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Review Article

Role of penicillin in the management of group A beta-hemolytic streptococcal pharyngitis

Ramesh Dargad*

Department of Cardiology, Lilavati Hospital, Bandra (West), Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Ramesh Dargad,
E-mail: rohitdargad@hotmail.com

ABSTRACT

Group A beta-hemolytic streptococcal (GABHS) infection is the most common bacterial cause of acute pharyngitis. GABHS is more commonly seen in the pediatric age group than in adults. The disease responds to antibiotics. Untreated GABHS leads to non-suppurative and suppurative complications. Penicillin is the drug of choice recommended by most guidelines. Most GABHS isolates are sensitive to penicillin including penicillin G. Penicillins play a very important role in preventing transmission rates of GABHS, resolution of symptoms, and prevention of GABHS complications. Intramuscular penicillin G benzathine is one of the treatment options for GABHS. Penicillin G potassium is a natural penicillin, with a narrow spectrum of activity, as is required for GABHS. This review aims to understand the role of penicillins in the treatment of GABHS and its complications.

Keywords: Penicillin G, Group A beta-hemolytic streptococcal pharyngitis, Suppurative complications, Narrow spectrum of activity, Transmission rate

INTRODUCTION

Group A beta-hemolytic streptococcal (GABHS) infection is the most common bacterial cause of acute pharyngitis.[1] GABHS is the cause of sore throats in 15% to 35% of children (5-15 years) and 5% to 15% of adults in the Western world; it is more common in the late winter and early spring.[1-3]

GABHS pharyngitis is significantly more likely in pediatric patients aged 5-15 years; it manifests as fever, tonsillar exudates, tender anterior cervical adenopathy, but no cough.[2] GABHS pharyngitis is considered as the sole precursor of acute rheumatic fever (ARF). A recent systematic review and meta-analysis reporting pooled prevalence of GABHS pharyngitis in Indian children aged 5-15 years estimated its prevalence to be 2.79% (95% confidence interval [CI]: 1.58-4.89) and 13% (95% CI: 3.18-41.97) in asymptomatic children and children with confirmed pharyngitis, respectively.[4] Prevalence rate of rheumatic fever in this age group was found to be 0.04% (95% CI: 0.01-0.17).[4]

GABHS pharyngitis is treatable via administration of appropriate antibiotics. Penicillin is the drug of choice recommended by most guidelines.[5-9] Most GABHS isolates are sensitive to penicillin including penicillin G.[10] Intramuscular penicillin G benzathine and oral amoxicillin (a class of penicillin) are the other treatment options for GABHS pharyngitis.[9]

Penicillin G potassium and penicillin V are natural penicillins, with a narrow-spectrum of activity as required for the management of GABHS pharyngitis.[3,11]

This review is undertaken to understand the role of penicillins in the treatment of GABHS pharyngitis and its complications.

DIAGNOSIS OF GABHS PHARYNGITIS

Diagnostic tests

The first step in the diagnosis of GABHS pharyngitis is elicitation of detailed history of the onset and symptoms of pharyngitis and careful physical examination.[3] Symptoms of GABHS pharyngitis typically include throat pain, fever, headaches, and chills; other symptoms like abdominal pain, nausea, and vomiting may be present. Cough, coryza, or conjunctivitis that are typically seen in viral pharyngitis are absent in GABHS pharyngitis.[3,12]

GABHS infection should not be diagnosed telephonically as it is important to examine the throat (pharynx) and neck for cervical lymph nodes.[13] Further, patients are often not very coherent and precise about their symptoms on phone.[14] Following physical examination, the next step is choosing the right diagnostic tool from the various diagnostic methods available to detect GABHS infection, which include the clinical scoring systems, rapid antigen detection tests (RADT), throat culture, nucleic acid amplification tests (NAATs), and machine learning (ML) and artificial intelligence (AI).[3]

Throat culture of swabs taken from posterior pharynx and tonsils is considered to be the reference standard for diagnosing GABHS pharyngitis.[3] However, results are available only after 48-72 hours. Hence, to clinically differentiate between GABHS pharyngitis and viral pharyngitis, diagnosis is substantiated by combining any clinical scoring system with selective use of RADT.[2] Though NAATs are more sensitive than RADT, they are not routinely used because of high cost.[3] ML and AI using cameras and smartphones have not yet been integrated into the mainstream diagnosis of GABHS pharyngitis.[3]

Clinical scoring tools

The Centor score helps differentiate between viral and bacterial pharyngitis.[2,16] In patients with score throat, one point is assigned each for absence of cough, swollen and tender anterior cervical nodes, temperature >100.4°F or 38°C, and tonsillar exudates or swelling. The McIsaac score adds or subtracts a point from Centor score based on age, i.e. 1 point for age 3-14 years, 0 points for age 15-44 years, and −1 point for age ≥45 years.[15,16] Table 1 shows the risk of and clinical decision rules for GABHS pharyngitis based on Centor scores. The FeverPAIN scale assigns one point each for fever in past 24 hours, intensely inflamed tonsils, absence of cough or coryza, presentation within 3 days of symptom onset, and purulent tonsils. Table 2 depicts the risk of and clinical decision rules for GABHS pharyngitis based on FeverPAIN scores.[2,15,16]

Guideline recommendations for diagnosing GABHAS pharyngitis

The Centor score or modified Centor score (McIsaac score) has been recommended by the Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians (AAFP) and the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) and ACP guidelines for diagnosing GABHAS pharyngitis in adults.[5-8,17] These three guidelines do not recommend any further testing for McIsaac scores 0-1. RADT and throat culture are recommended for scores ≥2. On the other hand, while the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) 2012 guidelines recommend Centor scores, they recommend RADTs only for Centor scores 3 and 4.[18]

However, according to ESCMID, Centor scores have lower diagnostic value in children than in adults, as the presentation of GABHS pharyngitis in children is different from that in adults.[18] The CDC, AAFP, ACP-ASIM and ESCMID guidelines do not recommend throat culture for negative RADT.[5,6,8,18] The Infectious Diseases Society of America (IDSA) guidelines do not endorse diagnosis of GABHAS pharyngitis based solely on scores but also recommend RADT/throat culture.[9] ISDA further recommends throat culture in children with negative RADT, but not in adults with negative RADT due to low incidence and risk of rheumatic fever complications in adults.[9]

Apart from this, the AAFP also recommends that the FeverPAIN score can be used to diagnose GABHS pharyngitis.[7] The guidelines do not recommend any test or treatment for scores 0 or 1, except in 3-15 years where a backup throat culture can be considered. The AAFP guidelines also recommend RADT for scores 2 or 3 and empiric antibiotic therapy to be started immediately without testing for scores 4 or 5.[7]

Thus, the guidelines significantly differ with regard to the time to perform additional testing like throat cultures. It is important to note that since RADT has specificity of 95%, no further testing is required if RADT is positive. However, the sensitivity of RADT ranges from 70% to 90%; therefore, in patients with high suspicion of bacterial infection, throat culture should be done even if RADT is negative to rule out GABHS pharyngitis.[19]

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of GABHS pharyngitis is viral pharyngitis, and many symptoms of the two conditions have a broad overlap.[3] The differential diagnosis of GABHS pharyngitis includes many infectious and non-infectious causes as listed in Table 3.[9,20,21]

MANAGEMENT OF GABHS PHARYNGITIS

Treatment for GABHS pharyngitis is aimed at providing symptomatic relief, shortening duration of illness, decreasing the risk of contagion, decreasing unnecessary antibiotics use and resultant development of antibiotic resistance, and preventing nonsuppurative and suppurative complications.[3]

Guidelines for management of sore throat

The ACP guidelines on appropriate antibiotic use strongly recommend that clinicians should prescribe antibiotics only for patients with confirmed diagnosis of streptococcal pharyngitis.[17] The CDC/AAFP/ACP-ASIM guidelines recommend a 10-day course of oral penicillin V as the first-choice antibiotic for managing GABHS pharyngitis.[5-8] The IDSA guidelines recommend a t10-day course of either penicillin or amoxicillin or a single intramuscular injection of benzylpenicillin G.[9] The "National Treatment Guidelines for Antimicrobial Use in Infectious Diseases" by the National Centre for Disease Control (NCDC)", India recommends oral penicillin V 500 mg twice daily or oral amoxicillin 500 mg thrice daily for 10 days.[22]

For people allergic to penicillin, CDC/AAFP/ACP-ASIM guidelines recommend the use of erythromycin, while IDSA suggests a 5-day course of azithromycin or 10-day course of clindamycin or clarithromycin for people with type 1 hypersensitivity to penicillin or amoxicillin and 10-day course of first generation cephalosporin for people with type IV hypersensitivity.[5-8,9] Similarly, for patients allergic to penicillin, NCDC, India, recommends azithromycin 500 mg once daily for 5 days or one dose of benzathine penicillin 12 lakhs or 1.2 million units intramuscularly.[22] The recommended doses of various antibiotics are outlined in Table 4.

The Indian Academy of Pediatrics (IAP) rheumatic fever guidelines caution against the use of antibiotics such as tetracycline, sulfonamide, and chloramphenicol due to widespread resistance to GABHS.[23]

Additionally, IDSA recommends acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) to control pain or fever associated with GABHS pharyngitis.[9] There is no recommendation to use corticosteroids as an adjunctive therapy.[2,9]

Role of penicillin in GABHS

Penicillins (oral and intramuscular) are the first choice of antibiotics for GABHS pharyngitis recommended by all the guidelines.[5-9] Penicillins (natural or synthetic) are oldest available bactericidal agents (antibiotics) derived from fungi.[24] Penicillin inhibits cell wall synthesis by binding to penicillin-binding proteins that produce the protein crosslinks in the bacterial cell wall.[24] The resulting structural weakness and activated autolytic enzymes contribute to the susceptibility of bacteria to penicillin and facilitate bacterial cell lysis.[24]

Penicillin has a narrow spectrum of activity, is effective, inexpensive and has a low side-effect profile. There is no known penicillin resistance to GABHS, and allergic reaction rate is low at <4%.[25,26] Thus, penicillins play a very important role in preventing transmission rates of GABHS, its symptom resolution and prevention of GABHS pharyngitis complications.[22,24,27-29]

Tolerability and resistance

All penicillins, except for the extended-spectrum penicillins are classified by the Food and Drug Administration (FDA) as pregnancy category B drugs.[24] Penicillin is excreted in very low concentrations in breast milk, and hence is considered safe in lactating mothers. However, breastfeeding infants of mothers on penicillin or its derivates may develop diarrhea or candidiasis.[30]

Adverse effects of penicillin are uncommon (seen in 0.1 to ≥1% cases) and can be classified as side effects of the gastrointestinal (most common are nausea and vomiting diarrhea; pseudomembranous colitis is less common), renal, nervous, integumentary, and hematologic systems and immune mediated hypersensitivity reactions (I [most severe] to IV/idiopathic [least severe] (Table 5).[24,31]

In general, GABHS is not resistant to penicillin.[25] However, other bacteria may be resistant to penicillin, and this resistance may be natural or acquired.[24] A type of natural resistance to penicillin may be seen in acute and relapsing GABHS pharyngo-tonsillitis co-infected with β lactamase producing bacteria (BLPB).[24,32] BLBP like staphylococcus destroy the beta lactam nucleus of penicillin and thereby inactivate the drug.[33] Another reason for bacterial resistance in GABHS is that often penicillin is not prescribed in penicillin-sensitive patients who self-report penicillin allergy.[24] Penicillin anaphylactic reactions are most commonly experienced with parenteral administration and are least common when penicillin is administered orally.[24,31] Detailed history of type of allergic reaction should be elicited, and adequate measures should be taken to detect hypersensitivity before prescribing penicillin in these patients. Inappropriate choice of antibiotic, inadequate dose and duration of therapy, poor compliance, reacquisition of GABHS from a contact or an object (i.e., toothbrush or dental braces), and carrier state are causes of recurrent GABHS, which is not ideally a case of resistance.[32]

Comparison of penicillin with other antibiotics in the treatment of GABHS

All penicillins contain a thiazoldine ring, an attached beta-lactam ring, and a side chain. Other antibiotics such as cepahalosporins, carbapenamines, and monobactams have the characteristic beta-lactam ring seen in penicillin; hence, all these antibiotics are collectively referred to as beta lactams.[24] Other antibiotics such as tetracycline, sulfonamide, and chloramphenicol cannot be used due to widespread resistance in GABHS pharyngitis.[23] Despite guidelines recommending the use of erythromycin in GABHS pharyngitis, GABHS isolates in Indian patients are found to be resistant to this antibiotic.[10,34]

The minimum inhibitory concentrations (MICs) of various antibiotics against GABHS show that penicillin is the most sensitive antibiotic against GABHS (Table 6).[35]

Table 1: Clinical decision rules for GABHS diagnosis based on Centor scores.

Centor score	Risk of GABHS pharyngitis (%)	Clinical course
1	1.0-2.5	No further testing or antibiotics indicated
2	5.0-10.0	No testing or antibiotics indicated if risk close to 5%; perform throat culture or RADT if risk close to 10% - if negative, no antibiotics indicated and if positive, treat with antibiotics
3	11.0-17.0	Perform throat culture or RADT if risk close to 10% - if negative, no antibiotics indicated and if positive, treat with antibiotics
≥4	28.0-35.0	Perform throat culture or RADT if risk close to 10% - if negative, no antibiotics indicated and if positive, treat with antibiotics
≤0	51.0-53.0	Consider empiric treatment with antibiotics

GABHS group A beta-hemolytic streptococcal; RADT: rapid antigen detection testing

Table 2: Clinical decision rules for GABHS diagnosis based on FeverPAIN scores.

FeverPAIN score	Risk of GABHS pharyngitis (%)	Clinical course
0 or 1	1.0-10.0	No further testing recommended; backup throat culture recommended in children aged 3-15 years
2	11.0-17.0	RADT
3	28.0-35.0	RADT
4 or 5	51.0-53.0	Empiric antibiotics

GABHS group A beta-hemolytic streptococcal; RADT: rapid antigen detection testing

Table 3: Causes of differential diagnosis of GABHS pharyngitis.

Infectious causes	Non-infectious causes
Bacterial infections	Allergies to pollen, indoor or outdoor pollutants or medications
Arcanobaceterium haemolyticum	Irritation due to gastroesophageal reflux disease or second-hand smoke exposure
Corynebacterium diphtheria	Trauma due to snoring, excessive shouting, or recent tracheal intubation
Fusobacterium necrophorum	Foreign body
Mycoplasma	Autoimmune disorders (Behçet syndrome and Kawasaki)
Neisseria gonorrhoeae	
Viral infections	
Respiratory viruses (parainfluenza, rhinovirus, coxsackievirus, and adenovirus)	
Epstein-Barr virus	
Acute HIV infection	
Coronavirus	
Others	
Chlamydia infection	
Treponema pallidum	

GABHS: group A beta-hemolytic streptococcal; HIV: human immunodeficiency virus

Table 4: Doses of various antibiotics used in GABHS.

Antibiotics	Dose	Duration (days)
Penicillin G	50 thousand units/kg/day in divided doses; contraindicated in penicillin allergy	10
Penicillin V (oral)	Children: 250 mg every 6 hours; adults: 500 mg thrice daily; contraindicated in penicillin allergy	10
Benzylpenicillin G (deep intramuscular)	1.2 million unit (>27 kg) after sensitivity test; 0.6 million unit (<27 kg) after sensitivity test	Single dose

Continued.

Antibiotics	Dose	Duration (days)
Amoxicillin (oral)	50 mg/kg, once daily with a maximum of 1000 mg per dose or 25 mg/kg twice a day with a maximum of 500 mg per dose	10
Clarithromycin (oral)	7.5 mg/kg/dose. twice daily; maximum of 250 mg/dose	10
Clindamycin (oral)	7 mg/kg/dose, 3 times daily; maximum of 300 mg/dose	10
Azithromycin (oral)	12.5 mg/kg/day one daily; maximum of 500 mg/dose	5
Erythromycin (oral)	20 mg/kg/dose; max: 500 mg; contraindicated in liver disorder	
First generation cephalosporin: cephalexin (oral)	15-20 mg/kg/dose twice a day	10

Table 5: Hypersensitivity reactions to penicillin.

Type	Time of onset (hours)	Presentation	Skin testing required?
I	<1	Anaphylaxis and/or angioedema, respiratory distress, hypotension	Yes
II	>72	Fever, arthralgia, splenomegaly, lymphadenopathy; typically self-limiting and resolves completely within days to weeks of stopping penicillin	No
III	>72	Autoimmune responses producing local ischemia and/or necrosis as a result of complement activation	No
IV	>72	Contact dermatitis	No
Idiopathic	>72	Maculopapular rash (most common reaction); no Stevens-Johnson syndrome (rare)	No

Table 6: MICs of various antibiotics.

Antibiotic	Sensitivity rate against GABHS (%)	MIC (µg/ml)
Penicillin	100	0.002-0.032
Vancomycin	100	0.125-2
Cephalothin	97.6	0.01-8
Chloramphenicol	88.8	1-32
Erythromycin	87.2	0.032-64
Tetracycline	75.2	0.125-128
Ciprofloxacin	92.8	0.125-4
Erythromycin	-	MIC_{50} for macrolide-resistant strain: 0.5 (range: 0.125-8) MIC_{90}: 8 (range: 0.125-8)

COMPLICATIONS OF GABHS

Untreated or poorly treated GABHS pharyngitis may lead to nonsuppurative and suppurative complications.[20] Nonsuppurative complications include acute rheumatic fever (ARF), rheumatic heart disease (RHD), acute glomerulonephritis, pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS), post-streptococcal reactive arthritis, scarlet fever, and streptococcal toxic shock syndrome.[20,36] Suppurative complications include tonsillopharyngeal (paratonsillar) cellulitis or abscess, otitis media, sinusitis, necrotizing fasciitis, jugular vein septic thrombophlebitis, bacteremia, meningitis, and brain abscess.[20]

Need to prevent GABHS pharyngitis complications

Though GABHS pharyngitis is considered self-limiting and most cases respond to treatment, untreated GABHS pharyngitis sequelae can cause significant acute and chronic systemic complications.[3,37] One of the goals of GABHS treatment is to prevent complications.[3] While the risk of serious complications is not high in developed countries, early diagnosis and antibiotic initiation is important to curtail the risk of developing both nonsuppurative and suppurative complications in developing countries where prevalence is high.[37-39] Poor socioeconomic and immunization status, overcrowding, and malnutrition contribute to increased risk of GABHS pharyngitis and its complications in developing nations.[37,39] Hence, it is important to diagnose and treat GABHS pharyngitis at the earliest.

Prevention of GABHS pharyngitis complications

ARF and RHD are significant sequels of untreated or poorly treated GABHS pharyngitis, and all efforts should be made to prevent these chronic sequels. Prevalence of ARF and RHD in Indian population varies from 0.5/1000

to 11/1000 in various studies.[23] Penicillin plays an important role in both primary and secondary prophylaxis against complications.[40] In patients who develop ARF, penicillin treatment is also effective in reducing the likelihood or severity of post ARF development of RHD.[36]

Primordial prevention

Preventing overcrowding, improving community and personal hygiene, and educating masses about GABHS pharyngitis and its sequelae can pave path for reducing the risk of transmission and risk of complications.[36]

Primary prevention

GABHS pharyngitis complications can be primarily prevented through timely diagnosis and management.[3,5,8,9,23,36] However, different guidelines advocate different diagnostic parameters, and clinicians have many options to choose from based on patient requirement.[3] All guidelines, however, concur that oral penicillin should be the first and primary choice of treatment. Again, there are many options for clinicians to choose from in patients not compliant to oral penicillin or those allergic to penicillin.[3]

Secondary prevention

Penicillin is the mainstay of secondary prophylaxis for preventing recurrence of ARF and progressive RHD.[23,36] In this setting, intramuscular benzathine penicillin is found to be superior to oral penicillin.[36] Both three weekly and four weekly regimens have been studied and are practiced. All efforts should be made to adhere to the selected dose regimen to prevent recurrent ARF/RHD.[36]

The appropriate duration of secondary prophylaxis is decided based on the time elapsed since the last ARF episode, presence or absence of carditis, severity of RHD, and age of the patient.[36] Based on these factors, secondary intramuscular benzathine penicillin prophylaxis is recommended for a minimum of 10 years since the last episode or until the age of 18-21 years, whichever duration is longer.[41]

Patients with moderate RHD should receive prophylaxis until the age of 30-35 years while those with severe RHD should receive until the age of 40 years.[41] Benzathine penicillin is, however, not recommended for endocarditis prophylaxis before catheterization or any surgical intervention.[23]

CONCLUSION

GABHS is the most common cause of bacterial pharyngitis in children. Antibiotic resistance to this organism has been changing in recent years, mostly due to inappropriate usage of wide spectrum antibiotics. The frequency of resistance of GABHS to antibiotics has been increasing worldwide. Penicillin still remains the drug of choice for GABHS pharyngitis treatment.

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