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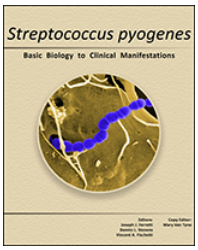
NLM Citation: Martin J. The *Streptococcus pyogenes* Carrier State. 2016 Jul 25. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes* : Basic Biology to Clinical Manifestations [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



The *Streptococcus pyogenes* Carrier State

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Created: July 25, 2016.

Abstract

The classical features of an individual said to be a carrier of *Streptococcus pyogenes* (Group A streptococcus) is the confirmed presence of the organism in their posterior pharynx, without any of the usual attendant clinical symptoms of acute pharyngitis. This chapter provides an overview and discussion of relevant topics of *S. pyogenes* carriage, including its prevalence, longitudinal studies, transmission from carriers, and identification of carriers in clinical practice. In addition, this chapter provides a distinction between recurrent infections and the carrier state, host and bacterial factors of carriage, and treatment and eradication of the carrier state.

Definition of Carrier

The classical clinical features that can be observed in a child who is believed to have an acute pharyngitis due to *Streptococcus pyogenes* include the abrupt onset of fever with sore throat, and the absence of diarrhea or respiratory symptoms, such as cough and rhinorrhea. In contrast, an asymptomatic child is considered to be a streptococcal pharyngeal carrier if a swab of the posterior pharynx is processed for a bacterial culture or rapid antigen detection test, and if such a test confirms the presence of *Streptococcus pyogenes* (Group A streptococcus). Since the child does not have symptoms of a sore throat and does not have inflammation of the tonsils or pharynx on physical examination, most experts would agree that the child most likely has pharyngeal carriage of the organism. In this circumstance, the pharynx is colonized with *S. pyogenes*, but it does not appear to be causing disease. This would likely be supported by the absence of a serologic antibody rise on serial testing of blood (Kaplan, 1980; Johnson, Kurlan, Leckman, & Kaplan, 2010; Kaplan, Gastanaduy, & Huwe, 1981). As it is not always practical to obtain multiple blood specimens from children, many experts make a presumption of *S. pyogenes* carriage based on the lack of clinical signs and symptoms observed at the time that a rapid test and/or throat culture is positive for *S. pyogenes* (Shulman, et al., 2012).

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Prevalence of *S. pyogenes* Carriage

Pharyngitis due to *S. pyogenes* is very common in school-aged children. A meta-analysis based on a systematic review of 29 studies provides a prevalence of information about this condition. When studies of children of all ages with sore throat were analyzed, there was a pooled prevalence of 37% (95% confidence interval (CI) 32-43%) of children who were found to have a positive diagnostic test performed on a pharyngeal swab for *S. pyogenes*. This analysis also demonstrated that the prevalence of *S. pyogenes* carriage among well children with no signs or symptoms of pharyngitis was 12% (95% CI 9–14%) (Shaikh, Leonard, & Martin, 2010). Several other studies support that 15–20% of asymptomatic school aged children are colonized with *S. pyogenes*, and that 25% of asymptomatic household contacts of children with streptococcal pharyngitis have throat cultures that revealed the presence of *S. pyogenes* (Schwartz, Wientzen, Pedreira, Feroli, Mella, & Guandolo, 1981; Shulman, 1994).

Longitudinal Studies of *S. pyogenes* Carriers

A longitudinal study was conducted in the United States of 100 school-aged children who were followed for up to four years. The mean age was 9.6 years, with a range of 5–15 years. These children had throat swabs cultured for the presence of *S. pyogenes* approximately every two weeks during the school year. An examination of the pharynx was performed at the time that the specimen was acquired, and the child was questioned about upper respiratory symptoms. If the throat culture revealed the presence of *S. pyogenes*, then a parent was contacted and another inquiry was made about the presence of a sore throat in the child. Children with classic symptoms that were consistent with streptococcal pharyngitis were treated with an antibiotic when the result of the throat culture demonstrated *S. pyogenes*. Children without signs or symptoms were not treated with antimicrobial therapy. Children were classified as having asymptomatic pharyngeal carriage if two or more sequential surveillance throat cultures positive for *S. pyogenes* were obtained more than one week apart, in the absence of respiratory symptoms. *S. pyogenes* carriers accounted for 27–32% of the cohort in each year of the study. The mean prevalence of carriers, calculated by month, was 15.9% (standard deviation 4.99%; range 4.2–26%). If children were identified as *S. pyogenes* carriers in the first year that they participated in the study, they were significantly more likely to be carriers in subsequent years, as compared with children who were not identified as *S. pyogenes* carriers in their first year of observation ($p<.0001$). Fifty-three percent of the children who were followed were *S. pyogenes* carriers at some point during their study participation (Martin, Green, Barbadora, & Wald, 2004).

All of the *S. pyogenes* isolates underwent molecular typing by field inversion gel electrophoresis (FIGE). A *S. pyogenes* isolate that represented each distinct FIGE pattern was sent to a reference laboratory for *emm* typing. It was common to find that the children who were *S. pyogenes* carriers switched from colonization with one *emm* type to colonization with another *emm* type. For the majority of the occurrences, there were no clinical signs or symptoms when the switching of *emm* types occurred. However, in 15% of the episodes where type switching occurred, the child reported clinical symptoms consistent with streptococcal pharyngitis at the same time. Occasionally, a child who was carrying one *emm* type had an apparent clinical disease due to a second type, and then resumed carriage with the original *emm* type (Martin, Green, Barbadora, & Wald, 2004). There was no association of *emm* type and carriage with clinical infection. In any given school year, there were 6–11 *emm* types identified in the study population. Each of the *emm* types was observed in children belonging to each clinical classification (Martin, Green, Barbadora, & Wald, 2004).

During the third year of this longitudinal study, there was a clonal outbreak of infections, due to an erythromycin-resistant *S. pyogenes* isolate. The strain was determined to have the M phenotype and was *emm* 6; it was observed in children who were symptomatic with typical symptoms (50%) and atypical symptoms (11%), as well as in asymptomatic children (39%). Typical symptoms were defined as those that occurred in children who had a sore throat as their predominant complaint. Atypical symptoms were defined as children who had

rhinorrhea, but no sore throat. This isolate was not observed in the previous two school years (Martin, Green, Barbadora, & Wald, 2002). The same isolate resulted in several different clinical manifestations, including colonization.

Transmission of Streptococcal Infection from Carriers

Immediately after acquisition of a new streptococcal organism, transmission of the bacteria from child to child is thought to occur by large respiratory droplets. However, after several weeks, the child is presumed to no longer be contagious even if they are still colonized. There are several reasons for making this assumption. Patients who are carriers are thought to have a lower density of *S. pyogenes* in their pharynx, compared to those with an acute infection due to *S. pyogenes* (Krause, Rammelkamp, Denny, & Wannamaker, 1962). This may reduce their ability to transmit infection to others. In addition, the lack of respiratory symptoms and therefore respiratory secretions may also impact on their ability to spread the bacteria to others in their environment (Johnson, Kurlan, Leckman, & Kaplan, 2010; Kaplan, Gastanaduy, & Huwe, 1981). Finally, the bacteria may change over time by becoming less virulent and losing the ability to cause infection (Davies, et al., 1996).

The bacteria that are most likely to colonize individuals are assumed to be less virulent. Davies conducted a population-based surveillance study of invasive disease due to *S. pyogenes* in 1992–1993. During this period, there were 323 cases of invasive disease identified with a variety of presentations. Specimens were obtained for bacterial culture of *S. pyogenes* from adult and child household contacts within two weeks of the identification of invasive disease in 46 patients: 12% had throat cultures which were positive for *S. pyogenes*. By molecular typing methods, all were identical to the strain that was identified in the index patient. Of these household contacts, 33% had pharyngitis at the time the culture was obtained. None had invasive disease or a skin or soft tissue infection. The univariate analysis demonstrated that a younger age and 4 or more hours of contact with the index patient were more likely to be associated with colonization with *S. pyogenes*. It was estimated that the risk of transmitting invasive disease to other household members was low, at 2.9 per 1000 (95% CI, 0.80 to 7.5 per 1000) (Davies, et al., 1996).

Complications from *S. pyogenes* Carriage

Children who are identified as *S. pyogenes* carriers are not thought to be at risk for complications due to *S. pyogenes* (Kaplan, 1980). While the pathogenesis of acute rheumatic fever is not completely understood, there is significant epidemiologic and immunologic evidence to support the theory that the immune response to a *S. pyogenes* infection is a critical factor. There is molecular mimicry between the immune response to the *S. pyogenes* and the heart, synovial, or brain tissue (Kaplan & Bisno, 2006; Stollerman, Lewis, Schultz, & Taranta, 1956; Zabriskie, Hsu, & Seegal, 1970; Krisher & Cunningham, 1985; Wannamaker, et al., 1951). Since *S. pyogenes* carriers do not have evidence of disease due to *S. pyogenes* or confirmation of an immune response to *S. pyogenes*, they are not believed to be at risk for non-suppurative complications (Johnson, Kurlan, Leckman, & Kaplan, 2010).

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (or PANDAS) is a term used to describe the potential relationship between infections with *S. pyogenes* and the abrupt onset of motor tics or obsessive compulsive disorder in children. (See the chapter by Orefici et al in this volume for more details.) Some authors believe that this may be a complication from an acute streptococcal infection and the resultant anti-brain autoantibodies. However, children who are *S. pyogenes* carriers may also be at risk. Murphy conducted a longitudinal school study that followed 693 children, aged 3 to 12 years. While only 4.6% had persistent positive throat cultures for *S. pyogenes*, these children had higher rates of neurologic symptoms, such as choreiform movements and behavioral findings (Murphy, et al., 2007). This data raises the question of a potential relationship of the carrier state to neuropsychiatric symptoms.

Identification of *S. pyogenes* Carriers in Clinical Practice

There are two primary ways that a patient may be recognized as being a streptococcal carrier. A child may have an episode of streptococcal pharyngitis, receive treatment, and have a follow-up throat culture for the presence of *S. pyogenes* at the end of their course of antibiotic therapy. If the follow-up throat culture demonstrates the presence of *S. pyogenes*, the patient is presumed to be a bacteriologic failure. There are several potential explanations for this occurrence. These include: 1) the presence of beta-lactamase–producing oral flora, which prevent the killing of *S. pyogenes*, or the absence of oral flora that are inhibitory to *S. pyogenes*; 2) tolerance of *S. pyogenes* to penicillin; 3) infection in the tonsillar crypts or other compartments where antimicrobial therapy is not effective; or 4) the presence of relatively non-replicating organisms (Smith, Huskins, Kim, & Kaplan, 1987; Roos, Grahn, & Holm, 1986; Gerber, 1994). However, many experts agree that the most likely explanation is that the children who experience bacteriologic failure following antibiotic therapy that is appropriate for streptococcal pharyngitis are *S. pyogenes* carriers (Kaplan, Gastanaduy, & Huwe, 1981; Shulman & Gerber, 2004). The child's initial episode of illness may in fact have been due to *S. pyogenes*; however, the bacteria were not eradicated by a course of antimicrobial therapy. The pharynx then becomes colonized with *S. pyogenes* without evidence of continuing disease or inflammation. Another possible explanation is that the initial clinical illness may not have been due to *S. pyogenes*, but rather that the symptoms may have been caused by a virus, and that the child was a carrier of this bacterium prior to the recent episode of pharyngitis.

True Recurrent Infections versus *S. pyogenes* Carriage

It is important to attempt to distinguish between children who are having true sequential recurrent episodes of streptococcal pharyngitis from the child who is a *S. pyogenes* carrier, as the management of these two conditions differ. A positive throat culture for *S. pyogenes* or a positive rapid antigen detection test at the time that a child has acute pharyngitis does not prove that the episode is due to *S. pyogenes*. Proof of streptococcal pharyngitis would require obtaining serial blood specimens and observing a rise in antibody titers over time (Kaplan, 1980; Johnson, Kurlan, Leckman, & Kaplan, 2010). This is not practical in the clinical care of children, and is confounded by the fact that prompt therapy may abort or blunt the antibody response. Instead, it is critical to obtain a careful history of the symptoms present with each episode of illness and the child's clinical response to antibiotic therapy.

The child with true recurrent episodes of streptococcal pharyngitis is likely to have classic symptoms with each illness (sore throat, without cough, rhinorrhea, hoarseness) and will experience a prompt resolution of symptoms with the initiation of antibiotic therapy (Nelson, 1984). In contrast, children with a viral illness whose throat cultures are positive for *S. pyogenes* who are actually streptococcal carriers are more likely to have viral symptoms (such as hoarseness, cough, and rhinorrhea) and are less likely to experience a rapid improvement of their symptoms with antibiotic therapy. While these clues are helpful, the best method to distinguish between these two possibilities is to obtain a throat culture after the patient has completed a course of antibiotic therapy, at a time that the patient is without any symptoms. The child with true recurrent infections will test negative for *S. pyogenes*, while the child who is a *S. pyogenes* carrier will have a positive throat culture at a time when they are well (Table 1).

Table 1: Characteristics to Distinguish a Child with True Recurrent Episodes from the Child who is a Streptococcal Carrier

True Recurrent Episodes	Streptococcal Carrier
Illness with classic symptoms: sore throat, fever, tender anterior cervical adenopathy, tonsillar erythema, tonsillar exudate, palatal petechiae	Illness not classic, may include respiratory symptoms such as hoarseness, cough and nasal congestion
Symptoms improve within 24-48 hours after initiation antibiotic therapy	Symptoms do not appear to improve with antibiotic therapy; Illness lasts longer than 5 days

Table 1 continued from previous page.

True Recurrent Episodes	Streptococcal Carrier
Throat culture or Rapid Antigen Detection Test is negative for *Streptococcus pyogenes* when the child is asymptomatic	Throat culture or Rapid Antigen Detection Test is positive for *Streptococcus pyogenes* when the child is asymptomatic

Eradication of the Carrier State

The child who is a *S. pyogenes* carrier presents challenges in clinical management. In the majority of instances, antimicrobial therapy is not indicated for children with asymptomatic pharyngeal colonization. The guidelines published by the Infectious Disease Society of America suggest that these children do not require antibiotic therapy, since these children are not at risk for developing complications, and that they are not likely to transmit infection to others (Shulman, et al., 2012). The American Academy of Pediatrics Committee on Infectious Diseases suggests several situations when it may be advantageous to eradicate *S. pyogenes* colonization. These include when there is a family history of rheumatic fever or rheumatic heart disease, when the family is extraordinarily anxious or is considering tonsillectomy solely because of the presence of *S. pyogenes* carriage, or when there are community outbreaks of *S. pyogenes* pharyngitis (Kimberlin, Brady, Jackson, & Long, 2015).

Several clinical studies suggest that certain antimicrobial agents are associated with a higher likelihood for successful *S. pyogenes* eradication than others, in the limited circumstances in which it appears desirable to attempt to eradicate carriage (Casey & Pichichero, 2004; Pichichero, et al., 2000; Kaplan, 1980; Kaplan & Johnson, 1988; Chaudhary, et al., 1985). There are two studies whose primary outcome was to determine the efficacy of antibiotics in eliminating *S. pyogenes* carriage. A ten-day course of oral clindamycin was found to be effective, with successful eradication in 85–90% of the children who were *S. pyogenes* carriers (Tanz, et al., 1991). An earlier study demonstrated success with a combination of benzathine penicillin G and oral rifampin (Tanz, Shulman, Barthel, Willert, & Yogev, 1985).

Alternatives that are commonly prescribed include a 10-day course of amoxicillin plus clavulanic acid, or a first-generation oral cephalosporin (Kaplan & Johnson, 1988). If *S. pyogenes* carriage is suspected, the child's subsequent episode of pharyngitis, which is associated with a throat swab positive for *S. pyogenes*, can be treated with one of these options in an attempt to eradicate the *S. pyogenes* (Brook, 2001) (See Table 2). There are no randomized controlled clinical trials to compare treatment regimens for children who are thought to have true recurrent episodes of streptococcal pharyngitis, or for those who are believed to have asymptomatic pharyngeal carriage.

Table 2: Antibiotic Dosages Commonly Used For Eradication of the Streptococcal Carrier State in Children

Agent	Route	Dosage	Duration
Clindamycin	oral	20-30 mg/kg/d in 3 doses (max.= 300 mg/dose)	10 days
Penicillin and Rifampin	oral	Pen V 50 mg/kg/d in 4 doses x10 days (max.=2000 mg/d) Rifampin: 20 mg/kg/d in 1 dose for each of the last 4 days of treatment (max.=600 mg/d)	10 days
Amoxicillin clavulanic acid	oral	40 mg /kg/d in 3 doses based on the amoxicillin (max.= 2000 mg amoxicillin/d)	10 days

Table 2 continued from previous page.

Agent	Route	Dosage	Duration
Benzathine penicillin G *Plus* Rifampin	IM	600,000 units for < 27 kg 1,200,000 units for ≥ 27 kg	1 dose
	oral	20 mg/kg/d in 2 doses (max.=600 mg/d)	4 days

mg = milligrams, kg = kilograms, d = days, max = maximum, IM= intramuscular

Host Factors for *S. pyogenes* Carriage

It is not clear if host factors, the specific characteristics of the bacterial isolates, or both play a role in determining whether a patient becomes a *S. pyogenes* carrier. It is believed that type-specific immunity does not prevent episodes of pharyngitis or asymptomatic carriage, particularly in view of the large number of different M types (Guirguis, Fraser, Facklam, El Kholy, & Wannamaker, 1982). From early studies, it is known that a patient who is not treated with an antibiotic for *S. pyogenes*, eradication of the *S. pyogenes,* presumably due to host response, occurs over several weeks in 50% of the patients (Brink, Rammelkamp, Denny, & Wannamaker, 1951; Catanzaro, et al., 1954; Krause, Rammelkamp, Denny, & Wannamaker, 1962). In her longitudinal study, Martin found that children who were *S. pyogenes* carriers were likely to remain carriers over time, while others never became carriers (Martin, Green, Barbadora, & Wald, 2004). In addition, children who also had siblings in the study were more likely to be a *S. pyogenes* carrier if their sibling was also colonized with *S. pyogenes* (unpublished data). Repeated environmental contact may also play a potential role. These observations suggest that there may be specific host and exposure factors that increase the likelihood that a child will become asymptomatically colonized with *S. pyogenes*.

Bacterial Factors

The M protein, which is encoded by the *emm* gene, is used for classifying types of *S. pyogenes* isolates. A longitudinal study did not demonstrate an association of *S. pyogenes emm* type with the likelihood of becoming a *S. pyogenes* carrier. Each *emm* type was observed in each clinical classification: typical infection, atypical infection, or carrier state (Martin, Green, Barbadora, & Wald, 2004). Mengeloglu studied clinical isolates from patients with infections due to *S. pyogenes* (n=79) and from carriers (n=60) and found no differences when the groups were compared by *emm* typing (Mengeloglu, et al., 2013). Some studies suggest that certain *emm* types are more likely to produce a biofilm than others (Ogawa, et al., 2011). *S. pyogenes* isolates may be able to evade host factors and antibiotics when contained within a biofilm, which may enable these isolates to be associated with asymptomatic colonization.

Some isolates of *S. pyogenes* have an external capsule and are described as mucoid. Capsule production can be upregulated, as seen in invasive infections, or can be downregulated. While mucoid strains of *S. pyogenes* have been associated with outbreaks of acute rheumatic fever, it is believed that isolates with less capsule production may be more likely to be isolated from children who are probable streptococcal carriers (Veasy, et al., 2004; Veasy, et al., 1987).

S. pyogenes is considered to be an extracellular pathogen. It can cause pharyngitis by adhering to epithelial cells, and several studies have demonstrated internalization into epithelial cells (Molinari & Chhatwal, 1998). There are several studies that demonstrate that children who are asymptomatic carriers of *S. pyogenes* are more likely to have a *S. pyogenes* isolate that contains the *prtF* genes (Neeman, Keller, Barzilai, Korenman, & Sela, 1998). PrtF1 and PrtF2 are considered to be major streptococcal virulence factors that may allow strains of *S. pyogenes* to enter respiratory epithelial cells. They are thought to play a role in the adherence and internalization of the bacteria, and may be critical in invasive *S. pyogenes* infections (Cunningham, 2000). Neeman examined the frequency of *prtF1* containing *S. pyogenes* isolates in children with pharyngitis. In 54 children with bacterial

eradication after a course of antibiotics, 16/54 (30%) of the isolates were *prtF1* positive, compared to 9/10 (90%) of the isolates recovered from children who were colonized with the same strain before and after treatment and were presumed to be *S. pyogenes* carriers (Neeman, Keller, Barzilai, Korenman, & Sela, 1998). Other studies support these findings (Molinari, Talay, Valentin-Wiegand, Rohde, & Chhatwal, 1997; Molinari & Chhatwal, 1998; Hotomi, et al., 2009). Musumeci compared *S. pyogenes* isolates obtained from patients with asymptomatic carriage (n=30) and with pharyngitis (n=32) and found no differences in *prtF1*-positive strains (70% vs. 69%). However, the proportion of isolates with the *prtF2* gene was higher in those isolates from asymptomatic carriers (80% vs. 53% $p < 0.05$) (Musumeci, et al., 2003). Investigators further examined *prtF1* positive *S. pyog*enes isolates using a HEp-2 cell model, and found that adherence and internalization were higher in the strains from *S. pyogenes* carriers, as compared to those who had experienced successful bacterial eradication (Sela, Neeman, Keller, & Barzilai, 2000), while other studies also support that *prtF2* positive isolates are associated with a greater efficiency for internalization (Gorton, Norton, Layton, Smith, & Ketheesan, 2005). This supports the hypothesis that internalization of *S. pyogenes* may contribute to bacteriologic failure and the persistent carriage of *S. pyogenes*.

There may also be an association between *S. pyogenes* isolates that are erythromycin resistant and their ability to invade respiratory epithelial cells. Facinelli found that erythromycin-resistant isolates were more likely to be *prtF1* positive (89%) than erythromycin-susceptible isolates (21%). The presence of *prtF1* was also associated with higher cell invasion efficiency (Facinelli, Spinaci, Magi, Giovanetti, & Varaldo, 2001). Cocuzza examined *S. pyogenes* isolates obtained from children with pharyngitis (n=837) both before and after antibiotic treatment. Overall, 33% were positive for *prtF1*. There was a higher prevalence of *prtF1* in isolates that were erythromycin-resistant (45%), with the highest proportion observed in the iMLS phenotype with inducible resistance (84%) (Cocuzza, Lanzafame, Sisto, Broccolo, & Mattina, 2004).

In asymptomatic carriage of *S. pyogenes*, complex and varied expression of virulence traits appear to be critical for allowing the bacteria to evade the host immune response. It appears that *prtF1* permits cell adherence and invasion. The presence of virulence factors and macrolide resistance genes may be associated with certain *emm* types, rather than with the source of the bacterial isolate (Creti, et al., 2005; Blandino, Puglisi, Speciale, & Musumeci, 2011; Baldassarri, et al., 2007; Ogawa, et al., 2011). This may explain the variety of clinical manifestations that may be observed within a population that has active infections with the same *emm* type of *S. pyogenes*.

Conclusion

S. pyogenes infections are common among school-aged children. The majority of positive throat cultures observed in a longitudinal study of school-aged children were obtained from children who were carriers of *S. pyogenes*. Carriers switched *emm* types, but tended to become carriers repeatedly during the study with different *emm* types. Practitioners should consider treating children known to be *S. pyogenes* carriers when they develop a new illness with symptoms that are consistent with streptococcal pharyngitis. This may represent a new infection leading to disease, and these children then may be at risk to transmit the infection, as well as for complications, such as rheumatic heart disease. Further investigations regarding host and bacterial factors will be needed to fully understand the asymptomatic carriage of *S. pyogenes*.

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