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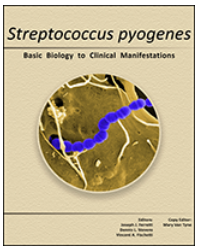

Pharyngitis and Scarlet Fever

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Abstract

Pharyngitis, or sore throat, is the most common manifestation of infection with *Streptococcus pyogenes*. Sore throat is a frequently presenting complaint for outpatient medical visits; as a result, infection with *S. pyogenes* is diagnosed in 20 to 40% of pharyngitis cases in children, and in 5 to 15% in adults. Scarlet fever denotes a clinical syndrome that is characterized by the presence of a rash along with an *S. pyogenes* infection, usually pharyngitis. In this chapter, the topics covered include pathogenesis of pharyngitis, animal models of *S. pyogenes* pharyngitis, adherence of *S. pyogenes* to epithelial cells, intracellular survival and persistence in the pharynx, regulation of capsule production, *S. pyogenes* survival in the pharynx, and immunity to pharyngitis. Finally, there is an overview and discussion of clinical features, complications, diagnosis, and treatment of these diseases.

Pharyngitis, or sore throat, is the most common manifestation of infection with *Streptococcus pyogenes*. Sore throat is a frequent presenting complaint for outpatient medical visits, and infection with *S. pyogenes* is diagnosed in 20 to 40% of pharyngitis cases in children and in 5 to 15% in adults (Ebell, Smith, Barry, Ives, & Carey, 2000; Shaikh, Leonard, & Martin, 2010). The peak incidence of *S. pyogenes* pharyngitis occurs in children 5 to 15 years of age (Danchin, et al., 2007). Infection is more common during winter and spring in temperate climates. Outbreaks may occur in households, schools, military facilities, and other settings in which there is close human-to-human contact. There is no known environmental reservoir or natural animal host of *S. pyogenes*, apart from human beings; and as a result, direct or indirect contact with an infected person is the source of human infection. Transmission is thought to occur primarily by large droplets from respiratory secretions, although spread through contaminated objects and food are well-described alternate routes of transmission. Unpasteurized milk and contaminated food have also been sources of several well-documented *S. pyogenes* outbreaks (Dublin, Rogers, Perkins, & Graves, 1943; Kemble, et al., 2013).

Scarlet fever, or streptococcal pharyngitis associated with a characteristic rash, has been recognized for centuries. “Scarlatina” was clearly distinguished from other febrile rash illnesses (such as measles, in particular) by Sydenham in the 17th century. Epidemics of scarlet fever with high mortality occurred in cities in Europe and North America as late as the latter part of the 19th century (Rolleston, 1928). The historical aspects of scarlet

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fever are described in detail in Chapter 1. Since the advent of penicillin treatment, scarlet fever has become less common and fatal cases are extremely rare. However, some large outbreaks have been reported in the 21st century, most notably in China and Hong Kong (Yang, et al., 2013).

Pathogenesis

Todd and Lancefield observed that *S. pyogenes* freshly isolated from patients with tonsillitis or scarlet fever grew as "matt" colonies (those that are large, with an irregular surface), a characteristic that was associated with production of "M substance;" that is, the M protein (Todd & Lancefield, 1928). The matt (or matte) colony type was subsequently shown to be a later stage of the mucoid colony morphology, which occurs due to abundant production of the hyaluronic acid capsular polysaccharide (Wilson, 1959). In contrast to strains associated with symptomatic infection, isolates from individuals undergoing tonsillectomy for enlarged tonsils yielded a mixture of matte and glossy (small, smooth) colonies. In vitro passage of matte isolates often resulted in their conversion to the glossy morphology, with the latter colony type being deficient in both the M protein and capsule. These observations suggested that expression of the M protein and capsule were associated with symptomatic *S. pyogenes* pharyngitis, although not necessarily with asymptomatic pharyngeal carriage. More recent studies on clinical isolates and in experimental infection in non-human primates have supported these early insights (see below).

Animal models of *S. pyogenes* pharyngitis

Human beings are the only known natural hosts for *S. pyogenes* infection, and for pharyngitis in particular, it has been difficult to mimic human infection in animal models. Studies in mice have demonstrated colonization of the upper airway after intranasal challenges, but either the organisms are cleared over a few days, or the animals develop rapidly progressive pneumonia and systemic infections (Husmann, Dillehay, Jennings, & Scott, 1996; Wessels & Bronze, 1994). A study in rats showed the persistence of low numbers of *S. pyogenes* in throat cultures for several weeks in approximately 50% of animals (Hollingshead, Simecka, & Michalek, 1993). Models in non-human primates are thought to most closely resemble the features of human infection. A high rate of colonization has been demonstrated in rhesus and cynomolgous macaques and in baboons after intranasal inoculation or direct introduction of *S. pyogenes* into the oropharynx (Ashbaugh, et al., 2000; Skinner, et al., 2011; Virtaneva, et al., 2005; Watson, Rothbard, & Swift, 1946). Although one study in cynomolgous macaques reported pharyngeal erythema and swelling during infection, other studies have observed only minimal erythema or no clinical signs of infection, despite persistent colonization. In a baboon model, an M-type 3 invasive clinical isolate colonized the pharynx of all six animals after oral inoculation and persisted for at least 42 days (Ashbaugh, et al., 2000). In marked contrast, in the same study, an isogenic M protein-deficient mutant colonized only 2 of 6 animals after inoculation and was cleared from both after 14 days. A mutant that produced wild-type amounts of M protein but lacked the hyaluronic acid capsule colonized 5 of 6 animals, but was cleared by 28 days. These results suggest that M protein is required both for initial colonization of the pharynx and for persistence. The capsule appears to be unnecessary for colonization, but its presence enhanced persistence in this model.

S. pyogenes adherence to epithelial cells

In vitro studies have attempted to identify the molecular basis for the adherence of *S. pyogenes* to the oropharyngeal epithelium. Experiments that tested the attachment of *S. pyogenes* to various cell lines in vitro have identified multiple bacterial surface molecules that appear to mediate or modulate adherence. A two-step model of adhesion has been proposed, in which an initial weak interaction involves lipoteichoic acid, and a second phase of more avid binding is mediated by *S. pyogenes* surface proteins (Hasty, Ofek, Courtney, & Doyle, 1992). The participation and relative importance of particular adhesins varies widely and depends on bacterial strain, growth phase, target cell type, and the presence or absence of potential bridging molecules, such as

fibronectin or fibrinogen. Certain M proteins contribute to *S. pyogenes* adherence to human cells, either directly or through binding with an intermediary integrin-binding protein, such as fibronectin. Types 6 and 24 M proteins mediated attachment to oropharyngeal keratinocytes in vitro, but type 18 did not (Schrager, Albertí, Cywes, Dougherty, & Wessels, 1998). On the other hand, type 1 M protein appears to inhibit adherence to oropharyngeal keratinocytes (Anderson, et al., 2014). The hyaluronic acid capsule can inhibit M protein-mediated adherence. However, the capsule itself mediates *S. pyogenes* attachment to CD44, a hyaluronic acid-binding glycoprotein that is expressed on many cell types, including oropharyngeal cells (Schrager, Albertí, Cywes, Dougherty, & Wessels, 1998). Eleven or more fibronectin-binding proteins are expressed by various strains of *S. pyogenes*. Binding of fibronectin can link surface proteins on the bacterial cell to fibronectin-binding $\alpha_5\beta_1$ integrins on human epithelial cells (Yamaguchi, Terao, & Kawabata, 2013). The level of expression of $\alpha_5\beta_1$ integrins on keratinocytes may be lower than on other cell types (Edwards, Potter, Meenan, Potts, & Massey, 2011), and the expression of fibronectin-binding protein F1 by *S. pyogenes* has been reported to direct bacterial binding to Langerhans cells in human skin tissue sections in vitro (Okada, Pentland, Falk, & Caparon, 1994).

Intracellular survival and persistence in the pharynx

Although *S. pyogenes* is considered an extracellular pathogen, multiple studies have demonstrated the internalization of the organism by human epithelial cells, including oropharyngeal keratinocytes, in vitro (LaPenta, Rubens, Chi, & Cleary, 1994; Molinari, et al., 1987; Ozeri, Rosenshine, Mosher, Fässler, & Hanski, 1998; Schrager, Rheinwald, & Wessels, 1996). Clinical isolates associated with pharyngitis or asymptomatic carriage appear to be internalized more efficiently than isolates associated with invasive infection, and it has been suggested that entry into epithelial cells may enhance persistent colonization by protecting intracellular bacteria from immune effectors and antibiotics (Molinari & Chhatwal, 1998). Conversely, strains that are associated with invasive infection tend to be internalized inefficiently, perhaps because they produce larger amounts of hyaluronic acid capsule and streptolysin O (SLO), both of which reduce *S. pyogenes* internalization by epithelial cells in vitro (Schrager, Rheinwald, & Wessels, 1996; Håkansson, Bentley, Shakhnovic, & Wessels, 2005). The production of SLO also influences the intracellular survival of *S. pyogenes* within epithelial cells. As they are both pore-forming toxins, SLO and streptolysin S (SLS) induce the formation of autophagosome-like compartments in epithelial cells (Nakagawa, et al., 2004; O'Seaghdha & Wessels, 2013). Streptococci are internalized into an early endosome; however, the production of SLO results in damage to the endosomal membrane and exposure of *S. pyogenes* to the cytosol, where they bind ubiquitin. Ubiquitination of the bacteria results in targeting of the autophagy pathway. In the absence of SLO, production of SLS can sufficiently damage the endosomal membrane to recruit galectin 8, a cytosolic lectin that binds to galactosides that are normally found on the interior surface of vacuolar compartments, but which become exposed upon SLS-mediated membrane injury (O'Seaghdha & Wessels, 2013). Galectin 8 binding to the endosome provides an additional means to traffic *S. pyogenes* to autophagosomes. Many *S. pyogenes* strains also produce NAD-glycohydrolase (NADase), an enzyme that is translocated into the cytosol of epithelial cells in an SLO-dependent fashion. NADase inhibits the fusion of lysosomes with *S. pyogenes*-containing autophagosomes, preventing their maturation into degradative autolysosomes and prolonging intracellular survival. In this way, SLO and NADase enhance the survival of *S. pyogenes* within epithelial cells and may contribute to its overall persistence in the pharynx.

Regulation of capsule production and *S. pyogenes* survival in the pharynx

The global two-component regulatory system CsrRS (or CovRS) appears to play a critical role in the adaptation of *S. pyogenes* for survival and persistence in the pharynx. Inactivating mutations are present in *csrS* or, less often, in *csrR* in approximately 40% of clinical isolates from patients with necrotizing fasciitis or streptococcal toxic shock. By contrast, such mutations are rarely observed among pharyngitis isolates—an observation that suggests CsrRS contributes to the survival of *S. pyogenes* in this host environment (Ikebe, et al., 2010; Shea, et al.,

2011). Further support for this view comes from studies that show a competitive advantage of wild-type *S. pyogenes*, as compared to CsrRS mutants during growth in human saliva (Treviño, et al., 2009). Experiments using a mouse model of upper airway colonization also showed reduced colonization with CsrRS mutants (Alam, Turner, Smith, Wiles, & Sriskandan, 2013). Along with several other virulence factors, synthesis of the hyaluronic acid capsule is regulated by CsrRS (Levin & Wessels, 1998). The overproduction of capsule by CsrRS mutants favors resistance to phagocytosis and survival in blood or deep tissues, but may impair persistence in the pharynx. A study of serial throat isolates from monkeys with experimental *S. pyogenes* pharyngeal infection showed an accumulation of mutations over time that resulted in reduced capsule expression, which is consistent with this hypothesis (Shea, et al., 2011). In addition, clinical isolates from patients with pharyngitis revealed a similar pattern of mutations that reduced capsule production. These observations seem inconsistent with the finding discussed above, in which an acapsular mutant strain was more rapidly cleared from the pharynx in a non-human primate model. These apparently contradictory results may be explained by the fact that the capsule not only impairs adherence to the pharyngeal mucosa and internalization by epithelial cells (thereby impairing colonization), but also helps to defend the bacteria against opsonophagocytic killing in the non-immune host (thereby resisting clearance). Highly encapsulated or mucoid strains of *S. pyogenes* have certainly been associated with outbreaks of pharyngitis and acute rheumatic fever (Marcon, et al., 1988; Veasy, et al., 1987; Westlake, Graham, & Edwards, 1990); however, the downregulation of capsule production may favor asymptomatic pharyngeal carriage.

Immunity to pharyngitis

Early studies in mice by Lancefield and others established that protective immunity to systemic *S. pyogenes* infection was conferred by opsonic serum antibodies against the M protein (Lancefield, 1962). Protective antibodies were type-specific, recognizing the antigenically variable amino terminal domain of M protein. Antibodies elicited from immunization with killed *S. pyogenes* bacteria protected against challenges by strains of the same, but not different, M types. Studies in non-human primates suggest that immunity to pharyngeal infection also is type-specific. Pharyngeal colonization of baboons with an M type 3 strain resulted in complete protection against subsequent rechallenge with the same strain, but no protection against infection with a type 1 strain (Ashbaugh, et al., 2000). The type-specificity of immunity in human pharyngitis is less well-defined. A prospective natural history study of the spread of several strains of *S. pyogenes* among families suggested that pre-existing type-specific serum antibodies did not prevent pharyngeal acquisition nor influence the duration of carriage (Guirguis, Fraser, Facklam, El Kholy, & Wannamaker, 1982). Fox et al. found that immunization with type 1 M protein had only a modest and statistically insignificant effect on pharyngeal colonization in volunteers after challenge with a type 1 strain, but that immunized subjects had a significantly lower rate of symptomatic infection, as compared to subjects in the control group (5% vs 47%) (Fox, Waldman, Wittner, Mauceri, & Dorfman, 1973). When taken together, these studies indicate that type-specific antibodies to M protein play an important role in protection against symptomatic infection. There is some evidence for type-specific immunity to pharyngeal colonization, although it is less clear whether such protection is mediated primarily or exclusively by type-specific serum antibodies. Local mucosal immunity induced by prior exposure or by a mucosal vaccine may also play a role in overall immunity to colonization.

Clinical features

The classical presentation of streptococcal pharyngitis begins with an abrupt onset of fever, malaise, and sore throat. Pain with swallowing and the presence of swollen, tender anterior cervical lymph nodes are typical features. Abdominal pain and vomiting is common, especially in younger children. Cough, rhinorrhea, hoarseness, conjunctival irritation, and diarrhea are notably absent in streptococcal pharyngitis, and the presence of these symptoms should suggest a non-streptococcal (usually viral) etiology. Physical findings include fever (often greater than 39 °C), erythema, and edema of the tonsils and posterior pharynx, which may be covered with a patchy white or yellowish exudate (Figure 1). Petechiae may be present on the soft palate.

Anterior cervical lymph nodes typically are enlarged, firm, and tender. The presence of most or all of these characteristic clinical features is suggestive of, but not specific to, *S. pyogenes* pharyngitis. Without treatment, sore throat usually resolves in 3 to 6 days, and fever abates within 1 week. Despite the resolution of symptoms, throat cultures often remain positive for several weeks in the absence of antibiotic treatment (Catanzaro, et al., 1954). Infectious mononucleosis from the Epstein-Barr virus can have a similar presentation, as can infection with adenovirus or other respiratory viruses. Less commonly, a similar syndrome can be caused by various bacterial or viral pathogens. Conversely, culture-proven *S. pyogenes* pharyngeal infection may be associated with milder signs and symptoms than those described above. For these reasons, a diagnosis on clinical grounds alone is unreliable. Exudative pharyngitis is uncommon in children younger than 3 years of age, although *S. pyogenes* infection can occur in this age group and may be manifested through fever, lymphadenopathy, and mucopurulent rhinitis.

Complications

Suppurative complications of streptococcal pharyngitis can arise from direct extension of pharyngeal infection to adjacent structures, or by hematogenous or lymphatic spread to more remote sites. Such complications include peritonsillar or retropharyngeal abscess, sinusitis, otitis media, cervical lymphadenitis, bacteremia, endocarditis, pneumonia, and meningitis. Local complications, such as peritonsillar or retropharyngeal abscess formation, should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance. Non-infectious autoinflammatory complications can include acute rheumatic fever and post-streptococcal glomerulonephritis, both of which are thought to result from immune responses to streptococcal infection (see the chapters on PANDAS and poststreptococcal glomerulonephritis). Treatment of streptococcal pharyngitis with penicillin has been shown to reduce the likelihood of acute rheumatic fever, but not to reduce the likelihood of post-streptococcal glomerulonephritis.

Scarlet fever

Scarlet fever denotes a clinical syndrome characterized by the presence of a rash along with an *S. pyogenes* infection, usually pharyngitis. The rash typically begins on the first or second day of illness, initially on the trunk, and spreads to involve the extremities, sparing the palms and soles of the feet. The rash is often accentuated in flexural creases, such as in the antecubital fossae and axillae (Pastia's lines). The cheeks are flushed, with sparing of the area around the mouth (circumoral pallor) (Figure 2). The rash is made up of minute papules, giving a characteristic "sandpaper" feel to the skin. Enlarged papillae may be seen on a coated tongue (strawberry tongue), which later may become denuded. The rash generally fades in 6–9 days, and is followed by desquamation of the palms and soles after several days, which typically begins on the fingertips at the free margin of the fingernails. The differential diagnosis of scarlet fever includes viral exanthems, Kawasaki disease, staphylococcal toxic shock syndrome, and allergic reactions.

The pathogenesis of scarlet fever is not completely understood. Studies in the 1920s by George and Gladys Dick and others implicated one or more secreted *S. pyogenes* proteins, which was previously called erythrogenic toxin, and which are now classified as pyrogenic exotoxins (Birkhaug, 1925; Dick & Dick, 1924; Dick & Dick, 1983). Injection of culture filtrates of scarlet fever-associated *S. pyogenes* evoked a rash in some naïve subjects, but not in those who had recovered from scarlet fever. Intradermal injection of antiserum to the scarlet fever strain caused blanching of the rash. Together, these observations suggested that the rash-associated illness was at least partially due to the effects of *S. pyogenes* products present in the culture supernatant. Subsequent research has identified erythrogenic toxin as a group of related streptococcal pyrogenic exotoxins (SPEs). Eleven such toxins have been identified, and an individual strain typically produces 4 to 6 of them (Spaulding, et al., 2013). No single toxin has been consistently implicated in scarlet fever, although SpeA, SpeC, and SSA, often in combination, have been associated with several outbreaks (Davies, et al., 2015; Silva-Costa, Carriço, Ramirez, & Melo-Cristino, 2014; Tyler, et al., 1992; Yu & Ferretti, 1989). The SPEs also appear to play an important role in

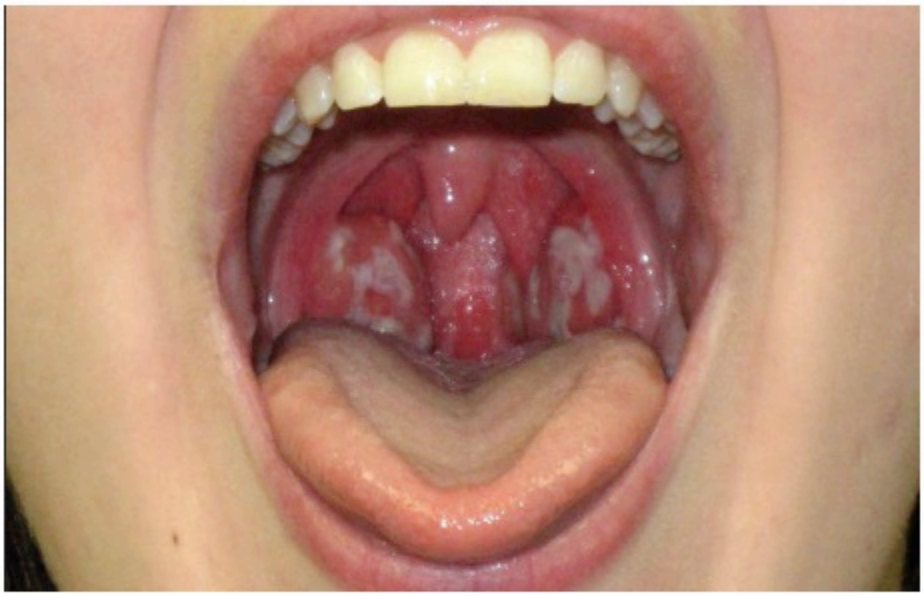

Figure 1. A 15-year-old girl with fever and exudative streptococcal pharyngitis (from (Block, 2014)).

the severe, systemic manifestations of streptococcal toxic shock syndrome through their activity as superantigens that are capable of stimulating cytokine secretion from a large population of T cells in an antigen-independent fashion (see the chapter on streptococcal superantigens).

Diagnosis

Scoring systems have been devised to improve the accuracy of clinical diagnoses of *S. pyogenes* pharyngitis. These systems assign points based on the presence or absence of suggestive clinical features, such as fever, absence of cough, presence of tonsillar exudates, and swollen, tender anterior cervical lymph nodes. The best-known clinical assessment tools are the Centor score and the very similar McIsaac score, which includes patient age as an additional criterion (Centor, Witherspoon, Dalton, Brody, & Link, 1981; McIsaac, White, Tannenbaum, & Low, 1998). A study analyzing data collected from more than 200,000 patients that were 3 years of age or older and were seen at a U.S. retail health chain found that the likelihood of a positive throat culture for *S. pyogenes* was 8% in individuals with a McIsaac score of 0, and rose to 55% in those with scores of 4 or 5 (Fine, Nizet, & Mandl, 2012). Algorithms based on such scoring systems have been used to limit the use of throat culture or rapid antigen detection tests in those patients in whom the probability of *S. pyogenes* infection is very low (McIsaac, Kellner, Aufricht, Vanjaka, & Low, 2004). For example, the clinical guidelines of the American College

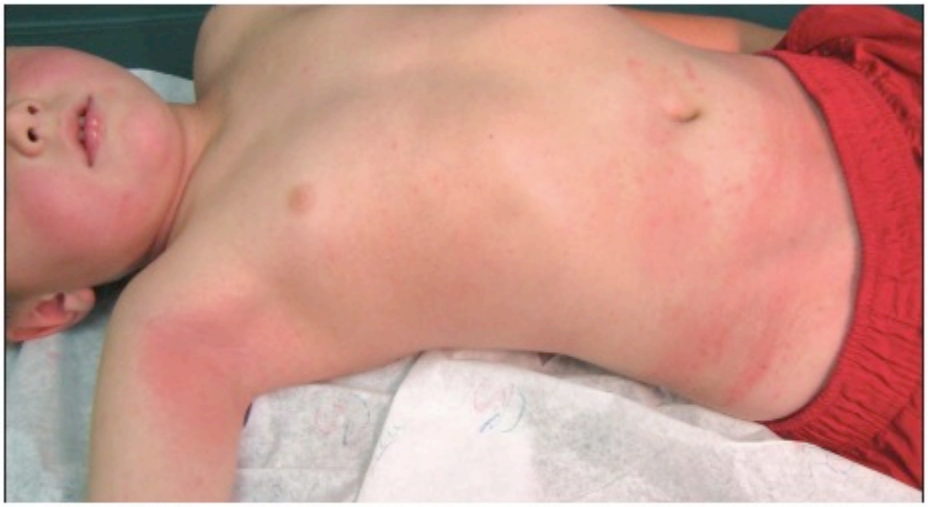

Figure 2. A 7-year-old boy with streptococcal pharyngitis and scarlet fever. Note the accentuation of the rash in skin folds and circumoral pallor (from (Block, 2014)).

of Physicians-American Society of Internal Medicine and the U.S. Centers for Disease Control and Prevention recommend not testing for *S. pyogenes* in adults with a Centor score of 0 or 1 in the absence of special risk factors (Cooper, et al., 2001).

The "gold standard" for diagnosis of *S. pyogenes* pharyngitis is a positive culture from a properly collected throat swab specimen, i.e., a swab rubbed on both tonsillar pillars, avoiding the lips and tongue. Faster and more convenient rapid antigen tests are widely used in many clinical settings. These tests are highly specific, generally 95% or higher, so a positive result provides an immediate diagnosis and obviates the need for culture. In children and adolescents, a negative rapid test should be confirmed with a throat culture, as the sensitivity of the culture method is higher than that of the rapid antigen tests. Most clinical guidelines do not recommend the routine confirmation of a negative antigen test in adults, since the risk of rheumatic fever is extremely low in adults without a prior episode. Serologic assays for antibodies to *S. pyogenes* antigens, such as SLO or DNase B, are useful for retrospective diagnosis of an antecedent *S. pyogenes* infection in cases of suspected acute rheumatic fever or post-streptococcal glomerulonephritis, but these tests are not useful for the acute diagnosis of *S. pyogenes* pharyngitis, as a rise in specific antibodies only begins 7 to 14 days after the onset of infection, reaching maximum levels at 3 to 4 weeks.

Treatment

Streptococcal pharyngitis is almost always a self-limited illness, and many have questioned whether antibiotic treatment is warranted. However, such treatment can be justified for three reasons:

1. Treatment shortens the duration and severity of illness. Several studies suggest that specific therapy reduces the duration of fever and sore throat by approximately 1 day, on average.
2. Treatment prevents rheumatic fever. Acute rheumatic fever is a potential complication of *S. pyogenes* pharyngitis, and studies conducted primarily on the U.S. military in the mid-twentieth century demonstrated that penicillin treatment reduced the risk of subsequent rheumatic fever. While this rationale for treatment remains compelling in many resource-poor countries where the incidence of acute rheumatic fever is high, in industrialized countries, the relative risks and benefits no longer clearly support this treatment goal in routine cases.
3. Treatment prevents the suppurative complications of pharyngitis. Antibiotic treatment has been shown to reduce the incidence of secondary infectious complications, such as otitis media and sinusitis (Spinks, Glasziou, & Del Mar, 2013). An additional benefit of treatment is that it reduces the spread of infection to others—an important consideration for outbreak control. Clinical practice guidelines in the U.S. recommend treatment for children and adults with proven *S. pyogenes* pharyngitis (Gerber, et al., 2009; Shulman, et al., 2012). Guidelines from some European countries are similar, while other countries do not recommend specific diagnostic testing or treatment, since treatment has a small impact on the natural history of pharyngitis, and the incidence of suppurative and non-suppurative complications is low in these populations (Van Brusselen, et al., 2014).

Penicillin has been the mainstay of treatment for *S. pyogenes* pharyngitis for many years. Clinical isolates remain universally susceptible to penicillin and to many other beta-lactam antibiotics. Amoxicillin is similarly effective and is often preferred for its longer half-life, especially in children. Once-daily dosing of amoxicillin appears to have similar efficacy to a twice-daily dosing regimen (Clegg, et al., 2006; Lennon, Farrell, Martin, & Stewart, 2008). A cephalosporin may be used in patients with a history of allergy to penicillin or amoxicillin that is not of the immediate hypersensitivity type. Macrolide antibiotics are an additional alternative, but resistance to these is relatively common (Liu, et al., 2009; Tamayo, Pérez-Trallero, Gómez-Garcés, Alós, & Spanish Group for the Study of Infection, 2005; Tanz, et al., 2004). Table 1 summarizes antibiotic regimens recommended in guidelines from the Infectious Diseases Society of America.

Some have argued that clinical and/or bacteriological cure rates are lower with penicillin (or amoxicillin) than with alternate agents, including cephalosporins (Casey & Pichichero, 2004; Pichichero, et al., 2000). The counter-argument has been that studies showing superiority of alternative agents have inadvertently included *S. pyogenes* carriers, and that penicillin is inferior for the eradication of carriage, but is comparable to other agents for treatment of true infection (Bisno, 2004; Shulman & Gerber, 2004). Penicillin continues to be recommended as a first line treatment in clinical practice guidelines because of its well-established record of safety and efficacy, narrow spectrum, and low cost.

Table 1: Antibiotic Regimens Recommended for Streptococcal Pharyngitis (adapted from (Shulman, et al., 2012))

Drug, Route	Dose or Dosage	Duration or Quantity	Recommendation Strength, Quality	References
For individuals without penicillin allergies				

Table 1 continued from previous page.

Drug, Route	Dose or Dosage	Duration or Quantity	Recommendation Strength, Quality	References
Penicillin V, oral	Children: 250 mg twice daily or 3 times daily; adolescents and adults: 250 mg 4 times daily or 500 mg twice daily	10 d	Strong, high	(Bass, Person, & Chan, 2000; Gerber, Spadaccini, Wright, Deutsch, & Kaplan, 1985)
Amoxicillin, oral	50 mg/kg once daily (max=1000 mg); alternate: 25 mg/kg (max=500 mg) twice daily	10 d	Strong, high	(Clegg, et al., 2006; Lennon, Farrell, Martin, & Stewart, 2008; Feder, Jr., Gerber, Randolph, Stelmach, & Kaplan, 1999; Gerber & Tanz, 2001; Shvartzman, Tabenkin, Rosentzwaig, & Dolginov, 1993)
Benzathine penicillin G, intramuscular	<27 kg: 600 000 U; ≥27 kg: 1 200 000 U	1 dose	Strong, high	(Bass, Person, & Chan, 2000; Bass, Crast, Knowles, & Onufer, 1976; Wannamaker, et al., 1951)
For individuals with penicillin allergies				
Cephalexin,[a] oral	20 mg/kg/dose, twice daily (max=500 mg/dose)	10 d	Strong, high	(Disney, Breese, Green, Talpey, & Tobin, 1971; Disney, et al., 1992; Stillerman & Isenberg, 1970; Stillerman, Isenberg, & Moody, 1972)
Cefadroxil,[a] oral	30 mg/kg once daily (max 1 g)	10 d	Strong, high	(Gerber, et al., 1986)
Clindamycin, oral	7 mg/kg/dose 3 times daily (max=300 mg/dose)	10 d	Strong, moderate	(Jackson, 1973)
Azithromycin,[b] oral	12 mg/kg once daily (max 500 mg)	5 d	Strong, moderate	(Hooton, 1991)
Clarithromycin,[b] oral	7.5 mg/kg/dose twice daily (max=250 mg/dose)	10 d	Strong, moderate	(Kafetzis, et al., 2004)

Abbreviation: Max, maximum.
[a] Avoid in individuals with immediate type hypersensitivity to penicillin.
[b] Resistance of *S. pyogenes* to these agents is well-known and varies both geographically and temporally.

References

Alam F. M., Turner C. E., Smith K., Wiles S., Sriskandan S. Inactivation of the CovR/S virulence regulator impairs infection in an improved murine model of Streptococcus pyogenes naso-pharyngeal infection. PLoS One. 2013;8(4):e61655. PubMed PMID: 23637876.

Anderson E. L., Cole J. N., Olson J., Ryba B., Ghosh P., Nizet V. The fibrinogen-binding M1 protein reduces pharyngeal cell adherence and colonization phenotypes of M1T1 group A Streptococcus. The Journal of Biological Chemistry. 2014;289(6):3539–3546. PubMed PMID: 24356958.

Ashbaugh C. D., Moser T. J., Shearer M. H., White G. L., Kennedy R. C., Wessels M. R. Bacterial determinants of persistent throat colonization and the associated immune response in a primate model of human group A streptococcal pharyngeal infection. Cell Microbiology. 2000;2(4):283–292. PubMed PMID: 11207585.

Bass J. W., Crast F. W., Knowles C. R., Onufer C. M. Streptococcal pharyngitis in children. A comparison of four treatment schedules with intramuscular penicillin G benzathine. JAMA. 1976;235(11):1112–1116. PubMed PMID: 765515.

Bass J. W., Person D. A., Chan D. S. Twice-daily oral penicillin for treatment of streptococcal pharyngitis: less is best. Pediatrics. 2000;105(2):423–424. PubMed PMID: 10654966.

Birkhaug K. E. STUDIES IN SCARLET FEVER: I. Studies Concerning the Blanching Phenomenon in Scarlet Fever. The Journal of Clinical Investigation. 1925;1(3):273–294. PubMed PMID: 16693652.

Bisno A. L. Are cephalosporins superior to penicillin for treatment of acute streptococcal pharyngitis? Clinical Infectious Diseases. 2004;38:1535–1537. PubMed PMID: 15156438.

Block S. L. Streptococcal pharyngitis: guidelines, treatment issues, and sequelae. Pediatric Annals. 2014;43(1):11–16. PubMed PMID: 24450315.

Casey J. R., Pichichero M. E. Meta-analysis of cephalosporin versus penicillin treatment of group A streptococcal tonsillopharyngitis in children. Pediatrics. 2004;113(4):866–882. PubMed PMID: 15060239.

Catanzaro F. J., Stetson C. A., Lorris A. J., Chamovitz R., Rammelkamp C. H. Jr, Stolzer B. L., et al. The role of the streptococcus in the pathogenesis of rheumatic fever. The American Journal of Medicine. 1954;17(6):749–756. PubMed PMID: 13207156.

Centor R. M., Witherspoon J. M., Dalton H. P., Brody C. E., Link K. The diagnosis of strep throat in adults in the emergency room. Medical Decision Making. 1981;1(3):239–246. PubMed PMID: 6763125.

Clegg H. W., Ryan A. G., Dallas S. D., Kaplan E. L., Johnson D. R., Norton H. J., et al. Treatment of streptococcal pharyngitis with once-daily compared with twice-daily amoxicillin: a noninferiority trial. Pediatric Infectious Disease Journal. 2006;25(9):761–767. PubMed PMID: 16940830.

Cooper R. J., Hoffman J. R., Bartlett J. G., Besser R. E., Gonzales R., Hickner J. M., et al. Principles of appropriate antibiotic use for acute pharyngitis in adults. Annals of Internal Medicine. 2001;134(6):509–517. PubMed PMID: 11255530.

Danchin M. H., Rogers S., Kelpie L., Selvaraj G., Curtis N., Carlin J. B., et al. Burden of acute sore throat and group A streptococcal pharyngitis in school-aged children and their families in Australia. Pediatrics. 2007;120(5):950–957. PubMed PMID: 17974731.

Davies M. R., Holden M. T., Coupland P., Chen J. H., Venturini C., Barnett T. C., et al. Emergence of scarlet fever Streptococcus pyogenes emm12 clones in Hong Kong is associated with toxin acquisition and multidrug resistance. Nature Genetics. 2015;47:84–87. PubMed PMID: 25401300.

Dick G. F., Dick G. H. Scarlet Fever. American Journal of Public Health. 1924;14(12):1022–1028. PubMed PMID: 18011382.

Dick G. F., Dick G. H. Landmark article Jan 26, 1924: The etiology of scarlet fever. JAMA. 1983;250(22):3096. PubMed PMID: 6358561.

Disney F. A., Breese B. B., Green J. L., Talpey W. B., Tobin J. R. Cephalexin and penicillin therapy of childhood beta-hemolytic streptococcal infections. Postgrad Medical Journal. 1971;47 Suppl:47–51. PubMed PMID: 5556190.

Disney F. A., Dillon H., Blumer J. L., Dudding B. A., McLinn S. E., Nelson D. B., et al. Cephalexin and penicillin in the treatment of group A beta-hemolytic streptococcal throat infections. American Journal of Diseases of Children. 1992;146(11):1324–1327. PubMed PMID: 1415072.

Dublin T. D., Rogers E. F., Perkins J. E., Graves F. W. Milk-borne Outbreaks Due to Serologically Typed Hemolytic Streptococci. American Journal of Public Health and the Nation's Health. 1943;33(2):157–166. PubMed PMID: 18015742.

Ebell M. H., Smith M. A., Barry H. C., Ives K., Carey M. The rational clinical examination. Does this patient have strep throat? JAMA. 2000;284(22):2912–2918. PubMed PMID: 11147989.

Edwards A. M., Potter U., Meenan N. A., Potts J. R., Massey R. C. Staphylococcus aureus keratinocyte invasion is dependent upon multiple high-affinity fibronectin-binding repeats within FnBPA. PLoS One. 2011;6(4):e18899. PubMed PMID: 21526122.

Feder H. M. Jr, Gerber M. A., Randolph M. F., Stelmach P. S., Kaplan E. L. Once-daily therapy for streptococcal pharyngitis with amoxicillin. Pediatrics. 1999;103(1):47–51. PubMed PMID: 9917438.

Fine A. M., Nizet V., Mandl K. D. Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. Archives of Internal Medicine. 2012;172(11):847–852. PubMed PMID: 22566485.

Fox E. N., Waldman R. H., Wittner M. K., Mauceri A. A., Dorfman A. Protective study with a group A streptococcal M protein vaccine. Infectivity challenge of human volunteers. The Journal of Clinical Investigation. 1973;52(8):1885–1892. PubMed PMID: 4719668.

Gerber M. A., Tanz R. R. New approaches to the treatment of group A streptococcal pharyngitis. Current Opinion in Pediatrics. 2001;13(1):51–55. PubMed PMID: 11176244.

Gerber M. A., Baltimore R. S., Eaton C. B., Gewitz M., Rowley A. H., Shulman S. T., et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular... Circulation. 2009;119(11):1541–1551. PubMed PMID: 19246689.

Gerber M. A., Randolph M. F., Chanatry J., Wright L. L., Anderson L. R., Kaplan E. L. Once daily therapy for streptococcal pharyngitis with cefadroxil. Journal of Pediatrics. 1986;109(3):531–537. PubMed PMID: 3091801.

Gerber M. A., Spadaccini L. J., Wright L. L., Deutsch L., Kaplan E. L. Twice-daily penicillin in the treatment of streptococcal pharyngitis. American Journal of Diseases of Children. 1985;139(11):1145–1148. PubMed PMID: 3933330.

Guirguis N., Fraser D. W., Facklam R. R., El Kholy A., Wannamaker L. W. Type-specific immunity and pharyngeal acquisition of group A Streptococcus. American Journal of Epidemiology. 1982;116(6):933–939. PubMed PMID: 6756129.

Håkansson A., Bentley C. C., Shakhnovic E. A., Wessels M. R. Cytolysin-dependent evasion of lysosomal killing. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(14):5192–5197. PubMed PMID: 15795386.

Hasty D. L., Ofek I., Courtney H. S., Doyle R. J. Multiple adhesins of streptococci. Infection and Immunity. 1992;60(6):2147–2152. PubMed PMID: 1587582.

Hollingshead S. K., Simecka J. W., Michalek S. M. Role of M protein in pharyngeal colonization by group A streptococci in rats. Infection and Immunity. 1993;61(6):2277–2283. PubMed PMID: 8500869.

Hooton T. M. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. The American Journal of Medicine. 1991;91(3A):23S–26S. PubMed PMID: 1656738.

Husmann L. K., Dillehay D. L., Jennings V. M., Scott J. R. Streptococcus pyogenes infection in mice. Microbial Pathogenesis. 1996;20(4):213–224. PubMed PMID: 8737491.

Ikebe T., Ato M., Matsumura T., Hasegawa H., Sata T., Kobayashi K., et al. Highly frequent mutations in negative regulators of multiple virulence genes in group A streptococcal toxic shock syndrome isolates. PLoS Pathogens. 2010;6(4):e1000832. PubMed PMID: 20368967.

Jackson H. Prevention of rheumatic fever. A comparative study of clindamycin palmitat and ampicillin in the treatment of group A beta hemolytic streptococcal pharyngitis. Clinical Pediatrics. 1973;12(8):501–503. PubMed PMID: 4579967.

Kafetzis D. A., Liapi G., Tsolia M., Aoudi H., Mathioudakis J., Paraskakis I., et al. Failure to eradicate Group A beta-haemolytic streptococci (GABHS) from the upper respiratory tract after antibiotic treatment. International Journal of Antimicrobial Agents. 2004;23(1):67–71. PubMed PMID: 14732316.

Kemble S. K., Westbrook A., Lynfield R., Bogard A., Koktavy N., Lappi V., et al. Foodborne outbreak of group a streptococcus pharyngitis associated with a high school dance team banquet--Minnesota, 2012. Clinical Infectious Diseases. 2013;57(5):648–654. PubMed PMID: 23868521.

Lancefield R. C. Current Knowledge of Type-Specific M Antigens of Group A Streptococci. The Journal of Immunology. 1962;89(3):307–313. PubMed PMID: 14461914.

LaPenta D., Rubens C., Chi E., Cleary P. P. Group A streptococci efficiently invade human respiratory epithelial cells. Proceedings of the National Academy of Sciences of the United States of America. 1994;91(25):12115–12119. PubMed PMID: 7991594.

Lennon D. R., Farrell E., Martin D. R., Stewart J. M. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Archives of Diseases in Children. 2008;93(6):474–478. PubMed PMID: 18337284.

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.

Liu X., Shen X., Chang H., Huang G., Fu Z., Zheng Y., et al. High macrolide resistance in Streptococcus pyogenes strains isolated from children with pharyngitis in China. Pediatric Pulmonology. 2009;44(5):436–441. PubMed PMID: 19360846.

Marcon M. J., Hribar M. M., Hosier D. M., Powell D. A., Brady M. T., Hamoudi A. C., et al. Occurrence of mucoid M-18 Streptococcus pyogenes in a central Ohio pediatric population. Journal of Clinical Microbiology. 1988;26(8):1539–1542. PubMed PMID: 3049658.

McIsaac W. J., Kellner J. D., Aufricht P., Vanjaka A., Low D. E. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. 2004;291(13):1587–1595. PubMed PMID: 15069046.

McIsaac, W. J., White, D., Tannenbaum, D., & Low, D. E. (1998). A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ•JAMC, 158*(1), 75-83.

Molinari A., Von Hunolstein C., Donelli G., Paradisi S., Arancia G., Orefici G. Effects of some capsular components on pathogenicity of type IV and provisional type V group B streptococci. FEMS Microbiology Letters. 1987;41(1):69–72.

Molinari G., Chhatwal G. S. Invasion and survival of Streptococcus pyogenes in eukaryotic cells correlates with the source of the clinical isolates. The Journal of Infectious Diseases. 1998;177(6):1600–1607. PubMed PMID: 9607839.

Nakagawa I., Amano A., Mizushima N., Yamamoto A., Yamaguchi H., Kamimoto T., et al. Autophagy defends cells against invading group A Streptococcus. Science. 2004;306(5698):1037–1040. PubMed PMID: 15528445.

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.

O'Seaghdha M., Wessels M. R. Streptolysin O and its Co-Toxin NAD-glycohydrolase Protect Group A Streptococcus from Xenophagic Killing. PLoS Pathogens. 2013;9(6):e1003394. PubMed PMID: 23762025.

Ozeri V., Rosenshine I., Mosher D. F., Fässler R., Hanski E. Roles of integrins and fibronectin in the entry of Streptococcus pyogenes into cells via protein F1. Molecular Microbiology. 1998;30(3):625–637. PubMed PMID: 9822827.

Pichichero M. E., Casey J. R., Mayes T., Francis A. B., Marsocci S. M., Murphy A. M., et al. Penicillin failure in streptococcal tonsillopharyngitis: causes and remedies. Pediatric Infectious Disease Journal. 2000;19(9):917–923. PubMed PMID: 11001127.

Rolleston J. D. The History of Scarlet Fever. The BMJ. 1928;2(3542):926–929. PubMed PMID: 20774279.

Schrager H. M., Albertí S., Cywes C., Dougherty G. J., Wessels M. R. Hyaluronic acid capsule modulates M protein-mediated adherence and acts as a ligand for attachment of group A Streptococcus to CD44 on human keratinocytes. The Journal of Clinical Investigation. 1998;101(8):1708–1716. PubMed PMID: 9541502.

Schrager H. M., Rheinwald J. G., Wessels M. R. Hyaluronic acid capsule and the role of streptococcal entry into keratinocytes in invasive skin infection. The Journal of Clinical Investigation. 1996;98(9):1954–1958. PubMed PMID: 8903312.

Shaikh N., Leonard E., Martin J. M. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. Pediatrics. 2010;126(3):e557–e564. PubMed PMID: 20696723.

Shea P. R., Beres S. B., Flores A. R., Ewbank A. L., Gonzalez-Lugo J. H., Martagon-Rosado A. J., et al. Distinct signatures of diversifying selection revealed by genome analysis of respiratory tract and invasive bacterial populations. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(12):5039–5044. PubMed PMID: 21383167.

Shulman S. T., Gerber M. A. So what's wrong with penicillin for strep throat? Pediatrics. 2004;113(6):1816–1819. PubMed PMID: 15173515.

Shulman S. T., Bisno A. L., Clegg H. W., Gerber M. A., Kaplan E. L., Lee G., et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2012;55(10):e86–e102. PubMed PMID: 22965026.

Shvartzman P., Tabenkin H., Rosentzwaig A., Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. The BMJ. 1993;306(6886):1170–1172. PubMed PMID: 8499823.

Silva-Costa C., Carriço J. A., Ramirez M., Melo-Cristino J. Scarlet fever is caused by a limited number of Streptococcus pyogenes lineages and is associated with the exotoxin genes ssa, speA and speC. The Pediatric Infectious Disease Journal. 2014;33(3):306–310. PubMed PMID: 24168973.

Skinner J. M., Caro-Aguilar I. C., Payne A. M., Indrawati L., Fontenot J., Heinrichs J. H. Comparison of rhesus and cynomolgus macaques in a Streptococcus pyogenes infection model for vaccine evaluation. Microbial Pathogenesis. 2011;50(1):39–47. PubMed PMID: 21035535.

Spaulding A. R., Salgado-Pabón W., Kohler P. L., Horswill A. R., Leung D. Y., Schlievert P. M. Staphylococcal and streptococcal superantigen exotoxins. Clinical Microbiology Reviews. 2013;26(3):422–447. PubMed PMID: 23824366.

Spinks A., Glasziou P. P., Del Mar C. B. Antibiotics for sore throat. Cochrane Database of Systematic Reviews. 2013;11:CD000023. PubMed PMID: 24190439.

Stillerman M., Isenberg H. D. Streptococcal pharyngitis therapy: comparison of cyclacillin, cephalexin, and potassium penicillin V. Antimicrobial Agents and Chemotherapy. 1970;10:270–276. PubMed PMID: 5000259.

Stillerman M., Isenberg H. D., Moody M. Streptococcal pharyngitis therapy. Comparison of cephalexin, phenoxymethyl penicillin, and ampicillin. American Journal of Diseases of Children. 1972;123(5):457–461. PubMed PMID: 4623690.

Tamayo J., Pérez-Trallero E., Gómez-Garcés J. L., Alós J. I.Spanish Group for the Study of Infection 2005; Resistance to macrolides, clindamycin and telithromycin in Streptococcus pyogenes isolated in Spain during 2004. Journal of Antimicrobial Chemotherapy.56(4):780–782. PubMed PMID: 16120627.

Tanz R. R., Shulman S. T., Shortridge V. D., Kabat W., Kabat K., Cederlund E., et al. Community-based surveillance in the united states of macrolide-resistant pediatric pharyngeal group A streptococci during 3 respiratory disease seasons. Clinical Infectious Diseases. 2004;39(12):1794–1801. PubMed PMID: 15578402.

Todd E. W., Lancefield R. C. Variants of hemolytic streptococci; their relation to type specific substance, virulence, and toxin. The Journal of Experimental Medicine. 1928;48(6):751–767. PubMed PMID: 19869519.

Treviño J., Perez N., Ramirez-Peña E., Liu Z., Shelburne S. A. III, Musser J. M., et al. CovS simultaneously activates and inhibits the CovR-mediated repression of distinct subsets of group A Streptococcus virulence factor-encoding genes. Infection and Immunity. 2009;77(8):3141–3149. PubMed PMID: 19451242.

Tyler S. D., Johnson W. M., Huang J. C., Ashton F. E., Wang G., Low D. E., et al. Streptococcal erythrogenic toxin genes: detection by polymerase chain reaction and association with disease in strains isolated in Canada from 1940 to 1991. Journal of Clinical Microbiology. 1992;30(12):3127–3131. PubMed PMID: 1452695.

Van Brusselen D., Vlieghe E., Schelstraete P., De Meulder F., Vandeputte C., Garmyn K., et al. Streptococcal pharyngitis in children: to treat or not to treat? European Journal of Pediatrics. 2014;173(10):1275–1283. PubMed PMID: 25113742.

Veasy L. G., Wiedmeier S. E., Orsmond G. S., Ruttenberg H. D., Boucek M. M., Roth S. J., et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. The New England Journal of Medicine. 1987;316:421–427. PubMed PMID: 3807984.

Virtaneva K., Porcella S. F., Graham M. R., Ireland R. M., Johnson C. A., Ricklefs S. M., et al. Longitudinal analysis of the group A Streptococcus transcriptome in experimental pharyngitis in cynomolgus macaques. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(25):9014–9019. PubMed PMID: 15956184.

Wannamaker L. W., Rammelkamp C. H. Jr, Denny F. W., Brink W. R., Houser H. B., Hahn E. O., et al. Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. The American Journal of Medicine. 1951;10(6):673–695. PubMed PMID: 14837911.

Watson R. F., Rothbard S., Swift H. F. Type-specific protection and immunity following intranasal inoculation of monkeys with group A streptococci. The Journal of Experimental Medicine. 1946;84(2):127–142. PubMed PMID: 19871558.

Wessels M. R., Bronze M. S. Critical role of the group A streptococcal capsule in pharyngeal colonization and infection in mice. Proceedings of the National Academy of Sciences of the United States of America. 1994;91(25):12238–12242. PubMed PMID: 7991612.

Westlake R. M., Graham T. P., Edwards K. M. An outbreak of acute rheumatic fever in Tennessee. The Pediatric Infectious Disease Journal. 1990;9(2):97–100. PubMed PMID: 2179847.

Wilson A. T. The relative importance of the capsule and the M antigen in determining colony form of group A streptococci. The Journal of Experimental Medicine. 1959;109(3):257–270. PubMed PMID: 13620853.

Yamaguchi M., Terao Y., Kawabata S. Pleiotropic virulence factor - Streptococcus pyogenes fibronectin-binding proteins. Cell Microbiology. 2013;15(4):503–511. PubMed PMID: 23190012.

Yang P., Peng X., Zhang D., Wu S., Liu Y., Cui S., et al. Characteristics of group A Streptococcus strains circulating during scarlet fever epidemic, Beijing, China, 2011. Emerging Infectious Diseases. 2013;19(6):909–915. PubMed PMID: 23735582.

Yu C. E., Ferretti J. J. Molecular epidemiologic analysis of the type A streptococcal exotoxin (erythrogenic toxin) gene (speA) in clinical Streptococcus pyogenes strains. Infection and Immunity. 1989;57(12):3715–3719. PubMed PMID: 2553612.

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