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REVIEW ARTICLE

# Group A ß-hemolytic Streptococcal Pharyngitis: An Updated Review

Alexander K.C. Leung[1,*], Joseph M. Lam[2], Benjamin Barankin[3], Kin F. Leong[4] and Kam L. Hon[5,6]

*[1]Department of Pediatrics, The University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada; [2]Department of Pediatrics and Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, British Columbia, Canada; [3]Department of Dermatology, Toronto Dermatology Centre, Toronto, Ontario, Canada; [4]Pediatric Institute, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia; [5]Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong, China; [6]Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong, China*

**Abstract:** ***Background*:** Group A ß-hemolytic *Streptococcus* (GABHS) is the leading bacterial cause of acute pharyngitis in children and adolescents worldwide.

***Objective*:** This article aims to familiarize clinicians with the clinical manifestations, evaluation, diagnosis, and management of GABHS pharyngitis.

***Methods*:** A search was conducted in December 2022 in PubMed Clinical Queries using the key term "group A β-hemolytic streptococcal pharyngitis". This review covers mainly literature published in the previous ten years.

***Results*:** Children with GABHS pharyngitis typically present with an abrupt onset of fever, intense pain in the throat, pain on swallowing, an inflamed pharynx, enlarged and erythematous tonsils, a red and swollen uvula, enlarged tender anterior cervical lymph nodes. As clinical manifestations may not be specific, even experienced clinicians may have difficulties diagnosing GABHS pharyngitis solely based on epidemiologic or clinical grounds alone. Patients suspected of having GABHS pharyngitis should be confirmed by microbiologic testing (*e.g.*, culture, rapid antigen detection test, molecular point-of-care test) of a throat swab specimen prior to the initiation of antimicrobial therapy. Microbiologic testing is generally unnecessary in patients with pharyngitis whose clinical and epidemiologic findings do not suggest GABHS. Clinical score systems such as the Centor score and McIssac score have been developed to help clinicians decide which patients should undergo diagnostic testing and reduce the unnecessary use of antimicrobials. Antimicrobial therapy should be initiated without delay once the diagnosis is confirmed. Oral penicillin V and amoxicillin remain the drugs of choice. For patients who have a non-anaphylactic allergy to penicillin, oral cephalosporin is an acceptable alternative. For patients with a history of immediate, anaphylactic-type hypersensitivity to penicillin, oral clindamycin, clarithromycin, and azithromycin are acceptable alternatives.

***Conclusion*:** Early diagnosis and antimicrobial treatment are recommended to prevent suppurative complications (*e.g.*, cervical lymphadenitis, peritonsillar abscess) and non-suppurative complications (particularly rheumatic fever) as well as to reduce the severity of symptoms, to shorten the duration of the illness and to reduce disease transmission.

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## 1. INTRODUCTION

"The art is long, life short, opportunity fleeting, experience fallacious, judgement difficult". Hippocrates

Group A ß-hemolytic *Streptococcus* (GABHS) is the leading cause of acute pharyngitis in both children and adolescents worldwide [1-3]. Nevertheless, even experienced clinicians cannot reliably distinguish GABHS pharyngitis from other causes of pharyngitis based on epidemiologic or clinical grounds alone. As such, microbiologic testing is often necessary to confirm the diagnosis. Clinical scoring systems such as the Centor and McIsaac scores have been developed to assist clinicians in identifying patients at increased risk for GABHS pharyngitis and those needing GABHS testing. The optimal management of GABHS pharyngitis is controversial and therapeutic dilemmas abound. Guidelines have been developed to guide clinicians in better diagnosing and managing GABHS pharyngitis, including those from the American Academy of Pediatrics (AAP), the Infectious Diseases Society of America (IDSA), the Centers

*Address correspondence to this author at the Department of Pediatrics, The University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada; Tel: (403) 230 3300; Fax: (403) 230 3322; E-mail: aleung@ucalgary.ca

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for Disease Control and Prevention (CDC), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP)-American Society of Internal Medicine (ASIM), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), and the American Heart Association (AHA) [4-12]. International guidelines differ substantially in opinions on whether the diagnosis should be based on microbiologic testing, though there is universal agreement that if antimicrobial therapy is indicated, penicillin V is the drug of choice [13]. Many physicians, however, do not adhere to the basic recommended guidelines [14-18]. This communication aims to familiarize clinicians with the clinical manifestations, evaluation, diagnosis, and proper management of GABHS pharyngitis. This review covers mainly literature published in the previous ten years.

## 2. THE CAUSATIVE ORGANISM

GABHS is a facultative anaerobic, non-motile, non-spore-forming, Gram-positive coccus that grows in chains [19]. These organisms form small grey-white colonies (1 to 2 mm in diameter) surrounded by a zone of complete (or clear) hemolysis on 5% sheep blood agar. The organism is inhibited by bacitracin. GABHS has a hyaluronic acid capsule, a cell wall, fimbriae, and a cytoplasmic membrane enclosing the cytoplasm. The cell wall comprises interwoven proteins, peptidoglycan, lipoteichoic acid, and the group-determining cell wall polysaccharide [20]. Group A carbohydrate is a polymer of *N*-acetyl glucosamine and L-rhamnose; the N-acetyl glucosamine is responsible for its group specificity. The major virulent factor is the M protein located on the cell surface and within fimbriae [20]. The hypervariable N terminus of the M protein provides the basis for type specificity. The M protein and the hyaluronic acid capsule are antiphagocytic [21, 22]. Lipoteichoic acid plays an essential role in the ability of GABHS to adhere to fibronectin-binding proteins on the surface of epithelial cells and is critical for colonization [22]. The peptidoglycan provides the cell wall with rigidity. More than 240 genotypes or serotypes of GABHS have been identified based on the M-protein gene sequence (coded by the *emm* gene) or M-protein serotype [4, 23]. GABHS produces various extracellular enzymes and toxins, including streptococcal pyrogenic exotoxins-certain exotoxins produced by GABHS act as superantigens by up-regulating T-cells [24]. Hyaluronidase, cysteine protease, and streptolysins produced by GABHS can destroy host tissues, allowing GABHS to spread through the host [21, 22]. Some strains produce erythrogenic exotoxins, which play an essential role in the pathogenesis of scarlet fever [22].

## 3. EPIDEMIOLOGY

Humans are the sole natural host for GABHS, and the pharynges of children are the major reservoir for GABHS [25]. GABHS pharyngitis occurs mostly in children between 5 and 15 years of age [26-28]. Though rare in children aged 3 years or younger [29-31], GABHS pharyngitis has been reported in infants [32]. GABHS accounts for 15 to 35% of all cases of acute pharyngitis in school-aged children, peaking at 7 to 8 years of age [26, 27, 33-35]. In temperate climates, GABHS pharyngitis peaks during the winter and early spring, accounting for 35 to 40% of all cases of acute pharyngitis in school-aged children [26, 36, 37]. The sex ratio is approximately equal. All races are affected.

The major route of spread is person-to-person by respiratory droplets of infected individuals [3]. Spread among family members is common, with a transmission rate of approximately 35% [38]. Crowding, close contacts (*e.g.*, in daycare centres, schools, dormitories), and contact sports facilitate transmission [39]. Other risk factors for GABHS pharyngitis include individuals with barriers to accessing primary healthcare, GABHS carriage, and a GABHS skin infection [40]. Foodborne outbreaks of GABHS pharyngitis caused by human food contamination and improper food preparation have rarely been reported [39, 41-43]. Household pets and fomites are not vectors of GABHS infection [3, 4]. The incubation period for GABHS pharyngitis is 2 to 5 days [4, 23]. Patients are not contagious during the acute stage of the illness and are usually not contagious 24 hours after initiating appropriate antimicrobial therapy [4].

## 4. CLINICAL MANIFESTATIONS

Children with GABHS pharyngitis typically present with an abrupt onset of fever, intense pain in the throat, and pain in swallowing [33]. The pain in the throat is often worse on one side [44]. Typical symptoms of GABHS pharyngitis are uncommon in children aged three years or younger [23]. Generally, fever is less pronounced in very young children [22, 45]. Symptoms such as headache, myalgia, nausea, vomiting, and abdominal pain may also be present, particularly in younger children [33, 44]. Rhinorrhea, nasal congestion, cough, hoarseness, and conjunctivitis are unusual and are much more compatible with viral pharyngitis [35, 46]. There may be a history of recent contact with an individual with GABHS pharyngitis.

Physical findings include a beefy red pharynx, enlarged and erythematous tonsils (with or without exudate) (Fig. **1**), a red and swollen uvula, enlarged tender anterior cervical lymph nodes, and sometimes palatal petechiae and a strawberry tongue (Figs. **2** and **3**) [47-50]. Early in the illness, the prominent lingual papillae are covered by a white coating, giving the appearance of a white strawberry tongue (Fig. **2**) [51]. The white coating is usually lost in 1 to 2 days, giving rise to a red strawberry tongue (Fig. **3**) [51]. Typically, exudates are greyish, whitish, or yellowish and can be localized to one or both tonsils [22]. Other less common findings include circumoral pallor [52], doughnut lesions (erythematous papules or follicular lesions with a pale center) over the soft and hard palate [53], and pharyngeal haemorrhage [54].

In a susceptible host, an erythematous, fine papular rash (scarlatiniform rash) (Fig. **4**) may be seen [37, 47, 50]. Typically, the rash starts in the neck, axilla and groin and spreads to the trunk and limbs [37]. The face is usually spared [44]. The rash has the texture of coarse sandpaper or gooseflesh and is better felt than seen [20]. It blanches on pressure and may be more prominent in flexor skin creases, especially in the antecubital fossae (Pastia lines or Pastia sign) [52]. Other

findings include circumoral pallor [52] and doughnut lesions (erythematous papules or follicular lesions with a pale center) over the soft and hard palate [53]. Resolution of the rash usually takes 3 to 4 days and occurs in the same order of appearance. Desquamation of the involved area may follow the resolution of the rash. A scarlatiniform rash caused by streptococcal erythrogenic exotoxins, when present, signifies scarlet fever [3, 52].

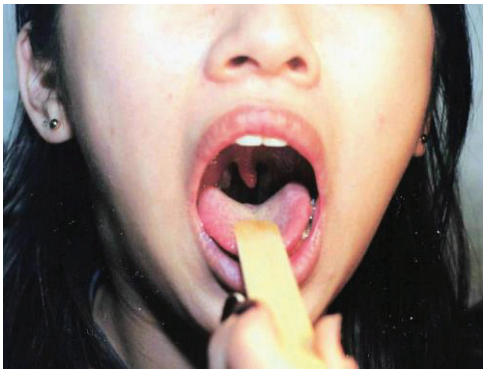

**Fig. (1).** Enlarged right tonsil with tonsillar exudate in a 13-year-old girl with streptococcal pharyngitis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

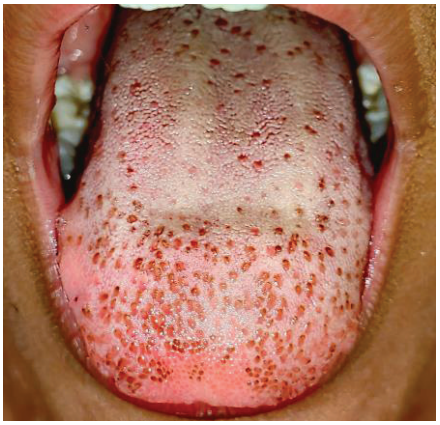

**Fig. (2).** White strawberry tongue. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

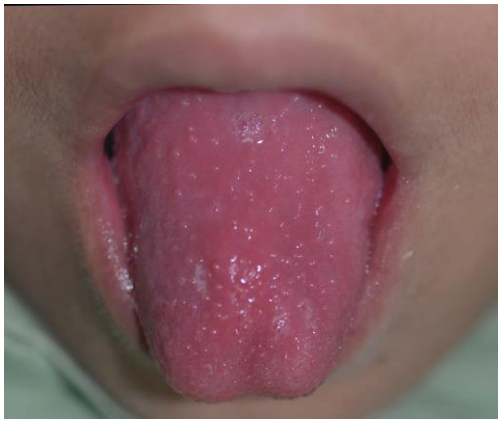

**Fig. (3).** Red strawberry tongue. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

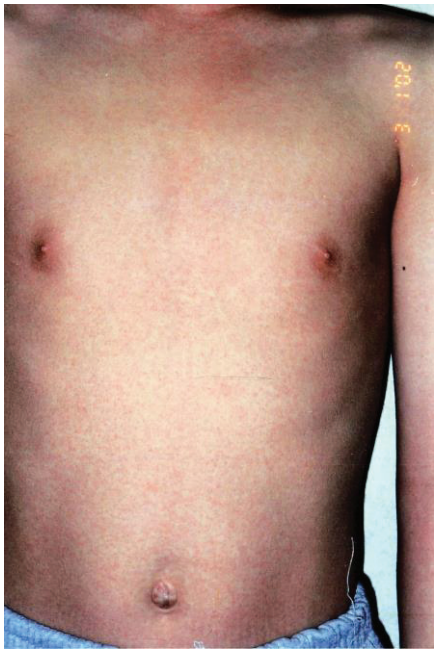

**Fig. (4).** A diffuse fine papular rash having the texture of goose-flesh or coarse sandpaper on the trunk of a 12-year-old boy with scarlet fever. The rash blanches on pressure. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

## 5. DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes viral pharyngitis (mild/no fever, sore throat, nasal congestion, runny nose, non-productive cough, hoarseness, concurrent conjunctivitis, stomatitis, ulcerative oropharyngeal lesion, “cobble-stoning” of the posterior pharynx) [38, 55], fungal pharyngitis (mouth numbness, loss of taste, painful smooth red patches or white curd-like plaques with the oropharynx, angular cheilitis) [55, 56], infectious mononucleosis (sore throat, fever, fatigue, erythematous morbilliform rash, pharyngitis, tonsillar exudates, palatine petechiae, palpebral/periorbital edema, posterior cervical adenopathy, generalized lymphadenopathy, splenomegaly, lymphocytosis, atypical lymphocytes) [57-59], epiglottitis (high fever, sore throat, toxic appearance, drooling, stridor) [60], diphtheria (fever, pharyngitis, thick, gray, adherent pseudomembrane over the tonsils and throat, airway compromise, tremendous enlargement of cervical lymph nodes) [61, 62], Kawasaki disease (prolonged fever, erythematous, fissured cracked lips, strawberry tongue, erythematous pharynx, cervical lymphadenopathy, bilateral nonexudative conjunctivitis, polymorphous rash, indurated edema of the dorsum of the hands and feet, diffuse erythema of their palms and soles, sharp demarcation at the ankles and wrists, periungual desquamation) [63, 64], herpangina (fever, sore throat, vesicular and ulcerative lesions on the soft palate, pharynx, and posterior mucosa, cervical lymphadenopathy) [65], rubeola (fever; erythematous maculopapular rash, coryza, cough, conjunctivitis) [66, 67], hand, foot, and mouth disease (low-grade fever, painful oral lesions, painless exanthem typically involves palms and soles) [68, 69], herpetic gingivostomatitis (fever, refusal to drink or eat, hyper-

salivation, halitosis, swollen, inflamed, friable gum that bleed easily, multiple oral ulcers), aphthous stomatitis (painful ulcer on the oral mucosa in otherwise healthy individuals), varicella (skin rash with lesions in varying stages of development, fever, pruritus, painful oral ulcers may occur) [70], Steven-Johnson syndrome (sudden onset of inflammatory bullous lesions on the skin with epidermal detachment involving less than 10% of total body surface area accompanied by involvement of two or more mucosal surfaces; ulceration and hemorrhagic crusting of lips), Behçet's disease (recurrent oral or genital ulcers, erythema nodosum-like lesions, relapsing uveitis, arthritis, thrombophlebitis) [71, 72], and PFAPA (periodic fever with aphthous stomatitis, pharyngitis and adenitis) syndrome [61, 73].

## 6. CLINICAL DIAGNOSIS AND CLINICAL SCORING SYSTEMS

A history of an abrupt onset of fever and sore throat, the absence of cough, and recent exposure to someone with GABHS pharyngitis and physical findings of an inflamed pharynx, enlarged and erythematous tonsils, tonsillar exudates, a red and swollen uvula, cervical lymphadenitis, a strawberry tongue, palatal petechiae, and an erythematous, fine papular rash that blanches on pressure with the texture of coarse or sandpaper are highly suggestive of GABHS pharyngitis [1, 20]. Except for the scarlatiniform rash, none of the clinical findings is specific to GABHS pharyngitis [22, 74]. On the other hand, the absence of a sore throat, signs of pharyngitis, and fever suggest another etiology. Clinical diagnosis can often be difficult because most patients with GABHS pharyngitis do not have the classic manifestations and infection due to many other agents that may be clinically indistinguishable from GABHS pharyngitis [75].

Several clinical scoring systems based on comparing composite features have been developed to assist clinicians in diagnosing GABHS pharyngitis [76-78]. The Centor score can be used to estimate the probability of a positive culture and applies to adults only [77]. The Centor scoring system assigns one point to each of four criteria: temperature >38ºC, tonsillar exudates, swollen tender anterior cervical nodes, and absence of cough. These points are then added to yield a composite score. The probability of a positive culture result with a Centor score of 0, 1, 2, 3, and 4 is 2.5%, 6.5%, 15%, 32%, and 56%, respectively [77]. The McIssac score, a modification of the Centor score that adjusts for age-related differences in the incidence of GABHS pharyngitis, has been validated for use in children and adults [78]. The McIssac scoring system assigns one point to each of five criteria: temperature >38ºC, tonsillar exudates, swollen tender anterior cervical nodes, absence of cough and age between 3 and 14 years [78]. One point is subtracted if the age is greater than 45 years. A higher McIssac composite score means a greater risk of GABHS pharyngitis. A score of ≥2 justifies microbiologic testing for evaluating GABHS pharyngitis.

Although scoring systems can help clinicians predict the probability of GABHS pharyngitis more accurately, these clinical scoring systems have a sensitivity of no greater than 80% and a specificity of approximately 80%. They, therefore cannot be reliably used to confirm or refute the diagnosis of GABHS pharyngitis [79, 80]. The IDSA recommends confirmatory microbiologic testing in all cases of pharyngitis except when a clear viral etiology is suspected [10, 11]. Overall, clinical scoring systems are useful in determining which patients should undergo microbiologic testing and reducing the unnecessary use of antibiotics [81-83].

## 7. MICROBIOLOGIC TESTING

Microbiologic testing (*e.g.*, culture, rapid antigen detection test, molecular point-of-care test) of a throat swab specimen is generally unnecessary for patients with acute pharyngitis and obvious viral symptoms such as coryza, cough, hoarseness and oral ulcers [5, 10, 11]. In general, microbiologic testing for GABHS is not recommended in patients ≤ 3 years because GABHS pharyngitis is uncommon in children in this age group unless the patients have appropriate symptoms, have positive contact with individuals with GABHS pharyngitis or signs of GABHS complications [33, 84]. In the absence of clinical and epidemiologic findings suggestive of GABHS pharyngitis, a positive microbiologic test most likely represents a GABHS carrier state with intercurrent viral pharyngitis [44]. As such, the judicious use of laboratory testing for GABHS cannot be over-emphasized [85, 86]. On the other hand, a clinical diagnosis of GABHS pharyngitis cannot be reliably made, even by the most experienced clinician. Thus, it is crucial to have bacteriologic confirmation of GABHS pharyngitis before antimicrobial treatment is started [5, 85]. Throat swab specimens should be obtained by swabbing the posterior pharyngeal wall and the surface of both tonsils [5]. The swab should be moved out of the mouth without touching the buccal mucosa or the tongue [37].

In general, microbiologic testing is unnecessary for asymptomatic patients after appropriate treatment [87, 88]. Microbiologic testing after treatment should be considered for individuals at risk for complications (in particular, rheumatic heart disease and rheumatic fever) [88].

### 7.1. Throat Culture

The culture of a properly taken throat swab specimen on a 5% sheep blood agar remains the gold standard for diagnosing GABHS pharyngitis [4, 5]. The sensitivity of a properly taken throat swab culture is 90 to 95% [5, 89]. A throat swab culture also allows antibiotic susceptibility to be tested. Generally, culture results are unavailable for 24 hours or even longer [21]. Negative plates should be reexamined after an additional 24 hours and, if necessary, over an additional 24 hours to maximize the sensitivity of the test [5]. False-positive cultures may result if other microorganisms are misidentified as GABHS. GABHS can be distinguished from other ß-hemolytic streptococci by the sensitivity of GABHS to bacitracin or by detecting the group-specific cell wall carbohydrate antigen using commercial kits containing group-specific antisera [5]. False-negative cultures may result from improper collection of specimens, improper inocu-

lation conditions, improper inoculation techniques, or recent or concurrent use of an antimicrobial.

### 7.2. Rapid Antigen Detection Tests

A rapid antigen detection test, also referred to as rapid streptococcal antigen test, *via* a throat swab performed in the physician's office can provide results in minutes [90-92]. All rapid antigen detection tests are based on acid or enzyme extraction of the group A carbohydrate antigen from the GABHS cell wall and detection of the antigen by using an immunoassay [37]. The specificity of rapid antigen detection tests has consistently been greater than 95% (very few false-positive results) [4, 75, 89]. Therefore, if the rapid antigen detection test is positive, a throat culture is unnecessary, and antimicrobial therapy can be initiated without much delay [10, 11]. On the other hand, the sensitivity of the rapid antigen detection tests ranges from 70 to 90% (*i.e.*, false negatives occur) [4, 37, 79]. In a 2016 meta-analysis of studies (105 test evaluations) in which 58,244 children underwent both rapid antigen detection tests and throat cultures for GABHS, the pooled sensitivity of rapid antigen detection tests was 85.6% (95% confidence interval: 83.3 to 87.6) [93]. The low sensitivity may be due to, at least in part, GABH carriage in some patients [94]. Also, rapid antigen detection tests using optical immunoassay (OLA), polymerase chain reaction (PCR), and DNA chemiluminescence DNA essays are more sensitive than those using latex agglutination (LA) assay and enzyme-linked immunosorbent assay (ELISA) [5, 33]. Some authors suggest using high-sensitivity rapid antigen detection testing without confirmatory cultures for negative results [95, 96]. On the other hand, if GABHS pharyngitis is highly suspected and the rapid antigen detection test is negative, a throat swab culture is necessary to make a diagnosis [4, 10, 11]. The AAP and IDSA recommend confirming a negative rapid antigen detection test with a throat culture unless the clinician has ascertained that the sensitivity of the rapid antigen detection test used in the office is comparable with that of a throat culture [4]. The drawback of a rapid antigen detection test is that most children with pharyngitis do not have GABHS pharyngitis and will therefore have a negative rapid antigen detection test which needs to be confirmed with throat culture [37]. This will add to the cost of microbiologic testing.

### 7.3. Molecular Assays

Molecular assays (*e.g.*, PCR assays, nucleic acid amplification tests [NAATs]) have superior specificity (97.4 to 100%) and sensitivity (95 to 100%) compared to rapid antigen detection tests and cultures [97-109]. Also, molecular assays have a much shorter turnaround time than cultures [97-109]. Despite these, their high cost and complexity of molecular assays preclude their widespread use as a replacement for rapid antigen detection tests or throat cultures [35, 102]. Molecular assays are complex tests requiring specialised equipment and personnel training before they can be implemented [102, 105]. They are not widely available, especially in outpatient settings [37]. If a molecular assay is negative, follow-up testing with a throat culture is not necessary because of the high sensitivity of molecular assays [37, 110].

## 8. SEROLOGY TESTS

Antistreptococcal antibody titers (such as anti-DNase, antihyaluronidase, and anti-streptolysin-O) are not useful in the diagnosis of acute GABHS pharyngitis because it takes 7 to 14 days after the onset of the infection for the antibody response to occur [46, 111]. The antibody titers usually peak at 3 to 6 weeks and remain elevated for months [46, 111]. As such, elevated antistreptococcal antibody titers reflect a past but not current GABHS infection [10, 11]. Antistreptococcal antibody titers are useful for diagnosing immune-mediated late complications of GABHS pharyngitis, such as acute rheumatic fever and poststreptococcal glomerulonephritis [44].

If infectious mononucleosis is suspected, a monospot test should be performed [112, 113]. Generally, complete blood cell count, absolute neutrophil count, C-reactive protein, and procalcitonin are higher in patients with acute GABHS pharyngitis than in asymptomatic controls [114, 115]. However, these infection markers are also higher in individuals with other kinds of infection. As the sensitivities and specificities of these infection markers are low, measurement of these markers does not add to the diagnostic accuracy of the clinical scoring systems [114].

## 9. COMPLICATIONS

Suppurative complications result when the infection spreads to adjacent structures. These complications, common in the pre-antibiotic era, are quite rare nowadays. Such complications include suppurative cervical lymphadenitis, peritonsillar cellulitis [88], peritonsillar abscess ("quinsy") [116], retropharyngeal abscess [106], parapharyngeal abscess [106], otitis media [88], pneumonia, sinusitis, and mastoiditis [27]. GABHS pharyngitis may very rarely result in streptococcal bacteremia [117], necrotizing fasciitis [118], phlegmonous gastritis [119], primary peritonitis [120], rhabdomyolysis [121], Lemierre syndrome (jugular vein septic thrombophlebitis) [122], meningitis [123], subdural empyema [124], and brain abscess [123].

Nonsuppurative complications include acute rheumatic fever [125-128], rheumatic heart disease [129-139], poststreptococcal glomerulonephritis [140-144], poststreptococcal reactive arthritis [123], microscopic polyangiitis [145], poststreptococcal uveitis [146], keratitis [147], maculopathy [148], corneal ulceration [147], streptococcal toxic shock syndrome [149], and pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus* (PANDAS) [150, 151].

GABHS pharyngitis is a common trigger for the development of psoriasis (particularly guttate psoriasis) (Fig. **5**) [152-154] and thyrotoxicosis [155]. It is an uncommon trigger for urticaria [156]. Henoch-Schönlein purpura is associated with GABHS pharyngitis in approximately 50% of cases [157-159].

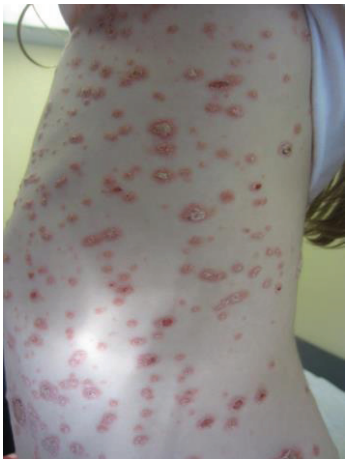

**Fig. (5).** A 6-year-old boy with guttate psoriasis precipitated by streptococcal pharyngitis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The global and economic burdens associated with GABHS pharyngitis can be considerable [160, 161]. In one study of 135 children with a single episode of GABHS pharyngitis, for a single episode of GABHS pharyngitis, on average, children missed a mean of 1.9 days of day care or school, and 42% of parents missed a mean of 1.8 days of work [162]. The economic burden should also consider health care dollars spent on laboratory testing, medications, and treatment of complications, if any.

## 10. MANAGEMENT

Once GABHS pharyngitis is diagnosed based on the results of a rapid antigen detection test, throat culture, or molecular assay, antimicrobial therapy should be initiated to prevent suppurative complications (*e.g.*, cervical lymphadenitis, otitis media) and some nonsuppurative complications or immune sequelae (particularly rheumatic fever), to reduce the severity of symptoms, to shorten the duration of the illness, and to reduce disease transmission [163-166]. Studies have shown that antimicrobial therapy started within 48 hours of the onset of GABHS pharyngitis hastens clinical recovery by 12 to 24 hours [3, 20]. Also, patients are not contagious after 24 hours of appropriate antimicrobial therapy [4].

Antimicrobial therapy should be considered in toxic patients or patients with a history of rheumatic fever and clinical features suggestive of GABHS pharyngitis while awaiting microbiologic confirmation [3, 5, 20]. Antimicrobial therapy should be discontinued if the microbiologic test results are negative, as indiscriminative use of antibiotics may lead to bacterial resistance [167, 168]. Routinely repeating microbiologic testing after antimicrobial therapy is usually unnecessary for asymptomatic patients [20].

### 10.1. Choice of Antimicrobials and Duration of Treatment

Because of its proven efficacy, safety, narrow spectrum of antimicrobial activity, and low cost, penicillin V given orally remains the drug of choice for GABHS pharyngitis, except in patients allergic to penicillin [4, 169-172]. The recommended oral dosage of penicillin V is 25 to 50 mg/kg (maximum 1000 mg) daily divided into 2 or 3 doses for 10 days, regardless of promptness of clinical recovery [4, 89].

For patients unwilling or unable to take the oral medication or when compliance is a concern, a single intramuscular injection of benzathine penicillin G should be considered; especially for patients at risk for rheumatic fever [173]. A benzathine penicillin G injection is painful and carries a risk of injection into nerves and blood vessels when it is not appropriately administered [3, 20]. The injection can be made less painful by warming benzathine penicillin G to room temperature before its injection and adding procaine to benzathine penicillin G [4, 106]. The combination of 900,000 units (562.5 mg) of benzathine penicillin G and 300,000 units (187.5 mg) of penicillin G procaine works for most children [4].

Amoxicillin is often preferred over penicillin V for children because of the better taste of the suspension and its availability as a chewable tablet and once-daily extended-release tablet [5, 88, 89, 174]. Skin rash and gastrointestinal side effects may be more common with amoxicillin. The recommended amoxicillin dose is 50 mg/kg/day (maximum 1200 mg per day), given orally once to thrice daily [175-178].

For patients who have a non-anaphylactic allergy to penicillin, a 10-day course of an oral cephalosporin (*e.g.*, cephalexin, 40 mg/kg/day divided into two doses; maximum 500 mg/dose) is an acceptable alternative [4]. Because of the possibility of cross-reactivity, patients with a history of immediate, anaphylactic-type hypersensitivity to penicillin should not be treated with cephalosporin [89]. Some investigators advocate using cephalosporins in all nonallergic patients because of better GABHS eradication and effectiveness against chronic GABHS carriage [89, 179]. Cephalosporins are more effective than penicillin, presumably because ß-lactamase copathogens that inactivate penicillin but not cephalosporins may be present in the tonsillopharynx [180]. Secondly, penicillin is more effective than cephalosporins in eradicating commensal α-streptococci in the tonsillopharynx, and these commensals represent ecological competitors of GABHS. Thirdly, cephalosporins achieve sustained adequate bactericidal drug levels throughout the course of therapy compared with penicillin [180].

For patients with a history of immediate, anaphylactic-type hypersensitivity to penicillin, oral clindamycin (20 mg/kg/day in 3 divided doses; maximum 900 mg/day), clarithromycin (15 mg/kg/day in two divided doses; maximum 500 mg/day), and azithromycin (12 mg/kg, once daily; maximum 500 mg/day) are acceptable alternatives [4, 79, 181]. Clindamycin and clarithromycin should be given for a total of 10 days, whereas azithromycin is usually given for 5 days owing to its extended half-life [88-183]. The use of oral clindamycin, clarithromycin, and azithromycin in the treatment of GABHS pharyngitis should be reserved for rare patients with a history of immediate, anaphylactic-type hypersensitivity to penicillin because of the potential for bacterial resistance to these microbials [174, 184].

Antimicrobials such as sulfonamides and tetracyclines have no role in treating GABHS pharyngitis because of the high prevalence of resistance, high incidence of treatment failure, and high adverse events [185-188].

Although some studies have shown that 5 to 7 days of antimicrobial treatment is equally effective for GABHS pharyngitis [189-193], other studies have shown that reducing the duration of treatment from 10 days has resulted in a higher failure rate and inferior bacteriologic eradication rates [4, 6, 33, 89, 194-196]. It is necessary to complete an entire 10-day course of therapy for most antimicrobials to maximize eradication rates of GABHS in the pharynx to reduce the risk of complications, except benzathine penicillin G and azithromycin [1, 10, 11, 21, 89]. A complete 10-day course of antimicrobial therapy for treating GABHS pharyngitis is also recommended by the IDSA, AAP, and ESCMID as per their respective guidelines [4, 8, 10, 11].

### 10.2. GABHS Carrier State

It is estimated that 5 to 13% of children are GABHS carriers [197-200]. The GABHS carriers are asymptomatic and pose little risk of active infection to these carriers and their contacts [198]. Neither the AAP nor the IDSA supports the routine use of antibiotics for GABHS carriers [4, 10, 11]. However, eradication of the GABHS carrier state may be considered under the following circumstances: (1) a local outbreak of acute rheumatic fever or poststreptococcal glomerulonephritis; (2) an outbreak of GABHS pharyngitis in a semi-closed or closed community; (3) a family history of rheumatic heart disease or rheumatic fever; (4) multiple episodes of documented GABHS pharyngitis that continue to occur within a family during a period of many weeks despite appropriate antibiotic therapy; or (5) parental anxiety or parents considering tonsillectomy solely because of GABHS carrier state [4, 19, 20]. The treatment of choice for eradicating GABHS carriage is oral clindamycin 20 to 30 mg/kg daily (maximum 900 mg/day) divided into 3 doses for 10 days [4]. Other antibiotics used to treat GABHS carriers include amoxicillin-clavulanate, cephalosporins, azithromycin, and a combination of penicillin V and rifampin [4].

### 10.3. Treatment Failure

Treatment failure may result from poor compliance, inadequate treatment, antimicrobial tolerance or resistance, or eradication of protective pharyngeal microflora such as α-streptococci and ß-lactamase-producing copathogens. Pseudo-treatment failure may result from a GABHS carrier state or reinfection. Children with treatment failure can be treated with the same antimicrobial agent, a narrow-spectrum cephalosporin, a macrolide, or amoxicillin-clavulanate [4]. For patients with inadequate treatment or poor compliance, an intramuscular injection of benzathine penicillin G should be considered [38]. A Cochrane systematic review of 19 randomized, double-blind trials (n = 5,839) comparing different antibiotics for GABHS pharyngitis showed cephalosporins were more effective than penicillin for relapse in children (odds ratio: 0.55; 95% confidence interval: 0.30 to 0.99; 4 studies, n = 1386) and in adults (odds ratio: 0.42; 95% confidence interval: 0.20 to 0.88; 2 studies; n = 770) [201].

### 10.4. Recurrent GABHS Pharyngitis

Children with recurrent pharyngitis with a positive throat culture for GABHS can present a diagnostic dilemma. From a clinical point of view, it is challenging to distinguish a GABHS carrier with recurrent viral pharyngitis from a patient with bona fide recurrent GABHS pharyngitis [202]. Clues in favor of GABHS pharyngitis include clinical findings or community or household epidemiologic factors suggestive of GABHS pharyngitis, a marked clinical response to antimicrobial therapy, negative throat cultures between episodes of pharyngitis, and a serologic response to GABHS extracellular antigens (*e.g.*, antistreptolysin O, antiDNase, and antihyaluronidase) [4, 20]. Isolation of the same type (*emm* typing) of GABHS suggests GABHS carrier statue with concomitant recurrent viral pharyngitis, whereas isolation of differing types of GABHS suggests bona fide recurrent GABHS pharyngitis [4]. However, typing (*emm* typing) of GABHS isolates is mainly for academic purposes and can only be performed in research laboratories. Recurrent GABHS pharyngitis can be treated with a narrow-spectrum cephalosporin, a macrolide, or amoxicillin-clavulanate [20]. Tonsillectomy is rarely indicated for the treatment of recurrent GABHS pharyngitis but may be considered if there are seven or more culture-documented episodes of GABHS pharyngitis in a single year, five or more episodes per year for two successive years, or three or more per year in each of three years [88, 203].

### 10.5. Adjunctive Therapies

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, may be administered for fever and pain control. Aspirin should be avoided in children due to the risk of Reye syndrome. The use of a systemic corticosteroid is not recommended because of the risk of potential adverse events [10, 11, 204]. Also, concurrent antibiotic-corticosteroid therapy does not improve the pain/discomfort associated with GABHS pharyngitis and might even prolong the recovery [10, 11, 55].

Various lozenges and throat sprays have been marketed to relieve the sore throat in adults and older children [205]. Lozenges containing active ingredients such as menthol, benzocaine, lidocaine, dyclonine, ambroxol, hexylresorcinol, amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA), or NSAIDs and throat sprays containing active ingredients such as benzocaine, phenol, benzydamine, or chlorhexidine gluconate may provide temporary symptomatic relief [206-225].

Foods containing honey may facilitate intake of other foods and provide temporary symptomatic relief of the sore throat associated with GABHS pharyngitis [205, 226]. In addition to being used as a demulcent, studies have shown that honey has antibacterial activities [227-232]. In various studies, the minimum inhibitory concentration (MIC) of honey on GABHS ranged from 12.5% to 73% [226, 232].

### 10.6. Alternative and Complementary Therapies

In some cultures, complementary and alternative therapies are popular for treating sore throat and GABHS pharyngitis [233]. A wide variety of products from medicinal plants have been shown to have bacteriostatic or bactericidal activity against GABHS and some therapeutic effects on GABHS pharyngitis [234-236]. These include green tea (major catechins include epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, and epicatechin), herbal teas from different herbs (licorice root, barberry root, marshmallow root, purple coneflower flower, purple coneflower stem, oregano flowering shoots, thyme, sage leaves, and slippery elm inner bark), essential oils (extracted from sage, oregano, cloves and ginger), and cranberry and sumac extracts [234-240]. These treatments have not yet been subjected to rigorous studies or randomized clinical trials. Until then, the use of these products as alternative or complementary therapies for GABHS pharyngitis cannot be recommended.

## 11. PREVENTION

Improving living conditions, avoiding overcrowding, preventing poverty, improving hand hygiene, and easy access to healthcare may help decrease the incidence of GABHS pharyngitis [88].

*Streptococcus salivarius* K12 (BLIS K12), an oral probiotic, is strongly antagonistic to the growth of GABH through the release of two bacteriocins (salivaricin A2 and salivaricin B) [241-249]. Preliminary studies have shown that daily administration of BLIS K12 to children significantly reduces GABHS pharyngitis [241-247]. Some authors suggest prophylactic daily administration of BLIS K12 to individuals at risk for recurrent GABHS pharyngitis and rheumatic fever [241-247, 249].

The economic burden of GABHS is substantial; hence the importance of developing a safe, safe, and affordable GABHS vaccine against the broad spectrum of GABHS organisms [250, 251]. There are currently several vaccine candidates, most in preclinical trials, for preventing GABHS pharyngitis [252-254]. Vaccine candidates in clinical trials include the 26-valent vaccine (StreptAvax), 30-valent vaccine (StrettAnova™) and J8 vaccine (MJ8VAX) [255-259]. Preliminary results are encouraging; the vaccine candidates are immunogenic and well-tolerated [259, 260]. No commercial vaccine against GABHS is available yet.

## 12. PROGNOSIS

The prognosis for adequately treated GABHS pharyngitis is excellent. Fever usually resolves within three days, and sore throat within one week with adequate treatment [44, 204]. Suppurative complications are uncommon and respond readily to treatment. Acute rheumatic fever has declined steadily over the past several decades. There is insufficient evidence to determine if antimicrobial therapy can prevent poststreptococcal glomerulonephritis, poststreptococcal arthritis, and PANDAS, hence the importance of preventing GABHS pharyngitis [260-262].

## CONCLUSION

Unnecessary or inappropriate use of antimicrobials is common and contributes to the development of resistance to antimicrobials. As such, bacteriologic confirmation of GABHS pharyngitis is necessary before starting antimicrobial treatment. A rapid antigen detection test is preferred because the result is available in minutes and can be performed in most clinical settings. Restricting diagnostic testing to patients with a greater pretest probability of GABHS can limit the over-diagnosis of GABHS, resulting in unnecessary treatment with antibiotics. Clinical scoring systems such as Centor and McIsaac scores have been developed to assist clinicians in identifying patients at increased risk for GABHS pharyngitis and the need for GABHS testing. Prompt and accurate diagnosis of GABHS pharyngitis is important to reduce sequelae of untreated infection and limit disease transmission to other individuals.

## AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| AAFP | = | American Academy of Family Physicians |
| AAP | = | American Academy of Pediatrics |
| ACP | = | American College of Physicians |
| AHA | = | American Heart Association |
| AMC | = | Amylmetacresol |
| ASIM | = | American Society of Internal Medicine |
| CDC | = | Centers for Disease Control and Prevention |
| DCBA | = | Dichlorobenzyl Alcohol |
| ELISA | = | Enzyme-Linked Immunosorbent Assay |
| GABHS | = | Group A ß-hemolytic *Streptococcus* |
| IDSA | = | Infectious Diseases Society of America |
| LA | = | Latex Agglutination |
| MIC | = | Minimum Inhibitory Concentration |
| NAATs | = | Nucleic Acid Amplification Tests |
| NSAIDS | = | Acetaminophen and Nonsteroidal Anti-inflammatory Drugs |
| OLA | = | Optical Immunoassay |
| PANDAS | = | Pediatric Autoimmune Neuropsychiatric Disorder Associated with *Streptococcus* |
| PCR | = | Polymerase Chain Reaction |
| PFAPA | = | Periodic Fever with Aphthous Stomatitis, Pharyngitis and Adenitis |

## CONSENT FOR PUBLICATION

Informed consent was taken before publishing human images.

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## CONFLICT OF INTEREST

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