

Worldwide comparison of treatment guidelines for sore throat

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Abstract

Introduction: Sore throat (acute pharyngitis) is globally one of the most frequent reasons for seeking healthcare. Its etiology is mostly viral. In 15%-30% of cases, group A streptococci (GAS) are detected, which may cause acute rheumatic fever. We have done a worldwide systematic review to compare diagnostic and therapeutic guidelines across countries and regions. Previous reviews of sore throat guidelines were limited to specific regions and/or language; this is the first global review.

Materials and Methods: Searches were performed in MEDLINE, EMBASE and COCHRANE (key words: sore throat, pharyngitis, tonsillitis or pharyngotonsillitis, and management, guidance, guideline or recommendation) and on the web sites of major health authorities and associated institutions from Africa, Asia, Europe, Middle East, North America, Oceania and South America.

Results: Thirty-six guidelines were identified from 26 countries. Most common are recommendations relying on the symptom- and age-based Centor or McIsaac scores. However, antibiotic treatment may be based on other symptomatic criteria; in the most extreme approach just sore throat in children. The recommendation of GAS-specific diagnostic tests is mainly limited to countries where such tests are readily available, although some countries choose not to use them. Penicillins are consistently recommended as first-line antibiotics. By contrast, guidance for symptomatic treatment is variable and mostly sparse or missing. African countries without sore throat guidelines and Asian countries bypassing them are afflicted by rising antibiotic resistance.

Conclusion: The availability of sore throat guidelines varies considerably by region and country. Moreover, important divergence is found among the guidelines regarding diagnostic and treatment criteria. This may be explained by the historical background or adoption of external guidelines, rather than local incidences of GAS infections or acute rheumatic fever. Absence of recommendations on symptomatic treatment in many guidelines is concerning, and raises issues about antimicrobial stewardship, as this should be the mainstay of sore throat management, rather than antibiotics.

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1 | INTRODUCTION

Sore throat (acute pharyngitis) is prevalent worldwide and one of the most frequent complaints in children and adults requiring healthcare.¹⁻³ The etiology of sore throat is in 70%-95% of cases viral.⁴ Rhinovirus, coronavirus and adenovirus account for at least 30% of all cases, while influenza or parainfluenza viruses are found in about 4%.⁵ Other viral pathogens in children and adults include Epstein-Barr virus, enteroviruses, respiratory syncytial virus, herpes viruses, cytomegalovirus and human immunodeficiency virus.^{1,3}

In approximately 15%-30% of all cases with sore throat (5%-15% in adults, 20%-30% in children), *Streptococcus pyogenes* (group A streptococcus, GAS) is detected.⁶⁻⁸ These numbers, however, also include healthy carriers and false positive test results (see below). GAS has been associated with acute rheumatic fever (ARF), which may lead to rheumatic heart disease (RHD).^{9,10} While similar proportions of GAS infection are reported in different regions,⁶⁻⁸ the incidence of ARF varies greatly; in most industrialized nations it is 100-200 times lower than in developing countries.¹¹ Less frequent bacterial causes of sore throat include group C or G streptococci (about 5%), chlamydia, mycoplasma, *Arcanobacterium haemolyticum*, *Neisseria gonorrhoeae* and *Corynebacterium diphtheriae* (all <1%).^{1,3,5}

The clinical distinction between GAS pharyngitis (including scarlet fever) and acute pharyngitis caused by viral or other pathogens is notoriously difficult.¹² Clinical scores have been developed to identify GAS infection, such as the Centor score for adults¹³ and the modified/McIsaac Centor score for children and adults.¹⁴ In the original Centor score, one point is given for each history of fever (>38°C), tonsillar exudates, tender anterior adenopathy and absence of cough.¹³ In the modified Centor score, one point is added to the original score for age 3-14 years, whereas one point is subtracted for age ≥45 years.¹⁴ Throat swab cultures are considered the gold standard for diagnosing GAS infection.^{7,15} As the results of cultures are not available before 1-2 days, rapid antigen detection tests (RADT) have been developed to identify GAS.^{16,17} However, false positive RADT results have been reported in about 5% of children¹⁸ and up to 15% of adults with acute pharyngitis.¹⁹ The addition of polymerase chain reaction (PCR) tests may increase sensitivity and specificity, with relatively rapid turnaround times.¹⁵ Yet neither RADT nor PCR or cultures can distinguish between GAS pharyngitis and GAS carriers with viral pharyngitis. The asymptomatic carriage rate of GAS is estimated to be around 6%-11% of the patient population.²⁰

The majority of adult and paediatric cases of sore throat, in particular those with viral infections that are self-limiting, do not require antibiotic treatment, but are amenable to systemic and/or local symptomatic treatments for pain, inflammation and fever.^{14,21} In bacterial throat infections, antibiotics may shorten the duration of symptoms by about a day. They also reduce the risk of ARF by about two thirds in communities where this complication is common.²²

Based on this etiological background and the different diagnostic tools and treatments, various guidelines have been developed around the world, to diagnose and treat sore throat. We have

What's known

- Searches for guidelines were performed in the COCHRANE Library (Systematic Reviews), EMBASE (entire database) and PUBMED (all databases, including MEDLINE), using the search terms, criteria and cut-offs defined in the manuscript. Further guideline searches were performed on the internet, with the Google search engine using the specified English search terms, and their translations in Arabic, Chinese, French, German, Portuguese, Russian and Spanish, as well as on the websites of the major health authorities and associated institutions of all regions worldwide.
- Only guidelines that provided recommendations for the diagnosis and the treatment of sore throat (acute pharyngitis) in general were considered and included. For Europe and the USA, where large numbers of guidelines are available, the most recent and representative published guidelines supported by the major national or regional health care organizations were selected.

What's new

- Sore throat is one of the commonest reasons for using antibiotics worldwide, although most cases are viral.
- There are major discrepancies across the guidelines, which are often not adapted to the actual, local incidence of group A streptococcus pharyngitis and its complications. Most guidelines do not provide any advice on symptomatic treatment.
- These issues are of clinical concern as they may cause unnecessary suffering of patients and drive the ineffective use of antibiotics.

performed a systematic search to compare such guidelines across countries and regions, identify significant differences and discuss reasons for the major discrepancies.

2 | METHODS

Searches for guidelines were performed in COCHRANE Library (Systematic Reviews), EMBASE (entire database), PUBMED (all databases, including MEDLINE) and on the internet, using the following search terms and specifications.

COCHRANE Library: SORE THROAT or PHARYNGITIS or TONSILLITIS or PHARYNGOTONSILLITIS from January 2010 through 19 May 2020 (67 items).

EMBASE: (SORE THROAT or PHARYNGITIS or TONSILLITIS or PHARYNGOTONSILLITIS) and (MANAGEMENT or GUIDANCE or GUIDELINE(S) or RECOMMENDATION(S)) in Title from 2010 through 19 May 2020 (130 items).

PUBMED (MEDLINE): (SORE THROAT or PHARYNGITIS or TONSILLITIS or PHARYNGOTONSILLITIS) and (MANAGEMENT or GUIDANCE or GUIDELINE(S) or RECOMMENDATION(S)) in Title from 01 January 2010 through 19 May 2020 (108 items).

Internet searches were performed up to 19 May 2020 with the GOOGLE search engine, using the English search terms of the literature searches and translations of SORE THROAT, ACUTE PHARYNGITIS and GUIDELINE in Arabic, Chinese, French, German, Portuguese, Russian and Spanish, as well as searches of the websites of the major health authorities and associated institutions of all the regions shown in Table 1. For the retrieval and analysis of guidelines published in other languages than English, French, German, Portuguese or Spanish, translations by GOOGLE TRANSLATE and YANDEX TRANSLATE were used.

Only guidelines that provided recommendations for the diagnosis and the treatment of sore throat (acute pharyngitis) in general were considered. For the Western countries, in particular Europe and the United States of America (USA), where large numbers of guidelines are available, the most recent and representative published guidelines supported by the major national or regional health-care organizations were selected.

3 | RESULTS

3.1 | Geographic origin and selection of the guidelines

A total of 36 guidelines from 26 countries were identified. Table 1 gives an overview of these guidelines by region and country; Figure 1 shows their origin on a world map. The highest number of guidelines were published in Europe; in addition to a European guideline,²³ a selection of the most recent and relevant published guidelines from Central (Germany),²⁴ Eastern (Russian Federation),²⁵ Northern (Netherlands²⁶ and Sweden²⁷), Southern (Italy²⁸ and Spain²⁹) and Western countries (France³⁰ and United Kingdom³¹) were included. Of a large number, the most recent and relevant published guidelines were selected from North America, including Canada,³² Mexico^{33,34} and the USA.^{35–37} and Asia, i.e. China^{38,39} (with Hong Kong⁸), India,⁴⁰ Japan,⁴¹ Malaysia⁴² and Thailand.⁴³ Regarding the Middle East, the principal recommendations were found from Iran,^{44,45} Israel,⁴⁶ Saudi Arabia⁴⁷ and Turkey.⁴⁸ For South America, recommendations from Argentina⁴⁹ and Brazil^{6,50} were included, in addition to a Latin American guideline.⁵¹ Guidance from the African continent was scarce; only two relevant, recent guidelines, one from Egypt⁵² and one from South Africa,⁵³ were included. Notably, there was no guideline for the management of sore throat in Nigeria,⁵⁴ Africa's most populated country. Two relevant guidelines were found for the Oceanian countries, one from Australia⁵⁵ and one from New Zealand.⁵⁶

3.2 | Clinical diagnosis of acute pharyngitis

Although not all cases of sore throat are actually acute pharyngitis,^{57,58} the terms are commonly used as synonyms. Acute pharyngitis is

hallmarked by the acute onset of throat pain, typically with odynophagia, and signs of pharyngeal inflammation, e.g. erythema.^{59,60} Beyond clinical history and clinical examination, environmental and epidemiologic factors should be considered in the clinical differential diagnosis of sore throat.⁶¹ However, none of the retrieved guidelines provides information to distinguish acute pharyngitis from other conditions. Instead, most guidelines discuss criteria of seriousness, bacterial origin or GAS infection, to support the decision about antibiotic treatment.

3.3 | Recommendations for antibiotic treatment

All the retrieved guidances provide criteria for antibiotic treatment, except one review of Chinese medicinal herbs for sore throat.³⁸ With regards to antibiotic treatment, three groups of recommendations can be distinguished: (1) only clinical criteria, not based on the Centor score (or similar); (2) only clinical criteria, based on Centor score (or similar); (3) criteria including laboratory tests. These groups were strongly clustered according to regions. Thus, all African guidelines are based solely on clinical criteria, including neither the Centor score, nor laboratory tests.^{62,52,53} By contrast, all European and North American guidelines recommend RADT, pending on clinical signs and symptoms mostly including the Centor score, with the exception of the recommendations from the Netherlands,²⁶ the United Kingdom³¹ and Mexico.³⁴ While the latter two rely on the Centor score (or similar) only, the Dutch guideline considers the distinction of viral and bacterial acute pharyngitis as usually irrelevant, given the low incidence of GAS in the Netherlands.²⁶ A mixed picture emerges from Asia (except China) and the Middle East, where wealthier countries, such as Japan,⁴¹ Israel⁴⁶ and Saudi Arabia,⁴⁷ but also Malaysia⁴² and a recent recommendation from Iran,⁴⁵ include RADT in their guidelines, while the other countries, and an earlier Iranian guideline,⁴⁴ recommend treatment according to clinical criteria, with^{48,40} or without^{43,44} using the Centor score. In China, the Special Administrative Region of Hong Kong recommends RADT,⁸ whereas Chinese National guidelines endorse antibiotic treatment based on clinical signs and symptoms only.³⁹ Regarding Oceania, antibiotic treatment for sore throat is based on the Centor score in Australia,⁵⁵ but on age, ethnic origin and socioeconomic circumstances in New Zealand.⁵⁶

With the exception of three guidances from China,³⁸ South Africa⁵³ and the USA,³⁵ all the sore throat guidelines give recommendations for antibiotic therapy. First-line treatment options are invariably penicillin-based medicines. Macrolides or cephalosporins are commonly recommended as second-line antibiotics; e.g. in case of penicillin allergy. While amoxicillin/clavulanate is infrequently recommended as second-line antibiotic in sore throat,^{33,34} it is the most common treatment prescribed for sore throat in children in Nigeria, which has no national guideline.⁶³ In Italy, amoxicillin/clavulanate is the most commonly prescribed antibiotic in children,⁶⁴ although the guidelines recommend amoxicillin as first-line antibiotic for sore throat,²⁸ where its combination with clavulanic acid offers no therapeutic advantage.⁶⁴

TABLE 1 Overview of worldwide treatment guidelines

Region	Country	Issuer of guideline or backing organizations	Criteria for antibiotic therapy	Antibiotic treatments	Symptomatic treatments
Africa					
Egypt		World Health Organization ⁵²	≥ 2 of following: <ul style="list-style-type: none"> Erythema White or yellow exudate Enlarged tender lymph node(s) 	Benzathine penicillin G injection	Paracetamol
South Africa		University of Cape Town ⁵³	No cough (1) + No rhinorrhea (1) + tonsillar swelling (2) + tonsillar exudate (1) ≥ 3 with tonsillar swelling	not specified	not specified
Asia					
China		Cochrane review ³⁸	not specified	not specified	Antiviral, anti-asthmatic, antitussive, and fever-relieving herbs
China		Chinese Medical Association ³⁹	Pharyngeal hyperemia, tonsillar swelling with purulent exudate, swollen and tender lymph nodes	Penicillin or first generation cephalosporins	Paracetamol; aspirin; ibuprofen
China (Hong Kong)		Centre for Health Protection ⁸	Treatment if modified Centor score ^{13,14} ≥ 4	First line: penicillin V or amoxicillin or cephalexin 5-7 days; second line: clarithromycin or azithromycin	not specified
India		University of Chennai ⁴⁰	Treatment if modified Centor score ^{13,14} ≥ 4	Penicillin	not specified
Japan		Ministry of Health ⁴¹	RADT if modified Centor score ^{13,14} ≥ 2 or if high risk for GAS infection	Amoxicillin for 10 days	not specified
Malaysia		Ministry of Health ⁴²	RADT based on modified Centor score ^{13,14} ; culture if modified Centor score ^{13,14} ≥ 2 ; culture or treatment if modified Centor score ≥ 4	Ampicillin for 10 days or benzathine penicillin G injection; if allergy erythromycin or clindamycin	Paracetamol; NSAIDs; lozenges or gargles
Thailand		Mahidol University Bangkok ⁴³	Treatment if ≥ 3 of the following: <ul style="list-style-type: none"> High fever in combination with sore throat Purulent tonsillar exudate or swollen red tonsils Enlarged, tender neck lymph nodes No symptoms of colds, such as cough or sneezing 	Penicillin V or amoxicillin for 10 days; if allergy cephalexin, roxithromycin, azithromycin, clarithromycin or clindamycin	not specified
Europe					
European Union		European Society of Clinical Microbiology and Infectious Diseases ²³	RADT if Centor score or modified Centor score ^{13,14} ≥ 3	Penicillin V, 2-3x daily for 10 days	Ibuprofen; paracetamol
France		Haute Autorité de Santé ³⁰	RADT if modified Centor score ^{13,14} ≥ 2	Amoxicillin 1 g 2x daily for 6 days; if allergies cefuroxime or josamycin	not specified
Germany		Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin ²⁴	Treatment if Centor score or modified Centor score ^{13,14} ≥ 3 ; RADT or culture only for intermediate scores	Penicillin; if allergy erythromycin	Paracetamol; ibuprofen
Italy		Italian Panel on the Management of Pharyngitis in Children ²⁸	RADT if modified Centor score ^{13,14} ≥ 2	Amoxicillin 50 mg/kg/d 2-3x daily for 10 days	Paracetamol; ibuprofen

(Continues)

TABLE 1 (Continued)

Region	Country	Issuer of guideline or backing organizations	Criteria for antibiotic therapy	Antibiotic treatments	Symptomatic treatments
	Netherlands	Dutch College of General Practitioners ²⁶	Not specified; antibiotics almost never indicated	Penicillin; if peritonsillar infiltrate suspected: amoxicillin/clavulanic acid	NSAIDs not recommended as standard treatment
	Russian Federation	Scientific Center of Children's Health ²⁵	RADT if signs of bacterial pharyngitis; confirmation by culture unless treatment is urgent	Penicillin or amoxicillin 10 days; if allergy cephalexin, cefadroxil, clindamycin, clarithromycin or azithromycin	NSAIDs; aspirin in adults
	Spain	Sociedad Española de Medicina de Familia y Comunitaria, Grupo de Estudio de la Infección en Atención Primaria de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, Sociedad Española de Médicos Generales y de Familia, Sociedad Española de Farmacia Familiar y Comunitaria, Sociedad Española de Médicos de Atención Primaria, Sociedad Española de Otorrino-laringología y Patología Cérvico-Facial ²⁹	Community outbreak, immunosuppression, previous ARF, severe symptoms; RADT or treatment if not available if Centor score ¹³ ≥ 3	Penicillin V; alternatively penicillin G, amoxicillin or cefadroxil for 8-10 days; if allergy josamycin or diacetyl-midecamycin	Ibuprofen; diclofenac; flurbiprofen
	Sweden	Medicinal Products Agency ²⁷	RADT if Centor score ¹³ ≥ 3	Penicillin V for 10 days; if allergy clindamycin	Paracetamol; NSAIDs; aspirin
	United Kingdom	National Institute for Health and Clinical Excellence ³¹	Treatment if Centor score ¹³ ≥ 3 (or use FeverPAIN score)	Penicillin V for 5-10 days; if allergy clarithromycin or erythromycin	Paracetamol; ibuprofen; medicated lozenges
Middle East					
	Iran	Islamic Azad University ⁴⁴	Exudate plus enlarged tender cervical nodes	Benzathine penicillin G injection or amoxicillin	not specified
	Iran	Iran University of Medical Science ⁴⁵	RADT followed by culture	Penicillin	not specified
	Israel	Ben-Gurion University ⁴⁶	RADT in children and adolescents culture, if RADT negative, for acute pharyngitis except if viral features (e.g. rhinorrhea, cough, oral ulcers, hoarseness), following IDSA ¹⁰⁵	Penicillin V, amoxicillin or benzathine penicillin G; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin ¹⁰⁵	Acetaminophen or NSAID; aspirin to be avoided in children ¹⁰⁵
	Saudi Arabia	Ministry of Health ⁴⁷	Treatment if modified Centor score ^{13,14} ≥ 4 ; culture or RADT if score 2-3	Penicillin V 500 mg 2x daily for 10 days; if allergy cephalexin 500 mg 2x daily	not specified
	Turkey	Osmangazi University ⁴⁸	Treatment if Centor score ¹³ ≥ 3	Penicillin and erythromycin	not specified
North America					
	Canada	College of Family Physicians ³²	Treatment if Centor score ¹³ ≥ 3 ; RADT if Centor score = 2	Penicillin V	NSAIDs
	Mexico	Instituto Mexicano del Seguro Social ³³	Treatment if Ebell score ¹⁰⁶ 4-5; RADT if Ebell score 1-3	Benzathine penicillin G injection; if allergy macrolides; second line: amoxicillin/clavulanic acid	not specified

(Continues)

TABLE 1 (Continued)

Region	Country	Issuer of guideline or backing organizations	Criteria for antibiotic therapy	Antibiotic treatments	Symptomatic treatments
Oceania	Mexico	Centro Nacional de Excelencia Tecnológica en Salud ³⁴	Treatment if modified Centor score ^{13,14} ≥ 4	Penicillin, clindamycin, amoxicillin/clavulanic acid, benzathine penicillin G, first generation cephalosporin	Paracetamol or ibuprofen; lidocain spray or solution for adults
	USA	American Academy of Family Physicians ³⁵	Treatment if modified Centor score ^{13,14} ≥ 4 ; RADT if score 1-3	not specified	not specified
	USA	American Heart Association ³⁶	RADT or culture if symptoms suggest GAS; no test if symptoms suggest viral infection	Penicillin V, amoxicillin or benzathine penicillin G 10 days; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin	not specified
	USA	Infectious Diseases Society of America ^{105,37}	RADT, in children and adolescents culture if RADT negative, for acute pharyngitis except if viral features are present (e.g. like rhinorrhea, cough, oral ulcers, and/or hoarseness)	Penicillin V, amoxicillin or benzathine penicillin G 10 days; if allergy cephalexin, cefadroxil, clindamycin, azithromycin or clarithromycin	Paracetamol or NSAIDs; aspirin to be avoided in children
South America	Australia	New South Wales Health ⁵⁵	Treatment if modified Centor score ^{13,14} ≥ 3 ; plus cultures optionally if score 3-4	Penicillin V 15 mg/kg/dose 12 hourly for 10 days; if allergy roxithromycin 4mg/kg/dose 12 hourly for 10 days	Paracetamol 15 mg/kg/dose (≤ 1 g) 4x daily for 1-2 days or ibuprofen 5 mg/kg/dose (≤ 400 mg) 3x daily for 1-2 days
	New Zealand	Heart Foundation ⁵⁶	Culture and start treatment if ≥ 2 of following: Maori or Pacific, age 3-35 years, crowded or low socioeconomic circumstances	Penicillin V or amoxicillin or benzathine penicillin G; if allergy roxithromycin or erythromycin	Paracetamol or NSAIDs; aspirin to be avoided in children
	Latin America	Asociación Panamericana de Infectología ⁵¹	Treatment if Centor score ¹³ ≥ 3 ; RADT if score = 2	Penicillin V for 10 days or benzathine penicillin G; if allergy erythromycin	Analgesics; NSAIDs; supportive treatment
	Argentina	Sociedad Argentina de Infectología, Sociedad Argentina de Pediatría, Sociedad Argentina de Medicina, Sociedad Argentina de Bacteriología, Micología y Parasitología Clínica ⁴⁹	Treatment if modified Centor score ^{13,14} ≥ 3 ; RADT if score 2-3	Penicillin 2x daily for 10 days, amoxicillin 1x daily for 10 days, if oral treatment not possible benzathine penicillin G; if allergy clarithromycin or clindamycin	NSAIDs; paracetamol; topical anaesthetics
	Brazil	Agência Nacional de Vigilância Sanitária ⁶	Clinical signs of bacterial pharyngotonsillitis	Benzathine penicillin G or penicillin V; if allergy erythromycin, azithromycin or clindamycin	not specified
	Brazil	Associação Brasileira de Otorrinolaringologia e Cirurgia Cérvico-Facial ⁵⁰	Pharyngotonsillitis with aggravating clinical or epidemiological factors	Amoxicillin, cefuroxime, amoxicillin-clavulanate for 10 days, or ceftriaxone	not specified

Abbreviations: ARF, acute rheumatic fever; NSAID, non-steroidal anti-inflammatory drug; penicillin G, benzylpenicillin; penicillin V, penicillin VK, phenoxymethyl-penicillin; RADT, rapid antigen detection test; USA, United States of America.

Eighteen of the 33 guidelines that give recommendations for antibiotics advise the duration of treatment. All indicate a 10-day course of antibiotics, except the guidelines from France, Spain,

the United Kingdom and China (Hong Kong), which recommend 6 days,³⁰ 8-10 days,²⁹ 5-10 days³¹ and 5-7 days of treatment,⁸ respectively.



FIGURE 1 Origin of worldwide treatment guidelines. Note: Numbers refer to the guidelines that are listed in the REFERENCES and shown in Table 1 (regional guidelines: Europe²³; Latin America⁵¹). Source of blanc world map: Wikimedia Commons¹⁰⁷

3.4 | Recommendations for other treatments

Although 33 of the 36 guidelines provide recommendations regarding antibiotics, only 20 discuss other sore throat treatments. Of these 20 guidelines, 11 recommend paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of fever and pain, four recommend only NSAIDs,^{32,46,29,25} one recommends only paracetamol⁵² and one advises against the standard use of NSAIDs, because of their potential systemic side effects.²⁶ Furthermore, four guidelines recommend topical treatments such as lozenges, gargles or sprays for analgesic treatment.^{42,49,34,31} The review of Chinese medicinal herbs describes antiviral, anti-asthmatic, antitussive and fever-relieving herbs as the basic elements of a traditional prescription for sore throat, detailing the therapeutic approaches for the different symptoms.³⁸

Among the guidelines recommending symptomatic therapies, only one, from Australia,⁵⁵ specifies the duration of the treatment (ie, 1 to 2 days).

4 | DISCUSSION

Several previous reviews have analysed guidelines for the management of sore throat in children and adults.⁶⁵⁻⁶⁸ These reviews include guidelines published up to 2006,⁶⁵ 2010,⁶⁶ 2012⁶⁸ and 2015 (date of latest reference),⁶⁷ respectively. The major limitations of these reviews are the restrictions to North American and European guidelines,⁶⁵⁻⁶⁷ to English language^{67,68} and to published literature.^{66,67} To our knowledge, the present work is the first review of sore throat guidelines that

has no geographic or linguistic restrictions, and includes guidelines not published in the literature. The fact that guidelines from either primary care or other fields of expertise were considered contributed to the diversity of the recommendations.

Major limitations of the present review include the restriction of literature searches to a limited string of key words and a 10-year limit. The use of wider criteria and of iterative techniques would have allowed identifying a larger number of guidelines. Guidelines published more than 10 years ago are likely to be out of date and no longer in use. The set of key words, which were used across different databases to increase the reach of the searches, was chosen to correspond to the words a general practitioner might use to search for up to date guidelines. The principal restraint for the internet searches was the use of English as principal language, although limited internet searches were also performed in Arabic, Chinese, French, Russian, Spanish, German and Portuguese; the first six correspond to the official languages of the World Health Organization. Although guidelines in any language were considered, the search methods may have introduced a bias in favour of the Western industrialized countries. Also in these areas guidelines tend to be published more frequently, both in the scientific literature and on the internet.

The review of the guidelines reveals important divergences regarding diagnostic and antibiotic treatment criteria in different countries. A large variety of clinical and/or laboratory criteria are proposed to identify and treat GAS infection. The reliance on merely clinical criteria in many of the recent guidelines is surprising, as few patients present with the typical signs and symptoms of GAS pharyngitis described in the guidelines, and neither clinical history nor physical examination

can differentiate between GAS infection and other causes of sore throat.⁶⁹ While lab tests may not be readily at hand in all regions (e.g. Africa), guidelines of many countries where the tests are available choose not to use them (e.g. several Middle East and Asian countries, Australia and New Zealand). Rather than by the availability of the lab tests, the large variability in the diagnostic criteria may be explained by the uncertainty of the scientific basis that underlies the different recommendations. In a well-documented ARF outbreak in the late eighties in Utah (USA), half of the cases did not have any symptoms of sore throat, and swab tests were negative in a large proportion of the patients.^{70,71} Furthermore, regarding the laboratory tests, neither RADT nor bacterial cultures can differentiate individuals with GAS pharyngitis from GAS carriers with intercurrent viral pharyngitis.³⁶

Comparing the guidelines from different regions, the most unexpected observation is that their differences in the antibiotic treatment criteria do generally not reflect the large variations in the risk of GAS infection and its complications across the world. While ARF and RHD have declined worldwide, they still remain major a cause of morbidity and mortality in some regions.^{9,72} The African, South-East Asia and Western Pacific regions are most affected, accounting for 84% of all prevalent cases and 80% of all estimated deaths because of RHD globally in 2015.⁷³ Yet, with the exception of New Zealand,⁵⁶ the guidelines from Africa (Egypt), South-East Asia (India, Malaysia, Thailand) and Western Pacific (Australia, New Zealand) appear to mirror those of Europe and North America, where the incidence of ARF and the prevalence of RHD are about 100 times lower.^{11,72} It might be argued that the systematic antibiotic treatment of sore throat has enabled reduction in the incidence of complications from GAS in the developed nations. If so, these guidelines would be particularly beneficial for the high risk countries. Yet, there is no evidence that the near disappearance of ARF and RHF in the industrialized countries, such as the United States of America, since the beginning of the last century was related to the wide use of antibiotics since the early fifties.⁷¹ Furthermore, the appropriate duration of antibiotic therapy for streptococcal pharyngitis is controversial regarding clinical efficacy, bacteriological eradication and complication rates.⁷⁴⁻⁷⁶ Notwithstanding these considerations, many guidelines give no indication for the duration of antibiotics, and only few suggest a shorter treatment than the 10-day standard regimen.^{29-31,8}

Based on the data from older trials, antibiotics can significantly reduce the incidence of ARF and other complications (including otitis media and tonsillar abscess), in patients with acute pharyngitis.²² However, in high-income countries, where not only the overall incidence of GAS infections is low, but also the rates of complications from the latter are reduced, the number needed to treat may exceed an acceptable limit to make treatment worthwhile to reduce these complications.²² Any use of antibiotics, but especially widespread and excessive use,^{77,78} and long treatment durations,⁷⁹ increase the risk of drug resistance. Rising antimicrobial resistance threatens the national health care systems and economics, including those of the industrialized countries.^{78,80} To prevent the unnecessary use of antibiotics, national and international treatment guidelines are of prime importance.⁸¹ Whilst most prescribers in the USA and in Europe have

easy access to antibiotic guidelines, many do not trust these guidelines.^{82,83} Only a minority of physicians in the USA^{84,85} and in many European countries^{86,87} follow current guidelines to treat sore throat and prevent ARF. By contrast, effective implementation of appropriate guidelines was shown to improve general practitioners' adherence and reduce unnecessary and inappropriate use of antibiotics.^{88,89}

In African countries where no national guidelines for the treatment of acute pharyngitis exist, such as Nigeria,⁵⁴ antibiotics are prescribed empirically for most patients presenting with sore throat.⁶³ Such practices may fuel deadly drug-resistant infections, such as bacterial pneumonia and diarrhoea.⁹⁰ Today, a large proportion of salmonella infections have become resistant to the most widely available antibiotics in Nigeria⁹¹ and Kenya.⁹² In Asian countries where many people take antibiotics for infections without any prescription,^{93,94} alarming levels of multidrug resistance have emerged.^{95,96} Thus, rather than helping vulnerable populations plagued by life-threatening infections, such as HIV, tuberculosis and certain respiratory viruses, excessive and irrational uses of antibiotics seriously compound their healthcare issues.

Besides GAS, group B, C or G beta-hemolytic streptococci and *Fusobacterium necrophorum* have been identified in sore throat. There is some doubt about whether they are truly pathogenic or require antibiotic treatment.⁹⁷⁻⁹⁹ Some of these infections have on rare occasions been associated with suppurative complications, e.g. peritonsillar abscess (quinsy), requiring specialist care (such as surgical drainage) and antibiotic treatment. Serious complications of the fusobacteria, such as thrombophlebitis of the internal jugular vein (Lemierre's syndrome), are exceedingly rare.⁹⁸ Beta-hemolytic streptococci other than GAS are not associated with ARF and RHD.

While well-targeted antibiotic treatments may prevent the spread of GAS pharyngitis, reduce cases of ARF where this is prevalent, and help treating suppurative complications of bacterial infections, their overall efficacy in reducing the duration of symptoms of sore throat is modest.^{100,22} Analgesics and in particular NSAIDs are more effective than antibiotics to treat sore throat symptoms such as pain and fever.^{101,100} Given the fact that symptomatic therapy represents the primary medical need for most patients,¹⁰² it is striking that many guidelines only provide guidance for antibiotic treatment of sore throat. Furthermore, besides throat pain and fever, acute pharyngitis may present with a variety of other symptoms, such as oral ulcers, difficulties in swallowing, hoarse voice, cough, rhinorrhoea, conjunctivitis, painful and swollen glands, skin rash, gastrointestinal symptoms and malaise.^{69,103} The only guidance, however, that discusses symptoms other than pain and fever is the review of Chinese traditional medicines.³⁸ Although the prolonged use of analgesics is associated with a risk of serious side effects, just a single guideline specifies their duration.⁵⁵

In conclusion, the important differences observed in the worldwide treatment guidelines for sore throat do not seem to have a rational basis. While the guidelines may reflect the historical background (such as the high prevalence of ARF in the USA during the 19th century) or the adoption of recommendations from external guidelines (e.g. by African, South-East Asia and Western Pacific countries), they have often not been adapted to the actual,

present-day local incidence of GAS pharyngitis or its complications. Yet wide variations are also observed within a single region, such as Europe. Some variation may reflect an evolving understanding of this common disease and reflect uncertainty. Another explanation might be related to the issuers' opinions and priorities, rather than scientific evidence, and these may be country specific or related to differences in systems of healthcare.¹⁰⁴ For healthcare providers, the lack of harmonization or consistency is likely to impact on the adoption of the guidelines and hence the quality of care.^{82,105}

Implementation of appropriate treatment guidelines can increase physicians' adherence and correct use of the available treatments. Although symptomatic treatments, rather than antibiotics, are the mainstay of the therapeutic management for sore throat, recommendations on symptomatic treatment are missing in many guidelines. This may cause unnecessary suffering and drive the ineffective use of antibiotics. As sore throat is one of the commonest reasons for using antibiotics worldwide, these omissions impede current international strategies to reduce antibiotic use as part of antimicrobial stewardship.^{87,88}

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