

Essential Drugs

WHO Model Prescribing Information

Streptococcal pharyngitis and prevention of rheumatic fever

Rheumatic fever and rheumatic heart disease are the delayed consequence of an untreated group A beta-haemolytic streptococcal infection of the upper respiratory tract. The disease can cause serious, debilitating damage to the heart and involve other tissues. Those people who have already suffered a rheumatic fever attack are extremely susceptible to a recurrence if they are again infected with group A streptococci.

Group A streptococcal infections are universally endemic. There is no available vaccine for group A infections, and preventive measures remain dependent upon accurate clinical diagnosis and appropriate antibiotic treatment. Although epidemics in nurseries and infection in younger children are reported, the majority of streptococcal infections occur in school-age children between 5 and 15 years of age. Adult infections are most frequently observed in establishments, military bases or residential facilities.

Group A streptococcal upper respiratory tract infection is spread by droplets, thus accounting for its high transmission rate where crowding is frequent. Most outbreaks are associated with this kind of transmission, but food-borne transmission has also been reported. In contrast to other infectious agents, there are approximately 100 recognized serotypes of group A streptococci. Therefore, although infection with a given serotype is thought to confer long lasting type-specific immunity, the abundance of serotypes makes the threat of new infections a continuous worldwide public health problem.

Diagnosis, treatment and management

Young children, school-age children, and adults may present with significantly different clinical manifestations. An accurate clinical diagnosis of group A streptococcal upper respiratory tract infec-

tion can be very difficult and laboratory confirmation of the infection should be sought whenever possible. The classical signs and symptoms — high fever, severe pain on swallowing often accompanied by abdominal pain, nausea and vomiting — may not always be present, especially in endemic situations. Likewise, in young children under three years of age the presentation of streptococcal upper respiratory tract infection varies.

As difficult as it may be to clinically establish a diagnosis of acute streptococcal tonsillitis or pharyngitis, the signs and symptoms of this bacterial infection typically are quite different from those associated with viral upper respiratory tract infections. Culture using throat swabs continues to be the most useful method for determining the presence of group A streptococci in the upper respiratory tract although prior administration of antibiotics may result in a false-negative test-result.

Rapid antigen detection tests are available which allow the detection from the throat swab. Although antibody tests such as antistreptolysin O (ASO) and anti-deoxyribonuclease-B (anti-DNase B) are very useful in confirming diagnosis of rheumatic fever or acute glomerulonephritis, they are not indicated for the diagnosis of patients with acute group A streptococcal pharyngitis.

1. Primary prevention of rheumatic fever

In general, once the condition has been diagnosed, antibiotic therapy is indicated.

Penicillins

Penicillin remains the treatment of choice for group A streptococcal upper respiratory tract infections, since it is the only antibiotic that has been evaluated in controlled studies. A single injection of intramuscular benzathine benzylpenicillin is the most effective treatment in eradicating group A streptococci, probably due to its long duration of action. It can also be used for mass prophylaxis.

Oral phenoxymethylpenicillin administration for streptococcal pharyngitis must be continued for 10 days. Other orally administered penicillins include ampicillin, amoxicillin and the semisynthetic penicillins.

Macrolides

For penicillin-allergic patients, treatment with oral erythromycin for 10 days is often used. Newer macrolides are reported to be associated with fewer adverse effects but are generally more expensive. Short-course therapy with these newer macrolides is effective, but more definitive data are required before use in primary prevention is recommended.

Cefalosporins

First and second generation cefalosporins have been used to treat group A streptococcal infections. As a rule, cefalosporins are more expensive than penicillin. Short-course therapy (less than 10 days) with some cefalosporins is also under evaluation.

Resistance

No clinical isolate of group A streptococci has shown resistance to penicillin but resistance to macrolide antibiotics (e.g. erythromycin) is increasing in some countries. None the less, group A streptococcal resistance to the macrolides remains at less than five percent. Clinical use of macrolides should be made in relation to local resistance rates. Resistance to sulfonamides and tetracyclines is known to occur.

Recommended antibiotics

Table 1 shows commonly recommended antibiotics for the treatment of acute streptococcal pharyngitis for primary prevention of rheumatic fever. Sulfonamides or tetracyclines are not acceptable therapy for group A streptococcal pharyngitis.

If individuals remain symptomatic following a complete course of antibiotic therapy in which compliance was assured, a second course may be indicated. In these relatively rare instances, laboratory confirmation of the organism is advisable.

2. Secondary prophylaxis of rheumatic fever

For all individuals who have had an initial attack of rheumatic fever, whether or not they have rheumatic heart disease, continuous administration of an antibiotic is mandatory to prevent acquisition and infection of the upper respiratory tract by group A streptococci. Secondary prophylaxis reduces the risk of recurrent attacks with their attendant morbidity and mortality.

Antibiotic regimens for secondary prophylaxis differ. The regular intramuscular injection of benzathine benzylpenicillin is the most effective available treatment. Although usually given every four weeks, recent data indicate that 1 200 000 units of benzylbenzathine penicillin given every three weeks may be more effective in preventing recurrences of rheumatic fever, especially in high-risk patients. Commonly recommended antibiotics are set out in Table 2.

Several technical factors related to the benzathine benzylpenicillin injection can affect its bioavailability. It is recommended that health workers are trained in the technique of giving injections. The injection should be made deep into the muscle as

Table 1: Treatment of Group A streptococcal pharyngitis (primary prevention of rheumatic fever)

Antibiotic	Route	Dose	Duration
For non-penicillin allergic patients:			
Benzathine benzylpenicillin	IM	<30 kg: 600 000 IU >30 kg: 1 200 000 IU	single injection
Phenoxyethylpenicillin	oral	<30 kg: 250 mg 2 or 3 times daily >30 kg: 500 mg 2 or 3 times daily	10 days
For penicillin allergic patients:			
Erythromycin ethylsuccinate	oral	40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days
Erythromycin estolate	oral	20–40 mg/kg/day (max. 1.5 g/day) 3 times daily	10 days

**Table 2: Prevention of recurrence of rheumatic fever
(secondary prophylaxis)**

Antibiotic	Route	Dose
For non-penicillin allergic patients:		
Benzathine benzylpenicillin	IM	<30 kg: 600 000 IU every 3–4 weeks >30 kg: 1 200 000 IU every 3–4 weeks
Phenoxymethylpenicillin	oral	250 mg twice daily
For penicillin allergic patients:		
Sulfonamide (sulfadiazine, * sulfadoxine, or equivalent)	oral	<30 kg: 500 mg daily >30 kg: 1 g daily
Erythromycin	oral	250 mg twice daily
* Contraindicated in late pregnancy		

recommended. Superficial injections lead to the benzathine benzylpenicillin remaining in the subcutaneous tissue, resulting in decreased absorption and lower serum levels. Care should be taken that the entire content of the vial is injected.

For patients who are not able to receive injections of benzathine benzylpenicillin, a less effective method is oral phenoxymethylpenicillin daily. The potential problems with oral prophylaxis are adherence and rheumatic fever recurrence rates, which have been shown to be higher with this regimen than with intramuscular benzathine benzylpenicillin.

For patients known to be allergic to penicillin, an oral sulfonamide is recommended for secondary prophylaxis. However, it is not effective for treating established group A streptococcal infection. For individuals who cannot take either penicillin or sulfadiazine, erythromycin in a dose of 250 mg twice daily may be used, although resistance to erythromycin has been reported.

Duration of secondary prophylaxis

There are several variables that affect the likelihood of recurrences of rheumatic fever, including the time since the most recent attack, the age of the patient and the risk posed by the environment. The duration of secondary prophylaxis should be adapted to the individual patient but some general principles can be stated. Patients without carditis in a previous attack should continue prophylaxis for a

minimum of five years after the last attack, and at least until age 18 and often longer if risk factors are high. Patients with cardiac involvement in the initial attack should continue prophylaxis at least until the age of 25 years, and longer if environmental conditions or other risk factors are present.

The general principles for secondary prophylaxis are :

Patient	Duration
No carditis/rheumatic heart disease	To 18 years of age and at least 5 years after last attack
Documented carditis	At least to 25 years of age and often longer
Chronic carditis	For life
+ Artificial valves	For life

For patients with chronic valvular rheumatic heart disease, secondary prophylaxis for prolonged periods, even for life, has sometimes been recommended. Antibiotic prophylaxis for secondary rheumatic fever should be continued through pregnancy. However, sulfonamides present a risk to the fetus and an alternative antibiotic (penicillin or erythromycin) should be substituted.

BENZATHINE BENZYL PENICILLIN

Powder for injection 1.44 g (2.4 million IU) in 5-ml vial

Benzylpenicillin is a natural substance derived from *Penicillium notatum*. It is a bactericidal agent against *streptococci*, *neisseriae*, many anaerobes and spirochaetes.

After intramuscular injection, peak plasma concentrations are usually reached within 12–24 hours and are usually detectable for 1–4 weeks. It is widely distributed throughout the body and excreted mainly in the urine.

Uses: Streptococcal pharyngitis. Primary and secondary prophylaxis of rheumatic fever.

Dosage and administration:**Primary prophylaxis**

Children <30 kg: 600,000 IU, in a single injection.
Children >30 kg and adults: 1,200,000 IU, in a single injection.

Secondary prophylaxis

Children <30 kg: 600,000 IU, every 3–4 weeks.
Children >30 kg and adults: 1 200 000 IU, every 3–4 weeks.

The contents of the vial should be diluted in sterile water to obtain a homogeneous suspension in order to avoid obstruction of the needle. A needle gauge of #19 or #20 is preferred. The injection should be deep into the gluteus maximus muscle. Superficial injections leave the benzathine benzylpenicillin in the subcutaneous tissue leading to decreased absorption and lower serum levels. Care should be taken that the entire content of the vial is injected.

Contraindications: Known hypersensitivity to penicillin or cephalosporins.

Precautions: Facilities should be available for treating anaphylaxis whenever penicillin is used. A full patient history should be obtained with regard to previous allergic reactions. If skin rashes develop, another antimicrobial should be given.

The overall incidence of hypersensitivity reactions reported with penicillin is from 2 to 5 %. Anaphylaxis occurs in approximately 1 in 10 000 injections. Death has been reported in approximately 1 in 30–50 000 injections. Many anaphylactic reactions occur in severely ill rheumatic heart disease pa-

tients at risk of life-threatening arrhythmias where an arrhythmia associated with shock mimics anaphylaxis.

Use in pregnancy: There is no evidence of teratogenicity with benzathine benzylpenicillin.

Adverse reactions: The most common adverse effects are hypersensitivity reactions ranging in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection.

Accidental injection into a peripheral nerve will cause pain and dysfunction.

Nephropathy manifested as interstitial nephritis has been reported.

Neutropenia and thrombocytopenia have occurred rarely.

Storage: Powder for injection should be stored at temperatures between 2 °C and 8 °C and protected from moisture.

PHENOXYMETHYL PENICILLIN

*Tablet, 250 mg, 500 mg (as potassium)
Powder for oral suspension, 250 mg, 125 mg (as potassium salt)/5 ml*

Phenoxyethylpenicillin is a semisynthetic derivative of penicillin for oral use. It is active against a wide variety of Gram-positive and Gram-negative cocci. Most strains of streptococci remain susceptible.

It is well absorbed from the gastrointestinal tract and distributed widely in tissues. It crosses the placenta, is excreted in the urine and in breast milk.

Uses: Treatment of streptococcal pharyngitis. Secondary prophylaxis of rheumatic fever.

Dosage and administration:

Children <30 kg: 250 mg, 2 or 3 times daily
Adults and children >30 kg: 500 mg, 2 or 3 times daily.

Contraindications: Known hypersensitivity to penicillin or cephalosporins.

Precautions: Facilities should be available for treating anaphylaxis whenever penicillin is used for the first time.

A full patient history should be obtained with regard to previous allergic reactions.

If skin rashes develop, the patient should be given another antimicrobial.

Use in pregnancy: Phenoxyethylpenicillin can be used in pregnancy.

Adverse reactions: The most common adverse effects are hypersensitivity reactions that range in severity from skin rashes to immediate anaphylaxis. Mild diarrhoea may also occur.

Storage: Should be stored in tightly closed containers.

ERYTHROMYCIN

Enteric coated tablets, 250 mg (as stearate or ethylsuccinate)

Oral suspension, 125 mg (as stearate or ethylsuccinate)/5 ml

Erythromycin is a macrolide antimicrobial produced by *Streptomyces erythreus*. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli. Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half life is approximately 90 minutes. It is partially demethylated in the liver and excreted largely via the bile and faeces.

Uses: Streptococcal pharyngitis in penicillin-allergic patients.

Dosage:

Primary prophylaxis of rheumatic fever

Adults: 40 mg/kg/day (max. 1.5 g/day), 3 times daily.

Children: 20–40 mg/kg/day (max. 1.0 g/day) 3 times daily.

Secondary prophylaxis of rheumatic fever
250 mg twice daily.

Contraindications: Known hypersensitivity to erythromycin.

Precautions: Hepatic function should be monitored in patients with a previous history of liver disease.

Adverse effects: Erythromycin is well tolerated by most patients at the dosages suggested. Large oral doses may produce nausea, vomiting and diarrhoea.

Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

Drug interactions: Erythromycin, chloramphenicol, and clindamycin have a similar bacteriostatic action and may be antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

Storage: Capsules and tablets should be stored in tightly closed containers.

SULFADIAZINE or SULFISOXAZOLE

Tablet, 500 mg

Injection, 250 mg (sodium salt)

Sulfadiazine and sulfisoxazole are intermediate-acting sulfonamides with broad spectrum activity against a wide range of Gram-positive and Gram-negative organisms. They are readily absorbed from the gastrointestinal tract and widely distributed in the body. The serum half-life is 10–12 hours. After partial acetylation in the liver they are excreted in the urine.

Uses:

Secondary prevention of rheumatic fever.

Dosage:

Adults: 1 g daily in 2 divided doses.

Children: 150 mg/kg/day in 2 divided doses.

Contraindications: Hypersensitivity to sulfonamides; severe renal or hepatic function impairment; porphyria; first trimester pregnancy.

Precautions: The red blood cell count should be monitored regularly throughout therapy to detect signs of bone-marrow depression. Any patient suspected of being sensitive to sulfonamides should never receive them again. Presumptive signs include skin rashes and evidence of haemolysis such as dark urine and purpura.

Sulfadiazine is less soluble in urine than many other sulfonamides. High urinary output must be maintained and patients should be advised to drink 1.0–1.5 litres of alkaline water daily.

Use in pregnancy: Sulfadiazine is contraindicated during the first trimester. Administration of sulfonamides can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein-binding sites has given rise to concern. Based on data derived from premature neonates, sulfonamides may promote kernicterus. Although they readily cross the placental barrier there is no conclusive evidence that the fetus is at risk.

Adverse effects: Nausea, vomiting, diarrhoea and headache sometimes occur.

Sulfonamide-induced hypersensitivity reactions, although uncommon, may be severe. They include rare life-threatening cutaneous reactions such as erythema multiform (Stevens–Johnson syndrome)

and toxic epidermal necrolysis. Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug Interactions: Concomitant administration of other drugs that interfere with folic acid metabolism (other than pyrimethamine) should be avoided whenever possible.

Overdosage: Continuous forced diuresis may be beneficial and an alkaline urine should be maintained. Treatment is otherwise symptomatic.

Storage: Preparations should be stored protected from light.