CLINICAL UPDATE

Treatment of sore throat in light of the Cochrane verdict: is the jury still out?

Margaret H Danchin, Nigel Curtis, Terence M Nolan and Jonathan R Carapetis

SORE THROAT is the second most common illness for which Australians seek medical attention. Recent data from the BEACH (Bettering the Evaluation and Care of Health) project show that 4% of all symptomatic presentations to general practitioners were for throat complaints, second only to cough at 7%.[1] Sore throat is also one of the most common reasons for prescribing antibiotics, with prescriptions resulting from 88.7% of consultations for sore throat in Australia in 2001.[2] Yet, there is a growing argument that antibiotic treatment of sore throat caused by group A streptococci (GAS) — the predominant cause for which antibiotics may be indicated — has limited value in relieving symptoms and preventing complications in settings where acute rheumatic fever is rare.[3] Published guidelines from the United Kingdom, Scotland and Australia reflect this approach.[4-6] However, guidelines from the United States and Canada continue to stress the importance of diagnosis and treatment of streptococcal pharyngitis.[7,8]

This article details the main arguments for and against the investigation and antibiotic treatment of GAS pharyngitis and gives recommendations for Australian clinicians. It also highlights deficiencies in the available literature and the need for accurate epidemiological and cost-effectiveness studies.

ABSTRACT

- There are few good-quality studies of the effectiveness of antibiotic treatment of proven group A streptococcal (GAS) pharyngitis in children; available data suggest that antibiotics may reduce symptom duration.
- While there is limited justification for antibiotic treatment of GAS pharyngitis to prevent acute rheumatic fever in non-Indigenous Australians, there is no justification for routine antibiotic treatment of all patients with sore throat.
- Two strategies are open to clinicians: not to treat GAS pharyngitis with antibiotics, in which case no investigations should be done; or to treat cases of sore throat with clinical features that suggest GAS, in which case diagnosis should be confirmed with a throat swab, and penicillin started while awaiting the result. Penicillin should be discontinued if the swab is negative, or continued for 10 days if it is positive for GAS.
- Surveillance of GAS infections and acute rheumatic fever is needed in Australia, as are further studies of effectiveness (including cost-effectiveness) of antibiotic treatment of proven GAS pharyngitis.

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Diagnosis

Bacterial causes for sore throat other than GAS are rare, while antibiotics are not indicated for viral causes. Therefore, the aim of diagnosis is to identify the approximately one-third of cases in children and the 5%–10% of cases in adults that are caused by GAS.[9,10] This is often difficult in primary care. Available options include clinical diagnosis, throat swab and culture, serological tests, and rapid antigen testing.

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The clinical features of GAS pharyngitis may be quite distinctive, but are rarely sufficient to allow a confident diagnosis without confirmatory laboratory tests. For example, pharyngeal exudate may be present in more than a third of patients with non-GAS pharyngitis.[11] Patient age may help: GAS pharyngitis occurs predominantly in school-aged children.[12] However, it can occur in younger children and adults. Moreover, the characteristic symptoms and signs are less specific in children aged under three years.[13] Even in older children and adults, clinical scoring systems predict positive results of throat cultures or rapid antigen detection tests 80% or less of the time (Box 1).[14-20]

A correctly cultured throat swab has a sensitivity of 90%–95%.[21] However, the limitations of routine throat swabbing include the 24–48-hour delay while awaiting the result, the cost of the test compared with empirical treatment (or of initiating and then ceasing treatment if the swab is negative), the discomfort of the test, false negative results from poorly performed or processed swabs, and the difficulty in differentiating between infection and carriage of GAS. A recent Australian study found that only 13% of 284 Australian general practitioners would have taken a throat swab from a child with classical clinical signs of bacterial pharyngitis (fever, tender cervical lymph nodes and pharyngeal exudate).[22] Streptococcal serological testing can distinguish

1: Clinical algorithms for diagnosing group A streptococcal (GAS) pharyngitis in patients with sore throat

Study author (year)	Features included in final algorithm	Age group (years)	Sample size	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Walsh† (1975)[14]	Recent exposure to GAS infection Pharyngeal exudate Tender or enlarged cervical lymph nodes	< 15 to > 40	418	55	74	28
Breese‡ (1977)[15]	Season (late winter or early spring) Age (5–10 years) Elevated white blood cell count Temperature > 38°C Sore throat Absence of cough Headache Pharyngeal erythema or oedema or exudate Tender or enlarged cervical lymph nodes	Children	670	68	85	84
Centor† (1981)[16]	History of fever Tonsillar exudate Tender and enlarged anterior cervical lymph nodes Absence of cough	> 15	234	NS	NS	56
Steinhoff† (1997)[17]	Pharyngeal/tonsillar exudate or enlarged anterior cervical lymph nodes	2–13	451	84	40	30
McIsaac† (1998)[18]	Tender and enlarged anterior cervical lymph nodes Tonsillar swelling or exudate Temperature > 38°C Absence of cough	3–14 15–76	90 413	63 24	67 98	51 57
Wald† (1998)[19]	Age (5–15 years) Season (winter–spring) Temperature ⩾ 38.3°C Tender or enlarged cervical lymph nodes Pharyngeal or tonsillar erythema or swelling or exudate No cough or conjunctivitis or rhinorrhoea	2–16	365	22	93	75
Attia† (2001)[20]	Tonsillar swelling Tender and enlarged cervical lymph nodes Scarlatiniform rash Absence of coryza	1–18	545	18	97	79

NS = not stated (and not able to be calculated from the data provided).
†Calculations are based on the presence of all listed features.
‡Calculations are for a score of 32 out of a possible score of 38, based on a complex weighted score using the nine features listed.

carriage from infection, but is of little value in diagnosing acute pharyngitis, as the peak antistreptolysin O titre occurs three to six weeks after symptom onset.[23]

Rapid antigen tests may be used for same-day diagnosis in primary care. These tests are highly specific (over 95%), and the newer optical immunoassay may be as sensitive as a throat swab.[24] A recent US study found the cost of a throat swab to be $2.40, compared with $6.50 for an optical immunoassay (in 1995 US dollars). It also found that throat swab with culture was the most cost-effective diagnostic strategy.[25] Although rapid antigen tests are widely used in the United States, they have not been embraced in Australia, perhaps because they are expensive and attract no Medicare rebate.

Antibiotic treatment

The potential benefits of antibiotic treatment are:

- decrease in symptom severity and duration;
- prevention of suppurative complications, such as otitis media and retropharyngeal abscess;
- decrease in infectivity and hence reduced numbers of secondary cases; and
- prevention of acute rheumatic fever.[26]

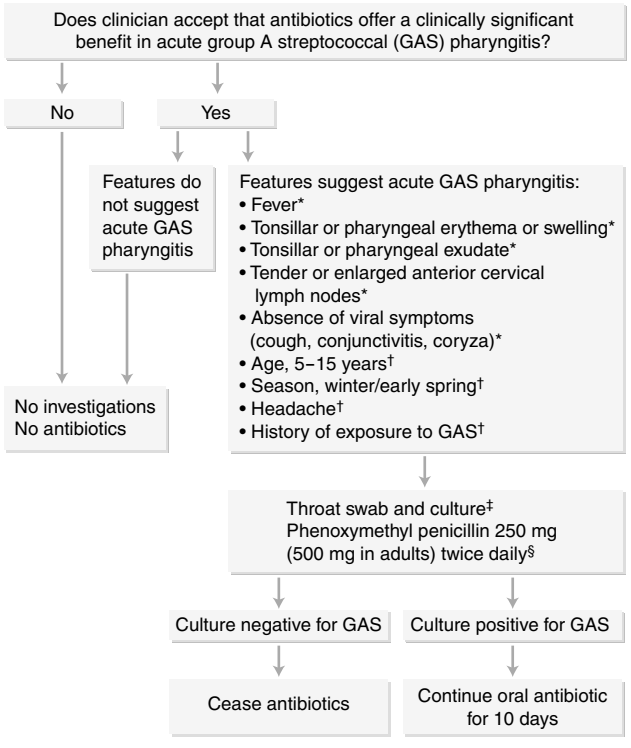
There is no definitive evidence that antibiotic treatment of GAS pharyngitis prevents acute post-streptococcal glomerulonephritis.[27] An important consideration is the need to minimise potential adverse effects from inappropriate antibiotic therapy.

If antibiotics are used, a 10-day course of oral penicillin (or a single dose of intramuscular benzathine penicillin G) is still the treatment of choice for GAS pharyngitis, because of its proven efficacy in eradicating the organism and preventing subsequent rheumatic fever, its safety, narrow spectrum and low cost.[28] Twice-daily dosing (250 mg of phenoxymethyl penicillin in children, 500 mg in adults) is as effective as three- or four-times-daily dosing and is now the preferred regimen.[29] Regimens using broader-spectrum antibiotics have comparable bacteriological and clinical cure rates with shorter courses, but are not recommended, as they promote resistance, are more expensive and have more side effects, particularly gastrointestinal.[30] The documented treatment failure rate with penicillin is 10%–15%.[31] This failure is not caused by antibiotic resistance (no clinical isolates resistant to penicillin have been reported). Possible explanations include antibiotic tolerance (a decrease in bactericidal effect of penicillin with maintenance of inhibition of further growth has been observed *in vitro*), modification of the response to penicillin by other organisms in the upper respiratory tract, or sequestration of GAS organisms within epithelial cells, out of reach of β-lactam antibiotics.[32] Penicillin-allergic patients should be treated

2: Recommendations for antibiotic treatment of sore throat in Australia

- Antibiotic treatment is not indicated for sore throat without a high suspicion of GAS pharyngitis, except in populations with a high incidence of acute rheumatic fever.
- In non-Indigenous Australians, the decision to treat GAS pharyngitis with antibiotics should not at present be based on prevention of acute rheumatic fever.
- On the available evidence, it is reasonable for clinicians to choose not to treat GAS pharyngitis (see algorithm, Box 3); in that case there is no point undertaking diagnostic tests.
- However, as antibiotic treatment of GAS pharyngitis may substantially reduce symptom duration, and as the effect on indirect costs and prevention of secondary cases has yet to be quantified, clinicians may also reasonably choose to treat cases of sore throat with features suggesting GAS pharyngitis (Box 1), particularly if signs of viral upper respiratory infection are absent (cough, conjunctivitis and rhinorrhoea).
- In such cases, we recommend confirming the diagnosis using a throat swab and culture, as clinical diagnosis of GAS pharyngitis is inaccurate (see algorithm, Box 3).
- Which of these two options is optimal cannot be decided until further population-based studies are undertaken.

3: Diagnosis and management of acute sore throat in settings with low incidence of post-streptococcal sequelae



* These features have been identified as indicating GAS pharyngitis in all or most studies and clinical algorithms. † These features have been identified as indicating GAS pharyngitis in some but not all studies and clinical algorithms. ‡ Optical immunoassay rapid streptococcal antigen test can be substituted for culture if available. § A single intramuscular injection of benzathine penicillin G may be used instead. Erythromycin is currently recommended if the patient is allergic to penicillin. Symptomatic treatment should be considered regardless of clinical pathway.

with macrolides.[28] As about 8% of GAS isolates in Australia are resistant to erythromycin,[6] and macrolide resistance continues to increase around the world, these recommendations may change.

However, should GAS pharyngitis be treated with antibiotics at all in non-Indigenous Australians?

A recent Cochrane meta-analysis assessed the benefits of antibiotics in management of sore throat, and included 25 studies with a total of 11 452 cases.[33] Antibiotics were found to reduce the risk of acute rheumatic fever by 70%, with a minimum reduction of 55% (odds ratio [OR], 0.30; 95% CI, 0.20–0.45). They also led to a 78% reduction in subsequent cases of acute otitis media (OR, 0.22; 95% CI, 0.11–0.43), and an 84% reduction in cases of quinsy (OR, 0.16; 95% CI, 0.07–0.35). The observed 54% reduction in cases of sinusitis had a wide 95% CI that included 1 (OR, 0.46; 95% CI, 0.10–2.05). Antibiotics also shortened the duration of pharyngitis symptoms, including headache, throat soreness and fever, by a mean of one day when assessed three days into the illness. The reviewers concluded that the effect of antibiotics on suppurative complications and symptom reduction was too small to justify antibiotic treatment of sore throat. However, they emphasised that the option of not treating GAS pharyngitis with antibiotics should be considered only in areas with low rates of acute rheumatic fever.

Opponents of antibiotic treatment of GAS pharyngitis frequently cite this Cochrane review, but its limitations should be made clear. The original analysis combined studies of confirmed GAS pharyngitis with those where the cause of sore throat was not determined, and also one that excluded patients with GAS isolated. A subgroup analysis in the most recent update of the review demonstrated a substantially greater reduction in pain among patients with GAS-positive swabs than among the GAS-negative group (pain at Day 3 reduced by 74% v 54%; OR, 0.26 [95% CI, 0.21–0.32] v 0.46 [95% CI, 0.33–0.64]). Very few of the studies were conducted in children, who made up only 61 of the 1334 patients in whom presence of fever was evaluated at Day 3. Therefore, the data analysis was weakest in the group for whom antibiotics may have the greatest effect: children with proven GAS pharyngitis. In addition, most of the studies were conducted in the 1950s and were of poor quality. They used diverse antibiotics at different doses and durations. Furthermore, the reviewers were able to estimate the effect of antibiotics on only the presence or absence of symptoms rather than their severity. Apart from symptom reduction and complications, other important outcome measures, including indirect costs (such as resource use and time off work and school), were not considered.

Conclusions

The limited Australian data suggest that Australians with sore throat rarely have throat swabs taken, but that most receive antibiotics. This is clearly at odds with the strategies of either treating based on a confirmed diagnosis of GAS

pharyngitis, or of not treating GAS pharyngitis with antibiotics at all.

There are no good-quality Australian data on the incidence and costs of GAS pharyngitis and current approaches to management, which makes it difficult to recommend management strategies that take into account clinical and public health needs and cost-effectiveness. Comprehensive studies in Australia are limited to the Indigenous population of the Northern Territory, where the incidence of acute rheumatic fever is the highest reported in the world, and it is clear that prevention and treatment of GAS skin and throat infections should remain a priority.[34] Studies of superficial GAS infections in urban Australian populations are uncommon and do not attempt to quantify the incidence or costs.[13,35] More data are needed on the effectiveness (including cost-effectiveness) of antibiotic treatment of proven GAS pharyngitis in children, and on the effectiveness of antibiotics in limiting spread of virulent organisms and secondary cases.

Recommendations for antibiotic treatment of sore throat in Australia are summarised in Box 2. In settings where antibiotics are not to be recommended, surveillance systems should be established to monitor the emergence of virulent GAS strains and cases of acute rheumatic fever. In the United States, during the 1980s, the incidence of acute rheumatic fever and invasive GAS disease increased after a steady decline in antibiotic prescriptions for GAS pharyngitis over the previous decade. It is now thought that the major contributing factor to these outbreaks was the emergence of new, virulent GAS strains,[36] but there is clearly a need for caution when adopting new treatment strategies. Monitoring systems will also allow sensible decisions about the use and effectiveness of GAS vaccines when they become available.

Competing interests

None identified.

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