AUCTORES
Globalize your Research

Journal of Surgical Case Reports and Images

Anthony Kodzo-Grey Venyo*

Open Access

Research Article

Invasive Group A Streptococcus: A Review and Update

Anthony Kodzo-Grey Venyo *

North Manchester General Hospital, Department of Urology, Manchester, M8 5RB. United Kingdom.

***Corresponding Author:** Anthony Kodzo-Grey Venyo. North Manchester General Hospital, Department of Urology, Manchester, M8 5RB. United Kingdom.

Received Date: April 04, 2023; **Accepted Date:** April 25, 2023; **Published Date:** May 08, 2023

Citation: Anthony Kodzo-Grey Venyo, (2023), Invasive Group A Streptococcus: A Review and Update, *J, Surgical Case Reports and Images* 6(3); **DOI:10.31579/2690-1897/153**

Abstract

Group A Streptococcus (GAS), or Streptococcus pyogenes, is the leading bacterial cause of tonsillopharyngitis in adults and children worldwide. GAS is one of the few causes of tonsillopharyngitis or pharyngitis for which antibiotic treatment is recommended. The incidence of group A Streptococcus (GAS) invasive infection has been increasing worldwide, and there is no obvious explanation for this phenomenon.

Recurrent GAS infections may trigger autoimmune diseases such as acute poststreptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease. Combined, these diseases account for over half a million deaths per year globally.

While GAS remains sensitive to all penicillins and cephalosporins, rising resistance to other antibiotics used in disease treatment is an increasing worldwide concern. Several GAS vaccine formulations that elicit protective immunity in animal models have shown promise in nonhuman primate and early-stage human trials. The development of a safe and efficacious commercial human vaccine for the prophylaxis of GAS disease remains a high priority.

Keywords: streptococcus pyogenes; invasive infections; group a streptococcus; invasive group a streptococcus (igas); bacteria; streptococci; public health; long-term care; infection control; disease outbreaks; whole-genome sequencing; wound infection; antibiotic resistance; beta-lactams resistance; penicillin; macrolides

Introduction and Definition

Group A streptococcus (GAS) e.g., Streptococcus pyogenes is an aerobic gram-positive coccus that is a common cause of acute bacterial pharyngitis and other cutaneous and invasive infections in children for which antibiotic is recommended [1, 2]. Invasive GAS infections are defined as bacteraemia, pneumonia, osteomyelitis, septic arthritis, or any other infection associated with the isolation of GAS from a normally sterile body site [2].

Invasive infections also include necrotizing fasciitis and spontaneous gangrenous myositis.

Group A Streptococcus (GAS) can cause symptomatic infection or can colonize the oropharynx.

- Active infection refers to symptomatic infection caused by GAS.
- Persistent infection refers to symptomatic infection caused by GAS that does not resolve after appropriate antibiotic treatment. This is synonymous with treatment failure.
- Recurrent infection refers to a new symptomatic infection with GAS that occurs after appropriate antibiotic treatment. Recurrent infection can be caused by the same GAS serotype that caused the initial infection or by a different serotype. Recurrent infections most often occur among members of the same household or in other settings such as schools or day care centres where close contact facilitates GAS transmission [3].
- Chronic carriage refers to asymptomatic colonization or the persistent presence of GAS in the oropharynx in the absence of symptoms or host immune response. The prevalence of chronic carriage has not been comprehensively studied, but reported rates are about 4 to 5 percent in healthy adults [4] and range from about 2 to 20 percent in children [4-11]. Carriage can persist for months to years [10,12].

Distinguishing among these states is important because only patients with symptomatic GAS infection require treatment. The ensuing article on Invasive Group A Streptococcus infections had been divided into two

parts: [A] Overview which has discussed general overview of Streptococcus and (B) which contains detailed review and update summations on various aspects of Invasive Group A Streptococcus infections.

Aims

In this review and update we have focussed on (A) an overview of Streptococcus infection generally and (B) we have focussed on the general aspects of GAS invasive infection, as well as on certain entities, such as bacterial pharyngitis. We have reviewed all therapeutic avenues, old and new, that are relevant to the treatment of GAS infections.

Methods

Internet data bases were searched including: Google; Google Scholar; and PUBMED. The search words that were used included: Streptococcus; Streptococcus pyogenes; Group A Streptococcus, invasive Group A Streptococcus (iGAS), two hundred and one (201) references were identified which were used to write the review and update of the literature on Streptococcus infections and the differential diagnoses of various conditions that tend to simulate Streptococcus infections. The article has been divided into two parts (A) Overview of Streptococcus infections and (B) Detailed discussions related to various aspects of Invasive Group A Streptococcus.

Results

[A] Overview

Definition / general statements [13]

- Streptococcus is a bacterial organism which stains positive upon Gram stain staining
- With regard to morphology Streptococci are cocci that are appear or are seen in Chains
- Streptococci generally are facultative anaerobes
- Non - pathogenic Streptococcal species generally are stated to be al flora of mucosal surfaces

Terminology [13]

- With regard to terminology, the name Streptococcus was derived from Greek "Strepto" (chain) + coccus, which is a utilized terminology referring to chain - like morphology of the bacterial organism that is demonstrated upon Gram staining by pathologists.

Streptococci tend to be grouped broadly according to the haemolytic pattern of the organism that is seen upon blood agar examination into alpha, beta and other subtypes of Streptococcus as follows:[13]

- **Alpha (α) haemolytic:** Streptococcus. pneumoniae, viridans group of Streptococcus
- **Beta (β) haemolytic Streptococcus which is:** further divided serologically utilizing Lancefield antigens into Groups A through V (some letters are not used)
- **Gamma (γ) haemolytic:** formerly Group D Streptococci, re-classified as Enterococcus faecalis and Enterococcus faecium
- "Streptococcus viridans" (viridans = "green") which is not a species, but a group of non - S. pneumoniae alpha haemolytic species including *S.* mutans, S. mitis, S. anginosus and others [14]
- It has been iterated that "Pyogenic Streptococci" is a terminology that refers not only to or is utilized not only for S. pyogenes, but for all beta haemolytic streptococci and a few non - beta haemolytic streptococci (S. dysgalactiae)
- Lancefield Group A Streptococci (GAS) is synonymously used for or = S. pyogenes
- Lancefield Group B Streptococci (GBS) is a terminology that is used for or = *S. agalactiae*
- "pneumococcus" is a terminology that is used for or = *Streptococcus pneumoniae*

Aetiology

With regard to the aetiology of or causative Streptococcal organisms that tend to be found as causative Streptococcus organisms in infections of various parts of the body, the following summations had been made: [13]

- S. pyogenes (Group A Streptococci): tend to be associated with: pharyngitis, necrotizing fasciitis, cellulitis, erysipelas, scarlet fever, streptococcal toxic shock syndrome; non - infectious immune sequelae includes post - infectious glomerulonephritis, acute rheumatic fever
- S. agalactiae (Group B streptococci) had tended to be associated with the causation of: pneumonia, sepsis, meningitis in newly-born individuals
- S. pneumoniae have tended to be found in association with the following types of infections: community - acquired pneumonia, meningitis, and otitis media
- Viridans Group streptococci tend to be found in the following types of infections: endocarditis, bacteraemia (particularly in the setting of oral mucosal disruption)

Laboratory tests

The following laboratory tests tend to be undertaken in various scenarios related to Streptococcus infections: [13]

- Culture conditions:
    - Blood agar (non-contaminated sites), colistin nalidixic acid agar (contaminated sites)
    - 35 - 37C
    - Ambient air or 5% CO2, anaerobic conditions enhance growth (particularly Viridans group)
- Gram positive cocci in chains (S. pneumoniae classically diplococci)
- Catalase negative
- Alpha or beta haemolytic upon blood agar, depending upon the species (gamma reclassified as Enterococcus)
- Bile solubility test (sodium deoxycholate) tends to be undertaken in order to distinguish alpha haemolytic species: Viridans group Strep; (bile insoluble) from *S.* pneumoniae (bile soluble)
- Latex agglutination card test for Lancefield serotyping of beta haemolytic strains
- S. pneumoniae: Quellung (Neufeld's quellung) reaction positive, optochin ("P" disc) sensitive
- S. pyogenes: positive PYR test (L-pyrrolidonyl-beta-naphthylamide), bacitracin sensitive, CAMP (Christie Atkins Munch-Petersen) test negative
- S. agalactiae*:* CAMP test positive, hippurate positive
- Biochemical identification tends to be especially useful for the Viridans group of Streptococcus
- Rapid antigen detection is utilized clinically for Group A Strep; culture is stated to be gold standard

Treatment

Some of the treatment options that had been utilized in some types of Streptococcus infections had been summarized as follows: [13]

- It has been stated that Penicillin medications tend to be used in the treatment of Streptococcus infections; nevertheless, it has been pointed out that resistance had been reported among beta haemolytic streptococci. [15
- It has also been pointed out that in the treatment of Streptococcus infections, Macrolide resistance has been increasing related to: mefA gene (drug efflux) or erm gene (methylation of macrolide binding site) [16]

Gross macroscopy description

The macroscopy gross examination findings that tend to be found in Streptococcus infections had been summarized to include the following: [13]

- Gray specimen that could be - white glistening, alpha or with beta haemolysis
- S. pneumoniae capsule does tend to give colonies that tend to be mucoid appearance, and may contain central depression

Molecular / cytogenetics description [13]

- It has been pointed out that PCR screening for group B streptococci (GBS) in tends to be undertaken in pregnant women [13] [17].
- It had also been pointed out that 16S rRNA is useful to speciate alpha haemolytic streptococcus. [13] [18].

Differential diagnosis

With regard to the differential diagnosis of Streptococcus infections, the following iterations had been made: [13]

- Distinctive morphology upon Gram-stained specimen examination tends to be found when chains are seen, and the distinction has tended to be more difficult among alpha strep species
- MALDI-TOF may discriminate often misdiagnosed alpha haemolytic streptococci [19].
- Other Gram-positive cocci may be mis-diagnosed as Streptococci

[B] Detailed Review and Update Related to Various Aspects of Invasive Group A Streptococcus Infections

Incidence

GAS bacteraemia usually occurs secondary to a primary site of infection, most commonly in the skin and soft tissues [20-22]. The estimated incidence of GAS bacteraemia and/or invasive infection in children is 1 to 3 cases per 100,000 per year [23-26] The incidence is greatest in children <1 year (3 to 5 cases per 100,000) [24,25].

Among hospitalized patients, invasive GAS infection accounts for approximately 0.3 to 0.9 percent of paediatric hospital admissions [27,28].

● United States – Invasive GAS attack rates have been relatively stable in the United States since the mid-1990s. Approximately 100 to 200 paediatric cases were reported to the Active Bacterial Core (ABC) surveillance at the Centres for Disease Control and Prevention (CDC) each year from 2015 through 2019 [25,26,29-32]. There were only 74 cases reported in 2020, likely due to the impact of social distancing and other infection control measures during the height of the COVID-19 pandemic [26]. Similarly, in a report from Texas Children's Hospital, there were considerably fewer hospital admissions for invasive GAS infections in 2020 compared with previous years, though the rate increased again by 2022 [28]. In December of 2022, the CDC issued a health advisory regarding an increase in the number of cases of paediatric invasive GAS infection reported to the ABC surveillance program in November through early December [33]. The CDC is investigating these reports. Based on preliminary data, the increase likely reflects that rates of invasive GAS infection appear to have returned to levels like those seen in pre-pandemic years [34].

● Europe – Several European countries have reported an increase in the number of invasive GAS infections among children <10 years old during the fall and winter of 2022 compared with prior years [35,36]. For example, in the United Kingdom (UK), there were 107 cases of invasive GAS infection in children <10 years reported from mid-September to early December 2022 (average of 11 cases per week) [36]. This rate is markedly higher than during and immediately following the height of the COVID-19 pandemic and it is also considerably higher than in pre-pandemic years. From mid-September to early December 2022, there were 13 deaths attributable to invasive GAS infection reported in children <15 years old in the UK, which is considerably more than reported in prior years [36].

Other European countries, including France, Ireland, the Netherlands, and Sweden have reported similar increases in rates of invasive GAS infection, particularly among children <10 years old [35]. The rise in invasive GAS infection parallels a >3-fold increase in reported cases of scarlet fever. The increase may reflect an early GAS season coinciding with an increase in circulating respiratory viruses. There have been no observed increases in antibiotic resistance among isolated GAS strains. Enhanced surveillance activities have been implemented in the affected areas and public health organizations are emphasizing the importance of early recognition of GAS infections, including scarlet fever, and prompt treatment.

Epidemiology of Group A streptococcal bacterial pharyngitis.

GAS is the most common cause of bacterial pharyngitis in children and adolescents. It accounts for 15 to 30 percent of all cases of pharyngitis in children between the ages of 5 and 15 years [37-40].

In temperate climates, the incidence of GAS pharyngitis peaks during the winter and early spring [41]. During these seasons, as many as 35 to 40 percent of cases of pharyngitis in children and adolescents are caused by GAS.

GAS pharyngitis is most common in school-age children but may occur in younger children, especially if they have contact with school-age children [41-42]. In a meta-analysis, the pooled prevalence of GAS among children (<18 years) who presented to an outpatient clinic or emergency department with sore throat was 37 percent (95% CI 32-43 percent) [11]. The prevalence among children <5 years was 24 percent (95% CI 21-26 percent).

Historical perspective

GAS was first described in 1874 by Billroth, who demonstrated its presence in wound infections and erysipelas. Pasteur identified GAS as the cause of puerperal sepsis in 1879. In 1884, Rosenbach gave it the name Streptococcus pyogenes. Lancefield made a major contribution in the field of epidemiology in 1933, when she classified β-haemolytic streptococci in different groups [43].

Throughout history, GAS has been responsible for major epidemics with catastrophic consequences [22]. With the advent of better hygiene, penicillin and modern medicine, there was a striking drop in the incidence of severe GAS infections [44,45]. Now, for unknown reasons, there has been a surge of severe, life-threatening infections, notably in developed countries [43].

In Sweden, the number of cases of GAS bacteraemia per 100 000 population jumped from 1.8 in 1987 to 2.4 in 1989 [46]. In Arizona, a

study conducted between January 1987 and March 1990 showed an annual age adjusted incidence of GAS invasive infections of 4.3 per 100 000 population. But the infection rate was much higher among native Americans (46 per 100 000) [47]. In 1992, the annual incidences in Ontario of invasive GAS infections and STSS were 1.15 and 0.19 per 100 000 population respectively [22]. In 1994, a definite increase in the number of cases of necrotizing fasciitis was noted compared with previous years [43].

Since end of year 2022, there have been more cases of GAS in the lower respiratory tract, including cases of empyema, and more cases of scarlet fever, which is a notifiable disease [48].

The pathogen and pathophysiology

GAS is a gram-positive coccus that produces and has numerous constituents, somatic and extracellular, capable of an important role in the pathogenesis of the invasive infection. First, certain proteins are produced and expressed at the surface of the bacterium, notably the M protein, which is a major virulence factor. This antigen has the ability to decrease phagocytosis by polymorphonuclear leukocytes and plays an important role in initiating the streptococcal diseases. There are about 80 different types of M protein. Not all group A streptococci carry the M protein, some are called non-typable and are considered to be less virulent. Another important surface antigen is called the serum opacity factor (SOF), so named because of its ability to opacify horse serum. For more precise typing and identification purposes, another protein called T protein has been identified by Griffith [49]. Apart from its epidemiologic importance, this protein has no virulence potential.

Extracellular toxins are produced by GAS and represent essential mediators of the bacterial virulence. Among them are the streptococcal pyrogenic exotoxins (SPEs). Three different types of SPEs have been characterized and named A, B and C. These toxins have been shown, experimentally, to induce cytotoxicity and to provoke symptoms comparable to those seen in the staphylococcal toxic shock syndrome. SPE-A and the staphylococcal toxic shock syndrome toxin-1 (TSST-1) have a similar molecular structure [50].

The pathophysiology of severe GAS infections is not fully understood, but SPEs are playing a key role as superantigens (bacterial products, mainly from gram-positive bacteria that have the ability to massively stimulate nonspecific T-cell proliferation) [2,51,52]. The T-cell proliferation, once activated, enhances the production of cytokines. Large production of tumour necrosis factor (TNF) and interleukins (1β and 6) mediate fever, shock, tissue injury and the spectacular inflammatory process seen in STSS. SPEs can trigger such a response because of their ability to cross-link the major histocompatibility complex (MHC) molecule on antigen-presenting cells, with the variable region of the T-cell receptor β chain [43,51]. Compared with conventional antigens, superantigens are unique in that they can activate a T cell without being previously processed by an antigen-presenting cell. Besides, specific interaction between conventional antigens and T cells is governed by the 5 variable regions of the T-cell receptor (Ja, Va, Jb, Db, Vb), whereas the coupling of superantigens with T cells is primarily under the control of only the Vb region, with little contribution from the other regions of the T-cell receptor. Thus, a conventional antigen usually activates less than 0.01% of all T cells; in contrast, a superantigen can stimulate between 5% and 40% of all T cells [51].

Manifestations and clinical Presentations of invasive Group A Streptococcus (iGAS).

Group A Streptococcus (GAS) is carried as a commensal in the nasopharynx of 5 – 15% of the population [52] and can cause pharyngitis and scarlet fever. iGAS is a rare but serious complication of infection with GAS and occurs when the bacteria infect a site that is usually sterile such as the blood, joints or lungs [48].

Clinical presentations of GAS may include a simple sore throat, tonsillitis or scarlet fever. Scarlet fever, which is a notifiable disease, presents in a typical way. The initial symptoms are non-specific (sore throat, headache, fever) and a rash will develop within two days. The rash is rough, described as like sandpaper, and it starts on the torso and spreads from there, but usually spares the palms and the soles. Pastia's lines may be seen – these are deep red lines where the rash is accentuated in the flexures [52,53].

Other features include a strawberry tongue – the tongue has a white coating which peels off after a few days, leaving the tongue looking red and swollen – enlarged cervical lymph nodes, general malaise, peeling skin on the fingertips and toes and a flushed face with pallor around the mouth [47,52, 53].

GAS is the most common cause of bacterial pharyngitis in children and adolescents. It accounts for 15 to 30 percent of all cases of pharyngitis in children between the ages of 5 and 15 years [37-40].

In temperate climates, the incidence of GAS pharyngitis peaks during the winter and early spring [41]. During these seasons, as many as 35 to 40 percent of cases of pharyngitis in children and adolescents are caused by GAS.

GAS pharyngitis is most common in school-age children but may occur in younger children, especially if they have contact with school-age children [41-42]. In a meta-analysis, the pooled prevalence of GAS among children (<18 years) who presented to an outpatient clinic or emergency department with sore throat was 37 percent (95% CI 32-43 percent) [11]. The prevalence among children <5 years was 24 percent (95% CI 21-26 percent).

Children ≥3 years — In children ≥3 years, GAS pharyngitis typically has an abrupt onset. Fever, headache, abdominal pain, nausea, and vomiting may accompany the sore throat, which can lead to poor oral intake [39,54,55]. Additional features may include exudative tonsillopharyngitis, with enlarged erythematous tonsils, enlarged tender anterior cervical lymph nodes, palatal petechiae, inflamed uvula (uvulitis), and scarlatiniform rash (erythematous, finely papular rash which characteristically starts in the groin and axilla and then spreads to the trunk and extremities, followed by desquamation) [39,54,56]. Viral features (eg, rhinorrhoea, conjunctivitis, cough, hoarseness, anterior stomatitis, discrete ulcerative lesions or vesicles, diarrhoea) are usually absent. Symptoms usually resolve spontaneously in three to five days.

Children <3 years — Children <3 years of age generally do not have the findings that are typical of older children [57]. Instead of a well-defined episode of pharyngitis, they may have protracted symptoms of nasal congestion and discharge, low-grade fever (e.g., <38.3°C [101°F]), and tender anterior cervical adenopathy [51]. This GAS symptom complex is called "streptococcosis."

Infants <1 year of age may present with nonspecific symptoms, including fussiness, decreased appetite, and low-grade fever. They often have older siblings or day care contacts with GAS infection.

Complications — Although most cases of GAS pharyngitis resolve without complications, serious nonsuppurative and suppurative complications may occur.

•Nonsuppurative complications of GAS pharyngitis include Acute rheumatic fever (ARF)

•Poststreptococcal reactive arthritis (PSRA)

•Acute rheumatic fever

•Poststreptococcal glomerulonephritis

•Paediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS)

•Suppurative complications of GAS pharyngitis

•Necrotizing fasciitis

•Bacteraemia

•Peritonsillar cellulitis or abscess

•Otitis media

•Sinusitis

Importance of accurate diagnosis — GAS is the most common cause of bacterial pharyngitis that benefits from antimicrobial therapy. Depending upon the season, as many as 35 to 40 percent of cases of pharyngitis in children and adolescents are caused by GAS. Timely treatment of GAS in children and adolescents is necessary to:

•Prevent suppurative complications and acute rheumatic fever (ARF)

•Prevent disease transmission, particularly if the patient is a contact of someone with a history of ARF [54]

•Reduce duration and severity of symptoms

Microbiologic confirmation of GAS in the pharynx before initiation of antibiotic therapy helps to prevent unnecessary prescription of antibiotics to children with viral pharyngitis (most children with pharyngitis) [59].

Diagnosis

Diagnostic criteria — The diagnosis of GAS pharyngitis is supported by a positive microbiologic test (throat culture, rapid antigen detection test [RADT], or molecular point-of-care test [POC] for GAS) in a patient with symptoms of GAS pharyngitis and absence of signs and symptoms of viral infections (e.g., rhinorrhoea, conjunctivitis, cough, hoarseness, anterior stomatitis, discrete ulcerative lesions or vesicles, diarrhoea). However, the presence of isolated viral features (e.g., cough, rhinorrhoea) does not preclude a diagnosis of GAS pharyngitis [59].

Although a positive test supports the diagnosis of GAS, between 5 and 21 percent of children between 3 and 15 years of age are pharyngeal carriers of GAS [4,9,11,60,61]. Neither throat culture, RADT, nor molecular POC test for GAS can differentiate patients with acute GAS pharyngitis from GAS carriage with intercurrent viral illness [39]. Such patients may fail to respond to appropriate therapy for GAS infection.

Approach to testing — The approach to testing for GAS pharyngitis is generally consistent with that of the Infectious Diseases Society of America, the American Heart Association, American Academy of Paediatrics, and other professional groups [39,54,60,61].

Whom to test — Microbiologic testing is suggested for GAS in children and adolescents with [39,54,60]:

1. Evidence of acute tonsillopharyngitis (erythema, oedema, and/or exudates) or scarlatiniform rash on physical examination and absence of multiple signs and symptoms of viral infections (e.g., rhinorrhoea, conjunctivitis, cough, hoarseness, anterior stomatitis, discrete ulcerative lesions or vesicles, diarrhoea).

2. Exposure to an individual with GAS at home or school or a high prevalence of GAS infections in the community and symptoms of GAS, including:

i. For children ≥3 years – Pharyngitis, fever, headache, abdominal pain, enlarged tender anterior cervical lymph nodes, palatal petechiae [39,54,55].

ii. For children <3 years – Prolonged nasal discharge, tender anterior cervical adenopathy, and low-grade fever (eg, <38.3°C [101°F]), particularly if they have exposure to contacts with GAS infection [42,57,58].

No single sign or symptom reliably identifies GAS pharyngitis in children with sore throats [39,54,56]. In a meta-analysis, although individual findings (e.g., scarlatiniform rash, palatal petechiae, tonsillar enlargement, tender cervical lymphadenopathy) increased the probability of GAS pharyngitis to >50 percent, they could not be used for definitive diagnosis [56].

Similarly, clinical scoring systems for GAS that consist of various constellations of clinical findings and epidemiologic features [62-65] are insufficiently sensitive or specific to eliminate the need for microbiologic testing in children and adolescents with suspected GAS [39,56, 66-68]

3. Suspected acute rheumatic fever (ARF) or poststreptococcal glomerulonephritis.

To prevent identification of GAS carriers with viral respiratory infection, microbiologic testing for GAS should be avoided in children and adolescents with multiple manifestations strongly suggestive of viral illness (e.g., rhinorrhoea, conjunctivitis, cough, hoarseness, anterior stomatitis, discrete ulcerative lesions or vesicles, diarrhoea) [39,60,69,70]. Nonetheless, in a child with fever, exudative pharyngitis, and isolated rhinorrhoea or cough, microbiologic testing may be warranted. Although viral features are usually absent in children with GAS pharyngitis, the presence of isolated viral features does not preclude a diagnosis of GAS pharyngitis. In a retrospective study of >60,000 children and adolescents (age 3 to 21 years) who were tested for GAS in a national network of retail clinics, the prevalence of GAS positivity was 28 percent among those with ≥1 feature of viral illness [71]. The prevalence of GAS positivity decreased with increasing numbers of viral features. Among children with viral features, the prevalence of GAS positivity was greater than the prevalence of GAS carriage (i.e., the prevalence of GAS positivity in asymptomatic children), which ranged from 5 to 21 percent in a systematic review [11], suggesting that some of the children with viral features had acute GAS pharyngitis.

Choice of test — The diagnosis of GAS pharyngitis is supported by a positive throat culture, RADT, or molecular assay for GAS.

For children and adolescents in whom microbiologic testing for GAS is necessary, we suggest performance of a RADT. Standard throat culture and molecular assays are acceptable alternatives [72].

If initial testing with RADT is negative in a child or adolescent, we recommend follow-up testing with standard throat culture because RADT may miss as many as 30 percent of cases of GAS pharyngitis [39,60, 73-75]. Confirmation of negative RADT with throat culture is not necessary in adults. The risk of an initial episode of ARF in an adult with GAS pharyngitis is extremely low, even if an episode of streptococcal pharyngitis is untreated [39].

If initial testing with a molecular assay is negative, follow-up testing with a standard throat culture is not necessary, given the high sensitivity of molecular assays [76].

Preference for initial testing with RADT is based upon practical considerations. RADT are available in almost all practice settings, and the immediate results are appealing to patients, caregivers, and clinicians given the advantages of early diagnosis and treatment, including earlier clinical cure and return to school (for children) and work (for caregivers). Although immediate results also are available with molecular assays, use of molecular assays is limited by cost and complexity. Despite the practical considerations, initial testing with RADT may be less cost effective than initial testing with standard throat culture. Most children

who require microbiologic testing for pharyngitis do not have GAS pharyngitis and will have a negative RADT. Given that negative RADT in children and adolescents must be confirmed with throat culture, if RADT is used as the initial test, the majority of children and adolescents who are tested will require both RADT and throat culture.

Specimen collection and processing — The key to optimizing detection of GAS in clinical specimens is appropriate collection and transport of the sample [75]:

●Specimens should be obtained before initiation of antimicrobial therapy because a single dose of antibiotics can result in a negative culture or RADT.

●If RADT is to be performed, it is suggested that the throat be swabbed with two swabs simultaneously [75]. One is used for RADT; if RADT is positive, the second swab can be discarded. If RADT is negative, the second swab can be used for standard culture.

●Specimens should be obtained by vigorous swabbing of both tonsils (or tonsillar fossae in patients who have undergone tonsillectomy) and the posterior pharynx. The swab(s) should be moved into and out of the mouth without touching the tongue or the buccal mucosa. The importance of obtaining an adequate specimen cannot be overstated; the sensitivity of both culture and RADT correlates with inoculum size [37,77,78].

Investigation in the Community

Throat swabs do not usually play a significant role in the management of sore throat, or the investigation of scarlet fever in the community – Strep A is a commensal, so its presence doesn't necessarily mean that it is the cause of a sore throat, and the results aren't back until some days after the decision on whether to treat has to be made [35,36]. The current guidance says that we should consider taking a throat swab where there is 'diagnostic uncertainty' or concerns about antibiotic resistance – presumably so that if first-line antibiotics don't help, we have sensitivities to guide the second choice. However, in some areas swabbing may be arranged as part of public health investigations – this is in line with the Government's advice on scarlet fever which says that we should consider swabbing if 'a case is suspected to be part of an outbreak — the local health protection team should advise primary care if a local outbreak is suspected and when testing is appropriate' [35,36].

Differential diagnosis

The differential diagnosis of GAS pharyngitis includes both infectious and non-infectious causes of pharyngitis.

Other infectious causes of pharyngitis — Acute infectious pharyngitis in children and adolescents is caused by a variety of agents. The frequency of these pathogens varies according to the age of the child, season, and geographic area.

Microbiologic testing may be necessary to differentiate GAS pharyngitis from other infectious causes of pharyngitis that require treatment or infection control and in children and adolescents whose symptoms worsen or persist for more than five to seven days (whether or not they were treated for GAS) [79].

Other bacterial infections

Other bacterial causes of pharyngitis that may require treatment are listed below. Although it is not necessary to exclude these infections in children with pharyngitis who test negative for GAS, microbiologic testing is warranted in children with compatible clinical or epidemiologic features.

● **Group C and G streptococci** – Group C and G streptococci have been reported to cause epidemic and sporadic pharyngitis in school-age children and adults, although there has been some controversy over their etiologic role [80-84]. Group C or G streptococci may be identified with standard throat culture, but most laboratories do not routinely identify them unless specifically requested to do so. Group C or group G streptococcal pharyngitis may warrant treatment if the patient remains symptomatic when the results of the culture are available. The diagnosis and treatment of group C and G streptococcal infections are discussed separately.

● **Neisseria gonorrhoeae** – N. gonorrhoeae is a relatively rare cause of pharyngitis but may occur in patients with oral-genital contact. Most cases are asymptomatic; when present, findings are nonspecific (e.g., pharyngeal erythema, oedema, or exudate). Evaluation for gonococcal pharyngitis with a nucleic acid amplification test or throat culture on media specific for N. gonorrhoeae may be warranted in patients with risk factors (e.g., unprotected oral-genital contact). If N. gonorrhoeae is detected, treatment is necessary to prevent transmission and disseminated disease [63].

● **Fusobacterium necrophorum** – F. necrophorum causes most cases of jugular vein suppurative thrombophlebitis (Lemierre syndrome). Lemierre syndrome predominantly affects previously healthy adolescents and young adults. Clinical features include high fever (>39°C [102.2°F]), rigors, respiratory symptoms, and unilateral neck swelling or pain, findings typically absent in GAS pharyngitis [63].

● **A. haemolyticum** – A. haemolyticum pharyngitis occurs predominantly in adolescents (85-87). Clinical features overlap with those of GAS and include fever, exudative pharyngitis, and rash on the extensor surfaces of the arms (86, 88). The rash occurs in approximately one-half of patients but, in contrast with the rash of scarlet fever, does not peel (85,86,88). A. haemolyticum grows slowly on sheep blood agar plates and produces a tiny zone of beta haemolysis after 48 to 72 hours. Detection is improved (larger colony size and wider zone of haemolysis) by culture on human or rabbit blood agar (89). In in vitro studies, A. haemolyticum was unresponsive to penicillin; erythromycin is the drug of choice (85).

● **Diphtheria** – Diphtheria is uncommon in developed countries but is important to consider in patients from endemic areas. In contrast with GAS pharyngitis, which has acute onset, the onset of symptoms in diphtheria is usually gradual, beginning with mild pharyngeal injection and erythema. The hallmark of diphtheria is the formation of a tightly adherent gray membrane in the nares and throat. This membrane occurs in at least one-third of patients and causes bleeding when it is dislodged [63].

● **Tularaemia** – Tularaemia is an uncommon cause of pharyngitis that should be considered in patients with pharyngitis unresponsive to penicillin. It is usually acquired by ingestion of poorly cooked wild animal meat or contaminated water. Clinical features of oropharyngeal tularaemia include fever, painful ulcerative-exudative pharyngitis, and cervical lymphadenitis [63].

● **Mycoplasma pneumoniae** – M. pneumoniae can cause pharyngitis and other respiratory tract illness in children ≥6 years. M. pneumoniae accounts for 5 to 16 percent of cases of pharyngitis; the wide range may be related to the cyclicity of M. pneumoniae epidemics [90,91].

Viral infections

Viruses are the most common cause of acute pharyngitis [92-94]. Clinical features suggestive of viral aetiology include concurrent conjunctivitis, rhinorrhoea, cough, hoarseness, anterior stomatitis, discrete ulcerative lesions, viral exanthems, and/or diarrhoea [39]. Most children and adolescents with negative microbiologic tests for GAS have viral pharyngitis, which is a self-limiting condition and can be treated symptomatically without additional testing.

Viral infections in the differential diagnosis of GAS pharyngitis in children and adolescents that have important management or infection control implications are listed below. Although it is not necessary to exclude these infections in children with pharyngitis who test negative for GAS, microbiologic testing may be warranted in children with compatible clinical or epidemiologic features.

●**Infectious mononucleosis** – Epstein-Barr virus (EBV) and cytomegalovirus account for most cases of infectious mononucleosis, a clinical syndrome that classically occurs in adolescents and is characterized by fever, severe pharyngitis (which lasts longer than pharyngitis due to GAS), and anterior and posterior cervical or diffuse lymphadenopathy, lymphocytosis, and increased aminotransferase levels [85-96]. Prominent constitutional symptoms include fatigue, anorexia, and weight loss. Examination findings may include periorbital or palpebral oedema, mild hepatomegaly, and splenomegaly. Patients who are treated with ampicillin, amoxicillin, or other antibiotics may develop a characteristic rash. Laboratory findings may include increased aminotransferases and predominance of atypical lymphocytes in the differential blood count.

Unlike adolescents, who typically present with classic symptoms, younger patients with EBV infection may have a more subtle presentation that can make diagnosis difficult.

Patients with infectious mononucleosis and splenomegaly require activity restriction to prevent splenic rupture.

●**Primary HIV infection** – Primary HIV infection may cause an acute retroviral syndrome (similar to infectious mononucleosis) in sexually active adolescents or rarely in children who have been sexually abused. The onset of symptoms usually occurs within days to weeks after the initial exposure. Clinical features of primary HIV infection include prominent cervical or generalized adenopathy and persistent constitutional complaints (e.g., fever, weight loss). Laboratory features may include lymphopenia and increased aminotransferase levels [92-94].

●**Herpes simplex virus** – Herpes simplex virus (HSV) pharyngitis should be considered in children and adolescents with the characteristic enanthem or ulcerative lip lesion. HSV is more common in adolescents than in younger children and is characterized by its severity and duration (frequently >7 days). HSV pharyngitis in children and adolescents may respond to acyclovir therapy [92-94].

●**Influenza** – Influenza infection is characterized by fever, cough, headache, and myalgias that occur in seasonal epidemics. Pharyngitis caused by influenza may be exudative. Influenza pharyngitis should be considered in children and adolescents with fever and severe illness (pharyngitis, cough, or both in the absence of another known cause of illness) during influenza season (regardless of influenza immunization status) [97]. Antiviral therapy is indicated for children at risk for complications or severe disease. Laboratory confirmation should not delay initiation of treatment [92-94].

●**Severe acute respiratory syndrome coronavirus 2** – Severe acute respiratory syndrome coronavirus 2 **(**SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), may cause pharyngitis in children [92].

●**Enteroviruses** – Enteroviruses, specifically coxsackie A viruses, cause herpangina, which is characterized by small vesicles in the posterior pharynx. In one series of 50 children (aged 1 to 10 years) with acute pharyngitis, enterovirus polymerase chain reaction was positive in 8 percent [98].

●**Adenovirus** – Adenovirus may manifest as pharyngitis, tonsillitis, or pharyngoconjunctival fever. There are no distinguishing characteristics of infections caused by adenovirus except in patients with pharyngoconjunctival fever. The presence of exudate is common but not invariable [92].

When pharyngitis is part of a viral syndrome that causes nasopharyngitis, nasal congestion and discharge may be more prominent than sore throat. These infections generally resolve with symptomatic therapy, and it is not usually necessary to identify the specific viral pathogen

Viruses that cause nasopharyngitis include [92-04]:

●**Rhinoviruses**

●**Coronaviruses**, including SARS-CoV-2, which causes COVID-19

●**Respiratory syncytial virus**

●**Parainfluenza viruses**

Non-infectious causes of pharyngitis — Non-infectious causes of sore throat include irritation or drying of the pharynx (often from mouth-breathing overnight secondary to nasal obstruction from viral infection or allergic inflammation), foreign body (e.g., fish bone), chemical exposure, referred pain from extrapharyngeal sources (e.g., dental abscess, otitis media). These can usually be differentiated from infectious pharyngitis through information from the history or physical examination [63].

Decision making tools in the Community

For those who have a sore throat or tonsillitis, but no signs of scarlet fever, and who are not so ill that you feel they need hospital review (using the tools already mentioned if needed to aid that judgment), the decision has to be made as to whether they need antibiotics. The NICE guidance on sore throat recommends two decision making tools – Centor and FeverPAIN [99] but the interim clinical guidance summary produced by NHSE, the UKHSA, the RCGP, the RCPCH, the Royal Pharmaceutical Society and NICE seems to focus on FeverPAIN because it is validated in primary care and suggests that we adjust our threshold for antibiotic prescribing to prescribe for those with a FeverPAIN score of 3 or more [48].

FeverPAIN/Centor criteria [99]

FeverPAIN criteria

• Fever (during previous 24 hours)

• Purulence (pus on tonsils)

• Attend rapidly (within 3 days after onset of symptoms)

• Severely Inflamed tonsils

• No cough or coryza (inflammation of mucus membranes in the nose)

Each of the FeverPAIN criteria score 1 point (maximum score of 5). Higher scores suggest more severe symptoms and likely bacterial (streptococcal) cause. A score of 0 or 1 is thought to be associated with a 13 to 18% likelihood of isolating streptococcus. A score of 2 or 3 is thought to be associated with a 34 to 40% likelihood of isolating streptococcus. A score of 4 or 5 is thought to be associated with a 62 to 65% likelihood of isolating streptococcus.

Centor criteria

• Tonsillar exudate

• Tender anterior cervical lymphadenopathy or lymphadenitis

• History of fever (over 38 degrees Celsius)

• Absence of cough

Each of the Centor criteria score 1 point (maximum score of 4). A score of 0, 1 or 2 is thought to be associated with a 3 to 17% likelihood of

isolating streptococcus. A score of 3 or 4 is thought to be associated with a 32 to 56% likelihood of isolating streptococcus.

This is a significant lowering of the threshold as the NICE guidance on sore throats usually advises only that we consider an immediate or back-up antibiotics with a FeverPAIN score of 4 or 5 and that we consider a back-up antibiotic or no antibiotic with a score of 2 or 3. In normal times, a FeverPAIN score of 2-3 is associated with a 34-40% likelihood of isolating streptococcus and a score of 4-5 is associated with a 62 – 65% chance, however increased incidence may mean that these predictive values are increased at the current time. The FeverPAIN score has been criticised for giving one point for those who attend within three days of the onset of symptoms. This is presumably meant to indicate severity of symptoms, however in an environment of public panic and the trend towards wanting immediate access to a doctor for all respiratory symptoms, it is arguable whether attending quickly is actually a marker of severity.

Treatment:

Goals of treatment — The goal of antibiotic therapy for streptococcal pharyngitis is multifold and includes:

●Reducing symptom severity and duration

●Prevention of acute complications, such as otitis media, peritonsillar abscesses, or other invasive infections

●Prevention of delayed complications or immune sequelae, particularly acute rheumatic fever

●Prevention of spread to others

Symptom reduction — Antibiotic treatment has been shown to reduce symptom severity and hasten the rate of recovery in patients with streptococcal pharyngitis [100,101]. However, even without antibiotic therapy, symptoms typically resolve in about three to five days for most patients [102] making the prevention of complications a key goal of care.

Prevention of complications — Complications of streptococcal pharyngitis can result from extension of infection beyond the oropharynx, termed suppurative complications, or as immune phenomena, termed nonsuppurative complications.

Suppurative complications

Rates of otitis media and peritonsillar abscesses are each reduced with antibiotic use. In a large meta-analysis of randomized trials comparing antibiotics to placebo in adults and children with streptococcal pharyngitis, antibiotics reduced the incidence of acute otitis media within 14 days (0.47 versus 2.0 percent; risk ratio [RR] 0.30, 95% CI 0.15-0.58) and peritonsillar abscess at two months (0.24 versus 2.3 percent; RR 0.15, 95% CI 0.05-0.47) [100]. Reduction in the rates of acute sinusitis were also observed but did not reach statistical significance. The effect on less common but severe suppurative complications including bacteraemia and necrotizing fasciitis has not been studied, though it is reasonable to surmise that antibiotics would have a protective effect.

Nonsuppurative complications

Acute rheumatic fever — The prevention of acute rheumatic fever is one of the main indications for antibiotic treatment of streptococcal pharyngitis. Acute rheumatic fever and rheumatic heart disease are important causes of cardiovascular death worldwide [103,104]. In a meta-analysis of 14 randomized trials comparing penicillin with placebo in over 8000 adults and children with sore throat, penicillin decreased the risk of rheumatic fever by about two-thirds [100]. The absolute risk reduction is likely highest in children aged 5 to 15 residing in developing nations, where incidence of rheumatic fever peaks [104,105].

Other nonsuppurative complications — Data on the benefits of antibiotics in preventing other nonsuppurative complications are limited. Antibiotics probably prevent poststreptococcal glomerulonephritis based on a meta-analysis of 10 randomized trials comparing antibiotics with placebo in adults and children with sore throat, though there were too few cases in these trials to conclude this with certainty [100]. The effect of antibiotics on other nonsuppurative complications such as poststreptococcal arthritis and paediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS) is not well studied.

Prevention of transmission — GAS can spread among close contacts, leading to clusters of cases and recurrent infections in households or other close-contact settings. The rate of GAS transmission from an infectious case to close contacts is estimated to be between 5 and 50 percent [106-108]. Although no studies have directly evaluated the effect of antibiotic treatment on transmission, antibiotic use appears to eliminate GAS from the oropharynx in about 80 to 90 percent of cases after 24 hours of therapy [109,110]. When untreated, historic epidemiologic data suggest approximately 50 percent of patients with streptococcal pharyngitis will continue to harbour GAS in the oropharynx three to four weeks after symptom onset [39,102].

WHOM TO TREAT — Antibiotic treatment is recommended for any patient with symptomatic pharyngitis or tonsillopharyngitis who has a positive rapid antigen test or culture for group A *Streptococcus* (GAS).

Empiric treatment is generally not recommended, as the clinical features of GAS pharyngitis and non-streptococcal pharyngitis broadly overlap [111-112]. Short delays in therapy (e.g., while awaiting culture results) have not been associated with increased rates of complications such as acute rheumatic fever [39]. However, whether such delays effect rates of other complications (e.g., development of peritonsillar abscess) is not known. If clinical suspicion for GAS pharyngitis is high and testing results cannot be obtained rapidly, it is reasonable to start antibiotic treatment while test results are pending [113]. If testing does not confirm the diagnosis, antibiotics should be discontinued.

Antibiotic treatment is not recommended for asymptomatic chronic GAS carriers or for GAS carriers who have superimposed viral infections [111, 112,114].

Treatment of initial episodes

Antibiotic treatment is the mainstay of care.

Supportive care measures such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen may be administered to relieve fever and pain.

Antibiotic treatment — The antibiotic treatment recommendations presented below are largely consistent with recommendations from the NICE Guidelines, Infectious Diseases Society of America, the American Heart Association, and the American Academy of Paediatrics [97, 111,114-116]. Guidelines from other regions vary [117-119].

Penicillin — Penicillin is the treatment of choice for group A *Streptococcus* (GAS) pharyngitis due to its efficacy, safety, narrow spectrum, and low cost. Resistance to penicillin among clinical GAS isolates has not been documented. Penicillin is the only antibiotic that has been studied and shown to reduce rates of acute rheumatic fever [100].

●For most adult patients, we use oral penicillin V 500 mg two to three times daily for 10 days. Oral amoxicillin is also a reasonable option [1, 43, 99].

●For most children, we use either oral penicillin V or amoxicillin. Amoxicillin is often preferred for young children because the taste of the amoxicillin suspension is more palatable than that of penicillin. Amoxicillin can also be given once daily, either immediate release or as an extended-release tablet. In several randomized trials, standard-dose and once-daily dosing of amoxicillin appeared to have equivalent efficacy as oral penicillin [120-124].

●For patients with a history of acute rheumatic fever (who are not receiving antibiotic prophylaxis), options include oral penicillin, oral amoxicillin, or single-dose intramuscular (IM) benzathine penicillin. Because adherence is critical for patients with a history of acute rheumatic fever, choice is based on patient values and preferences. While IM benzathine penicillin can be given as a single dose, the drug is expensive in some regions, frequently unavailable, and causes injection site pain. In contrast, oral options are readily available but carry the risk of incomplete adherence [1].

The duration of therapy for oral penicillin or amoxicillin is 10 days. Although symptoms typically improve within the first few days of treatment [102,125,126), treating for 10 days appears to enhance the rate of GAS eradication from the oropharynx when compared with 5 or 7 days [5, 99,111,127-129]. Because complications, particularly immune sequelae, are likely related to the presence of GAS in oropharynx and can be severe, treating with a 10-day course seems prudent.

IM penicillin appears to be more effective than oral penicillin at eradication of GAS from the oropharynx [130] and has been most well studied for the prevention of acute rheumatic fever [100]. However, as noted above, IM penicillin is expensive in some regions and not always available. Thus, for patients with a history of acute rheumatic fever (who are high risk for cardiac complications compared with those without this history), we discuss the risk and benefits of its use on an individual basis [131].

Alternatives to penicillin — Cephalosporins, clindamycin, and macrolides are alternatives for patients who are allergic to penicillin or who cannot otherwise tolerate penicillin. Dosing and duration of therapy should be based on age and type of medication, usually between 5 to 10 days. Selection of an agent depends on the type of allergy, local antibiotic resistance rates, and patient values and preferences [39,132, 133].

The approach to antibiotic selection for patients with penicillin allergy varies among experts:

●For patients with mild, non-IgE-mediated reactions to penicillin (eg, maculopapular rash beginning days into therapy), generally a first-generation cephalosporin such as cephalexin is preferred because of its narrow spectrum and the low likelihood of cross-reactivity [1].

For patients with mild, possibly IgE-mediated reactions (eg, urticaria or angioedema but not anaphylaxis), a second- or third-generation cephalosporin with a side chain that is dissimilar to penicillin, such as cefuroxime, cefdinir, or cefpodoxime is recommended [1].

When using an oral cephalosporin, treatment is generally for 10 days. A 5-day treatment course with cefdinir or cefpodoxime is also acceptable. These shorter treatment courses are US Food and Drug Administration approved and, in randomized trials, had similar clinical and microbiologic efficacy as 10-day courses of oral penicillin [134-137].

●For patients with a history of severe angioedema and/or anaphylaxis or with serious delayed reactions or for patients who cannot take cephalosporins, a macrolide, such as azithromycin is generally used. A major advantage of azithromycin is that it can be given for a three- or five-day course due to its extended half-life [138].

A key consideration when using a macrolide is potential drug resistance. Macrolide resistance rates are growing and vary with geography [139-144]. Generally, higher macrolide resistance rates have been observed in Asia and Europe when compared with the United States. Clinicians should take into account local resistance patterns or consult local antibiograms when prescribing macrolides, if possible.

●For patients with known or suspected macrolide-resistant GAS who cannot tolerate cephalosporins, treat with a 10-day course of clindamycin.

The above approach is generally consistent with recommendations from both the American Academy of Paediatrics and the Infectious Diseases Society of America [39,116].

Other experts prefer to perform a test-dose procedure before prescribing cephalosporins to patients with penicillin allergies. Because this is generally not feasible in the outpatient clinic, a more conservative approach to treatment is an option for patients with mild, non-IgE-mediated reactions or IgE-mediated reactions [1]:

●For patients with mild, non-IgE-mediated reactions, a third-generation cephalosporin, such as cefpodoxime or cefdinir, is selected.

●For patients with any possible IgE-mediated reactions (including anaphylaxis), an alternative to cephalosporins such as a macrolide or clindamycin is selected.

Broad use of cephalosporins may promote antimicrobial resistance and are generally more costly than penicillins. No trial has evaluated the use of alternatives to penicillin for the prevention of acute rheumatic fever; thus, penicillin remains the treatment of choice when feasible [1].

Tetracyclines, sulphonamides, and fluoroquinolones should not be used for treatment of streptococcal pharyngitis due to the high prevalence of resistance [139-144], potential for clinical failure, and/or high side-effect profile [145].

Adjunctive treatment — We offer supportive care (rest, adequate fluid intake, avoidance of respiratory irritants, soft diet) to all patients and systemic agents such as NSAIDs or acetaminophen for patients who desire medication for fever or pain control. We avoid using systemic glucocorticoids for symptom relief because antibiotics and systemic analgesics are generally effective, and the addition of systemic glucocorticoids increases the likelihood of adverse events [1].

Response to therapy

Resolution of symptoms — Fever and constitutional symptoms typically resolve within one to three days of starting treatment [102,146-150]. Follow-up visits are not needed for most patients.

Most patients can return to work or school after completing one full day of treatment, provided they are afebrile and otherwise well. This recommendation is based on a small cohort study in children that showed that about 80 percent of patients with culture-proven group A streptococcal (GAS) pharyngitis clear the organism from the oropharynx within 24 hours of starting therapy [109]. A second cohort study evaluating 111 children with pharyngitis and a positive rapid antigen detection test (RADT) showed that 91 percent of patients treated with amoxicillin by 5:00 PM on the day of therapy had negative follow-up RADTs the following morning [110].

Indications for test of cure — For patients who are asymptomatic at the end of a course of antibiotic therapy, a test of cure is typically not needed [151]. We generally perform a test of cure (culture or RADT) in the following patients, who are at risk for complications, recurrent infection, or spreading infection to others:

●Patients with a history of acute rheumatic fever

●Patients who acquired infection during an outbreak of acute rheumatic fever or poststreptococcal glomerulonephritis

●Patients who acquired infection during a cluster of cases in their household or other close-contact setting

For patients who test positive in these circumstances, we repeat a full 10-day course of therapy. Usually, an antibiotic that has greater beta-lactamase stability than the one used for the initial treatment course should be selected. As examples, if penicillin was used for initial treatment, we use either amoxicillin-clavulanate or a first-generation cephalosporin; if a first-generation cephalosporin was used, we select a later-generation cephalosporin. The rationale for this strategy is based on clinical data that suggest relapse rates may be lower with cephalosporin use, as well as scientific observations that antibiotics with greater beta-lactamase activity may be more effective in eradicating GAS from the oropharynx [1].

Patients who are asymptomatic following an appropriate course of therapy who test positive but lacked an appropriate indication for a test of cure are not usually treated. The patients are likely chronic carriers.

Persistent or recurrent symptoms

Evaluation — For patients who have persistent or recurrent symptoms consistent with GAS pharyngitis after completing a course of antibiotic therapy, we generally repeat testing for GAS. Because chronic GAS carriage can occur after antibiotic therapy [4-11], we generally avoid testing in patients whose symptoms are highly consistent with viral pharyngitis (e.g., sore throat accompanied by cough, conjunctivitis, or rhinorrhoea) or other aetiology. For patients with persistent or recurrent symptoms consistent with GAS pharyngitis, a positive test result should raise suspicion for any of the following:

●Nonadherence with the prescribed antimicrobial regimen

●Recurrent infection, which refers to new infection with the initial infecting strain or a new strain

●Persistent infection, also termed treatment failure

●Infection with a different pathogen superimposed on chronic GAS carriage

●Presence of a suppurative complication, such as a peritonsillar abscess

Distinguishing among these states is typically based on epidemiologic and clinical history, which can be challenging as symptoms overlap and GAS testing can be positive in all.

-Suspicion for recurrent infection should be raised when clusters of GAS infections are occurring within the patient's household, school, workplace, or other close-contact setting. Symptoms associated with recurrent infection with the same serotype may be milder than with the initial infection [152]. Persistent infection is rare but most often occurs in children, particularly those under age 5 [153]. Initial antibiotic choice may also influence the likelihood of recurrent or persistent infection. Selection of an antibiotic to which there is potential GAS resistance, such as a macrolide or clindamycin, increases the likelihood of treatment failure. Additionally, some studies suggest that cephalosporins may be more effective than penicillin for preventing relapse [154].

-The presence of persistent or recurrent symptoms should also raise suspicion for an alternate initial diagnosis or new infection with a different pathogen in a chronic GAS carrier. For patients with repeated episodes of pharyngitis, culturing for GAS when patients are between episodes may help distinguish chronic carriage from active infection. A positive culture in an asymptomatic patient suggests that the patient is a carrier and that symptoms are due to an alternate cause as outlined in differential diagnosis section [1].

A persistent, severe sore throat accompanied by fever, trismus, or a muffled voice suggests a local complication such as peritonsillar cellulitis or abscess.

Antibiotic treatment — We generally repeat a 10-day course of antibiotic treatment for patients with persistent or recurrent streptococcal pharyngitis. The selection of an antibiotic varies based on patient history.

●For patients who were nonadherent to the initial antibiotic regimen, typically they can be treated with intramuscular penicillin. Injections of penicillin G benzathine provide bactericidal levels against GAS for 21 to 28 days. For those who are allergic or who cannot otherwise tolerate penicillin, antibiotic selection should be based on the patient's preferences and reasons for nonadherence [1].

●For patients with persistent infection or an initial recurrence, we usually select an antibiotic that has greater beta-lactamase stability than the one used for the initial treatment course. As examples, if penicillin was used for initial treatment, we use either amoxicillin-clavulanate or a first-generation cephalosporin; if a first-generation cephalosporin was used, we select a later-generation cephalosporin [1].

The approach is based on a meta-analysis of four randomized trials evaluating over 1300 adults and children with GAS pharyngitis that showed decreased clinical relapse rates when comparing cephalosporins with penicillins (25 versus 46 percent; odds ratio 0.55, 95% CI 0.30-0.99) [155]. Additional studies suggest that bacteriologic cure rates may be higher for cephalosporins compared with penicillin [156-159]. Scientific observations also support the selection of antibiotics with beta-lactamase stability when treating persistent or recurrent GAS infection [160-162]. Some bacteria that colonize the oropharynx, such as Staphylococcus aureus, Haemophilus influenza, and Moraxella catarrhalis, produce beta-lactamases that inactivate penicillin, leading to decreased activity of penicillin against GAS [163-185]. Penicillin also decreases the quantity of alpha-streptococci in the oropharynx, which naturally protect against GAS infection [166-168]. Cumulatively, these effects may inadvertently promote the survival and persistence of GAS in the oropharynx. By contrast, antibiotics with beta-lactamase activity may have a more balanced effect on the oropharyngeal flora, resulting in greater likelihood of GAS eradication.

A small number of patients experience multiple recurrences, which may be related to the infecting GAS strain [169-171], host immune response [147,172], or other factors that are not yet well characterized.

●For patients with multiple recurrences of GAS pharyngitis, treatment should be with an antibiotic from a class that has not been used previously, such as clindamycin.

●For patients with frequent, mild to moderate recurrent infections, delaying the start of antibiotic therapy by two to three days is an alternate approach. This approach is derived from observational data that suggest delaying therapy may allow the development of immunity against the infecting strain, resulting in higher eradication rates [147,153,172] without increasing the risk of acute rheumatic fever [173,174]. This approach is generally avoided in patients with severe symptoms or when GAS is actively circulating in the community, as it prolongs symptom duration and may increase the risk of suppurative complications and/or transmission of GAS to others.

●For patients with frequent, severe episodes of GAS pharyngitis that recur despite appropriate antibiotic treatment, tonsillectomy should be considered.

It is not necessary to perform follow-up testing for persistent or recurrent infection unless the patient becomes symptomatic after antibiotic treatment or special circumstances as outlined above are present.

When recurrent infections are thought to be due to ongoing GAS circulation among household members, consider testing all household members and treating those who test positive. When recurrent infections are thought to be due to ongoing GAS circulation in other close-contact settings such as day care centres or workplaces, determine the best management approach on a case-by-case basis.

Tonsillectomy — Tonsillectomy is rarely indicated for patients with recurrent GAS pharyngitis. The need for tonsillectomy should be determined in each individual case based on the patient age, the frequency and severity of infections, history of antibiotic use, and patient values and preferences [1,39].

Prevention

General prevention

Hand hygiene — Hand hygiene is a key measure for preventing spread to others, especially after coughing or sneezing and before preparing foods or eating, and we remind all patients of its importance.

Postexposure prophylaxis — Testing and treatment of asymptomatic persons who have been exposed to a patient with group A Streptococcus (GAS) pharyngitis are not routinely recommended [30], except for patients with a history of acute rheumatic fever, during outbreaks of acute rheumatic fever and/or poststreptococcal glomerulonephritis, or when GAS infections are recurring in households or other close-contact settings.

Special populations

Patients with a history of acute rheumatic fever — Patients with a history of acute rheumatic fever are at high risk for recurrent rheumatic fever and the development of chronic valvular heart disease with any subsequent GAS infection. We educate these patients on the risk of recurrence and its complications and recommend long-term antibiotic prophylaxis. Antibiotic selection and duration of therapy vary based on patient characteristics and medication availability.

Chronic carriers have GAS in their pharynx but are asymptomatic and have little or no immunologic response to the organism. Carriers are unlikely to spread GAS to their close contacts and are at very low, if any, risk for developing suppurative or nonsuppurative complications [150,174,175-178]. Treatment is generally not recommended for the carrier state (39), although it may be considered for close contacts in scenarios such as invasive disease outbreaks [178]. Tonsillectomy is not recommended solely for the purpose of reducing GAS pharyngitis [39]

However, we do consider treating carriers during outbreaks of acute rheumatic fever and/or poststreptococcal glomerulonephritis or when GAS infections are recurring in households or other close-contact settings [178-179].

Oral options for treatment of chronic carriage include clindamycin, amoxicillin-clavulanate, and penicillin plus rifampin; the duration of treatment is usually 10 days [39]. When used with either oral or parenteral penicillin, rifampin is typically given only during the last four days of therapy [39].

Prevention of foodborne illness — Streptococcal contamination of food has been implicated in foodborne outbreaks of pharyngitis [180-184], and foodborne transmission of GAS pharyngitis by asymptomatic food service workers with nasopharyngeal carriage has been reported [183,185,186]. Factors that can reduce foodborne transmission of GAS pharyngitis include thorough cooking, complete reheating, and use of gloves while handling food [180,187].

Vaccination — No vaccine against GAS is available for clinical use. However, research on GAS vaccine development is ongoing [188-192]. An important area of uncertainty is whether vaccine-induced antibodies may cross-react with host tissue to produce nonsuppurative sequelae in the absence of clinical infection.

Isolation Parents may ask us whether their children with scarlet fever or a sore throat should isolate or stay off school – there have been no changes in the law or new rules issued, as happened during the pandemic, recent guidance advises that a person is infectious for 2-3 weeks if antibiotics are not used, but that exclusion from school or nursery need only be for 24 hours after starting antibiotics [193].

Prognosis — GAS bacteraemia remains a serious infection. The estimated mortality rate associated with invasive GAS infections in children ranges from 2 to 8 percent [194-201]. Long-term disability occurs in an additional 3 to 8 percent of children following invasive GAS infection [194, 198].

Summary and conclusions

Early recognition of potential GAS infections is essential, as survival depends on rapid initiation of appropriate treatment. Antibiotics, surgery, and probably intravenous administration of human immunoglobulins are all indicated in cases of severe infection. In spite of modern therapy, the death rate remains high, and new therapeutic alternatives have to be found in order to reduce this rate.

Streptococci are ubiquitous, and their significance in medicine is remarkable. Exciting advances are being made in the diagnosis and in the understanding of the mechanisms of the pathogenesis of Streptococcus infections, as well as in control of these well-known organisms. Problems with antibiotic resistance must preclude complacency in dealing with these common pathogens.

Conflict of Interest – Nil

References:

1. Michael E Pichichero, Section Editors: Daniel J Sexton, Morven S Edwards, Deputy Editors: Sheila Bond, Jane Givens, https://www.uptodate.com/contents/treatment-and-prevention-of-streptococcal-pharyngitis-in-adults-and-children (last accessed on April 10 2023).
2. https://academic.oup.com/cid/article-abstract/14/1/2/354272
3. Efstratiou A, Lamagni T. Epidemiology of Streptococcus pyogenes. 2016 Feb 10 [updated 2017 Apr 3]. 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–. PMID: 26866237.
4. Gunnarsson RK, Holm SE, Söderström M. The prevalence of beta-haemolytic streptococci in throat specimens from healthy children and adults. Implications for the clinical value of throat cultures. Scand J Prim Health Care 1997; 15:149.
5. Schwartz RH, Wientzen RL Jr, Pedreira F, et al. Penicillin V for group A streptococcal pharyngotonsillitis. A randomized trial of seven vs ten days' therapy. JAMA 1981; 246:1790.
6. https://www.sciencedirect.com/science/article/pii/S0165587616300490
7. https://www.researchgate.net/profile/Alemseged-Abdisa/publication/51528378_Throat_carriage_rate_and_antimicrobial_susceptibility_pattern_of_group_A_Streptococci_GAS_in_healthy_Ethiopian_school_children/links/551c40c90cf20d5fbde4aac4/Throat-carriage-rate-and-antimicrobial-susceptibility-pattern-of-group-A-Streptococci-GAS-in-healthy-Ethiopian-school-children.pdf

8. Nayiga I, Okello E, Lwabi P, Ndeezi G. Prevalence of group a streptococcus pharyngeal carriage and clinical manifestations in school children aged 5-15 yrs in Wakiso District, Uganda. BMC Infect Dis. 2017 Apr 5;17(1):248. doi: 10.1186/s12879-017-2353-5. PMID: 28381239; PMCID: PMC5382413.
9. Marshall HS, Richmond P, Nissen M, Lambert S, Booy R, Reynolds G, Sebastian S, Pride M, Jansen KU, Anderson AS, Scully IL. Group A Streptococcal Carriage and Seroepidemiology in Children up to 10 Years of Age in Australia. Pediatr Infect Dis J. 2015 Aug;34(8):831-8. doi: 10.1097/INF.0000000000000745. PMID: 25961895.
10. Martin JM, Green M, Barbadora KA, Wald ER. Group A streptococci among school-aged children: clinical characteristics and the carrier state. Pediatrics. 2004 Nov;114(5):1212-9. doi: 10.1542/peds.2004-0133. PMID: 15520098.
11. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. Paediatrics. 2010 Sep;126(3): e557-64. doi: 10.1542/peds.2009-2648. Epub 2010 Aug 9. PMID: 20696723.
12. Kaplan EL. The group A streptococcal upper respiratory tract carrier state: an enigma. J Pediatr. 1980 Sep;97(3):337-45. doi: 10.1016/s0022-3476(80)80178-8. PMID: 6997450.
13. Hale C. Streptococcus-other. Pathology Outlines.com website. https://www.pathologyoutlines.com/topic/microbiologystreptococci.html. Accessed April 9th, 2023.
14. Doern CD, Burnham CA. It's not easy being green: the viridans group streptococci, with a focus on pediatric clinical manifestations. J Clin Microbiol. 2010 Nov;48(11):3829-35. doi: 10.1128/JCM.01563-10. Epub 2010 Sep 1. PMID: 20810781; PMCID: PMC3020876.
15. Longtin J, Vermeiren C, Shahinas D, Tamber GS, McGeer A, Low DE, Katz K, Pillai DR. Novel mutations in a patient isolate of Streptococcus agalactiae with reduced penicillin susceptibility emerging after long-term oral suppressive therapy. Antimicrob Agents Chemother. 2011 Jun;55(6):2983-5. doi: 10.1128/AAC.01243-10. Epub 2011 Mar 7. PMID: 21383092; PMCID: PMC3101384.
16. Desjardins M, Delgaty KL, Ramotar K, Seetaram C, Toye B. Prevalence and mechanisms of erythromycin resistance in group A and group B Streptococcus: implications for reporting susceptibility results. J Clin Microbiol. 2004 Dec;42(12):5620-5623. doi: 10.1128/JCM.42.12.5620-5623.2004. PMID: 15583291; PMCID: PMC535282.
17. Emonet S, Schrenzel J, Martinez de Tejada B. Molecular-based screening for perinatal group B streptococcal infection: implications for prevention and therapy. Mol Diagn Ther. 2013 Dec;17(6):355-61. doi: 10.1007/s40291-013-0047-2. PMID: 23832874.
18. Davies AP, Reid M, Hadfield SJ, Johnston S, Mikhail J, Harris LG, Jenkinson HF, Berry N, Lewis AM, El-Bouri K, Mack D. Identification of clinical isolates of α-hemolytic streptococci by 16S rRNA gene sequencing, matrix-assisted laser desorption ionization-time of flight mass spectrometry using MALDI Biotyper, and conventional phenotypic methods: a comparison. J Clin Microbiol. 2012 Dec;50(12):4087-4090. doi: 10.1128/JCM.02387-12. Epub 2012 Sep 19. PMID: 22993176; PMCID: PMC3502998.
19. Ikryannikova LN, Lapin KN, Malakhova MV, Filimonova AV, Ilina EN, Dubovickaya VA, Sidorenko SV, Govorun VM. Misidentification of alpha-hemolytic streptococci by routine tests in clinical practice. Infect Genet Evol. 2011 Oct;11(7):1709-1715. doi: 10.1016/j.meegid.2011.07.010. Epub 2011 Jul 21. PMID: 21798371.
20. Megged O, Yinnon AM, Raveh D, Rudensky B, Schlesinger Y. Group A streptococcus bacteraemia: comparison of adults and children in a single medical centre. Clin Microbiol Infect. 2006 Feb;12(2):156-62. doi: 10.1111/j.1469-0691.2005.01311. x. PMID: 16441454.
21. Kiska DL, Thiede B, Caracciolo J, Jordan M, Johnson D, Kaplan EL, Gruninger RP, Lohr JA, Gilligan PH, Denny FW Jr. Invasive group A streptococcal infections in North Carolina: epidemiology, clinical features, and genetic and serotype analysis of causative organisms. J Infect Dis. 1997 Oct;176(4):992-1000. doi: 10.1086/516540. PMID: 9333158.
22. Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F, Walmsley S, Low DE. Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. Clin Infect Dis. 1993 Jun;16(6):792-800; discussion 801-2. doi: 10.1093/clind/16.6.792. PMID: 8329511.
23. Tapiainen T, Launonen S, Renko M, Saxen H, Salo E, Korppi M, Kainulainen L, Heiskanen-Kosma T, Lindholm L, Vuopio J, Huotari T, Rusanen J, Uhari M. Invasive Group A Streptococcal Infections in Children: A Nationwide Survey in Finland. Pediatr Infect Dis J. 2016 Feb;35(2):123-8. doi: 10.1097/INF.0000000000000945. PMID: 26440814.
24. Nelson GE, Pondo T, Toews KA, Farley MM, Lindegren ML, Lynfield R, Aragon D, Zansky SM, Watt JP, Cieslak PR, Angeles K, Harrison LH, Petit S, Beall B, Van Beneden CA. Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005-2012. Clin Infect Dis. 2016 Aug 15;63(4):478-86. doi: 10.1093/cid/ciw248. Epub 2016 Apr 22. PMID: 27105747; PMCID: PMC5776658.
25. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs). ABCs Report: group A Streptococcus, 2019.
26. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs). ABCs Report: group A Streptococcus, 2020. Available at: https://www.cdc.gov/abcs/downloads/GAS_Surveillance_Report_2020.pdf (Accessed on March11, 2023).
27. Canetti M, Carmi A, Paret G, Goldberg L, Adler A, Amit S, Rokney A, Ron M, Grisaru-Soen G. Invasive Group A Streptococcus Infection in Children in Central Israel in 2012-2019. Pediatr Infect Dis J. 2021 Jul 1;40(7):612-616. doi: 10.1097/INF.0000000000003087. PMID: 34097654.
28. McNeil JC, Flores AR, Kaplan SL, Hulten KG. The Indirect Impact of the SARS-CoV-2 Pandemic on Invasive Group a Streptococcus, Streptococcus Pneumoniae and Staphylococcus Aureus Infections in Houston Area Children. Pediatr Infect Dis J. 2021 Aug 1;40(8):e313-e316. doi: 10.1097/INF.0000000000003195. PMID: 34250979; PMCID: PMC8279221.
29. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs). ABCs Report: group A Streptococcus, 2015. Available at: (Accessed on March 11, 2023).
30. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs). ABCs Report: group A Streptococcus, 2016, available at: (Accessed on March 11, 2023).

DOI: 10.31579/2690-1897/153