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ESCMID Guideline for the Management of Acute Sore Throat

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Guideline for the management of acute sore throat

ESCMID Sore Throat Guideline Group

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Abstract

The European Society for Clinical Microbiology and Infectious Diseases established the Sore Throat Guideline Group to write an updated guideline to diagnose and treat patients with acute sore throat. In diagnosis, Centor clinical scoring system or rapid antigen test can be helpful in targeting antibiotic use. The Centor scoring system can help to identify those patients who have higher likelihood of group A streptococcal infection. In patients with high likelihood of streptococcal infections (e.g. 3–4 Centor criteria) physicians can consider the use of rapid antigen test (RAT). If RAT is performed, throat culture is not necessary after a negative RAT for the diagnosis of group A streptococci. To treat sore throat, either ibuprofen or paracetamol are recommended for relief of acute sore throat symptoms. Zinc gluconate is not recommended to be used in sore throat. There is inconsistent evidence of herbal treatments and acupuncture as treatments for sore throat. Antibiotics should not be used in patients with less severe presentation of sore throat, e.g. 0–2 Centor criteria to relieve symptoms. Modest benefits of antibiotics, which have been observed in patients with 3–4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on microbiota, increased antibacterial resistance, medicalisation and costs. The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat. If antibiotics are indicated, penicillin V, twice or three times daily for 10 days is recommended. At the present, there is no evidence enough that indicates shorter treatment length.

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Background

Acute sore throat is a symptom often caused by an inflammatory process in the pharynx, tonsils or nasopharynx. Most of these cases are of viral origin and occur as a part of the common cold. Adults average two to four and children six to eight upper respiratory tract infections per year usually during the colder months of the year. In addition to viral pathogens, bacterial pathogens may also cause pharyngeal infections. These pathogens include *Streptococcus pyogenes* (group A β-haemolytic streptococcus), but groups C or G β-haemolytic streptococci as well as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been suggested to be pathogens. Although rare today in Europe, streptococcal pharyngitis can be complicated by acute rheumatic fever or acute glomerulonephritis. Fear of these complications, or a wish to relieve pain or to satisfy patients often lead physicians to use antibiotic treatment for sore throat.

Acute sore throat is itself a symptom, and pain or discomfort in the pharynx is not always caused by an

infectious agent. Conversely, infectious agents are often found in the pharyngeal area in asymptomatic patients. There is an apparent lack of studies on sore throat with simultaneous identification of a wide spectrum of different infectious agents, both bacterial and viral, alone or mixed, in symptomatic or asymptomatic children or adults, and during different seasons.

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) established the ESCMID Sore Throat Guideline Group to write an updated guideline to diagnose and treat patients with acute sore throat. This guideline answers questions concerning the use of clinical diagnostic criteria and laboratory diagnostics to detect possible bacterial infection. In addition to diagnostic recommendations, the first-choice treatment regimen is also evaluated and recommendations are given.

The following text is a summary of the recommendations themselves and a discussion of the evidence on which the recommendations are based.

Guideline approach

To limit the scope of this guideline we restrict our recommendations to diagnosis and treatment of acute (duration of symptoms <14 days), uncomplicated sore throat in adults and children in Europe. The recommendations concern first-line diagnostics as well as symptomatic and antibiotic treatment.

The guideline does not cover recurrent or persistent cases of sore throat, complicated pharyngitis (peritonsillar abscesses, Lemierre disease, Vincent's angina), severe comorbidity, immunosuppression or history of acute rheumatic fever. Moreover, special circumstances, such as sore throat after travel outside Europe, sore throat linked to sexual transmission or rare epidemics (e.g. diphtheria), are not debated.

Methods for literature search

We retrieved the main keywords/MeSH terms from previous clinical guidelines and reviews on sore throat. We defined separate search strings according to different topics, and performed systematic literature searches in the Medline database, using PubMed, and the Cochrane Database.

As various guidelines and reviews on sore throat were published between 2000 and 2002, providing several materials that were considered in this investigation, we decided to limit our search to the period 2002–2009. More than 1000 articles were reviewed. Abstracts and unpublished studies were excluded. No studies were excluded a priori for weakness of design or data quality. Detailed search methods are described in the Appendix.

Grading criteria of evidence

The appraisal of the available evidence was performed following the same lines of reasoning used in the previously developed guidelines for the management of adult lower respiratory tract infections [1]. Studies were evaluated according to their design as well as their potential bias or validity, to define the strength of evidence they provided. A checklist for the critical appraisal of each selected publication was used to assess the validity of selected studies, and their level of clinical evidence was summarized using criteria described in Table 1.

A few changes were made to the checklist used by Woodhead *et al.* [1], by including specific questions aimed at the evaluation of potential bias and flaws of randomized clinical trials, which was particularly useful for the section on treatment. The evaluated studies were included in various evidence matrices developed to answer specific questions on diagnosis, prognosis and treatment of acute sore throat. Clinical evidence was translated into recommendations using a protocol described in Table 2.

TABLE 1. Checklist for levels of evidence in literature search

Evidence levels
- 1 Systematic reviews and meta-analyses
- 2 Randomized trials
- 3 Prospective cohort
- 4 Case–control, cross-sectional, retrospective cohort
- 5 Case reports
- 6 Expert opinions, consensus statements, other

First suffix
- A Low risk of biased results; all or most of the validity criteria are met (i.e. at least four out of six flaws are unlikely, for randomized trials)
- B Moderate risk of biased results; half of the validity criteria are met (i.e. at least three out of six flaws are unlikely, for randomized trials)
- C High risk of biased results; most of the validity criteria are not met (i.e. two or fewer out of six flaws are unlikely, for randomized trials)

Second suffix
- + Numerical results unequivocally support a positive answer to the research question (i.e. determinant-outcome relation of interest clearly established)
- – Numerical results unequivocally do not support a positive answer to the research question (i.e. determinant-outcome relation of interest not established)
- ? Numerical results are unclear

TABLE 2. Checklist for grading recommendations

A Consistent evidence: clear outcome
B Inconsistent evidence: unclear outcome
C Insufficient evidence: consensus

Suffixes

For preventive and therapeutic intervention studies (including harm of intervention)
- 1 Systematic reviews (SR) or meta-analyses (MA) of randomized controlled trials (RCT)
- 2 One RCT or more than one RCT but no SR or MA
- 3 One cohort study or more than one cohort study but no SR or MA
- 4 Other

For other studies
- 1 Systematic reviews (SR) or meta-analyses (MA) of cohort studies
- 2 One cohort study or more than one cohort study but no SR or MA
- 3 Other

Recommendation summary

Clinical assessment of acute sore throat

What is the role of clinical scoring in the diagnosis of group A streptococcal infections?

The Centor clinical scoring system can help to identify those patients who have a higher likelihood of group A streptococcal infection (A-3). However, its utility in children appears lower than in adults because of the different clinical presentation of sore throat in the first years of life.

Laboratory tests for sore throat

Is throat culture considered a necessary clinical instrument for diagnosis of group A streptococci?

Throat culture is not necessary for routine diagnosis of acute sore throat to detect group A streptococci (C-3).

What is the validity and accuracy of near patient diagnostic tests for group A streptococcus? Is it necessary to perform a throat culture after a negative rapid antigen test (RAT) for the diagnosis of group A streptococci?

If RAT is performed, throat culture is not necessary after a negative RAT for the diagnosis of group A streptococci in both children and adults (B-2).

Is the diagnostic value of RAT increased when tests are performed in subjects with high clinical scores for group A streptococci, i.e. indicators that increase likelihood of strep throat, as Centor score or modified Centor score?

In patients with high likelihood of streptococcal infections (e.g. 3–4 Centor criteria) physicians can consider the use of RATs. In patients with lower likelihood of streptococcal infections (e.g. 0–2 Centor criteria) there is no need to routinely use RATs (B-3).

Is there a role for additional tests (e.g. C-reactive protein, procalcitonin measurements) in the assessment of severity of acute sore throat? Does clinical information combined with biomarker information provide better prognostic information?

It is not necessary to routinely use biomarkers in the assessment of acute sore throat (C-3).

Does improved diagnosis or the use of near patient tests improve antibiotic use?

Clinical scoring systems and rapid tests can be helpful in targeting antibiotic use (B-2).

Treatment

Are analgesics effective in sore throat?

Either ibuprofen or paracetamol are recommended for relief of acute sore throat symptoms (A-1).

What are the indications for use of glucocorticoids in sore throat?

Use of corticosteroids in conjunction with antibiotic therapy is not routinely recommended for treatment of sore throat. It can however be considered in adult patients with more severe presentations, e.g. 3–4 Centor criteria (A-1).

What are the indications for use of zinc gluconate in sore throat?

Zinc gluconate is not recommended for use in sore throat (B-2).

What are the indications for complementary treatments, e.g. herbal treatments or acupuncture, in sore throat?

There is inconsistent evidence of herbal treatments and acupuncture as treatments for sore throat (C-1 to C-3).

What is the average benefit from antibiotics and which groups of patients do benefit from antibiotic treatment?

Sore throat should not be treated with antibiotics to prevent the development of rheumatic fever and acute glomerulonephritis *in low-risk patients* (*e.g. patients with no previous history of rheumatic fever*) (A-1). The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat (A-1). Clinicians do not need to treat most cases of acute sore throat to prevent quinsy, acute otitis media, cervical lymphadenitis, mastoiditis and acute sinusitis (A-3).

Do antibiotics relieve symptoms in sore throat?

Antibiotics should not be used in patients with less severe presentation of sore throat, e.g. 0–2 Centor criteria, to relieve symptoms (A-1). In patients with more severe presentations, e.g. 3–4 Centor criteria, physicians should consider discussion of the likely benefits with patients. Modest benefits of antibiotics, which have been observed in group A β-haemolytic streptococcus-positive patients and patients with 3–4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on the microbiota, increased antibacterial resistance, medicalization and costs (A-1).

Which antimicrobial agent is the first choice in patients with acute sore throat?

If antibiotics are indicated, penicillin V, twice or three times daily for 10 days, is recommended (A-1). There is not enough evidence that indicates shorter treatment length.

Bacterial pathogens in sore throat

Group A β-haemolytic streptococcus

The role of group A β-haemolytic streptococcus as a bacterial pathogen in sore throat is evident and is not questioned. Reviews and guidelines considering the diagnosis of sore throat have therefore been focused mainly or exclusively on group A streptococci and related symptomatic presentation.

Asymptomatic carriage of β-haemolytic streptococci is frequent, especially in children. According to Tanz and Shulman [2], over 20% of asymptomatic school children may be carriers of group A streptococcal infection during the winter and spring. Several European investigations examined the carriage rates in children and adults. The highest rate was found in subjects aged 14 years or less (10.9%), whereas rates were 2.3% in patients aged 15–44 years and 0.6% in those aged 45 years or older [3].

Similar results emerged in a Swedish study [4], reporting carriage rates of 11.3% in 4-year–old children, 5.9% in school children and 0.8% in adults. In a study from Croatia [5], carriage rate of group A streptococci was 8.3% overall, with highest rates being reported for subjects aged 6–14 years. Higher rates were found in a prospective study conducted in Turkey on 351 asymptomatic primary school children, as about 26% of them were group A streptococcal infection carriers [6].

Complications of group A β-haemolytic streptococcal pharyngitis are generally rare in both children and adults (Tables 3 and 4; [7–14]). Potential adverse outcomes include both suppurative (i.e. quinsy, acute otitis media, cervical lymphadenitis, mastoiditis, acute sinusitis) and non-suppurative (i.e. acute rheumatic fever, acute glomerulonephritis) complications. In particular, acute rheumatic fever has been widely investigated during the last decades, but its incidence is very low in Europe. Prevention of acute rheumatic fever depends on effective control of group A streptococcal pharyngitis [7] and is important for patients at high risk (e.g. those who have had rheumatic fever before). Acute glomerulonephritis is another rare consequence of sore throat, following group A streptococcal pharyngitis after a latency period of a few weeks. Quinsy, a complication that occurs mainly in young adults, is a polymicrobial infection but group A streptococcus is the main organism associated with the disease (Tables 5 and 6; [7–9,11,15–17]).

Tanz and Shulman [2] conclude that pharyngeal carriers of group A streptococci show an extremely low risk of post-streptococcal complications, and their likelihood of transmitting the infection is also small.

Group C and G β-haemolytic streptococci

A number of studies are available on the symptomatic presentation of β-haemolytic streptococci other than group A streptococci. Two observational studies (one cohort study, one case–control study) supported a milder clinical presentation of group C or group G streptococcal pharyngitis than group A streptococcal pharyngitis (Table 7; [17–25]). On the other hand, five observational studies (three cohort, two case–control) and one case series investigation reported a similar clinical picture.

At least 12 original studies, mostly case series and case reports, described severe symptoms or complications following acute sore throat associated with group C and group G streptococci (Table 8; [12,25–35]). Cases of severe or recurrent pharyngitis because of group C streptococci have been reported. A case–control study of college students found that patients with group C streptococci had exudative tonsillitis and anterior cervical adenopathy more frequently than subjects negative for this infection [29]. On the other hand, there is little evidence to address the issue of whether there is an association between group G streptococci and severe or recurrent pharyngitis.

Uncommon complications of pharyngitis caused by group C or G streptococci that have been reported include reactive arthritis, subdural empyema and acute glomerulonephritis, but a causal relationship was not clearly established. In 1997, Efstratiou reported consistent results of group C and G septicaemia over a 10-year period [36].

TABLE 3. Summary information on group A streptococci and prognosis of sore throat from papers

First author	Type of study	Objective	Evidence level
Gerber [7]	Scientific statement	Develop evidence-based recommendations for the prevention of primary and secondary (recurrent) rheumatic fever	6+
Talmon [8]	Case series	Describe 11 cases of acute myopericarditis complicating acute tonsillitis	5+
Galioto [9]	Review	To review diagnosis and treatment of peritonsillar abscess	6+
Abdel-Haq [10]	RCS	Identify the predisposing factors and the microbiology of RPA	4C?
Martin [11]	Review	Review of GAS, with focus on its complications	6+
Almroth [12]	Case series	Study an epidemic of acute glomerulonephritis associated with throat infections	5?
Gerber [13]	Review	Review on pharyngitis in children	6+
Hanna [14]	RCS	To describe the epidemiology of peritonsillar abscess disease in Northern Ireland	4B+

GAS, group A streptococci; RCS, retrospective cohort study; RPA, retropharyngeal abscess.

TABLE 4. Summary information on group A streptococci and prognosis of sore throat from guidelines

Guideline	Country	Conclusions	Age group	Evidence level
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)	France	There are potentially severe post-streptococcal complications, i.e. ARF, acute glomerulonephritis and local or systemic septic complications. However, the risk for ARF is extremely low in industrialized countries and post-streptococcal acute glomerulonephritis is rarely the consequence of GAS pharyngitis	Adults	6+
NHS Clinical Knowledge Summaries (CKS)	UK	Possible complications of streptococcal pharyngitis (rare) were listed as: otitis media; acute sinusitis; peritonsillar abscess; para/retropharyngeal abscess; streptococcal pneumonia; mastoiditis; streptococcal toxic shock syndrome; Lemierre disease; rheumatic fever; glomerulonephritis	All	6+
National Institute for Health and Clinical Excellence (NICE)	UK	Potential complications of sore throat are ARF, glomerulonephritis, peritonsillar abscess, acute otitis media, acute rhinosinusitis)	All	6+
Scottish Intercollegiate Guidelines Network (SIGN)	UK	Incidence of ARF is a potential complication following sore throat, but it is extremely low in the UK	All	6+
Infectious Diseases Society of America (IDSA)	USA	The risk of a first attack of ARF is extremely low in adults	All	6+
Centers for Disease Control and Prevention (CDC)	USA	In the vast majority of cases, acute pharyngitis in an otherwise healthy adult is self-limiting and rarely produces significant sequelae	Adults	6–

ARF, acute rheumatic fever; GAS, group A streptococci.

TABLE 5. Summary information on clinical risk groups in relation to prognosis of sore throat from selected papers

First author	Type of study	Objective	Evidence level
Gerber [7]	Scientific statement	Develop evidence-based recommendations for the prevention of primary and secondary (recurrent) rheumatic fever	6+
Talmon [8]	Case series	Describe 11 cases of acute myopericarditis complicating acute tonsillitis	5+
Galioto [9]	Review	To review diagnosis and treatment of peritonsillar abscess	6+
Steer [15]	Review	Review GAS infection in children	6+
Martin [11]	Review	Review of GAS, with focus on its complications	6+
Hahn [75]	Review	Review focused on complications of GAS infection	6+
Dunn [17]	Case–control	To identify which variables predict the development of quinsy	4A+

GAS, group A streptococci.

TABLE 6. Summary information on clinical risk groups in relation to prognosis of sore throat from guidelines

Guideline	Country	Conclusions	Age group	Evidence level
NHS Clinical Knowledge Summaries (CKS)	UK	Subjects at increased risk of complications were defined as those: with increased risk of severe infections; at risk of immunosuppression; with history of valvular heart disease; with history of rheumatic fever	All	6+
UK National Institute for Health and Clinical Excellence (NICE)	UK	Specific evidence for complications following sore throat was that male patients aged 21–40 years who are smokers are significantly more likely to develop peritonsillar abscess after initial presentation of uncomplicated sore throat in primary-care settings	All	6+

TABLE 7. Summary information on group C and group G streptococci and symptomatic presentation of sore throat

First author	Type of study	Objective	Evidence level
Fretzayas [18]	PCS	To identify the clinical features of GCS pharyngitis	3B+
Lindbaek [19]	PCS	To analyse clinical features of patients with large colony GCS or GGS compared with patients with GAS and negative cultures	3A–
Zwart [20]	Case–control	Measure the association between β haemolytic streptococci and sore throat	4A–
Dagnelie [21]	PCS	To assay the bacterial growth in patients with sore throat	3B–
Turner [22]	Case–control	Association between GCS and clinical features of pharyngitis	4A–
Gerber [23]	PCS	Describe an outbreak of GGS pharyngitis	3A–
Meier [24]	Case–control	To determine whether non-GAS is associated with endemic pharyngitis	4A+
Corson [25]	Case report and case series	Review of cases of pharyngitis in relation to β-haemolytic streptococci	5–

GAS, group A streptococci; GCS, group C streptococci; GGS, group G streptococci; PCS, prospective cohort study.

While sore throat caused by group A streptococci is known to be rarely associated with acute rheumatic fever in developed countries, this has not been reported as a complication following group C or group G streptococcal infection [37]. There are, however, studies and expert opinions indicating that group C and group G streptococci might

TABLE 8. Summary information on group C and group G stretptococci and prognosis of sore throat

First author	Type of study	Objective	Evidence level
Severe or recurrent pharyngitis			
Shah [26]	Case report	Description of a case of severe GCS pharyngitis	5+
Turner [27]	PCS	Association between GCS and exudative pharyngitis	3A+
Dudley [28]	Case series	Report of cases of tonsillitis due to non-GAS	5+
Turner [29]	Case–control	To determine whether non-GAS is associated with endemic pharyngitis	4A+
Morgan [30]	Case report	Report of a case of recurrent tonsillopharyngitis due to GCS	5+
Fulginiti [31]	Case report	Report of a case of recurrent GCS tonsillitis	5+
Reactive arthritis			
Jansen [32]	Case series	To investigate reactive arthritis secondary to throat infection	5+
Young [33]	Case report	A case of reactive arthritis after GGS pharyngitis	5+
Other adverse outcomes			
Almroth [12]	Case series	Study an epidemic of acute glomerulonephritis associated with throat infections	5?
Natoli [34]	Case report	Report of a case of streptococcal toxic shock-like syndrome caused by a GCS strain	5+
Gettler [35]	Case report	GCS subdural empyema after pharyngitis	5+
Corson [25]	Case report and case series	Review of cases of pharyngitis in relation to β-haemolytic streptococci	5+

GAS, group A streptococci; GCS, group C streptococci; GGS, group G streptococci; PCS, prospective cohort study

contribute to acute rheumatic fever pathogenesis in high-incidence settings [38,39].

Group C streptococci can cause severe or recurrent pharyngitis, but there is insufficient evidence for a role of group C streptococci in other adverse outcomes. There is insufficient evidence for a role of group G streptococci in severe/recurrent pharyngitis and other adverse outcomes.

Mycoplasma pneumoniae* and *Chlamydia pneumoniae

Mycoplasma pneumoniae and *C. pneumoniae* infection has been associated with non-streptococcal acute pharyngitis in selected studies [40]. It is not clear whether pharyngitis due to these infections may have an unwanted outcome, including longer duration or recurrence of symptoms and occurrence of other complications. The available evidence is scanty and limited to paediatrics (Table 9; [40–44]). Two observational studies (one prospective cohort, one case–control) reported increased risk of recurrence of symptoms after *M. pneumoniae* infection. One prospective cohort study reported an increased risk of recurrence of respiratory illness after *C. pneumoniae* infection. Case reports and case series found a possible association between *M. pneumoniae* infection and Bell's palsy or Stevens–Johnson syndrome.

Clinical assessment of acute sore throat

What is the role of clinical scoring in the diagnosis of group A streptococcal infections?

The Centor score for the diagnosis of group A streptococcal throat infections was proposed in 1981 [45]. It was based on the study of 286 adult patients with sore throat who presented to the Emergency Department at the University College of Virginia. Centor and colleagues identified four signs and symptoms to estimate the probability of acute group A streptococcal pharyngitis in adults with sore throat.

The four signs and symptoms were tonsillar exudate, swollen tender anterior cervical nodes, the lack of cough and fever. According to the Centor score [45], the risk of group A streptococcal infection depends on the number of signs and symptoms, as described in Box 1.

BOX 1.

Number of signs and symptoms	Risk of group A streptococcal infection (%)
4	56
3	32
2	15
1	6.5
0	2.5

This clinical decision rule was validated only in adults and not in children.

The Centor score was later modified by adding age, and was validated in about 600 adults and children (3–15 years old) in a Canadian study [46]. The modified Centor score was based on a total sore throat score that determines the likelihood of group A streptococcal pharyngitis. To determine the patient's total sore throat score it is necessary to assign points using the criteria detailed in Box 2.

BOX 2.

Criteria	Point
Temperature >38°C	1
No cough	1
Tender anterior cervical adenopathy	1
Tonsillar swelling or exudate	1
Age 3–14 years	1
Age 15–44 years	0
Age >44 years	−1

The risk of group A streptococcal infection depends on the total sore throat score (Box 3) [46].

TABLE 9. Summary information from papers on *Mycoplasma pneumoniae* and *Chlamydia trachomatis* infection and prognosis of sore throat

First author	Type of study	Objective	Evidence level
Esposito [40]	PCS	To evaluate the natural history of acute tonsillopharyngitis associated with atypical bacterial infections	3B+
Esposito [41]	Case–control	To establish the role of atypical bacteria in acute pharyngitis	4A+
Levy [42]	Case series + review of case reports	Analyse the relation between *M. pneumoniae* infection and SJS	5+
Klar [43]	Case report	Case report of an infant who developed bilateral facial paresis 4 weeks after a febrile illness associated with tonsillitis	5+
Volter [44]	Case series	Analyse the relation between Bell's palsy and *M. pneumoniae* infection	5+

PCS, prospective cohort study; SJS, Stevens–Johnson syndrome.

BOX 3.

Total score	Risk of group A streptococcal infection (%)
4	38–63
3	27–28
2	10–12
1	4–6
0	2–3

The modified Centor score was further adapted in 2004 [47]. Although the criteria remained the same, the estimated risk of group A streptococcal infection was updated as follows (Box 4):

BOX 4.

Total score	Risk of group A streptococcal infection (%)
≥4	51–53
3	28–35
2	11–17
1	5–10
≤0	1–2.5

Children with acute sore throat have a higher rate of asymptomatic carriage of group A streptococci than adults and commonly present with a temperature >38°C, tender anterior cervical adenopathy and tonsillar swelling (e.g. modified Centor score 3); it is difficult to differentiate children with streptococcal pharyngitis on the basis of these scores.

The Centor clinical scoring system can help to identify those patients who have higher likelihood of group A streptococcal infection (A-3). However, its utility in children appears lower than in adults because of the different clinical presentation of sore throat in the first years of life.

Laboratory tests for sore throat

Is throat culture considered a necessary clinical instrument for diagnosis of group A streptococci?

The major disadvantage of throat culture in clinical practice is the delay in obtaining the results (18–24 h or longer). Further, there is debate as to whether negative cultures should be re-examined after an additional day to increase the sensitivity of the test (Tables 10 and 11 [48,49]). Most of the reviews and guidelines considered do not support throat culture as a necessary clinical instrument for routine diagnosis of group A streptococci (Tables 12 and 13; [37,49–53]).

Throat culture is not necessary for routine diagnosis of acute sore throat to detect group A streptococci (C-3).

What is the validity and accuracy of near patient diagnostic tests for group A streptococcus? Is it necessary to perform a throat culture after a negative RAT for the diagnosis of group A streptococci?

A wide variety of RATs are available for diagnosing group A streptococcal pharyngitis, with different diagnostic properties [37,55].

The great majority of RATs have a high specificity (≥95%) compared with culturing a throat swab on a sheep blood agar plate culture [37]. The negative predictive values of the

TABLE 10. Summary information from papers analysing the optimal duration of incubation of throat cultures

First author	Type of study	Objective	Evidence level
Kocoglu [48]	PCS	Evaluation of accuracy of throat culture at 24, 48 and 72 h of incubation	3A+
Shulman [49]	Review	Diagnosis and treatment of acute streptococcal pharyngitis	6+

PCS, prospective cohort study.

TABLE 11. Summary information from guidelines analysing the optimal duration of incubation of throat cultures

Guideline	Country	Conclusions	Age group	Evidence level
Infectious Diseases Society of America (IDSA)	USA	It is advisable to examine plates that yield negative results at 24 h again at 48 h	All	6+

RATs are high, ranging between 93% [52] and 97% [53], and generally being around 95% [54]. The sensitivity of most RATs is around 90% (ranging between 86% and 94.8% [37]) compared with culturing a throat swab on sheep blood agar plate cultures. As reported in several diagnostic accuracy studies on a specific RAT, the RATs are less sensitive than declared by the manufacturer [52,55,56]. The positive predictive values of the RATs ranged between 77% [52] and 97% [57], generally being around 90% [58].

However, the performance of RATs for group A streptococci is influenced by the skill, experience and expertise of the individual obtaining the throat swab and performing the RAT. The performance is also a function of the clinical characteristics of the illness of the patients selected for testing. As a result of this bias, often called 'spectrum bias', the performance of RAT is not an absolute feature of a given test [37,59]. To improve the accuracy of RAT, the RAT should be performed by trained staff [60] and performed in the posterior pharyngeal wall and both tonsils (Tables 14 and 15; [49,61,62]).

TABLE 12. Summary information from papers evaluating the use of throat culture in diagnosis of group A streptococcal sore throat

First author	Type of study	Objective	Evidence level
Gieseker [50]	PCS	Accuracy study to evaluate two specific RATs by comparing with a rigorous throat culture	3A?
Gerber [37]	Review	Review of availability data with respect to the accuracy of RATs and their use	6–
Lindbaek [51]	PCS	Accuracy study to evaluate a specific RAT by comparing with two throat cultures	3A?
Matthys [74]	Review	Comparison of guidelines on pharyngitis	6–
Choby [70]	Review	Diagnosis and treatment of streptococcal pharyngitis. Comparison of guidelines	6–
Shulman [49]	Review	Diagnosis and treatment of acute streptococcal pharyngitis	6+

PCS, prospective cohort study; RAT, rapid antigen test.

TABLE 14. Summary information from papers evaluating the optimal sites where throat culture should be performed

First author	Type of study	Objective	Evidence level
Fox [61]	PCS	Comparison between testing throat swab in mouth and throat	3A+
van der Veen [62]	PCS	Comparison between testing throat swab on the tonsillar surface and posterior pharyngeal wall	3A+
Shulman [49]	Review	Diagnosis and treatment of acute streptococcal pharyngitis	6+

PCS, prospective cohort study.

As already asserted for the first generation of RAT [63], the new generation of RAT may have an additional value for the management of sore throat. In children, eight observational studies (five prospective cohort, three retrospective cohort) and two guidelines supported the need for confirmation by a throat culture after a negative RAT. One clinical trial, two observational studies (both were prospective cohorts) and one guideline did not consider confirmation by a throat culture necessary (Tables 16 and 17; [47,50,52,56,57,64–70]). In adults, except for one prospective study, the observational study and two guidelines did not support the need to perform a throat culture after a negative RAT.

If RAT is performed, throat culture is not necessary after a negative RAT for the diagnosis of group A streptococci in both children and adults (B-2).

Is the diagnostic value of RAT increased when tests are performed in subjects with high clinical scores for group A streptococci, i.e. indicators that increase the likelihood of strep throat, as Centor score or modified Centor score?

In children and adults, all the observational studies and the guidelines considered supported higher accuracy of RATs when these were performed in patients with a high probability of strep throat (Tables 18 and 19; [54,55,64,66,67,71]). In conclusion, accuracy of RAT increases in patients with clinical criteria for group A streptococci, in both children and adults.

TABLE 13. Summary information from guidelines evaluating the use of throat culture in diagnosis of group A streptococcal sore throat

Guideline	Country	Conclusions	Age group	Evidence level
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)	France	Use of throat culture is not recommended	Adults	6–
NHS Clinical Knowledge Summaries (CKS)	UK	Throat swabs have poor sensitivity and results take up to 48 h to be reported	All	6–
Scottish Intercollegiate Guidelines Network (SIGN)	UK	Throat swabs should not carried out routinely in sore throat	All	6–
Centers for Disease Control and Prevention (CDC)	USA	The use of throat culture for clinical decision making is not included in the recommendations	Adults	6–
Infectious Diseases Society of America (IDSA)	USA	Culture of a throat swab remains the standard and if done correctly, has a high sensitivity	All	6+
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA)	Sweden	Throat cultures provide support to a suspected clinical diagnosis of group A streptococci	All	6+

TABLE 15. Summary information from guidelines evaluating the optimal sites where throat culture should be performed

Guideline	Country	Conclusions	Age group	Evidence level
British Columbia Guideline	Canada	The sterile throat swab should be used by contacting the posterior pharyngeal wall and the surface of both tonsils	All	6+
Infectious Diseases Society of America (IDSA)	USA	Throat swab specimens should be obtained from the surface of both tonsils or tonsillar fossae as well as the posterior pharyngeal wall	All	6+
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA)	Sweden	The swab is rubbed over both tonsils	All	6+

TABLE 16. Summary information from papers analysing the use of rapid antigen tests in diagnosis of group A streptococcal sore throat

First author	Type of study	Objective	Evidence level
Gieseker [50]	PCS	Accuracy study to evaluate two specific RATs by comparing with a rigorous throat culture	3A?
Maltezou [64]	RCT	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	2B–
Camurdan [57]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3B–
Humair [54]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3A–
Forward [52]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3A+
Van Limbergen [65]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3B+
Edmonson [66]	RCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	4A+
Hall [67]	RCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	4A+
McIsaac [47]	PCS	Empirical validation of guidelines for the management of pharyngitis	2A+
Armengol [68]	RCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	4B+
Cohen [69]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3B–
Gieseker [50]	PCS	Accuracy study to evaluate two specific RATs by comparing with a rigorous throat culture	3A+
Nerbrand [56]	PCS	Evaluation of two RATs in the diagnosis of streptococcal pharyngitis	3A+
Choby [70]	Review	Diagnosis and treatment of streptococcal pharyngitis. Comparison of Guidelines	6?

PCS, prospective cohort study; RAT, rapid antigen test; RCS, retrospective cohort study; RCT, randomized-controlled trial.

TABLE 17. Summary information from guidelines analysing the use of rapid antigen tests in diagnosis of group A streptococcal sore throat

Guideline	Country	Conclusions	Age group	Evidence level
Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)	France	Negative RAT with low risk for acute rheumatic fever does not require control culture	All	6–
Infectious Diseases Society of America (IDSA)	USA	The negative result of a RAT in children should be confirmed using throat culture unless physicians can guarantee that RAT sensitivity is similar to that of throat culture in their practice	Children	6?
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA)	Sweden	If the RAT is negative and suspicions remain that the aetiology is streptococcal, a throat swab should be taken for culture	All	6+
Finnish Medical Society Duodecim	Finland	If a RAT is used, a negative result should be verified by culture	Children	6+

RAT, rapid antigen test.

TABLE 18. Summary information from papers analysing the combination of use of rapid antigen tests and clinical scores for diagnosis of group A streptococcal sore throat

First author	Type of study	Objective	Evidence level
Tanz [55]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3A+
Maltezou [64]	RCT	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	2B+
Humair [54]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3A+
Edmonson [66]	RCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	4A+
Hall [67]	RCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	4A+
Atlas [71]	PCS	Evaluation of a specific RAT in the diagnosis of streptococcal pharyngitis	3B+

PCS, prospective cohort study; RAT, rapid antigen tests; RCS, retrospective cohort study; RCT, randomized-controlled trial.

In patients with a high likelihood of streptococcal infections (e.g. 3–4 Centor criteria) physicians can consider the use of RATs. In patients with lower likelihood of streptococcal infections (e.g. 0–2 Centor criteria) there is no need to routinely use RATs (B-3).

Is there role for additional tests (e.g. C-reactive protein, procalcitonin measurements) in the assessment of severity of

TABLE 19. Summary information from guidelines analysing the combination of use of rapid antigen tests and clinical scores for diagnosis of group A streptococcal sore throat

Guideline	Country	Conclusions	Age group	Evidence level
Centers for Disease Control and Prevention (CDC)	USA	Testing only patients with at least two clinical criteria by using a RAT	Adults	6+
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA)	Sweden	Testing only patients with at least two clinical criteria by using a RAT	All	6+

RAT, rapid antigen test.

acute sore throat? Does clinical information combined with biomarker information provide better prognostic information?

There is no evidence that C-reactive protein levels are helpful in the diagnosis of acute group A streptococcal sore throat [72,73]. Anti-DNase B provides useful evidence of invasive disease but because serial tests are needed, they cannot be recommended for routine diagnosis in sore throat [74]. We could find only one review, focused on complications of group A streptococcal pharyngitis, concluding that laboratory testing (e.g. erythrocyte sedimentation rate and C-reactive protein) might be indicated for suspected post-streptococcal adverse outcomes [75] (Table 20). Further, we found no evidence of whether clinical information combined with biomarker data provides better prognostic information for sore throat.

TABLE 20. Summary information from papers on biomarkers to predict prognosis of sore throat

First author	Type of study	Objective	Evidence level
Hahn [75]	Review	Review focused on complications of GAS infection	6+

GAS, group A streptococci.

It is not necessary, based on current evidence, to routinely use biomarkers in the assessment of acute sore throat (C-3).

Does improved diagnosis or the use of near patient tests improve antibiotic use?

One of the major points of disagreement between international guidelines on the management of acute pharyngitis is related to indications of the use of rapid tests [74]. In particular, from the available guidelines, it is still not clear whether a clinical decision alone, the use of rapid tests, or a combination of clinical score with rapid tests, should drive the decision on the use of antibiotics in patients presenting in the primary-care setting with acute pharyngitis. Hence, physicians in the USA, France and Finland will generally adopt a diagnostic test to decide on treatment, while in the UK and the Netherlands the decision will be driven by the severity of the disease [74]. In the UK and the Netherlands no diagnostic tests are used at all.

A number of studies have been published on the issue since 2002. As most investigations provided results stratified according to age group, we were able to separate the available data for children (Table 21; [47,49,64]) and adults (Table 22; [47,54,71,76]). When this was not possible, studies were considered apart (Table 23; [58,78,79]). Findings in children and adults were similar. Overall, four studies indicated that the use of rapid tests (alone) could reduce antibiotic use, whereas three studies indicated that a

TABLE 21. Papers considering the effect of use of rapid antigen tests/throat swabs/clinical score on antibiotic use in children

First author	Type of study	Outcome	Grade
Maltezou [64]	RCT	Comparison of three groups: A: private-practice paediatrician, clinical diagnosis; B: private-practice paediatrician, diagnosis by RAT and culture; C: hospital paediatrician, diagnosis by RAT and culture	Use of RAT only: 2B+ Clinical score: 2B–
McIsaac [47]	PCS	Total and unnecessary antibiotics. Comparison of recommendations of two guidelines with RAT alone, clinical rules, and treatment for culture positive St 1: Culture all St2: IDSA/ASIM1 St3: ASIM2 St4: ASIM3 St5: Modified Centor score and culture approach St6: RAT approach	Use of RAT only: 2B+ Clinical score: 2B–
Shulman [49]	Review		Use of RAT and clinical score: 6+

ASIM, American Society of Internal Medicine; IDSA, Infectious Diseases Society of America; PCS, prospective cohort study; RAT, rapid antigen tests; RCT, randomized-controlled trial.

TABLE 22. Papers considering the effect of use of rapid antigen tests/throat swabs/clinical score on antibiotic use in adults

First author	Type of study	Outcome	Grade
Worrall [76]	RCT, four arms (A: usual practice; B: decision rules only; C: RAT only; D: decision rules + RAT)	Prescribing rates and type of AB prescribed	Use of RAT only: 2B+ Clinical score: 2B–
Humair [54]	PCS	Appropriate AB use with five strategies: A: symptomatic treatment; B: systematic RAT; C: selective RAT; D: empirical AB use; E: systematic culture	Clinical score: 3A– Use of RAT and clinical score: 3A+
Atlas [71]	1-year PCS	For each patient with symptoms of acute pharyngitis was performed a RAT and culture. AB prescriptions at the clinical encounter were compared among patients with positive or negative RAT	Use of RAT and clinical score: 3B+
McIsaac [47]	PCS	Total and unnecessary AB. Comparison of recommendations of two guidelines with RAT alone, clinical rules, and treatment for culture positive St 1: Culture all St2: IDSA/ASIM1 St3: ASIM2 St4: ASIM3 St5: Modified Centor score and culture approach St6: RAT approach	Use of RAT only: 2B+ Clinical score: 2B–
Linder [77]	RCS	A retrospective analysis to determine if clinicians in actual practice use clinical criteria or microbiological testing to reduce AB prescriptions	Use of RAT and clinical score: 4A+

AB, antibiotic; ASIM, American Society of Internal Medicine; IDSA, Infectious Diseases Society of America; PCS, prospective cohort study; RAT, rapid antigen test; RCS, retrospective cohort study; RCT, randomized-controlled trial.

TABLE 23. Papers considering the effect of use of rapid antigen tests/throat swabs/clinical score on antibiotic use in children and adults (when it was not possible to separate the results)

First author	Type of study	Outcome	Grade
Johansson [58]	PCS 3 months	The physicians estimated probability of infection with GAS (6 grading). They also noted management that would have been used before receiving any test results. The group in which a majority of the patients were given AB without prior testing was considered the only clinically positive group in the analysis	Clinical score only: 3A+
McIsaac [78]	RCT Control group: a clinical check list Intervention group: chart stickers that prompted them to calculate a score based on clinical findings and provided management recommendations linked to score totals	Unnecessary AB prescriptions given to patients with a negative throat culture	Prompting clinical score only: 2A–
Rosenberg [79]	PCS	Use of AB according to results of tests	Use of RAT only: 3A+

AB, antibiotic; GAS, group A streptococci; PCS, prospective cohort study; RCT, randomized-controlled trial.

strategy involving a combination of clinical score and rapid test use could reduce antibiotic use.

In conclusion, there is inconsistent evidence on which diagnostic strategy is best to reduce (unnecessary) antibiotic use. A strategy based on the use of clinical scores alone may be associated with higher antibiotic use as compared with either (i) a combination of clinical score and rapid tests use; or (ii) use of rapid tests alone.

Clinical scoring systems and rapid tests can be helpful in targeting antibiotic use (B-2).

Treatment

Are analgesics effective in sore throat?

A systematic review [80] and six randomized-controlled trials (RCTs) [16,80–85] found that non-steroidal anti-inflammatory drugs and paracetamol are more effective than placebo for reducing acute sore throat symptoms in adults. Ibuprofen and diclofenac are slightly more effective than paracetamol for pain relief (Table 24; [4,16,80–113]). Paracetamol and ibuprofen were the safest. In a large RCT, ibuprofen, when used in accordance with the usual contraindications, was as well tolerated as paracetamol for the short-term treatment of the pain of cold and flu symptoms and of sore throat in adults [94,95]. No trials were found comparing ibuprofen and diclofenac. A systematic review showed that ibuprofen and paracetamol are more effective than placebo for reducing acute sore throat symptoms in children [80]. Another systematic review assessed the efficacy and safety of single doses of ibuprofen and paracetamol for short-term treatment of children's pain or fever [96]. The results did not indicate any difference between the drugs in analgesic efficacy or safety.

TABLE 24. Evidence table for studies on treatment of acute sore throat

First author	Objective	Type of study	Evidence level
Timmer [87]	To assess the efficacy and safety of *Pelargonium sidoides* for the treatment of acute respiratory infections in children and adults	MA	1A+
Shi [88]	To assess the efficacy and safety of Chinese herbal medicines for patients with sore throat	SR	1A+
Brinckmann [89]	To investigate the safety and efficacy of Throat Coat, a traditional demulcent herbal tea, in comparison with a placebo tea in the symptomatic treatment of acute pharyngitis	RCT	2A+
Gunsberger [90]	To examine the value of acupuncture in the treatment of such common childhood illnesses as pharyngitis, tonsillitis, and upper respiratory infections	ICS	3C–
Hubbert [91]	To compare the efficacy and tolerability of spray (containing a *Salvia officinalis* fluid extract) against placebo in the treatment of patients with acute viral pharyngitis	RCT	2B+
Rau [92]	To study the effectiveness of the herbal preparation (combination of *Capsicum annuum*, *Guajacum officinale* and *Phytolacca americana*)	OS	3C+
Wiesenauer [93]	To study the efficacy of three plants (combination of *Capsicum annuum*, *Guajacum officinale* and *Phytolacca americana*) used in homeopathy	ICS	3C–
Thomas [80]	To estimate the benefits of treatments other than antibiotics for acute sore throat, and the differences between non-antibiotic interventions and controls in patient-perceived pain of sore throat	SR	1A+
Burnett [82]	To determine the time to onset of pain relief from a single dose of a tablet formulation of paracetamol containing sodium bicarbonate	RCT	2A+
Gehanno [84]	To compare the anti-pyretic and analgesic effects of a single oral dose of diclofenac potassium 6.25, 12.5 or 25 mg with paracetamol 1000 mg and placebo in patients with fever resulting from acute febrile sore throat	RCT	2A+
Eccles [83]	To investigate the efficacy and safety of acetylsalicylic acid (ASA) for the treatment of sore throat pain associated with upper respiratory infections	RCT	2A+
Schachtel [85]	To identify and compare the analgesic activity of a single flurbiprofen lozenge (2.5, 5.0 and 12.5 mg) with placebo in patients with sore throats	RCT	2A+
Watson [16]	To study the efficacy of flurbiprofen lozenges compared with placebo	RCT	2A+
Benrimoj [81]	To determine the single dose efficacy of flurbiprofen 8.75 mg lozenges in comparison with placebo, over 6 h in patients with sore throat	RCT	2A+
Boureau [86]	To validate a slightly modified sore throat pain model by comparing the analgesic efficacy of ibuprofen with that of paracetamol	RCT	2A+
Moore [94]	To identify and quantify factors associated with the occurrence of adverse events in users of analgesic drugs	RCT	2A+
Moore [95]	To study the tolerability of ibuprofen, aspirin and paracetamol in patients suffering from cold/flu or sore throat	RCT	2A+
Perrott [96]	To summarize studies testing the efficacy and safety of single-dose acetaminophen and ibuprofen for treating children's pain or fever	MA	1A+
Hayward [97]	To evaluate whether systemic corticosteroids improve symptoms of sore throat in adults and children	MA	1A+
Mossad [98]	To test the efficacy of zinc gluconate lozenges in reducing the duration of symptoms caused by the common cold	RCT	2A+
Macknin [99]	To determine the efficacy of zinc gluconate lozenges treatment of colds in children and adolescents	RCT	2A+
Spinks [100]	To assess the benefits of antibiotics for sore throat	MA	1A+
Cooper [101]	To examine the available evidence regarding the diagnosis and treatment of acute GABHS pharyngitis in adult patients	SR	1A+
Spurling [102]	To evaluate clinical outcomes, adverse effects, antibiotic use and patient satisfaction associated with delayed antibiotic prescribing compared with immediate prescribing or no antibiotics for acute respiratory infections	SR	1A+
Altamimi [103]	To summarize the evidence regarding the effect of 2–6 days of oral antibiotics in treating children with acute streptococcal pharyngitis, compared with a 10-day course of oral penicillin, on duration of symptoms, eradication of the organism, and recurrence and complication rates	MA	1A+
Casey [104]	To compare the relative efficacy of cephalosporins with that of penicillin in the treatment of GABHS tonsillopharyngitis in adults in all available RCTs	MA	1A+
Casey [105]	To compare the relative efficacy of cephalosporin and penicillin treatment of GABHS tonsillopharyngitis in children in all available RCTs	MA	1A+
Casey [106]	To compare the relative efficacy of short-course antibiotic treatment with standard 10-day treatment courses for GAS tonsillopharyngitis	MA	1A+
Ioannidis [107]	To compare azithromycin with other antibiotics that typically require longer treatment courses	MA	1A+
Esposito [108]	To evaluate the efficacy and safety of short-course cefaclor therapy in paediatric GABHS pharyngitis by comparing 5 days of treatment with a cefaclor suspension and 10 days of treatment with an amoxycillin suspension	RCT	2A+
Sakata [109]	To compare a 5-day course of cefcapene-pivoxil with a 10-day course of amoxicillin and a 10-day course of cefcapene-pivoxil for the treatment of GAS pharyngitis in children	RCT	2B+
Pichichero [110]	To compare the amoxicillin sprinkle administered daily for 7 days with penicillin VK four times a day for 10 days in children with tonsillopharyngitis secondary to *Streptococcus pyogenes*	RCT	2A+
Gerber [111]	To compare the effectiveness of a short (5-day) course of penicillin V potassium with the conventional 10-day oral administration of this antibiotic	RCT	2B+
Schwartz [112]	To evaluate the effect of duration of orally administered penicillin V potassium on the bacteriological and clinical cure of GAS pharyngitis	RCT	2B+
Stromberg [4]	To investigate the possibility of decreasing the length of treatment of GAS pharyngotonsillitis by comparing the bacteriological and clinical outcomes of a 5-day course of penicillin V with those of a 10-day course	RCT	2A+
Zwart [113]	To assess whether treatment with penicillin for 3 days and the traditional treatment for 7 days were equally as effective at accelerating resolution of symptoms in patients with sore throat compared with placebo	RCT	2A+

GABHS, group A β-haemolytic streptococcus; GAS, group A streptococcus; ICS, interventional cohort study ; MA, meta-analysis; OS, observational study; RCT, randomized controlled trial; SR, systematic review.

Either ibuprofen or paracetamol are recommended for relief of acute sore throat symptoms (A-1).

What are the indications for use of glucocorticoids in sore throat?

A systematic review and meta-analysis including eight trials showed that adults with severe or high Centor scoring sore throat would benefit from a single dose of corticosteroids in conjunction with antibiotic therapy [97]. No evidence of significant benefit was found in children. However, studies included in the systematic review were not sufficiently powered to detect adverse effects of short courses of oral corticosteroids. In addition, steroids might have a considerably smaller effect in a typical primary-care population, where most patients do not have severe or high Centor scoring sore throat [97,114]. The effect of steroids was also smaller when administered by oral route (Table 24).

Use of corticosteroids in conjunction with antibiotic therapy is not routinely recommended for treatment of sore throat. It can, however, be considered in adult patients with severe presentations, e.g. 3–4 Centor criteria (A-1).

What are the indications for use of zinc gluconate in the treatment of sore throat?

The trials on the effectiveness of zinc gluconate provided conflicting results [98,99]. In both trials patients in the zinc group had more adverse effects (Table 24). According to the Cochrane review zinc administered within 24 h of onset of symptoms reduces the duration and severity of the common cold in healthy people. However, it is difficult to make firm recommendations about the dose, formulation and duration that should be used [115].

Zinc gluconate is not recommended to be used in the treatment of sore throat (B-2).

What are the indications for complementary treatments, e.g. herbal treatments or acupuncture in sore throat?

There are no reliable data on the efficacy of alternative treatment (herbal treatment and acupuncture) on sore throat [87–93]. In a Cochrane systematic review, the efficacy of *Pelargonium sidoides* for the treatment of acute respiratory tract infections has been studied in two trials on sore throat [87]. However, both were excluded because of high risk of bias (Table 24).

Another systematic review on the efficacy of Chinese herbal medicine for treating sore throat included seven trials [88]. All trials were of methodologically poor quality. In particular, it was highly likely that there was selection bias or detection bias, or both, in all of the included trials [88].

One RCT looking at the effectiveness of Throat Coat, a demulcent herbal tea, in comparison with a placebo tea was carried out in a small number of patients [89]. Throat Coat was found to be more effective than placebo for short-term relief of pain in patients with acute pharyngitis. However, total pain relief over the first 30 min was not different between the two groups.

Other studies on the efficacy of herbal treatment and acupuncture included restricted samples of patients [91] or were of methodologically poor quality. These three studies [90,92,93] did not randomize patients between treatment arms, failing to minimize the effects of selection bias on study results. In the study by Rau, liquid or tablet formulation of a herbal compound of *Phytolacca*, *Guajacum* and *Capsicum* were compared. In the study by Wiesenauer, combination of three plant substances (*Phytolacca americana*, *Guajacum officinale*, *Capsicum annuum*) was used in either solid (tablet) or liquid (drop) formulation. Efficacy is hard to judge from these studies as they were not placebo-controlled.

There is inconsistent evidence of herbal treatments and acupuncture as treatments for sore throat (C-1 to C-3).

What is the average benefit from antibiotics and which groups of patients benefit from antibiotic treatment?

A Cochrane systematic review and meta-analysis included 27 RCTs assessing the benefits of antibiotics in the management of sore throat [100]. There was a beneficial effect of antibiotics in reducing the incidence of rheumatic fever and acute glomerulonephritis following an episode of sore throat. However, this effect was present only in trials conducted in the 1950s and 1960s, during which time the rates of these complications (especially acute rheumatic fever) were much higher than now. The absolute risk of developing these complications following sore throat is extremely small in the Western world in the first decade of the twenty-first century and although antibiotic treatment of higher-risk patients is justified (those with previous rheumatic fever) antibiotic treatment of lower-risk patients to prevent non-suppurative complications is not justified [101] (Table 24).

Antibiotics reduced the incidence of acute otitis media and quinsy (peritonsillar abscess), but did not reduce the incidence of acute sinusitis in the Cochrane meta-analysis. However, the relative benefit exaggerates the absolute benefit because the event rates of suppurative complications are low. The number needed to treat to benefit was 27 or higher to prevent one case of quinsy [100,101]. In modern primary-care settings the number needed to treat to benefit is between 50 and 200 [113,114].

Sore throat should not be treated with antibiotics to prevent the development of rheumatic fever and acute glomerulonephritis *in low-risk patients* (A-1). The prevention

of suppurative complications is not a specific indication for antibiotic therapy in sore throat (A-1). Clinicians do not need to treat most cases of acute sore throat to prevent quinsy, acute otitis media, cervical lymphadenitis, mastoiditis or acute sinusitis (A-3).

Do antibiotics relieve symptoms in sore throat?

Antibiotics have a modest beneficial effect over placebo in reducing the symptoms of sore throat [100]. In the Cochrane meta-analysis, antibiotics reduced symptoms of sore throat on day 3 (pooled Relative Risk 0.72, 95% CI 0.68–0.76) [54]. However, at 1 week, only the group A β-haemolytic streptococcus-positive subgroup showed a beneficial effect of antibiotics over placebo (Table 24). In trials where the Centor criteria were used there was a modest benefit of antibiotics (1–2 days) [113].

In a systematic review on appropriate antibiotic use for acute pharyngitis in adults, treatment of antibiotics within 2–3 days of symptom onset hastened symptomatic improvement by 1–2 days in patients with group A β-haemolytic streptococcal pharyngitis [101]. In the recommendations, the working group combined this information with our statement that the Centor criteria are helpful in assessing the presence of a bacterial pharyngitis.

It is not necessary to start antibiotics immediately. A Cochrane review including ten RCTs compared delayed antibiotics (more than 48 h after the initial consultation) with antibiotics used immediately or no antibiotics for acute respiratory tract infections [102]. No significant differences were found in complication rates for the three prescribing strategies. In children, only one RCT of sufficient size and quality was performed, showing no relevant effects [116].

Antibiotics should not be used in patients with less severe presentation of sore throat, e.g. 0–2 Centor criteria, to relieve symptoms (A-1). In patients with more severe presentations, e.g. 3–4 Centor criteria, physicians should consider discussion with patients. Modest benefits of antibiotics (1–2 days), which have been observed in group A β-haemolytic streptococcus -positive patients and in patients with 3–4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on the microbiota, increased antibacterial resistance, medicalization and costs (A-1). Using delayed prescribing of antibiotics is a valid option (A-1).

Which antimicrobial agent is the first choice in patients with acute sore throat?

Penicillin has been the treatment of choice for group A β-haemolytic streptococcal pharyngitis for five decades and is recommended by North American and many European guidelines as first choice for acute sore throat [74]. Penicillin is chosen because of its proven efficacy, safety, narrow spectrum and low cost. Amoxicillin is often used in younger children in place of penicillin V because of taste considerations and its availability as syrup or suspension in some countries, but in older children amoxicillin is a poor first choice because of the risk of severe rash among patients with Epstein–Barr virus infection. Group A β-haemolytic streptococci have not developed resistance to any of the penicillins or shown an increase in penicillin minimal inhibitory concentrations over at least five decades [117] (Table 24).

Although newer antibiotics seem to be more effective than penicillin in reducing sore throat symptoms, the differences in efficacy are not clinically important. Five systematic reviews addressed the question of whether penicillin should remain the treatment of choice. In adults, a meta-analysis of nine RCTs (2113 patients) comparing cephalosporins with penicillin (10 days) was performed [104]. The likelihood of bacteriological and clinical failure in the treatment of group A β-haemolytic streptococcal tonsillopharyngitis was two times higher for oral penicillin than for oral cephalosporins; the OR for clinical cure rate was 2.29 (95% CI 1.61–3.28) favouring cephalosporin treatment. In children, 35 trials including 7125 patients were included in a meta-analysis [105]. The OR for clinical cure rate was 2.34 (95% CI 1.84–2.97) favouring cephalosporins. Although clinical cure rates favoured cephalosporins, the magnitude of the differences in both meta-analyses was small and not clinically relevant. Major flaws of these reviews were discussed by Shulman and Gerber [118] and Bisno [119]. Another meta-analysis by the same authors [118,119] compared bacterial and clinical cure rates in children and adults with group A streptococcal tonsillopharyngitis treated with oral β-lactam or macrolide (other than azithromycin) antibiotics [106]. Twenty-two trials with 7470 patients were included in four separate analyses. Four or 5 days of cephalosporin therapy was superior to 10 days of penicillin therapy in terms of bacterial cure rate: OR 1.47 (95% CI 1.06–2.03). The overall clinical cure rate, however, was 1.35 (95% CI 0.90–2.03) and it was even lower in the studies of good quality.

A systematic review comparing efficacy and safety of azithromycin against other antibiotics for acute pharyngitis in adults and children found no evidence of differing efficacy between azithromycin and comparator agents [107]. Comparator drugs were penicillin (***n*** = 7), clarithromycin (***n*** = 3), cefaclor (***n*** = 3), erythromycin (***n*** = 1), roxythromycin (***n*** = 1) and co-amoxiclav (***n*** = 1), all typically prescribed for 10 days.

Apart from the aforementioned reviews, two RCTs compared efficacy of cephalosporins and amoxicillin in

children [108,109]. No significant differences in clinical cure rate were found in both trials. Another RCT compared the efficacy of amoxicillin and penicillin in children with acute streptococcal tonsillopharyngitis [110]. The clinical cure rates for amoxicillin and penicillin were 86% and 92%, respectively, confirming that amoxicillin could be an alternative regimen for the treatment of streptococcal tonsillopharyngitis in children. Penicillin and amoxicillin are also supported by their sufficient antibacterial spectrum and lower cost.

Traditionally, a regimen of penicillin for 10 days was recommended for the treatment of sore throat to maximize eradication of bacteria. In western countries in 2011, penicillin is prescribed primarily to shorten the course of the sore throat and not to prevent complications.

If shorter duration therapy is as effective as 10-day treatment, shortening the duration could improve compliance and reduce adverse effects. The aforementioned review by Casey and Pichichero [104] also reviewed trials comparing 5-day courses of penicillin with 10-day courses of penicillin and saw small clinical differences in outcome favouring 10 days of treatment. Another RCT assessed the clinical and bacteriological effects of a 3-day and a 7-day regimen of penicillin V in adult patients with sore throat, selected by clinical criteria [113]. Penicillin treatment for 7 days was superior to treatment for 3 days or placebo in resolving the symptoms of sore throat.

A Cochrane review and meta-analysis [103] summarized the evidence regarding the efficacy of short-duration newer antibiotics (2–6 days) compared with 10 days of oral penicillin in treating children with acute group A β-haemolytic streptococcal pharyngitis. Twenty studies were included with 13 102 cases of acute group A β-haemolytic streptococcal pharyngitis. The short-duration treatment showed slightly better clinical outcome: shorter periods of fever [mean difference −0.30 days, 95% CI −0.45 to −0.14] and throat soreness (mean difference −0.50 days, 95% CI −0.78 to −0.22); lower risk of early clinical treatment failure (OR 0.80, 95% CI 0.67–0.94), no significant difference in early bacteriological treatment failure (OR 1.08, 95% CI 0.97–1.20) or late clinical recurrence (OR 0.95, 95% CI 0.83–1.08). More side effects were seen in the short-duration treatment group (OR 1.85, 95% CI 1.55–2.21). Most of the events involved the gastrointestinal system (diarrhoea, vomiting and abdominal pain) in both treatment groups. The two lengths of treatment were difficult to compare because different types of antibiotics were compared in most trials and differences found in clinical outcomes were small.

If antibiotics are indicated, penicillin V, twice or three times daily for 10 days, is recommended (A-1). There is not enough evidence that indicates shorter treatment length.

Author contribution

Claudio Pelucchi, Larissa Grigoryan and Carlotta Galeone contributed to systematic literature review and interpretation. Susanna Esposito is expert in paediatrics. Pentti Huovinen is expert in clinical microbiology and chair of the Guideline Group. Paul Little and Theo Verheij are expert in general practice.

Transparency declaration

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Appendix: Search methods

Diagnosis

We searched the scientific literature, with restrictions according to year of publication and language, as follows:

(sore throat OR pharyngitis OR tonsillitis OR pharyngotonsillitis OR tonsillopharyngitis) AND (rapid antigen OR rapid test OR rapid tests OR swab OR swabs OR throat culture) AND (streptococcus OR streptococcal OR strep) AND ((English[lang])) AND (('2002'[PDat]: '2010'[PDat])).

On 15 April 2009, we retrieved 182 papers (including 14 reviews) using PubMed. Potentially relevant articles were assessed by one reviewer, who excluded those that were not in the scope for this topic of the guideline (e.g. studies on antibiotic use, investigations focused on prognosis or on diseases other than those of the upper respiratory tract, studies that were clearly not conducted in the primary-care setting, those from developing countries, etc.) on the basis of title, abstract (when available), and keywords (MeSH

terms). From the first selection, 113 papers were eliminated. Sixty-nine papers were selected for further consideration. Two other papers of interest were found in the Cochrane Database, and two were found by looking at the reference list of the selected papers, for a total of 73 articles (see Appendix for the full list). All of these papers were carefully considered for the development of guideline indications, though not all provided relevant information.

Prognosis—streptococci

We searched the scientific literature, with restrictions according to year of publication and language, as follows:

((prognosis OR complication * OR outcome * OR rheumatic fever) AND (sore throat OR pharyngitis OR tonsillitis OR pharyngotonsillitis OR tonsillopharyngitis) AND (streptococcus OR streptococcal OR strep) AND ((English[lang])) AND (('2002'[PDat]: '2010'[PDat]))).

On 15 September 2009, we retrieved 372 papers (including 71 reviews). Potentially relevant articles were assessed by one reviewer, who excluded those that were not in the scope for this topic of the guideline (e.g. those not focused on upper respiratory tract infections, studies on treatment or diagnosis, investigations from developing countries, studies on socio-economic costs, etc.) on the basis of title, abstract (when available), and keywords (MeSH terms). From the first selection, 327 papers were eliminated. Forty-five papers were selected for further consideration. Two further articles were retrieved by looking at reference lists of the papers selected for consideration (see Appendix for the full list). All these papers were carefully considered for the development of guideline indications, though not all provided relevant information.

Prognosis—*Mycoplasma pneumoniae* or *Chlamydia pneumoniae*

We searched the scientific literature with a specific string for *M. pneumoniae* or *C. pneumoniae* infections, with restriction according to language but not year of publication, as follows:

((prognosis OR complication * OR outcome * OR rheumatic fever) AND (sore throat OR pharyngitis OR tonsillitis OR pharyngotonsillitis OR tonsillopharyngitis) AND (*M. pneumoniae* OR *C. pneumoniae*) AND ((English[lang]))).

On 15 September 2009, we retrieved 33 papers (including eight reviews). Potentially relevant articles were assessed by one reviewer, who excluded those that were not in the scope for this topic of the guideline (e.g. those focused on other agents involved in upper respiratory tract infections, studies on treatment or diagnostic tests, studies on socio-economic costs, reports of outbreaks, etc.) on the basis of title, abstract (when available), and keywords (MeSH terms). From the first selection, 24 papers were eliminated. Nine papers were selected for further consideration (see Appendix for the full list). All these papers were carefully considered for the development of guideline indications, though not all provided relevant information.

Infection with group C or group G streptococci

We searched the scientific literature, with restrictions according to language and year of publication (limited to studies published from 1980 onwards), as follows:

(sore throat OR pharyngitis OR tonsillitis OR pharyngotonsillitis OR tonsillopharyngitis) AND (((C) OR (G)) AND group) AND (streptococcus OR streptococcal OR strep) AND ((English[lang])).

On 15 September 2009, we retrieved 295 papers (including 27 reviews). Potentially relevant articles were assessed by one reviewer, who excluded those that were not in the scope for this topic of the guideline (mostly, those investigating group A streptococci, studies not focused on upper respiratory tract infections, studies on treatment, molecular and mechanistic studies) on the basis of title, abstract (when available), and keywords (MeSH terms). From the first selection, 233 papers were eliminated, and 62 papers were selected for further consideration (see Appendix for the full list). All these papers were carefully considered for the development of guideline indications, though not all provided relevant information.

Treatment

We searched the scientific literature for studies conducted in the primary-care setting, with restrictions according to language (English), and excluding studies conducted in developing countries, using the following search strategy (combined MeSH and text word search) and abstract appraisal criteria:

#1 sore throat
#2 ***pharyngitis***
#3 tonsillitis
#4 pharyngotonsillitis
#5 tonsillopharyngitis
#6 nasopharyngitis
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 complementary treatment OR ***complementary therapies*** OR complementary medicine
#9 alternative treatment OR alternative treatments OR alternative medicine OR traditional medicine
#10 phytotherapy OR herbal OR herb OR herbs
#11 medicinal plant OR medicinal plants

#12 Echinacea OR chamomile OR eucalyptus OR garlic OR sage OR raspberry OR licorice root

#13 marshmallow root OR Althaéa officinális OR pelargonium OR calendula

#21 #8 OR #9 OR #10 OR #11 OR #12 OR #13

#22 #7 AND #21 (**307 hits**)

 # 22 is the final search strategy for the part on complementary treatment.

#23 symptomatic treatment OR symptomatic treatments

#24 analgesic OR ***analgesics***

#25 acetaminophen OR paracetamol

#26 ***Anti-inflammatory agents, Non-steroidal*** OR nonsteroidal anti-inflammatory OR nonsteroidal anti-inflammatory OR NSAID OR NSAIDs

#27 aspirin OR acetylsalicylic acid

#28 ibuprofen

#29 #23 OR #24 OR #25 OR #26 OR #27 OR #28

#30 #7 AND #29 (**480 hits**)

#30 is the final search strategy for the part on symptomatic treatment.

#31 ***Anti-bacterial agents*** OR antimicrobial OR antimicrobials OR anti-microbial OR anti-microbials OR antibiotic OR antibiotics OR anti-bacterial OR antibacterial OR antibacterials

#32 penicillin

#33 erythromycin

#34 amoxicillin

#35 cephalosporin OR cephalosporins OR azithromycin OR clarithromycin OR quinolone OR tetracycline OR doxycycline OR co-trimoxazole

#36 #31 OR #32 OR #33 OR #34 OR #35

#37 #7 AND #36 (**3097 hits**)

#37 is the final search strategy for the part on antibiotic treatment (questions 3–6).

#38 ***mouthwashes*** OR mouthwash OR throat spray OR lozenge Or lozenges OR gargle OR gargles OR mouth rinse OR mouth rinses

#39 #7 AND #38 (**86 hits**)

#39 is additional search strategy

Abstract appraisal criteria:

- title or abstract addresses one or more of the study questions;
- title or abstract identifies primary research or systematically conducted secondary research

Appendix – List of selected references

Diagnosis

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