Management of Treatment Failure and GAS Recurrence

Revisions to Clinical Question 7, March 2019

Introduction

The *Group A Streptococcal Sore Throat Management Guideline Update 2014*[1] was published in June 2014 following extensive consultation and international peer review. Clinical Question 7 relating to how treatment failure and/or recurrence of group A streptococcal (GAS) pharyngitis is managed, was updated at that time. This section has since been reformatted and revised to address the management of patients depending on whether they are at **high or low** risk for developing acute rheumatic fever (ARF). This revision has been incorporated into the latest update: *Group A Streptococcal Sore Throat Management Guideline Update 2019*.

The following guidance and algorithm has been developed by the Heart Foundation and the Ministry of Health.

This guidance focuses on the management of **recurrent treated GAS positive sore throats in children and adolescents at high-risk for rheumatic fever.** For the management of GAS sore throat (where antibiotic regimens differ if it is the patient's first or second GAS sore throat), refer to the 2019 Guideline Update, available online at: www.heartfoundation.org.nz.

Revision of Question 7. How should treatment failure and/or the recurrence of GAS pharyngitis be managed?

Awareness of a patient's risk for developing ARF will have an important effect on the management of pharyngitis, including how to address possible treatment failure and/or recurrence (see Sore Throat Algorithm, page 14 and Clinical Question 3, page 25).

Treatment Failure

Treatment failure is strictly defined as the recurrence of symptomatic pharyngitis caused by the same serotype (*emm*) of GAS, accompanied by a corresponding rise in serial streptococcal serology.[2] It is a failure to eradicate pharyngeal GAS in a symptomatic individual and occurs more frequently in individuals treated with oral penicillin (or amoxicillin) in comparison with intramuscular benzathine penicillin.[3-5]

While treatment failure can be carefully identified in the research setting, this is much more difficult in the primary care setting. Serotyping (*emm*-typing) is not readily available in everyday practice, and while paired serology (acute and convalescent titres taken at least 14 days apart) are feasible, they are rarely performed even in antibiotic trials[2, 3] and should not delay prompt treatment (see Clinical Question 4, page 29 in the Guideline Update 2019).

A repeat throat swab at the end of treatment is not usually routinely recommended. Interpretation can be difficult (i.e. re-infection, carriage with viral infection). However, end of treatment throat swabbing is recommended where the risk of ARF is high and further treatment of possible re-infection or carriage is justified (see page 2 and Clinical Question 6 and 14 (pages 39 and 47) in the Guideline Update 2019).

Recurrence of GAS Pharyngitis

Recurrence of GAS pharyngitis is **defined as the patient's third or more consecutive treated symptomatic GAS positive pharyngitis within a three-month period. i.e. with NO negative GAS throat swabs in between positives.**

Patients at High-Risk of ARF

Those at high-risk for ARF are individuals who have a personal, family or household history of ARF, or who have two or more of the following criteria; Māori or Pacific ethnicity, age 3-35 years ***with an emphasis on children and adolescents****, or living in crowded circumstances or in lower socioeconomic areas of the North Island. Emphasis is on children and adolescents (aged 4-19 years old) as they are at particularly high-risk of developing ARF.*

The main objective in treating GAS pharyngitis is ARF prevention. In a study in a high-risk population, the determining factor for development of ARF was the persistence of pharyngeal GAS.[6]

Important considerations in the **HIGH ARF RISK** population are whether the infection is a result of poor adherence with treatment (relapse) or re-infection of the patient by the same or a new strain of GAS from a family, household or other contact. A second episode of pharyngitis by the original infecting strain of GAS is less common.[7] A recent study from a United States population highlighted careful management of repeated episodes, which were found in many cases to be due to a new serotype.[8] In a New Zealand study in a high risk population, approximately two thirds of GAS positive swabs at the end of treatment were a new serotype or a relapse (i.e. with symptoms) of the original serotype.[3]

Clinical Prediction Rules

Using clinical prediction rule (CPR) is not recommended in the management of GAS pharyngitis in a population at high-risk of ARF in either general practice or the school-clinic setting. Application in the school-clinic population showed a 50% prediction i.e. 50% GAS positive pharyngitis cases were missed. There is limited testing of CPR's in the general practice population in New Zealand at high ARF risk.[9] (See Clinical Question 1, page 20 in the Guideline Update 2019)

Treatment

In an environment where **ARF is endemic** and streptococcal pharyngitis occurs repetitively in some individuals, the third or further GAS recurrences can be treated using IM benzathine penicillin or oral amoxicillin.

Collect post-treatment swab from the index case, three to six days[2] after completion of 10 days of amoxicillin or one month after IM benzathine penicillin. If the patient remains GAS positive on throat swabbing, seek paediatrician, adult infectious disease specialist or clinical microbiologist advice (refer to antibiotic table and footnotes on page 6 or Appendix 10, page 70, in the Guideline Update 2019). Following consultation and peer review, this table is to be used for the antimicrobial management of a patient's third or more consecutive symptomatic treated GAS episode in a three-month period i.e. no GAS negative throat swabs in between. These regimens differ from the antibiotic regimens recommended for a patient's first or second GAS pharyngitis in a three-month period (see Clinical Question 5, page 30 in Guideline Update 2019).

Adherence

Adherence to treatment may be improved by the use of once-daily oral amoxicillin if not already used.[10, 11] Daily observed therapy in special situations may be helpful. Where compliance is likely to be problematic, a single dose of IM benzathine penicillin should be considered, see Clinical Question 11, page 45.

It is important to treat every GAS throat infection in the high ARF group, for the following reasons:

1. It is impossible to always ascertain on clinical grounds which throat infections are viral or GAS.[12] Most sore throats are diagnosed clinically and/or with throat swabs and not with repeated serology. In New Zealand, the population (which includes all household members) at high-risk of ARF also has high rates of respiratory illnesses, including bronchiolitis, poorly controlled asthma and bronchiectasis.[13, 14] Determining a likely viral origin of a sore throat on the basis of accompanying symptoms such as cough may not be reliable in the high ARF risk New Zealand population.
2. Repeated GAS infections have been linked to ARF so the authors cannot say they are 'safe' for the individual to have. Refer to Clinical Question 7, page 41 and Proposed Rheumatic Fever Primary Prevention Programme Guideline,[15] available on the Heart Foundation website.
3. The risk of developing ARF in GAS carriers is unclear; the literature is very poor and further studies are needed (see Clinical Question 6, page 39 on GAS Carriage in Guideline Update 2019). However, GAS in carriers can spread to others, albeit less likely to than those with symptomatic pharyngitis.

4. GAS in the throat is still infectious for others (see Clinical Question 6, page 39 in Guideline Update 2019).

Based on the current knowledge, the Writing Group considers the risk/benefit of treating apparent recurrent episodes to favour treating in the best interests of the patient in a population at high-risk of ARF. It is acknowledged that in some situations GAS pharyngeal carriage (not infection) will be treated but it is considered that carriage itself poses some risk to both the patient and the household. See Clinical Question 6, page 39 on GAS carriage.

Household contacts of patients experiencing recurrences should be assessed as per the Household Sore Throat Management Algorithm and Clinical Question 19, page 51 in Guideline Update 2019.

Recommendation 1:	Treat recurrent GAS pharyngitis using algorithm on page 5 and treat with IM benzathine penicillin or directly observed therapy of 10 days of oral amoxicillin.
Recommendation grade:	Expert opinion

Recommendation 2:	Collect post-treatment swab from index case three to six days after completion of 10 days of amoxicillin or one month after IM benzathine penicillin.
Recommendation grade:	Expert opinion

Recommendation 3:	If patient's post treatment swab is GAS positive, seek paediatrician, or adult infectious disease specialist or clinical microbiologist advice and/or refer to antibiotic table on page 6.
Recommendation grade:	Expert opinion

Recommendation 4:	Swab **ALL** household members (symptomatic and asymptomatic) with emphasis on children and adolescents (4-19 year olds), and treat if GAS positive.
Recommendation grade:	Expert opinion

Patients at Low-Risk of ARF

Those at low-risk for ARF are individuals who are non-Māori and non-Pacific people, children under three years old and adults older than 35 years old, those not living in crowded circumstances or lower socioeconomic areas of the North Island and with no personal, family or household history of ARF.

The main objective in treating GAS pharyngitis is ARF prevention. **Avoidance of unnecessary antibiotics in this population is an important public health factor to limit unnecessary use of antimicrobials.** Most patients at low-risk of ARF will not require antibiotic treatment (see Sore Throat Algorithm, page 14 in Guideline Update 2019). However, it is advisable to follow up severe cases of GAS pharyngitis to ensure treatment should suppurative sequelae be suspected.

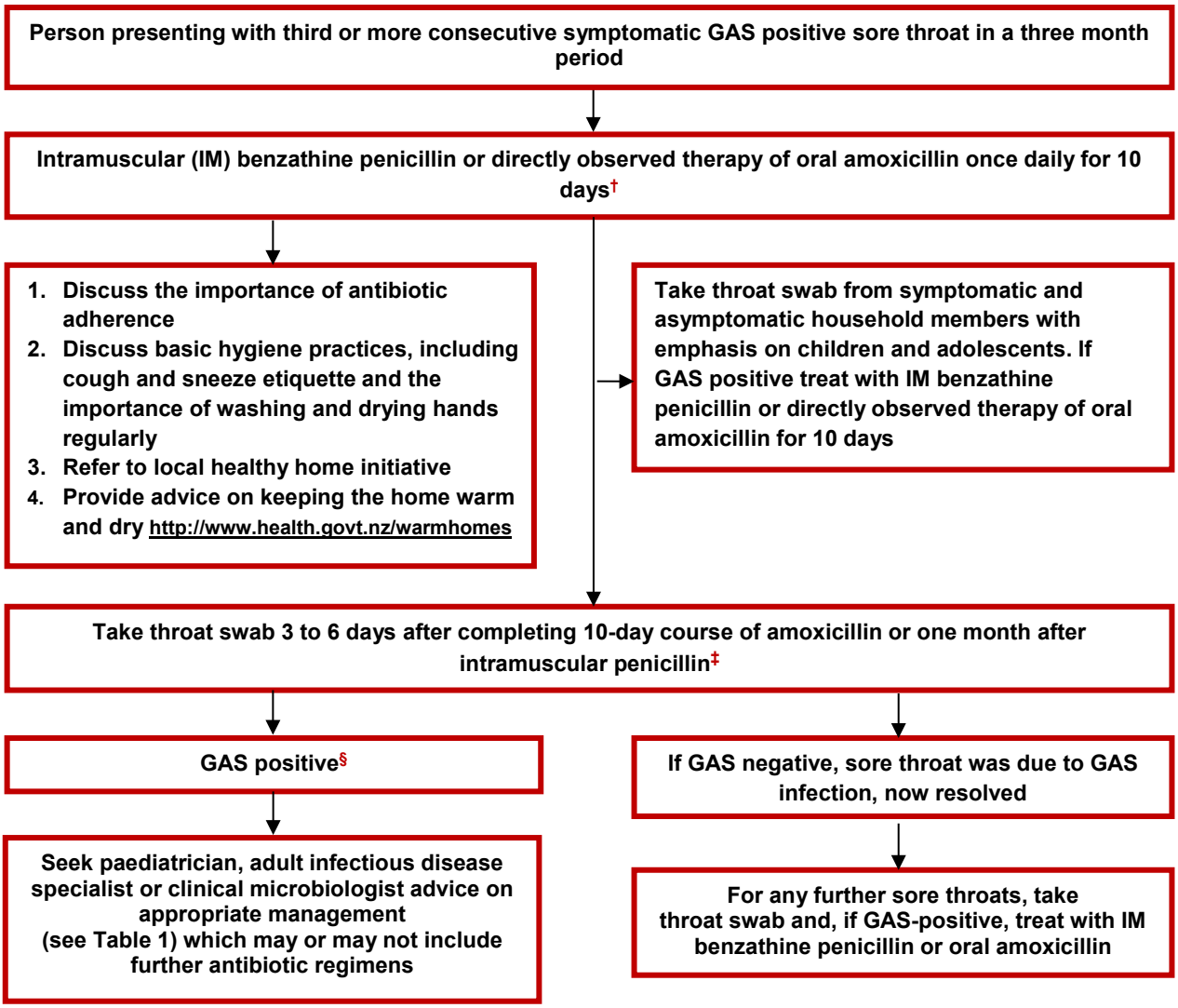
Gerber et al, studying patients in an environment where ARF was very uncommon, considered the possibility that GAS cultured at the end of a treatment course, when symptoms still persist, may be GAS isolated from the throats of chronic carriers actually suffering from viral upper respiratory tract infections.[7] In this type of environment the risk of ARF to the patient is very low, and the transmission of the GAS to others is likely to be of very minor importance.

Recommendation 1:	Throat swabbing and/or antibiotic treatment may **not** be required for **mild** symptoms **unless** the patient is at increased risk of spreading GAS e.g. healthcare and residential care workers, food handlers, school and early childhood teachers and students. Instead consider analgesia.
Recommendation grade:	Expert opinion

Recommendation 2:	Follow up severe cases of GAS pharyngitis to ensure treatment should suppurative sequelae be suspected.
Recommendation grade:	Expert opinion

Recommendation 3:	Avoid swabbing at the end of treatment in most patients (see Clinical Question 14, page 47 of Guideline Update 2019) and especially those patients at low risk of developing ARF who still have a sore throat.
Recommendation grade:	Expert opinion

Algorithm: Management of Recurrent Treated Group A Streptococcal (GAS) Positive Sore Throats in Children and Adolescents at HIGH-Risk* of Rheumatic Fever



Footnotes:

* Those at high-risk for ARF are individuals who have a personal, family or household history of rheumatic fever or who have two or more of the following criteria: Māori, Pacific ethnicity, age 3-35 years (particularly children and adolescents aged 4-19 years old), or living in crowded circumstances or in lower socioeconomic areas of the North Island.

† **IM benzathine penicillin:** For children <30kg: 450mg (600,000U); and for adults and children ≥30kg: 900mg (1,200,000U) as a single dose. Benzathine penicillin can be given with lignocaine to reduce injection site pain (see Appendix 4, page 62 in Guideline Update 2019).

Amoxicillin: If weight <30kg: 750mg once daily; and if weight ≥30kg: 1000mg once daily; for 10 days.

If concerned about allergic response to penicillin, use erythromycin ethyl succinate under directly observed therapy. Adults and children: 40mg/kg/day in 2-3 divided doses for 10 days.

‡ A throat swab in a patient at the end of antibiotic regimen is not required for routine (first or second) sore throat but for recurrent GAS pharyngitis an end of treatment throat swab is done as an **exception to usual practice**. (See Question 14, page 47 in Guideline Update 2019)

If end of treatment throat swab is **GAS negative**, this indicates successful treatment of GAS infection and allows the patient to be managed using IM penicillin or oral amoxicillin (page 4) should they present again with further symptoms or signs of pharyngitis.

§ If the end of treatment throat swab is **GAS positive**, seek paediatrician or adult infectious diseases specialist or clinical microbiologist advice on appropriate management and refer to Table 1 on page 6. An alternative antibiotic may be suggested if compliance and the household measures have been addressed. In this situation if the person is **asymptomatic** then by definition this may be treating "carriage". This is considered appropriate in this high risk population (see Appendix 12, page 74 in Guideline Update 2019).

Recommendations for Antibiotics Regimens Following the Treatment of a Patient's Third or More Consecutive Symptomatic GAS Pharyngitis in a Three Month Period

These antibiotic regimens are for the treatment of the patient who is GAS positive following treatment for recurrent GAS pharyngitis (i.e. they are GAS positive following treatment with IM benzathine penicillin or directly observed therapy of oral amoxicillin once daily for 10 days). **These antibiotic regimens are to be used on advice from a paediatrician, adult infectious diseases specialist or clinical microbiologist.**

Table 1. Recommendations for Antibiotics Regimens Following the Treatment of a Patient's Third or More Consecutive Symptomatic Episode of GAS Pharyngitis in a Three Month Period

Antibiotic	Route	Dose	Durat-ion	References	IDSA Evidence Rating 2012*
Benzathine penicillin†,‡ and rifampicin§	PO and IM	**Benzathine penicillin:** **Children <30kg:** 450mg (600,000 U) **Adults & children ≥30kg:** 900mg (1,200,000 U) **Plus** **Rifampicin** starting day of benzathine penicillin injection for 4 days: 20mg/kg/day orally in two divided doses *Max dose 600mg daily*	One dose 4 days	Tanz 1985[16]	Strong, high
Penicillin V† and rifampicin§	PO	**Penicillin:** 50mg/kg/day in 4 divided doses for 10 days *Max dose 2000mg daily* **Plus** **Rifampicin** for last 4 days (days 7-10): 20mg/kg/day in one single dose daily *Max dose 600mg daily*	10 days	Chaudhary 1985,[17] Shulman 2012[18]	Strong, high
Amoxicillin†, ‖ with rifampicin§	PO	**Amoxicillin** for 10 days: **Once daily:** 50mg/kg once daily **Or** Weight < 30kg: 750mg once daily Weight ≥ 30kg: 1000-1500mg once daily **Twice daily:** 25mg/kg twice daily *Max dose 1000-1500mg daily* **Plus** **Rifampicin** for last 4 days (days 7-10): 20mg/kg/day in one single dose daily *Max dose 600mg daily*	10 days	¶	
Clindamycin **	PO	150mg three times a day *Max dose 450mg a day*	10 days	Tanz 1991,[19] Shulman 2012[18]	Strong, high
Amoxicillin,†, ‖ , †† clavulanic acid	PO	40mg/kg/day of amoxicillin divided into 3 doses daily *Max 2000mg of amoxicillin daily*	10 days	Kaplan 1988[20]	Strong, moderate
Ask about adherence to antibiotic regimen, recommend family/household screening and consider end of treatment swab.					

Source: Modified from Table Two in Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012; 55: 1279-1282[18] © by permission of Oxford University Press.

* The IDSA used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (see Appendix 3, page 61 in Guideline Update 2019 for description).

† **Do not** give beta lactam antibiotics if patient has suspected immediate or type 1 hypersensitivity (anaphylaxis) to penicillin or amoxicillin. Up to 5% of patients who are allergic to penicillin or amoxicillin will also be allergic to 1st generation cephalosporins.[20] Clindamycin may be offered as alternative, as tabled.[21]

‡ Benzathine penicillin can be given with lignocaine to reduce injection site pain. (see Clinical Question 5, page 30 and Appendix 4, page 62 in Guideline Update 2019).

§ Rifampicin relatively contraindicated in pregnancy. Rifampicin interacts with many drugs and should be checked before being prescribed, in particular care with prescribing in combination with oral contraceptives, anti-convulsants and warfarin.

‖ Amoxicillin can be given with food.

¶ Once daily amoxicillin has been shown to be non-inferior to oral penicillin but has not been trialled specifically with rifampicin.

** No elixir available in New Zealand.

†† Maximum dose in amoxicillin with clavulanic acid is 2000mg of amoxicillin per day.[18]

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