

Differences Among International Pharyngitis Guidelines: Not Just Academic

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ABSTRACT

PURPOSE Many countries have national guidelines for the treatment of pharyngitis. We wanted to compare the recommendations and the reported evidence in national guidelines for the management of acute sore throat in adults.

METHODS Guidelines were retrieved via MEDLINE and EMBASE and through a Web-based search for guideline development organizations. The content of the recommendations and the underlying evidence were analyzed with qualitative and bibliometric methods.

RESULTS We included 4 North American and 6 European guidelines. Recommendations differ with regard to the use of a rapid antigen test and throat culture and with the indication for antibiotics. The North American, French, and Finnish guidelines consider diagnosis of group A streptococcus essential, and prevention of acute rheumatic fever remains an important reason to prescribe antibiotics. In 4 of the 6 European guidelines, acute sore throat is considered a self-limiting disease and antibiotics are not recommended. The evidence used to underpin these guidelines was different in North America and Europe. North American guidelines cited more North American references than did European guidelines (87.2% vs 48.0%; odds ratio, 4.6-11.9; $P < .001$).

CONCLUSION Although the evidence for the management of acute sore throat is easily available, national guidelines are different with regard to the choice of evidence and the interpretation for clinical practice. Also a transparent and standardized guideline development method is lacking. These findings are important in the context of appropriate antibiotic use, the problem of growing antimicrobial resistance, and costs for the community.

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INTRODUCTION

In many countries, clinical practice guidelines are developed to bridge the gap between research and practice.¹ In an era of easy access to international research data, we would expect guideline recommendations on the same clinical topic to be similar.²⁻⁴ Several authors, however, have pointed to differences that could be explained by insufficient evidence, different interpretations of the evidence, unsystematic guideline development methods, the influence of professional bodies, patient preferences, cultural and socioeconomic factors, or characteristics of health care systems.⁵⁻¹⁸ Three studies explored differences of content in relation to differences of the cited scientific evidence supporting the recommendations.⁷⁻⁹ Selective use of evidence can lead to differences in practice recommendations and, consequently, to important disparities in patient care and outcome. The World Health Organization (WHO) and other organizations recommend using a rigorous procedure to ensure that practice guidelines are supported by the best available evidence.¹⁹⁻⁴⁰ Nineteen key components of guidelines for guidelines are proposed to improve the use of research evidence.

In this study we focus on guidelines for managing acute sore throat, a relatively straightforward condition for which agreement can be antici-

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pated. The treatment recommendations have public health implications through the use of antibiotics and antibiotic resistance rates. We explore the content of these guidelines and investigate whether potential differences can be explained by variation in the use of scientific evidence. We also evaluate whether the guidelines are in agreement with the WHO recommendations.¹⁰⁻³⁴

METHODS

We performed a Web-based search for organizations that develop guidelines⁴¹ on acute sore throat, including the TRIP database, the Cochrane Library, Sumsearch, DARE, Clinical Evidence, EMBASE and MEDLINE (from 1970 to May 2006). We used the MeSH terms "pharyngitis," "sore throat," and "practice guidelines." Systematic reviews and evidence reports without specific practice recommendations were excluded.

The quality of the development method of pharyngitis guidelines was assessed by means of the 19 WHO key components.

The recommendations concerning the use of diagnostic tests, treatment (indications for antibiotics, dose,

and duration), and criteria for referral were extracted and independently analyzed by 2 authors (M.D.M., J.M.) who have experience in the domain of acute sore throat research.^{42,43} Discrepancies were resolved through discussion.

We compared the cited references for the recommendations in each guideline. The number of references and the overlap of citations was quantified by calculating the proportion of shared references among guidelines according to the publication dates of the guideline and its references.⁷ For each reference we determined the study design (meta-analysis, review, randomized controlled trial, other) and the country of origin (North America, Europe, other). Citations (expressed as proportions) were compared using Fisher's exact test. For statistical analysis we used SPSS 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Selection of Guidelines

We identified 14 guidelines and included 10 in our analysis: 6 from Western Europe, 3 from the United States, and 1 from Canada (Table 1).⁴⁴⁻⁵³ Four guide-

Table 1. Characteristics of Selected Guidelines on Acute Sore Throat

Country (+ code)	Organization Responsible for Guideline Development	Web Sites of the Selected Guidelines	Title in English	Year of Publication (No. of Pages)	Levels of Evidence or Grades of Recommendation
Belgium (BE01) ⁴⁴	Scientific Organisation of Flemish GPs, WVVH	http://www.health.fgov.be/antibiotics/	Acute Sore Throat: Guidelines for Good Clinical Practice	1999 (11)	No
The Netherlands (NL02) ⁴⁵	Dutch College of General Practitioners, NHG	http://nhg.artsennet.nl	Standard Acute Sore Throat	1999 (8)	No
France (FR03) ⁴⁶	Agence du Médicament	http://agmed.sante.gouv.fr	Antibiotic Therapy by General Way in General Practice: ENT Infections	1999 (8)	Yes
Finland ⁴⁷ (FI04)	Duodecim	http://www.guideline.gov	Sore Throat and Tonsillitis	2001 (4)	Yes
England ⁴⁸ (E05)	National Health Service, PRODIGY	www.prodigy.nhs.uk	Acute Sore Throat	2004 (9)	Yes
Scotland ⁴⁹ (SC06)	Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk	Management of Sore Throat and Indications for Tonsillectomy	1999 (24)	Yes
Canada ⁵⁰ (CA07)	Canadian Medical Association (CMA)	http://www.hlth.gov.bc.ca	Diagnosis and Management of Sore Throat	2001 (4)	No
United States ⁵¹ (US08)	Institute for Clinical Systems Improvement (ICSI)	www.guideline.gov	Acute Pharyngitis	2005 (33)	Yes
United States ⁵² (US09)	Infectious Disease Society of America (IDSA)	www.guideline.gov	Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis	2002 (13)	Yes
United States ⁵³ (US10)	American College of Physicians & American Society of Internal Medicine-Centers for Disease Control and Prevention (ACP/ASIM)	www.guideline.gov	Principles of Appropriate Antibiotic Use for Acute Pharyngitis in Adults (+ Background)	2001 (12)	Yes

lines aimed at children only were excluded (United Kingdom, Finland, Michigan, Singapore). All the European guidelines—Belgium (BE01), the Netherlands (NL02), France (FR03), Finland (FI04), England (E05), and Scotland (SC06)⁴⁴⁻⁴⁹—were national guidelines. The Canadian guideline (CA07) was disseminated by the Government of British Columbia.⁵⁰ The US guidelines (US08, US09, US10) were identified through the National Guideline Clearinghouse.⁵¹⁻⁵³

Comparison of Recommendations

Points of Agreement

The guidelines are in agreement on the general management of patients with acute sore throat in the following recommendations (Table 2). Group A β -hemolytic streptococcus (GABHS) is accepted as a pathogen for the diagnosis. No internationally accepted clinical scoring system (based on history and physical examination) can sufficiently predict a positive throat culture and guide antibiotic treatment without further investigation. Serologic tests (antistreptolysin O, C-reactive protein, leukocyte count) are not recommended. For the treatment of acute sore throat, narrow-spectrum penicillin is the first choice of antibiotic for the treatment of GABHS. Nearly all agree that antibiotics aim to shorten the clinical evolution, relieve symptoms, and limit the spread of GABHS in the case of high-risk and very ill patients. Antibiotics are not indicated for the prevention of acute glomerulonephritis.

Differences Among Guidelines

For the diagnosis of GABHS, the Centor criteria⁵⁴ (fever greater than 38.5°C, absence of cough, tonsillar exudate, and enlarged cervical glands) are used in only 4 guidelines (US08-10, CA07). In the clinical decision model of US10, the rapid antigen test is recommended when 2 or 3 Centor criteria are present. There is no international consensus on the use of the rapid antigen test: it is recommended in the 3 US guidelines and in the French and Finnish guidelines. The others do not recommend its use because of the high prevalence of streptococcal carriers (5% to 20%) and its modest sensitivity (65% to 80%) in primary health care (BE01, NL02, SC06). Recommendations on the use of a throat culture also differ. A throat culture is advised in 2 US (US08, US09), the Canadian, and Finnish guidelines. One US guideline recommends a throat culture when the rapid antigen test result is negative for GABHS or when the test is not available (US08). According to the Belgian, Dutch, French, Scottish, English, and 1 North American guideline (US10), the results of a throat culture arrive too late to have a major influence on the clinical course, and a throat culture is therefore not recommended.

For treatment, there is no consensus on the use of

antibiotics. Prevention of acute rheumatic fever is a major reason to recommend antibiotics in the North American (CA07, US08, US09, US10), French, and Finnish guidelines. Prevention of local complications (retrotonsillar abscess, sinusitis, otitis media) is another reason to prescribe antibiotics in 2 US (US09 and US10) and the Canadian (CA07) guidelines. In the North American, French, and Finnish guidelines, antibiotics are advised when a rapid antigen test result or throat culture is positive for GABHS. All guidelines recommend penicillin as first choice; however, French guidelines recommend aminopenicillins and cephalosporins.

Quality of Assessed Guidelines

It was not possible to score the guideline development method according to the 19 WHO key components, because they were seldom explicitly mentioned in the clinical guidelines (priority setting; group composition and consultations; declaration and avoidance of conflicts of interest; group processes; identification of important outcomes; explicit definition of the questions and eligibility criteria; type of study designs for different questions; identification of evidence; synthesis and presentation of evidence; specification and integration of values; making judgments about desirable and undesirable effects; taking account of equity; grading evidence and recommendations; taking account of costs; adaptation, applicability, and transferability of guidelines; structure of reports; methods of peer review; planned methods of dissemination and implementation; and evaluation of the guidelines). It was also impossible to infer these components. We therefore evaluated only 1 key component, ie, identification of evidence.

Comparison of Evidence

The 10 guidelines included a total of 544 references of which 308 were different. Fifty-eight references were shared by 2 guidelines. Eight guidelines used the same 2 references to studies on rheumatic fever that were published in the 1950s.^{55,56} Not one of the available meta-analyses (eg, Cochrane review) or landmark studies was used in all the guidelines. Most first authors of the studies cited in the guidelines (63.8%) originated from North America. North American guidelines cited more North American publications than did European guidelines (87.2% vs 48.0%; odds ratio, 4.6-11.9; $P < .001$) (Table 3). In 2 North American guidelines (US08, US09) only 2% of the references referred to non-American studies; no mention was made of the 3 European randomized placebo controlled clinical trials published in the 1990s^{42,57,58} or the Cochrane review. Only 1 US guideline (US10) referred to 21 European references (of a total of 72 references), including the 3 European trials.^{42,57,58}

Table 2. Comparison of the Recommendations in Acute Sore Throat Guidelines

Diagnosis and Treatment	European Guidelines						North American Guidelines			
	Belgium ⁴⁴ BE01	The Netherlands ⁴⁵ NLO2	France ⁴⁶ FR03	Finland ⁴⁷ FI04	England ⁴⁸ E05	Scotland ⁴⁹ SC06	Canada ⁵⁰ CA07	ICSI ⁵¹ US08	IDSA ⁵² US09	Position Paper (ACP) ⁵³ US10
Diagnosis										
History	+	+	+	+	+	+	+	+	+	+
Clinical examination	+	+	+	+	+	+	+	+	+	+
Centor criteria	-	-	-	-	-	-	+	+	+	+
GABHS (rapid antigen or strep) test	-	-	+	+	-	-	-	+	+	+
Culture	-	-	-	+	-	-	+	+	+	-
Treatment										
Prescribe antibiotics										
High-risk and very ill patients	+	+	+	-	+	+	+	+	+	+
Centor criteria	-	-	-	-	-	-	-	-	-	+
GABHS test result positive	-	-	+	+	-	-	-	+	+	+
GABHS test result negative; culture positive	-	-	+	+	-	-	-	+	+	-
Culture positive	-	-	-	+	-	-	+	+	+	-
Reason for antibiotics										
Shorten clinical evolution	+	+	+	+	-	-	+	+	+	+
Prevent ARF	-	-	+	+	-	-	+	+	+	+
Prevent GNF	-	-	-	-	-	-	-	-	-	-
Prevent local complications	-	-	-	-	-	-	+	-	+	+
Limit spread of GABHS	-	+	+	+	+	+	+	+	+	+
Small-spectrum penicillin	+	+	+	+	+	+	+	+	+	+

ACP = American College of Physicians; ARF = acute rheumatic fever; GABHS = group A β -hemolytic streptococci; GNF = glomerulonephritis; ICSI = Institute for Clinical Systems Improvement; IDSA = Infectious Disease Society of America.

* If a rapid antigen (strep) test is not available.

DISCUSSION

We have identified fundamental differences in the recommendations for the management of acute sore throat, in particular among guidelines from North America, France, and Finland on the one hand, and from Belgium, The Netherlands, England, and Scotland on the other. Recommendations differ with regard to the use of a rapid antigen test or throat culture and the indication for antibiotics. North American, French, and Finnish guidelines consider diagnosis of GABHS necessary, and prevention of acute rheumatic fever remains an important reason to recommend antibiotics. In 4 of the 6 European guidelines, acute sore throat is considered a self-limiting disease, and antibiotics are not recommended. The evidence used to underpin the guidelines was different in North America and Europe. Our bibliographic analysis shows that North American guidelines mainly rely on publications from authors of the same region.

To our knowledge, this study is the first that simul-

taneously compares the clinical content of the recommendations and the evidence of guidelines on acute sore throat. Although many national sore throat guidelines are easily available on the Internet, not all existing guidelines could be identified through the indexed literature or the Internet. Consequently, a potential limitation of our study is that we included only a selection of all national guidelines and omitted regional or local guidelines. Also, the effect of guidelines on public health in specific regions still needs to be studied. Even a well-constructed guideline is a hypothesis that needs to be tested unless it has been based on the results of practice-based effectiveness trials.

Explaining Differences in Recommendations

The North American, French, and Finnish guidelines recommend prescribing antibiotics to prevent acute rheumatic fever if streptococcal pharyngitis is suspected. This recommendation is most likely based on

Table 3. Type of Studies and European or American Articles Cited in the 10 Guidelines on Acute Sore Throat

Type of Study	BE01	NL02	FR03	FI04	E05	SC06	CA07	US08	US09	US10	Total
Cochrane, No.	1	1	0	3	2	0	1	0	0	1	9
Other systematic reviews, No.	9	6	4	1	4	5	0	4	0	1	34
Randomized controlled trial, No.	23	20	26	1	0	22	1	7	26	17	143
Guidelines, No.	1	4	4	0	5	2	1	2	7	3	29
Overview/others	43	54	35	0	5	44	9	26	63	50	329
Total cited, No.	77	85	69	5	16	73	12	39	96	72	544
European, No. (%)	35 (45.5)	46 (53.5)	27 (39.1)	1 (20.0)	13 (81.3)	31 (42.5)	0	1 (2.6)	3 (3.1)	21 (29.2)	178 (32.7)
American, No. (%)	40 (52.0)	36 (41.9)	39 (56.5)	1 (20.0)	2 (12.5)	38 (52.1)	11 (91.7)	38 (97.4)	92 (95.8)	50 (69.4)	347 (63.8)
Other, No. (%)	2 (2.5)	3 (4.6)	3 (4.4)	3 (60.0)	1 (6.2)	4 (5.4)	1 (8.3)	0	1 (1.1)	1 (1.4)	19 (3.5)

the findings of the Fort Warren studies in the United States in the 1950s.^{55,56,59-62} They found a 0.3% to 3% reduction of the incidence of acute rheumatic fever if streptococcal angina was treated with parenteral penicillin. These findings, however, have never been confirmed in other trials with penicillin,⁶³⁻⁶⁵ nor have they been confirmed in consecutive prospective studies.⁶⁶⁻⁶⁹ Almost a half-century ago, an editorial claimed:

The statement that 3% of such streptococcal infections will be followed by ARF [acute rheumatic fever] rests mainly on the extensive work at Fort Warren, and it is not at all certain that conditions reflect these in general practice. There can therefore be no hard and fast rule that 3% of streptococcal infections are followed by ARF.⁷⁰

By the 1980s acute rheumatic fever was considered a vanishing disease that had disappeared in the Western world.^{71,72} Some local revivals of acute rheumatic fever were registered in the United States (N = 164) and in Italy (N = 21), but closer analysis suggested that antibiotics did not play an important role.^{73,74} The morbidity and mortality rates for acute rheumatic fever in Western countries had clearly been declining before the use of antibiotics in the 1950s, and an effect of antibiotic use could not be shown.^{75,76} That some guidelines rely on the results of the Fort Warren studies, whereas others do not, may explain the observed differences. Likewise, regional variation of the incidence of acute rheumatic fever could contribute. The guidelines in our survey, however, did not originate from countries where acute rheumatic fever is still endemic (Aboriginal population of northern Australia, some developing countries, and tropical regions).

Where some guidelines recommend penicillin to prevent acute rheumatic fever (FR03, FI04, CA07, US08-10), other guidelines (BE01, NL02, E05, SC06) consider acute sore throat, even a streptococcal infection, as a self-limiting disease and state that antibiotics

have only a limited effect on shortening the clinical evolution.^{42,57,58,75-79}

Guidelines also differ with regard to the use of diagnostic tests. Those promoting outpatient tests, either a rapid antigen test or a throat culture (FR03, FI04, CA07, US08-10), recommend penicillin to treat GABHS. Others (BE01, NL02, E05, SC06) discourage diagnostic testing, and reserve antibiotics for high-risk patients only.

Important Differences of Evidence

Two North American (US08, US09) and the Canadian guidelines do not refer to relevant European trials. Both North American guidelines do not cite the Cochrane review (Table 3). Other authors have mentioned that only a few guidelines use formal, systematic methods to combine scientific data.¹³ Also, Cochrane reviews are not always used even though they may be among the most relevant sources of evidence.¹² It was not possible to assess the methods used by guideline developers to select scientific evidence supporting the guidelines.

Perhaps the lack of European trials^{42,57-58} in most North American guidelines is caused by selection bias. A recent study found that open review of abstracts (when authors' names and institutions are included) favors authors from the United States or from English-speaking countries outside the United States and from prestigious academic institutions.⁸⁰ This finding cannot explain why the Cochrane review was not included, however.

We found that evidence is not interpreted in the same way, perhaps because North American guidelines are often developed by (ear, nose, and throat) specialists, whereas the first authors of the Belgian, Dutch, English, and Scottish guidelines are family physicians. Finally, although we have identified fundamental differences between most North American and European guidelines, 2 European guidelines, the French and Finnish, comply

with the American guidelines. The French guideline does not refer to the Cochrane review, whereas the Finnish guideline mentions it as 1 of its 5 references. As a result, in Europe the different management recommendations are also a topic for further research.⁸¹

Differences among guidelines are not merely academic; they have important consequences for daily practice.⁸² A patient consulting a family physician for acute sore throat will be managed differently according to the country. In France, North America, or Finland, a diagnostic test will be performed, and the treatment will depend on its result. In England, Scotland, Belgium, or the Netherlands, physicians will not use a diagnostic test, and the decision to prescribe penicillin will depend mainly on the patient's illness severity. Both approaches are based on scientific evidence. The differences seem to be related to selection or interpretation of the available studies. More uniform development methods could lead to more uniform guidelines, and when implemented, to more uniform practice. Our findings support the need for a transparent development procedure as recommended by WHO. The next step would be to convene guideline developers from various countries and learn more about how they weigh the evidence and how they formulate conclusions.

National guidelines on acute sore throat promote different clinical approaches, recommend different treatments, and cite different evidence. There is no evidence that regional variation is appropriate. Introduction of an explicit guideline development method for both European and North American guidelines may lead to more uniformity in the diagnosis and management of acute sore throat.

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