be resistant (Yun, et al., 2003). Retapamulin, a novel pleuromutilin antibacterial, has recently been approved by the FDA for treatment of bullous and non-bullous impetigo caused by *S. pyogenes* and methicillin-susceptible strains of *S. aureus* in children 9 months of age or older (Yang & Keam, 2008). In vitro data have suggested that it may be more effective than mupirocin against methicillin-resistant *Staphylococcus aureus* (MRSA).

Improved living conditions, improved personal hygiene and topical treatment of impetiginous lesions can prevent the spread of impetigo to susceptible individuals. In addition, a recent molecular study provided evidence that scabies mite proteins act as complement inhibitors and enhance *S. pyogenes* growth in whole blood assays, presumably by the inhibition of host innate immunity. Based on this groundwork data, we hypothesize that the complement-inhibitory functions of excreted gut molecules promote the growth of bacterial pathogens in the microenvironment of the epidermal burrows.

Complications

Suppurative complications are uncommon, but cutaneous infections with nephritogenic strains of *S. pyogenes* predispose patients to post-streptococcal AGN in many areas of the world. As yet, there are no conclusive data to indicate that treatment of an individual case of pyoderma prevents the subsequent occurrence of nephritis in these patients. Such therapy is nevertheless important as an epidemiologic measure in eradicating nephritogenic strains from the environment. For as-yet unexplained reasons, rheumatic fever has never been shown to occur after streptococcal pyoderma.

Erysipelas

Streptococci were first demonstrated in cases of erysipelas and wound infections by Billroth in 1874 and in the blood of a patient with puerperal sepsis by Pasteur in 1879. In 1883, Fehleisen showed that hemolytic streptococci fulfilled Koch's postulates when he isolated chain-forming organisms in pure culture from erysipelas lesions and then demonstrated that these organisms could induce typical erysipelas in humans. Rosenbach applied the designation *Streptococcus pyogenes* to these organisms in 1884. In 1938, Lancefield gave them the distinction of group A streptococcus.

Erysipelas is a superficial cutaneous process that is usually restricted to the dermis, but with prominent lymphatic involvement. It is distinguished clinically from other forms of cutaneous infection by three features: the lesions are raised above the level of the surrounding skin, there is a clear line of demarcation between involved and uninvolved tissue, and the lesions are a brilliant salmon-red color. This disorder is more common in infants, young children, and older adults, and is almost always caused by β-hemolytic streptococci. In most cases, the infecting agent is *S. pyogenes*, but similar lesions can be caused by groups C or G streptococci. Rarely, group B streptococci or *S. aureus* may be the culprits. In older reports, erysipelas was described as

characteristically involving the butterfly area of the face, but at present, the lower extremities are more frequently involved. In patients with facial erysipelas, there is frequently a history of preceding streptococcal sore throat, although the exact mode of spread to the skin is unknown. When erysipelas involves the extremities, breaks in the cutaneous barrier serve as portals of entry; these include surgical incisions, trauma or abrasions, dermatologic diseases (such as psoriasis), or local fungal infections.

The cutaneous lesion begins as a localized area of erythema and swelling and then spreads rapidly with advancing red margins, which are raised and well demarcated from adjacent normal tissue. There is marked edema, often with bleb formation, and in facial erysipelas, the eyes are frequently swollen shut. The lesion may demonstrate central resolution while continuing to extend on the periphery. The cutaneous inflammation is accompanied by chills, fever, and toxicity.

The differential diagnosis is limited. Early on, the lesions of facial herpes zoster, contact dermatitis, or giant urticaria may be confused with erysipelas. Lesions that resemble erysipelas may occur in patients with familial Mediterranean fever. Cutaneous lesions similar in appearance to those of erysipelas may occur on the hands of patients who sustain cuts or abrasions while handling fish or meats. This entity, which is known as erysipeloid of Rosenbach and caused by *Erysipelothrix rhusiopathiae*, is usually unaccompanied by fever or systemic symptoms.

With early diagnosis and treatment, the prognosis is excellent. Rarely, however, the process may spread to deeper levels of the skin and soft tissues. Penicillin, either parenterally or orally, depending on clinical severity, is the treatment of choice. If a staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or cephalosporin should be selected. In a randomized, prospective multicenter trial (Bernard, et al., 1992), roxithromycin, a macrolide antimicrobial, was equivalent to penicillin. However, increased levels of macrolide resistance among *S. pyogenes* have been detected in certain areas of the United States (Martin, Green, Barbadora, & Wald, 2002; York, Gibbs, Perdreau-Remington, & Brooks, 1999).

Streptococcal cellulitis

Streptococcal cellulitis, an acute spreading inflammation of the skin and subcutaneous tissues, usually results from infection of burns, wounds, or surgical incisions, but may also follow mild trauma. Clinical findings include local pain, tenderness, swelling, and erythema. The process may rapidly extend to involve large areas of skin. Systemic manifestations include fever, chills, and malaise, and there may be associated lymphangitis, bacteremia, or both. In contrast to erysipelas, the lesion is not raised, the demarcation between involved and uninvolved skin is indistinct, and lesions are more pink than salmon-red in color. Often, however, the clinical differentiation between these entities is not clear-cut.

Two predisposing causes of streptococcal cellulitis deserve special mention. One is the parenteral injection of illicit drugs (Lentnek, Giger, & O'Rourke, 1990; Barg, Kish, Kauffman, & Supena, 1985). These cases are often associated with bacteremia and deep tissue infections, such as septic thrombophlebitis, suppurative arthritis, osteomyelitis, and occasionally infective endocarditis. Second, patients who have impaired lymphatic drainage from upper or lower extremities are prone to recurrent episodes of streptococcal cellulitis. Examples include individuals with filariasis and women who have undergone radical mastectomy with axillary node dissection (Simon & Cody, 1992). It is speculated that repetitive infection further damages local lymphatics and worsens lymphatic stasis (de Godoy, de Godoy, Valente, Camacho, & Paiva, 2000).

Recurrent episodes of severe cellulitis have also been reported in certain patients who have undergone coronary artery bypass grafting (Baddour & Bisno, 1982). The lesion invariably occurs in the extremity from which the saphenous vein was removed, and at times, may exhibit features of erysipelas. Patients with tinea pedis of the venectomy limb appear to be particularly at risk (Baddour & Bisno, 1984; Semel & Goldin, 1996). As with other forms of cellulitis, pathogenic bacteria are difficult to recover during these episodes, but the appearance of the lesions and the response to penicillin therapy suggest a streptococcal cause. The few β-hemolytic streptococci

that have been recovered and characterized often belong to serogroups other than group A (Baddour & Bisno, 1985).

Disruption of the cutaneous barrier (leg ulcers, wounds, dermatophytosis) is a risk factor for the development of cutaneous streptococcal infection (Dupuy, et al., 1999). There is suggestive evidence that local dermatophyte infection (such as athlete's foot) may serve as a reservoir for β-hemolytic streptococci that initiate episodes of erysipelas or cellulitis of the lower extremities (Semel & Goldin, 1996; Roldan, Mata-Essayag, & Hartung, 2000). Thus, care should be taken to eradicate such fungal infections in patients who experience recurrent bouts of erysipelas or cellulitis. Another potential reservoir is anal streptococcal colonization (Eriksson B. K., 1999). Other risk factors include venous insufficiency, edema, and obesity (Dupuy, et al., 1999). An increased risk of recurrent cellulitis has been associated with a lack of foot hygiene, and has also been reported in homeless persons (Lewis, Peter, Gómez-Marín, & Bisno, 2006).

Cellulitis may be caused by infection with a variety of bacterial pathogens, but most cases are caused by *S. pyogenes* (or, occasionally, streptococci of groups B, C, or G) or by *S. aureus. S. aureus* infection of the skin is usually associated with a pyogenic, fluctuant focus with surrounding erythema and has been referred to as "purulent cellulitis;" however, a better term would be purulent skin and soft tissue infection with surrounding erythema. In these cases, the erythema is entirely due to the host response to the purulent focus. The reddened skin is not itself infected, since simple drainage and no antibiotics are usually enough to resolve the infection. In the absence of positive blood cultures, which are present in only 5% of cases of non-purulent cellulitis, a specific microbiologic diagnosis is often not possible. Aspirate or biopsy samples from sites of active cellulitis are helpful when positive on smear or culture, but unfortunately, such specimens are usually negative in adult patients (Hook, et al., 1986; Howe, Eduardo Fajardo, & Orcutt, 1987; Newell & Norden, 1988).

Treatment

In some cases, it may be difficult to differentiate streptococcal from staphylococcal skin and soft tissue infection on initial presentation. In this case, a semi-synthetic penicillinase-resistant penicillin should be used. In penicillin-allergic patients, a first-generation cephalosporin may be used if the hypersensitivity is not of the immediate type. Clindamycin, linezolid, or vancomycin may be used in patients who manifest anaphylactic hypersensitivity to β-lactam antibiotics, and these agents should be administered later if there is reason to suspect infection with MRSA strains. Patients with milder cases of streptococcal cellulitis may be switched to oral medications after an initial favorable response to parenteral therapy.

The role of continuous antimicrobial prophylaxis (Wang, et al., 1997; Sjöblom, Eriksson, Jorup-Rönström, Karkkonen, & Lindqvist, 1993; Kremer, Zuckerman, Avraham, & Raz, 1991) in patients prone to frequent recurrences remains unsettled. At present, such prophylaxis seems justified only for patients with very frequent or severe episodes, and an optimal regimen has not been established.

Other Streptococcal Infections with Skin Manifestations

Suppurative soft-tissue complications following streptococcal pharyngitis

Inflammation in the facial area induced by acute streptococcal infection may affect structures that are directly contiguous to the pharynx or that drain that site. Such relatively rare complications include peritonsillar cellulitis, peritonsillar abscess, retropharyngeal abscess, and suppurative cervical lymphadenitis, as well as mastoiditis, acute sinusitis, and otitis media (Dajani, Taubert, Ferrieri, Peter, & Shulman, 1995). However, peritonsillar or retropharyngeal abscesses, frequently contain a variety of other oral flora, including anaerobes, with or without *S. pyogenes. S. pyogenes* are responsible for only a small minority of cases of otitis media or sinusitis.

Scarlet fever

Scarlet fever results from infection with a streptococcal strain that elaborates streptococcal pyrogenic exotoxins (erythrogenic toxins). Although this disease is usually associated with pharyngeal infections, it may follow streptococcal infections at other sites, such as wound infections or puerperal sepsis. The clinical syndrome is similar in most respects to that associated with non-toxigenic strains, except for the characteristic scarlatina-type rash. The latter must be differentiated from those of viral exanthems, drug eruptions, staphylococcal toxic shock syndrome, and Kawasaki disease.

The rash usually appears on the second day of clinical illness as a diffuse red blush, with many points of deeper red that blanch on pressure. It is often first noted over the upper part of the chest, and then spreads to the remainder of the trunk, neck, and extremities. The palms, soles, and usually the face are spared. Skin folds in the neck, axillae, groin, elbows, and knees appear as lines of deeper red (Pastia's lines). There are scattered petechiae, and the Rumpel-Leeds test of capillary fragility is positive. Occlusion of sweat glands imparts a sandpaper texture to the skin—a particularly helpful finding in dark-skinned patients.

The face appears flushed, except for marked circumoral pallor. In addition to findings of exudative pharyngitis and tonsillitis, patients display an exanthem that is characterized by small, red, hemorrhagic spots on the hard and soft palates. The tongue is initially covered with a yellowish-white coating, through which may be seen the red papillae (white strawberry tongue). Later, the coating disappears, and the tongue is beefy red in appearance (red strawberry tongue). The skin rash fades over the course of one week and is followed by extensive desquamation that lasts for several weeks. A modest eosinophilia may be present early in the course of the illness.

Severe forms of scarlet fever, associated with either local or hematogenous spread of the organism (septic scarlet fever) or with profound toxemia (toxic scarlet fever), are characterized by a high fever and marked systemic toxicity. The course may be complicated by arthritis, jaundice, and, very rarely, hydrops of the gallbladder. Such severe forms of the disease are infrequent in the antibiotic era. However, in the late 1800s, scarlet fever was associated with mortalities of 20% in Chicago, New York and Scandinavia. During the American Civil War, epidemics of surgical scarlet fever, also called "hospital gangrene," developed among soldiers after amputation for wounds. Recently, an epidemic of 900 cases of scarlet fever occurred in China in 2011 between January and July that was associated with *emm*-12 strains of *S. pyogenes* (Luk, et al., 2012).

Lymphangitis

Lymphangitis may accompany cellulitis or may occur after clinically minor or inapparent skin infection. Lymphangitis is readily recognized by the presence of red, tender, linear streaks directed toward enlarged, tender, regional lymph nodes. It is accompanied by systemic symptoms, such as chills, fever, malaise, and headache.

Puerperal sepsis and infection of the genitalia

Puerperal sepsis follows abortion or natural childbirth when streptococci that colonize the vaginal vault or are transmitted from medical personnel invade the endometrium and surrounding structures, lymphatics, and bloodstream. The resulting endometritis and septicemia may be complicated by pelvic cellulitis, septic pelvic thrombophlebitis, peritonitis, or pelvic abscess. This disease was associated with high mortality in the pre-antibiotic era. Vaginal wall tears during delivery or episiotomy sites can also be infected with *S. pyogenes* and can cause cellulitis of the perineum or necrotizing fasciitis. Clostridial species can also cause necrotizing infection under these conditions, but can be distinguished from *S. pyogenes*, because the latter does not produce gas.

S. pyogenes perianal cellulitis and vulvo-vaginitis are symptomatic but benign disorders that primarily affect children (Petersen, Kaltoft, Misfeldt, Schumacher, & Schønheyder, 2003; Mogielnicki, Schwartzman, & Elliott, 2000). Asymptomatic carriage of *S. pyogenes* in the vagina, anus, scalp or, rarely, the upper respiratory tract of

adults has, however, been the source of some outbreaks of nosocomial streptococcal infection (Mastro, et al., 1990).

Streptococcal Virulence Factors Associated with SSTI

Adhesins

A number of somatic streptococcal components play critical roles in the first step of colonization, namely, adherence to the surface of human epithelial cells. At least 17 adhesin candidates have been described (Courtney, Hasty, & Dale, 2002; Hasty, Itzhak, Courtney, & Doyle, 1992), but the most extensively studied have been lipoteichoic acid (LTA), M protein, and fibronectin-binding proteins. Through hydrophobic interactions, LTA serves as a "first-step" adhesin, which brings the organisms into close contact with host cells and then allows other adhesins to promote high-affinity binding (Hasty, Itzhak, Courtney, & Doyle, 1992). Although M protein does not appear to promote adhesion to human buccal or tonsillar epithelial cells (Ofek, Beachey, Jefferson, & Campbell, 1975; Caparon, Stephens, Olsén, & Scott, 1991), it does mediate the adherence to skin keratinocytes via the attachment of the C repeat region to keratinocyte membrane cofactor CD46 (Okada, Pentland, Falk, & Caparon, 1994; Okada, Liszewski, Atkinson, & Caparon, 1995). *S. pyogenes* surface proteins that bind fibronectin have been studied extensively and are important in adherence to both throat and skin. These include protein F1 (PrtF1) (Hanski & Caparon, 1992), also known as SfbI (streptococcal fibronectin-binding protein I) (Talay, Valentin-Weigand, Jerlström, Timmis, & Chhatwal, 1992); and related proteins known as SbfII (Kreikemeyer, Talay, & Chhatwal, 1995), FBP54 (Courtney, Dale, & Hasty, 1996), protein F2 (Jaffe, Natanson-Yaron, Caparon, & Hanski, 1996), and PFBB (Rocha & Fischetti, 1999).

Moreover, the expression of these adhesins has been reported to be environmentally regulated (Gibson, et al., 1995). Expression of protein F1 is enhanced in an O_2-rich environment, whereas that of M protein is greater at higher partial pressures of CO_2 (Caparon, Geist, Perez-Casal, & Scott, 1992). Thus, teleologically, it might be postulated that the organism displays protein F1 on its surface when it seeks to adhere to the cutaneous surface, but expresses M protein in the deeper tissues, where it is more likely to encounter phagocytic cells.

Exotoxins

During the course of growth either in vitro or in vivo, *S. pyogenes* elaborates numerous extracellular products, only a limited number of which have been well characterized. Two distinct hemolysins have been described. The first is streptolysin O (SLO)—a member of the cholesterol-binding family of cytolysins (reviewed in (Alouf & Geoffroy, 1999)). Like several of its family members, SLO derives its name from its oxygen lability. It is reversibly inhibited by oxygen and irreversibly inhibited by cholesterol. In addition to its ability to lyse erythrocytes, it is toxic to a variety of cells and membrane-bound cell fractions, including leukocytes, platelets, endothelial cells, dermal fibroblasts, lysosomes, and isolated mammalian and amphibian cardiomyocytes. SLO is produced by virtually all strains of *S. pyogenes* (as well as many group C and G streptococci) and is antigenic. Measurement of anti-SLO (ASO) antibodies in human sera is useful as an indicator of recent streptococcal infection, but is of less value in patients with impetigo.

Other *S. pyogenes* extracellular products may facilitate the liquefaction of pus and the spreading of streptococci through tissue planes characteristic of streptococcal cellulitis and necrotizing fasciitis. These include: (1) four antigenically distinct deoxyribonucleic acid-degrading enzymes (DNases A, B, C, and D); (2) hyaluronidase, which degrades hyaluronic acid found in the ground substance of connective tissue; (3) streptokinase, which promotes the dissolution of clots by catalyzing the conversion of plasminogen to plasmin; (4) streptococcal pyrogenic exotoxin B (SpeB), which is a potent protease; and (5) C5a peptidase, which specifically cleaves the human chemotaxin C5a at the PMNL binding site (Ji, McLandsborough, Kondagunta, & Cleary, 1996; Wexler, Chenoweth, & Cleary, 1985). SpeB also cleaves IgG bound to *S. pyogenes*, thus interfering with ingestion and killing by phagocytes (Eriksson & Norgren, 2003).

Several members of the streptococcal pyrogenic exotoxin (Spe) family have been associated with StrepTSS, necrotizing fasciitis, and other severe *S. pyogenes* infections. This family of superantigens includes the bacteriophage-encoded SpeA and SpeC (historically known as the scarlatina toxins), as well as the cysteine protease SpeB and several of the more recently identified pyrogenic exotoxins, such as mitogenic factor (MF and SpeF), and streptococcal superantigen (SSA), as reviewed in (Bisno, Brito, & Collins, 2003). Superantigens are potent immunostimulators that cause the clonal proliferation of T cells and watershed production of pro-inflammatory cytokines that mediate tissue destruction, shock, and organ failure.

Genetic Control of Virulence Factors

Control of virulence factor gene expression over time and under diverse environmental conditions depends on multiple complex and interrelated genetic systems (reviewed in (Bisno, Brito, & Collins, 2003). Of the known transcriptional regulators in *S. pyogenes*, the most intensively studied include Mga (**m**ultiple virulence gene regulator of **g**roup **A** streptococcus) (McIver, 2009), Mry (**M** protein **R**NA **y**ield) (Perez-Casal, Caparon, & Scott, 1991), and a two-component regulatory system known as CsrRS (**c**apsule **s**ynthesis **r**egulator, **R**esponse and **S**ensor components) (Levin & Wessels, 1998) or, alternatively, as CovRS (**c**ontrol **of** **v**irulence genes) (Federle, McIver, & Scott, 1999), which represses the synthesis of the hyaluronic acid capsule and several exotoxins. The **r**egulator of **p**roteinase **B** (RopB) has also been shown to have multiple polymorphisms that control the virulence of *S. pyogenes* (Carroll, et al., 2011).

References

Adams B. B. Dermatologic disorders of the athlete. Sports Medicine. 2002;32(5):309–321. PubMed PMID: 11929358.

Alouf, J. E., & Geoffroy, C. (1999). The Family of the Antigenically-Related, Cholesterol-Binding ("Sulphydryl-Activated") Cytolytic Toxins. In J. E. Alouf, & J. H. Freer (Eds.), The Comprehensive Sourcebook of Bacterial Protein Toxins, Second Edition (pp. 147-186). New York: Academic Press.

Anthony B. F., Kaplan E. L., Wannamaker L. W., Chapman S. S. The dynamics of streptococcal infections in a defined population of children: serotypes associated with skin and respiratory infections. American Journal of Epidemiology. 1976;104(6):652–666. PubMed PMID: 793381.

Baddour L. M., Bisno A. L. Recurrent cellulitis after saphenous venectomy for coronary bypass surgery. Annals of Internal Medicine. 1982;97(4):493–496. PubMed PMID: 6982013.

Baddour L. M., Bisno A. L. Recurrent cellulitis after coronary bypass surgery. Association with superficial fungal infection in saphenous venectomy limbs. JAMA. 1984;251(8):1049–1052. PubMed PMID: 6607365.

Baddour L. M., Bisno A. L. Non-group A beta-hemolytic streptococcal cellulitis: association with venous and lymphatic compromise. The American Journal of Medicine. 1985;79(2):155–159. PubMed PMID: 3875287.

Barg N. L., Kish M. A., Kauffman C. A., Supena R. B. Group A streptococcal bacteremia in intravenous drug abusers. The American Journal of Medicine. 1985;78(4):569–574. PubMed PMID: 3885729.

Barnett B. O., Frieden L. J. Streptococcal skin diseases in children. Seminars in Dermatology. 1992;11(1):3–10. PubMed PMID: 1550713.

Barton L. L., Friedman A. D. Impetigo: a reassessment of etiology and therapy. Pediatric Dermatology. 1987;4(3):185–188. PubMed PMID: 3122189.

Barton L. L., Friedman A. D., Sharkey A. M., Schneller D. J., Swierkosz E. M. Impetigo contagiosa III. Comparative efficacy of oral erythromycin and topical mupirocin. Pediatric Dermatology. 1989;6(2):134–138. PubMed PMID: 2501775.

Bernard P., Plantin P., Roger H., Sassolas B., Villaret E., Legrain V., et al. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. British Journal of Dermatology. 1992;127(2):155–159. PubMed PMID: 1390144.

Bessen D. E. Population biology of the human restricted pathogen, Streptococcus pyogenes. Infection, Genetics and Evolution. 2009;9(4):581–593. PubMed PMID: 19460325.

Bisno A. L., Brito M. O., Collins C. M. Molecular basis of group A streptococcal virulence. The Lancet Infectious Diseases. 2003;3(4):191–200. PubMed PMID: 12679262.

Bisno A. L., Nelson K. E., Waytz P., Brunt J. Factors influencing serum antibody response in streptococcal pyoderma. Journal of Laboratory and Clinical Medicine. 1973;81(3):410–420. PubMed PMID: 4686957.

Britton J. W., Fajardo J. E., Krafte-Jacobs B. Comparison of mupirocin and erythromycin in the treatment of impetigo. The Journal of Pediatrics. 1990;117(5):827–829. PubMed PMID: 2121951.

Caparon M. G., Geist R. T., Perez-Casal J., Scott J. R. Environmental regulation of virulence in group A streptococci: transcription of the gene encoding M protein is stimulated by carbon dioxide. Journal of Bacteriology. 1992;174(17):5693–5701. PubMed PMID: 1512202.

Caparon M. G., Stephens D. S., Olsén A., Scott J. R. Role of M protein in adherence of group A streptococci. Infection and Immunity. 1991;59(5):1811–1817. PubMed PMID: 2019444.

Carapetis J. R., Steer A. C., Mulholland E. K., Weber M. The global burden of group A streptococcal diseases. The Lancet Infectious Diseases. 2005;5(11):685–694. PubMed PMID: 16253886.

Carroll R. K., Shelburne S. A., Olsen R. J., Suber B., Sahasrabhojane P., Kumaraswami M., et al. Naturally occurring single amino acid replacements in a regulatory protein alter streptococcal gene expression and virulence in mice. The Journal of Clinical Investigation. 2011;121(5):1956–1968. PubMed PMID: 21490401.

Courtney H. S., Dale J. B., Hasty D. I. Differential effects of the streptococcal fibronectin-binding protein, FBP54, on adhesion of group A streptococci to human buccal cells and HEp-2 tissue culture cells. Infection and Immunity. 1996;64(7):2415–2419. PubMed PMID: 8698460.

Courtney H. S., Hasty D. L., Dale J. B. Molecular mechanisms of adhesion, colonization, and invasion of group A streptococci. Annals of Medicine. 2002;34(2):77–87. PubMed PMID: 12108578.

Dagan R., Bar-David Y. Comparison of amoxicillin and clavulanic acid (augmentin) for the treatment of nonbullous impetigo. American Journal of Diseases of Children. 1989;143(8):916–918. PubMed PMID: 2667333.

Dajani A., Taubert K., Ferrieri P., Peter G., Shulman S. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Pediatrics. 1995;96(4 Pt 1):758–764. PubMed PMID: 7567345.

de Godoy J. M., de Godoy M. F., Valente A., Camacho E. L., Paiva E. V. Lymphoscintigraphic evaluation in patients after erysipelas. Lymphology. 2000;33(4):177–180. PubMed PMID: 11191659.

Demidovich C. W., Wittler R. R., Ruff M. E., Bass J. W., Browning W. C. Impetigo. Current etiology and comparison of penicillin, erythromycin, and cephalexin therapies. American Journal of Diseases in Children. 1990;144(12):1313–1315. PubMed PMID: 2244610.

Dupuy A., Benchiki H., Roujeau J.-C., Bernard P., Vaillant L., Chosidow O., et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. The BMJ. 1999;318:1591. PubMed PMID: 10364117.

Eriksson A., Norgren M. Cleavage of antigen-bound immunoglobulin G by SpeB contributes to streptococcal persistence in opsonizing blood. Infection and Immunity. 2003;71(1):211–217. PubMed PMID: 12496168.

Eriksson B. K. Anal colonization of group G beta-hemolytic streptococci in relapsing erysipelas of the lower extremity. Clinical Infectious Diseases. 1999;29(5):1319–1320. PubMed PMID: 10524984.

Federle M. J., McIver K. S., Scott J. R. A response regulator that represses transcription of several virulence operons in the group A streptococcus. Journal of Bacteriology. 1999;181(12):3649–3657. PubMed PMID: 10368137.

Fehrs L. J., Flanagan K., Kline S., Facklam R. R., Quackenbush K., Foster L. R. Group A beta-hemolytic streptococcal skin infections in a US meat-packing plant. JAMA. 1987;258(21):3131–3134. PubMed PMID: 2959800.

Ferrieri P., Dajani A. S., Wannamaker L. W., Chapman S. S. Natural history of impetigo. 1. Site sequence of acquisition and . The Journal of Clinical Investigation. 1972;51(11):2851–2862. PubMed PMID: 5080412.

Fiorentino T. R., Beall B., Mshar P., Bessen D. E. A genetic-based evaluation of the principal tissue reservoir for group A streptococci isolated from normally sterile sites. The Journal of Infectious Diseases. 1997;176(1):177–182. PubMed PMID: 9207364.

Gibson C., Fogg G., Okada N., Geist R. T., Hanski E., Caparon M. Regulation of host cell recognition in Streptococcus pyogenes. Developments in Biological Standardization. 1995;85:137–144. PubMed PMID: 8586164.

Gonzalez A., Schachner L. A., Cleary T., Scott G., Taplin D., Lambert W. Pyoderma in childhood. Advances in Dermatology. 1989;4:127–141discussion 142. PubMed PMID: 2518352.

Hanski E., Caparon M. Protein F, a fibronectin-binding protein, is an adhesin of the group A streptococcus Streptococcus pyogenes. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(13):6172–6176. PubMed PMID: 1385871.

Hasty D. L., Itzhak O., Courtney H. S., Doyle R. J. Minireview: multiple adhesions of streptococci. Infection and Immunity. 1992;60:2147–2152. PubMed PMID: 1587582.

Hook E. W., Hooton T. M., Horton C. A., Coyle M. B., Ramsey P. G., Turck M. Microbiologic evaluation of cutaneous cellulitis in adults. Archives of Internal Medicine. 1986;146(2):295–297. PubMed PMID: 3947189.

Howe P. M., Eduardo Fajardo J., Orcutt M. A. Etiologic diagnosis of cellulitis: comparison of aspirates obtained from the leading edge and the point of maximal inflammation. The Pediatric Infectious Disease Journal. 1987;6(7):685–686. PubMed PMID: 3302921.

Jaffe J., Natanson-Yaron S., Caparon M. G., Hanski E. Protein F2, a novel fibronectin-binding protein from Streptococcus pyogenes, possesses two binding domains. Molecular Microbiology. 1996;21(2):373–384. PubMed PMID: 8858591.

Ji Y., McLandsborough L., Kondagunta A., Cleary P. P. C5a peptidase alters clearance and trafficking of group A streptococci by infected mice. Infection and Immunity. 1996;64(2):503–510. PubMed PMID: 8550199.

Kaplan E. L., Wannamaker L. W. Suppression of the anti-streptolysin O response by cholesterol and by lipid extracts of rabbit skin. The Journal of Experimental Medicine. 1976;144(3):754–767. PubMed PMID: 182898.

Kaplan E. L., Anthony B. F., Chapman S. S., Ayoub E. M., Wannamaker L. W. The influence of the site of infection on the immune response to group A streptococci. The Journal of Clinical Investigation. 1970;49(7):1405–1414. PubMed PMID: 5432372.

Kreikemeyer B., Talay S. R., Chhatwal G. S. Characterization of a novel fibronectin-binding surface protein in group A streptococci. Molecular Microbiology. 1995;17(1):137–145. PubMed PMID: 7476200.

Kremer M., Zuckerman R., Avraham Z., Raz R. Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. The Journal of Infection. 1991;22(1):37–40. PubMed PMID: 2002231.

Lentnek A. L., Giger O., O'Rourke E. Group A beta-hemolytic streptococcal bacteremia and intravenous substance abuse. A growing clinical problem? Archives of Internal Medicine. 1990;150(1):89–93. PubMed PMID: 2404484.

Levin J. C., Wessels M. R. Identification of csrR/csrS, a genetic locus that regulates hyaluronic acid capsule synthesis in group A streptococcus. Molecular Microbiology. 1998;30(1):209–219. PubMed PMID: 9786197.

Lewis S. D., Peter G. S., Gómez-Marín O., Bisno A. L. Risk factors for recurrent lower extremity cellulitis in a U.S. Veterans Medical Center population. The American Journal of the Medical Sciences. 2006;332(6):304–307. PubMed PMID: 17170620.

Luk E. Y., Lo J. Y., Li A. Z., Lau M. C., Cheung T. K., Wong A. Y., et al. Scarlet fever epidemic, Hong Kong, 2011. Emerging Infectious Diseases. 2012;18(10):1658–1661. PubMed PMID: 23018120.

Martin J. M., Green M., Barbadora K. A., Wald E. R. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. The New England Journal of Medicine. 2002;346:1200–1206. PubMed PMID: 11961148.

Mastro T. D., Farley T. A., Elliott J. A., Facklam R. R., Perks J. R., Hadler J. L., et al. An outbreak of surgical-wound infections due to group A streptococcus carried on the scalp. The New England Journal of Medicine. 1990;323:968–972. PubMed PMID: 2205801.

McIver K. S. Stand-alone response regulators controlling global virulence networks in streptococcus pyogenes. Contributions to Microbiology. 2009;16:103–119. PubMed PMID: 19494581.

Mika, A., Reynolds, S. L., Pickering, D., McMillan, D., Sriprakash, K. S., Kemp, D. J., et al. (2012). Complement inhibitors from scabies mites promote streptococcal growth--a novel mechanism in infected epidermis? PLoS Neglected Tropical Diseases, 6(7), e1563.

Mogielnicki N. P., Schwartzman J. D., Elliott J. A. Perineal group A streptococcal disease in a pediatric practice. Pediatrics. 2000;106(2 Pt 1):276–281. PubMed PMID: 10920151.

Newell P. M., Norden C. W. Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. Journal of Clinical Microbiology. 1988;26(3):401–404. PubMed PMID: 3356783.

Ofek I., Beachey E. H., Jefferson W., Campbell G. L. Cell membrane-binding properties of group A streptococcal lipoteichoic acid. The Journal of Experimental Medicine. 1975;141(5):990–1003. PubMed PMID: 236356.

Okada N., Liszewski M. K., Atkinson J. P., Caparon M. G. Membrane cofactor protein (CD46) is a keratinocyte receptor for the M protein of the group A streptococcus. Proceedings of the National Academy of Sciences of the United States of America. 1995;92(7):2489–2493. PubMed PMID: 7708671.

Okada N., Pentland A. P., Falk P., Caparon M. G. M protein and protein F act as important determinants of cell-specific tropism of Streptococcus pyogenes in skin tissue. The Journal of Clinical Investigation. 1994;94(3):965–977. PubMed PMID: 8083381.

Perez-Casal J., Caparon M. G., Scott J. R. Mry, a trans-acting positive regulator of the M protein gene of Streptococcus pyogenes with similarity to the receptor proteins of two-component regulatory systems. Journal of Bacteriology. 1991;173(8):2617–2624. PubMed PMID: 1849511.

Petersen J. P., Kaltoft M. S., Misfeldt J. C., Schumacher H., Schønheyder H. C. Community outbreak of perianal group A streptococcal infection in Denmark. The Pediatric Infectious Disease Journal. 2003;22(2):105–109. PubMed PMID: 12586971.

Rocha C. L., Fischetti V. A. Identification and characterization of a novel fibronectin-binding protein on the surface of group A streptococci. Infection and Immunity. 1999;67(6):2720–2728. PubMed PMID: 10338474.

Roldan Y. B., Mata-Essayag S., Hartung C. Erysipelas and tinea pedis. Mycoses. 2000;43(5):181–183. PubMed PMID: 10948816.

Semel J. D., Goldin H. Association of athlete's foot with cellulitis of the lower extremities: diagnostic value of bacterial cultures of ipsilateral interdigital space samples. Clinical Infectious Diseases. 1996;23(5):1162–1164. PubMed PMID: 8922818.

Simon M. S., Cody R. L. Cellulitis after axillary lymph node dissection for carcinoma of the breast. The American Journal of Medicine. 1992;93(5):543–548. PubMed PMID: 1364813.

Sjöblom A. C., Eriksson B., Jorup-Rönström C., Karkkonen K., Lindqvist M. Antibiotic prophylaxis in recurrent erysipelas. Infection. 1993;21(6):390–393. PubMed PMID: 8132369.

Stevens, D. L. (2015). Infections of the Skin, Muscles, and Soft Tissues. In D. Kasper, A. Fauci, S. Hauser, D. Longo, J. Jameson, & J. Loscalzo, Harrison's Principles of Internal Medicine (19th ed., pp. 827-838). New York: McGraw Hill Education.

Stevens D. L., Bisno A. L., Chambers H. F., Dellinger E. P., Goldstein E. J., Gorbach S. L., et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the . Clinical Infectious Diseases. 2014;59(2):e10–e52. PubMed PMID: 24973422.

Talay S. R., Valentin-Weigand P., Jerlström P. G., Timmis K. N., Chhatwal G. S. Fibronectin-binding protein of Streptococcus pyogenes: Sequence of the binding domain involved in adherence of streptococci to epithelial cells. Infection and Immunity. 1992;60(9):3837–3844. PubMed PMID: 1386839.

Wang J. H., Liu Y. C., Cheng D. L., Yen M. Y., Chen Y. S., Wang J. H., et al. Role of benzathine penicillin G in prophylaxis for recurrent streptococcal cellulitis of the lower legs. Clinical Infectious Diseases. 1997;25(3):685–689. PubMed PMID: 9314462.

Wasserzug O., Valinsky L., Klement E., Bar-Zeev Y., Davidovitch N., Orr N., et al. A cluster of ecthyma outbreaks caused by a single clone of invasive and highly infective Streptococcus pyogenes. Clinical Infectious Diseases. 2009;48(9):1213–1219. PubMed PMID: 19331587.

Wexler D. E., Chenoweth D. E., Cleary P. P. Mechanism of action of the group A streptococcal C5a inactivator. Proceedings of the National Academy of Sciences of the United States of America. 1985;82(23):8144–8148. PubMed PMID: 3906656.

Yang L. P., Keam S. J. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. Drugs. 2008;68(6):855–873. PubMed PMID: 18416589.

York M. K., Gibbs L., Perdreau-Remington F., Brooks G. F. Characterization of antimicrobial resistance in Streptococcus pyogenes isolates from the San Francisco Bay area of northern California. Journal of Clinical Microbiology. 1999;37(6):1727–1731. PubMed PMID: 10325315.

Yun H. J., Lee S. W., Yoon G. M., Kim S. Y., Choi S., Lee Y. S., et al. Prevalence and mechanisms of low- and high-level mupirocin resistance in staphylococci isolated from a Korean hospital. Journal of Antimicrobial Chemotherapy. 2003;51(3):619–623. PubMed PMID: 12615863.

License