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LITERATURE REVIEW

Systematic review of factors contributing to penicillin treatment failure in *Streptococcus pyogenes* pharyngitis

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OBJECTIVE: Review the evidence for various explanations for microbiologic treatment failure following use of penicillin in group A streptococcal (GAS) tonsillopharyngitis.

DATA SOURCE: Systematic review of the literature based on Medline and EMBASE searches, and review of reference lists of included studies.

RESULTS: The explanations for penicillin treatment failure in GAS tonsillopharyngitis include 1) carrier state, 2) lack of compliance, 3) recurrent exposure, 4) in vivo copathogenicity of β-lactamase–producing normal pharyngeal flora, 5) in vivo bacterial coaggregation, 6) poor antibiotic penetration to tonsillopharyngeal tissue, 7) in vivo eradication of normal protective flora, 8) early initiation of antibiotic therapy resulting in suppression of an adequate host immune response, 9) intracellular localization of GAS, 10) GAS tolerance to penicillin, 11) contaminated toothbrushes or orthodontic appliances, and 12) transmission from the family pet. There is very little type I or II evidence to support any of the above-cited explanations for treatment failure in GAS tonsillopharyngitis; available studies are mostly observational (in patients) or laboratory-based without clinical confirmation.

CONCLUSION: Multiple explanations have been offered by investigators to explain penicillin treatment failures in GAS tonsillopharyngitis, but the evidence base to support the proposed explanations is generally weak by current standards. Further research is needed to better understand the mechanism(s) of penicillin treatment failure in GAS tonsillopharyngitis.

Group A streptococcal (GAS) microbiologic treatment failure following penicillin use was reported in 4 to 8 percent of children with GAS pharyngitis in the 1950s.[1,2] Whereas, in the past 15 years, most studies find treatment failure in the range of 20 to 40 percent.[3] In this review, various proposed explanations for microbiological treatment failures following penicillin will be discussed. The explanations include 1) carrier state,[4,5-12] 2) lack of compliance, 3) recurrent exposure (family or peers), 4) in vivo copathogenicity of β-lactamase–producing flora (BLPF),[13-36] 5) in vivo bacterial coaggregration,[37] 6) poor tonsillar penetration of antibiotic,[38-43] 7) in vivo eradication of protective throat microflora,[14,26,29,36,44-52] 8) early initiation of antibiotics resulting in inadequate host immune response,[53-55] 9) intracellular localization of GAS,[56-65] 10) streptococcal tolerance to penicillin,[66-72] 11) fomites,[73,74] and 12) family pet[75-78] (Table 1). In addition, there may be other factors acting alone or in concert that result in the phenomenon of microbiologic treatment failure, such as host and/or characteristics specific to the strain of GAS.

METHODS

The streptococcal pharyngitis literature was accessed with a Medline search from 1960 to 2006, and an EMBASE search from 1980 to 2006. Search terms included streptococcal pharyngitis, streptococcal carrier, recurrence, and treatment failure. There was no language restriction. To search for articles published prior to 1960, the extensive library of one of the authors (Pichichero) was searched and all relevant articles were reviewed. Reference lists of included articles were searched to identify any articles missed in the online searches.

Inclusion criteria for studies included in this systematic review were 1) studies of recurrent streptococcal pharyngitis including randomized clinical trials, epidemiological trials, case studies, and literature reviews; 2) in vitro studies examining the microbiology of patients with recurrent streptococcal pharyngitis; 3) animal trials; 4) no age restrictions of the patient population.

Exclusion criteria for articles were 1) randomized trials evaluating the efficacy of a treatment in a nonrecurrent streptococcal pharyngitis; 2) treatment trials that did not discuss explanations for recurrences.

All articles were examined for indicators of quality by both authors. For particular recommendations and statements, the strength of the supporting evidence and quality of the data were rated by a modification of The Infectious Diseases Society of America—United States Public Health

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Table 1
Explanations for recurrent streptococcal pharyngitis

Explanation	Number of studies with evidence type				
	I	II	III	In vitro	Animal studies
Carrier state; no disease[4-12]	1[10]	3[5,9,12]	8[4,5-8]	0	0
Poor patient compliance	0	4	0	0	0
Recurrent exposures	0	3	1	0	0
Copathogenicity[13-36]	1[33]	7[14,16,21,22,27,28,35]	11[13,17,20,21,24,25,30-34]	3[15,18,26]	2[29,37]
Coaggregation[37]	0	0	0	1[37]	0
Poor tonsillar penetration[37-43]	0	0	1[39]	5[38,40-43]	0
Eradication of protective nonpathogenic pharyngeal flora[14,26,29-36,44-52]	3[58,59,62]	3[45,47,51]	1[14]	3[26,44,46]	3[29,36,50]
Early antibiotic treatment[53-55]	3[63-65]	0	0	0	0
Intracellular localization of GAS[56-58]	0	2[59,65]	0	7[56-58,60-64]	0
Penicillin tolerance[66-72]	0	2[69,70]	1[71]	3[66-68]	0
Toothbrush or orthodontic appliance contamination[73-74]	0	0	0	2[73-74]	0
Family pets as source of reinfection[75-78]	0	1[75]	2[76,77]	0	1[78]

GAS, Group A streptococcal.

Service grading system.[79] Roman numerals I-III indicate the quality of the supporting evidence. The articles were classified as "I" if it was a randomized, clinical trial; "II" if the trial was an epidemiological study without randomization; "III" if the trial was a case study or a review of the literature; "in vitro" if the manuscript was of in vitro studies of patient samples (such as throat culture specimens); and "animal studies" if the manuscript involved an animal model to evaluate a hypothesis to examine a possible explanation for recurrent streptococcal pharyngitis.

RESULTS

The literature searches, personal library search, and reviews of the identified manuscripts' reference lists yielded >900 articles related to streptococcal pharyngitis. The majority of the articles were excluded because they were not about recurrent streptococcal infections. A total of 96 articles fulfilled the inclusion criteria; however, 10 articles could not be obtained for review.

Eighty-six articles were reviewed and quality of the evidence recorded by both authors (Table 1). Eight randomized clinical trials were graded as I, 26 nonrandomized epidemiological trials as II, 26 case studies or reviews as III. There were 22 in vitro studies and six animal studies.

Explanations of Penicillin Treatment Failure

The carrier. Twelve studies were identified that discussed the streptococcal carrier as the explanation of recurrent GAS pharyngitis. One study[10] was a randomized clinical trial, three studies[5,9,12] were nonrandomized clinical trials of epidemiological trials, and eight[4,6-8,11] were case studies and/or reviews of the literature (Table 1). The majority of the evidence for this explanation of penicillin treatment failures relies on nonrandomized trials, epidemiological studies, case studies, and reviews.

Identifying the carrier. Carriers of GAS harbor the organism in their noses or throats but display no symptoms of acute infection and do not mount an antibody response to the organism (Table 2). It may be possible, although not practical in the routine setting, to distinguish between a patient with acute GAS infection and a streptococcal carrier by comparing the titers of antibody to GAS antigens (usually antistreptolysin) in acute and convalescent serum specimens. Unfortunately, the initiation of early antibiotic treatment of GAS pharyngitis will significantly dampen or completely prevent a rise in antistreptococcal antibodies. A

Table 2
Definition of the group A streptococcal (GAS) tonsillopharyngeal carrier

Positive GAS throat culture or rapid antigen detection test, plus
Clinically well with no symptoms or signs of acute GAS throat infection, plus
If measured, no detectable immune response to GAS strain

low antibody titer in two consecutive specimens may suggest continuous carriage of GAS rather than an acute GAS infection.

See the Appendix for discussions of prevalence and significance of carriers, how children become carriers, treatment of the carrier, and other explanations for penicillin treatment failure.

Copathogens

Twenty-four trials were identified that discussed copathogenicity as the explanation of penicillin failures[13-36] (Table 1). One trial[33] was a randomized clinical trial, seven[14,16,21,22,27,28,35] were nonrandomized clinical trials or epidemiological studies, 11[13,17,20,21,24,25,30-34] trials were either case studies or reviews of the literature, three[15,18,26] trials were in vitro studies of patient specimens, and two[27,37] trials studied animal models of copathogenicity.

Copathogenicity has become an acknowledged mechanism to explain penicillin treatment failure.[82] The presence of co-colonizing bacteria, termed copathogens, that elaborate β-lactamase in the tonsillopharynx has been proposed as a possible mechanism by which penicillin is inactivated prior to bactericidal action on GAS.[13-36] *Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis,* and β-lactamase–producing anaerobic species are common flora in the pharynx. The prevalence of these β-lactamase–producing bacteria may be increased as a consequence of penicillin treatment of patients with GAS pharyngitis, thereby leading to increased penicillin failures. Indirect evidence suggests that when copathogens are present in the pharynx, use of antibiotics that are effective despite the presence of β-lactamase may enhance bacteriological and clinical success[3,13,35,82,97,98] although this is not a universal finding.[84] It is not necessary to eradicate the copathogens that produce β-lactamase. Rather, it is necessary for the antibiotic employed to remain active despite the presence of β-lactamase in vivo. Patients who have recurrent bouts of GAS pharyngitis and/or in whom penicillin does not eradicate GAS might be colonized with copathogens. Selecting an alternative antibiotic that is β-lactamase stable and can be bactericidal to GAS despite the presence of β-lactamase, in some cases, proves an important therapeutic strategy in copathogen-colonized patients who experience GAS pharyngitis.

Coaggregation

Another explanation for penicillin failure may involve an interaction of GAS with *Moraxella catarrhalis*. One in vitro study was identified.[37] Colonization with *M catarrhalis* can facilitate GAS pharyngeal attachment because GAS can attach to *M catarrhalis* adhesins. In this way, a high concentration of β-lactamase to inactivate penicillin in the tonsillopharyngeal tissues may occur. In a recent study, Brook and Gober[105] evaluated the cohabitation of the tonsillopharynx by GAS and certain other bacterial species that may contribute to the inflammatory process and the failure of penicillin therapy. The study evaluated the recovery of *H influenzae*, *M catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* in association with acute tonsillopharyngitis. An association between the recovery of GAS and *H influenzae* and *M catarrhalis* from patients with acute tonsillopharyngitis and *M catarrhalis* from healthy children was found.

Poor Tonsillar Penetration of Antibiotic

Eradication failure might be due to the lack of sufficient antibiotic concentration at the site of infection during the recommended treatment time.[38-43] Six studies identified this phenomenon as a possible mechanism of penicillin treatment failures. One trial[39] was a case study and five were in vitro studies.[38,40-43]

Alteration of Microbial Ecology/Bacterial Interference

Eradication of the normal pharyngeal flora, especially α-hemolytic streptococci, may enhance the susceptibility of patients to subsequent infection with GAS; their presence has been shown to be associated with resistance to GAS infection by a mechanism termed "bacterial interference."[14,26,29,36,44-52] Thirteen trials were identified that discussed bacterial interference as a possible explanation of penicillin treatment failures. Three trials[48,49,52] were randomized clinical trials, three trials[45,47,51] were nonrandomized clinical trials, one trial[14] was a review, and three trials each were in vitro studies[26,44,46] or animal studies.[29,36,50] Penicillin may eradicate or suppress host indigenous bacterial flora. Such alterations may result in clinical or subclinical superinfections, resulting in quantitative and qualitative changes in the pharyngeal ecosystem. Penicillin treatment causes a significant quantitative decrease in α-hemolytic streptococci, γ-hemolytic streptococci, peptostreptococci, and *Prevotella* in the throat; thereby the ecological balance in the throat is disturbed. These effects can persist weeks after therapy. Elimination of α-streptococci from the throat eliminates their ability to produce bacteriocins, which are a part of the natural host resistance to GAS colonization. Using throat gargles of live α-streptococci prepared from a patient's own throat bacteria has been suggested as a possible therapeutic strategy for prevention of GAS infection, particularly in prevention of relapse or recurrent disease.[48-51] The role of bacterial interference in eradication failure has not always been observed.

Early Treatment Suppresses Immunity

Prompt initiation of penicillin treatment with the onset of acute symptoms may suppress the antistreptolysin and anti-DNase B antibody rise typically observed to follow GAS infections. Three articles, all randomized clinical trials, were identified.[53-55] Antibody suppression has been associated with GAS pharyngitis relapse and recurrence.[53-54] These observations have been challenged[84,85]; however, no study of similar design with a placebo control has produced contrary results. Although delaying treatment is probably not necessary in most cases of GAS pharyngitis, it may be

a useful strategy for patients who have frequent, recurrent mild-to-moderate infections.

Intracellular Localization

A number of published reports now describe the capacity of various GAS strains to enter and survive within epithelial and macrophage-like cells of the upper respiratory tract cells.[56-65] Nine such trials were identified: Two were nonrandomized trials[59,65] and seven were in vitro studies[56-58,60-64] (Table 1). Consequently, it has been suggested that the cell entry by GAS may enable the bacterium to survive in an environment that is shielded from the bactericidal effect of penicillin, as well as other β-lactams, which cannot reach bactericidal intracellular concentrations.

The first genes implicated with high-efficiency internalization of various GAS strains were sfbI and prtF1, which encode for a closely related fibronectin-binding protein.[64,65] The prevalence of the prtF1 gene in GAS strains derived from asymptomatic patients with eradication failure following penicillin therapy has been compared with the prevalence in strains derived from patients with successful bacterial eradication. A strong correlation between the presence of prtF1 and GAS eradication failure was found.[52]

Penicillin Tolerance

Despite the extensive use of penicillin in the past six decades, no resistance has emerged among GAS.[86,87] Tolerance, whereby bacteria repeatedly or continuously exposed to sublethal concentrations of penicillin become increasingly resistant to eradication, has been suggested to cause penicillin treatment failure.[66-72] Six such articles were identified. Two articles[69,70] were nonrandomized clinical trials, one article[71] was a review of the literature, and three articles[66-68] were in vitro studies (Table 1). Sporadic reports correlated in vitro penicillin tolerance (ie, significantly decreased bactericidal effect of penicillin) with GAS eradication failure, but conflicting findings have been reported by others. Disagreement on a uniform and accepted method of testing penicillin tolerance in GAS may explain the conflicting results. Of importance are stored versus freshly isolated strains; the number of colonies selected for subculture; phase of growth; size of inoculum; macrobroth or microbroth method; composition of the test medium including the pH; length of incubation; mixing of tubes during the test; volume of subculture taken from liquid medium; use of β-lactamase for minimal bactericidal concentration (MBC) determination; ratio of MBC to minimum inhibitory concentration (MIC) used to define tolerance. An ineffective bactericidal effect might be associated with the growth phase of GAS. GAS might survive in a stationary-like phase, in which cell-wall synthesis is minimal (Eagle effect). Several penicillin-binding proteins of GAS are lost when the bacterium enters the stationary phase in vitro.

Toothbrushes and Orthodontic Appliances

A limited amount of research has been done on the ability of GAS to adhere to toothbrushes and orthodontic appliances[73,75] (Table 1). The studies were in vitro simulations to demonstrate the possibility of the organism to contaminate these objects that go in the mouth and results of a study of 104 children, but there is no direct evidence to link GAS recurrences to use of the same toothbrush before and after acute infection nor to a benefit by disinfecting orthodontic retainers.

Family Pet

Small, descriptive reports and one animal study have suggested that, in rare instances, dogs or cats may be carriers of GAS although GAS are not a normal colonizer of these animals; however, this possibility has not been corroborated in other investigations[75-78] (Table 1).

Host and Strain Factors

Explanations for susceptibility to GAS tonsillopharyngitis have been elusive. Some data suggest differences in expression of oropharyngeal epithelial cell receptors that allow GAS attachment.[88,89] There may be pharmacogenomic variation in penicillin pharmacokinetics[90] similar to that for amoxicillin.[91,92]

Some GAS strains express a thicker polysaccharide capsule (so-called mucoid strains). These strains have been associated with acute rheumatic fever (ARF) outbreaks[93]; notably about 40 percent of the patients experiencing ARF during the Salt Lake City[94,101] and western Pennsylvania/northeast Ohio outbreaks[99,100] had received penicillin or amoxicillin.

CONCLUSION

Factors that may contribute to penicillin treatment failure include the carrier state, a lack of compliance, recurrent exposure, in vivo copathogenicity of β-lactamase–producing normal pharyngeal flora, in vivo bacterial coaggregation, poor antibiotic penetration into tonsillopharyngasal tissue, in vivo eradication of normal protective flora, early initiation of antibiotic therapy resulting in suppression of an adequate host immune response, intracellular localization of GAS, GAS tolerance, contaminated toothbrushes or orthodontic appliance, and transmission of GAS from a family pet. There is a need for type I or II evidence to support the above explanations. However, it is very clear and the evidence base is abundant that microbiological treatment failure with penicillin has been reported with increased frequency since around 1970,[97,98] coincident with the explosion of β-lactamase–producing normal oropharyngeal flora and early initiation of antibiotic treatment (owing to rapid antigen detection testing), which may result in suppression of an adequate host immune response and reduce antibiotic penetration. Although all guidelines continue to advocate penicillin as the sole treatment of choice and argue that penicillin treatment failures are occurring in only carriers, this argument has no evidence base. That is, there is no evidence that more children are GAS carriers today or since

1970 compared with the 1950s and 1960s. Nor is there evidence that, during the past 35 years, more GAS carriers have enrolled in clinical trials of GAS tonsillopharyngitis in which treatment with penicillin or amoxicillin was rendered.

Despite increasing microbiological treatment failures with penicillin, rheumatic fever has not returned to the developed world as a consequence. However, rheumatic fever occurs in the specific and special circumstance when GAS infection of the throat involves a rheumatogenic strain and illness occurs in a genetically susceptible host—often in a circumstance of poorly defined environmental factors that may influence the inoculum of GAS and/or the ability to mount an appropriate immune response. In this regard, Shulman et al[95] recently reported that the reason we are not seeing an increase in rheumatic fever is because we have not had widespread circulation of rheumatogenic GAS strains in the United States since around 1950. Besides the new morbidity of GAS, tonsillopharyngitis is related to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[96,102-104] and the need to limit contagion and to return children to school and parents to work with the lowest risk possible of treatment failure.[80,81]

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Michael E. Pichichero and **Janet R. Casey**, study concept, literature review, writing, and revision.

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APPENDIX

Prevalence of Carriers

In longitudinal surveys among children in such closed or semiclosed populations such as residential homes, orphanages, and schools, carrier rates vary from 10 to 40 percent.[A11-A17] An overall average might be 15 to 20 percent. If one were to assume that at least 15 to 20 percent of all children with pharyngitis have a positive culture for GAS on a carrier basis alone, then a conclusion might be reached that about half of all patients from whom GAS can be isolated are carriers. However, review of these studies clarifies why this logic is not applicable to the patient encountered in private practice.

Detection of carriage of GAS will occur much more commonly in a longitudinal survey of children in which multiple throat cultures are taken from a child over a time span of months in a closed or semiclosed population. Such findings do not reflect the prevalence of carriage in a community-based practice or clinic. Studies from our private practice suggest that about 2.5 percent of well 5- to 10-year-olds can be detected as GAS carriers during well-child visits.[A17] If a schoolage child has a sore throat along with an apparent viral upper respiratory infection (URI) (cough, rhinitis, hoarseness), the carrier prevalence increases to about four to eight percent.[A17] Other practice settings have described similar results regarding carrier prevalence. [A18-A22] Our group[A40] has documented a positive GAS rapid antigen detection test or throat culture rate of 25 to 30 percent among children suspected to have GAS pharyngitis. Therefore, in a practice among the 25 to 30 percent of children with positive rapid tests/cultures, there may be about five percent who are carriers with a viral URI mimicking GAS pharyngitis, leaving about 20 to 25 percent with likely bona fide GAS infections.

Significance of the Carrier

There is disagreement with regard to the significance of the carrier state. The widely held notion that GAS carriers are harmless to themselves and to others is not disingenuous, but it is an oversimplification.[A13,A23-A26] Kuttner and Krumwiede[A41] described a number of GAS outbreaks caused by carriers on the rheumatic fever wards at the Irvington House on the Hudson River, NY, prior to the advent of antibiotics. They showed in their institutional setting that a newly established GAS carrier (defined as a person who was asymptomatic but GAS-positive on culture, with cultures being regularly taken) could be an important vector for GAS infections. Some major and minor acute rheumatic fever outbreaks were introduced by asymptomatic children who carried newly acquired strains of GAS (Table 3). Similarly, in a family setting, James et al[A37] showed that children with clinical illness due to GAS pharyngitis infected other members of the family approximately 25 percent of the time, whereas children who were carriers infected other members of the family about nine percent of the time. The contagion of carriers was found to occur during the first two to four weeks after acquisition of a GAS strain; thereafter, contagion was minimal.[A37,A26] More recently, the same GAS strains prevalent among carriers and patients with symptomatic pharyngitis in a community have been described to be responsible for invasive, toxic shock, and necrotizing fasciitis infections; transmission of these strains from the carriers likely occurred.[A1-A8]

How Children Become Carriers

From studies in the preantibiotic era, school surveys, and family studies since the 1950s already referenced in this paper, we know that some children who become colonized in their nasopharynx or oropharynx with GAS, do not show evidence of illness, and do not demonstrate an immune response to the acquisition of the bacteria. These children would be classified as carriers. A second common mechanism whereby a child becomes a carrier is after antibiotic treatment of an acute GAS pharyngitis episode. In this regard, there are data indicating that about 12 percent of children treated with penicillin for acute GAS pharyngitis emerge as carriers after treatment (Table 4).[A44-A46] Cephalosporins, macrolides, and clindamycin less frequently are followed by development of the carrier state (Table 4).[A44,A46]

Treatment of the Carrier

There are some circumstances in which antibiotic treatment of the GAS carrier has been endorsed (Table 5).[A9,A10,A31] Penicillin is generally ineffective in eradicating GAS from carriers.[A9,A10] Cephalosporins, specifically cefprozil[A28] and cefixime[A29] are more effective.

Table 3
Contagion of carriers

Household study: Clinically ill family member infected 20% of family members, carriers infected 9% of family members.[A37]
Good Samaritan Hospital in Boston and Irvington House on The Hudson studies showed importance of carrier as agent of transmission of GAS early on when carrier state first established.[A25,A41]
Nasal carriers of GAS are more contagious.[A24]
Carrier contagiousness is highest within 2-4 weeks after acquisition of a GAS strain.[A37,A41]

GAS, Group A streptococcal infection.

Table 4
Group A streptococcal tonsillopharyngitis posttreatment carrier rates

Penicillin	41/300 (13.6%)[A44] 81/718 (11.3%)[A46]
Cephalosporin	22/508 (4.3%)[A46]
Macrolide	10/140 (7.1%)[A46]
Clindamycin	10/285 (3.5%)[A44]

Clindamycin[A27,A43] or a combination of penicillin and rifampin[A45,A47] are the best regimens for eradication of GAS from carriers,[A28,A28,A42-A46] perhaps owing to the capability of clindamycin and rifampin to penetrate inside pharyngeal cells (discussed later) and/or their bactericidal activity even when GAS are not replicating.

Other Explanations of Penicillin Treatment Failure

Compliance. Poor patient compliance could be an explanation for penicillin treatment failures. Four studies address patient compliance as a cause of penicillin failures; all four studies were nonrandomized clinical trials or epidemiological trials.[A32-A35] For optimal absorption, oral penicillin V should be administered one hour before or two hours after meals. The 3-times-daily dosing and administration away from meal time recommended by the American Heart Association for penicillin represents a significant compliance barrier. Three-times-daily dosing typically is associated with 30 to 50 percent compliance, whereas 1- to 2-times-daily dosing produces 70 to 90 percent compliance. Intramuscular benzathine penicillin injections obviate compliance issues, but the most recent study that included treatment with benzathine penicillin reported a 37 percent bacterial eradication failure rate.[A30]

Table 5
When to treat Group A streptococcal (GAS) carriers

Definitely
With a history of ARF
Carriers living with a person who has ARF
Carriers working in hospitals, nursing homes, chronic care facilities
Carriers in communities experiencing an ARF outbreak
Possibly
Carriers in families exhibiting "ping-pong" spread of GAS
Carriers with particularly anxious family members regarding GAS infection
Recently established carriers (within 1 month of onset)

ARF, Acute rheumatic fever.

Repeated Exposure. Four trials were identified that studied recurrent GAS exposures as an explanation of penicillin treatment failure[A36-A39] (Table 1). Three trials were classified as type II evidence, nonrandomized clinical trials, or epidemiological studies; one trial was a literature review.

Some patients with GAS tonsillitis treatment failure represent cases of successful antibiotic treatment, that is, resolution of signs and symptoms and complete eradication of the original infecting strain followed by reinfection with the same strain or a new one.

The symptoms of GAS tonsillopharyngitis symptomatically resolve spontaneously within two to five days of onset even when the patient is untreated. Infected individuals remain contagious for several weeks thereafter. Crowded living conditions encourage the transmission of GAS within the family, at work, at school, or in day care settings. After treatment, if there is a recurrence of GAS tonsillopharyngitis and the infection involves the same serotype, then patients may display milder symptoms.[A47] These individuals are contagious to others in their environment and are, themselves, susceptible to rheumatic fever. Because it is not feasible for the routine bacteriological laboratory to subtype GAS strains, the physician cannot determine whether the etiological source for recurrent infection represents a true eradication failure or reinfection.

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