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A scoring system for management of acute pharyngo-tonsillitis in adults

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Abstract

Objectives: The aim of this study was to develop and evaluate a scoring system for the management of acute pharyngo-tonsillitis.

Methods: We conducted a prospective study between May 2004 and June 2005. Patients with acute pharyngo-tonsillitis were evaluated for causative pathogens and were assessed clinical symptoms and pharyngo-tonsillar finding by a clinical scoring system.

Results: A total 214 adult patients were enrolled in this study. *Streptococcus pyogenes* were identified at 13.6%. Thirty-one viruses were also identified by PCR. They were adenovirus (4.8%), influenza virus (1.0%), RS virus (6.3%), and human metapneumovirus (2.9%). Numbers of total white blood cells and levels of C-reactive protein showed a significant positive correlation with clinical scores ($p < 0.001$) and were also higher in cases with *S. pyogenes*. The clinical scores rapidly improved after the antimicrobial treatments in moderate cases and severe cases.

Conclusion: The current study strongly suggested that the clinical scoring system reflected disease severity well and would be very useful for evaluating clinical course and decision making for the antimicrobial treatment of acute pharyngo-tonsillitis.

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Keywords: Acute pharyngo-tonsillitis; Clinical score; *Streptococcus pyogenes*; CRP; WBC

1. Introduction

Sore throat is one of the commonest respiratory symptoms in general practice and the vast majority of adults presenting sore throat have acute pharyngitis. Acute tonsillitis also accompanies acute pharyngitis and is obvious from typical appearances of tonsils as crypts studded with purulent material or purulent exudations covering palatine tonsils [26,27].

The management of acute pharyngo-tonsillitis is an important issue for quality of care because this infectious disease is frequent in outpatients setting. Most of cases are caused by viral infections and are self-limiting by only symptomatic treatments. Approximately 5–15% of cases in

adults are caused by *Streptococcus pyogenes* (*S. pyogenes*) and prescribed antimicrobial agents [3,5,6,10,19–21]. In contrast to the rationale of managements for pharyngo-tonsillitis, antibiotics are actually prescribed to a majority of adult patients at approximately 75% [1,16]. The best way to manage adult patients with pharyngo-tonsillitis has still been controversial among countries [8,12,23–25,34]. Optimal management depends on both the clinical likelihood of infections with *S. pyogenes* and the relative importance assigned to the criteria to avoid over-use and/or under-use of antibiotics with preventing complications. It is important to develop a clinical scoring system easy to use and to assess accurate clinical features of acute pharyngo-tonsillitis with special emphasis on infections with *S. pyogenes* in adults [7,9].

We organized a nationwide prospective surveillance study group (Pharyngo-Tonsillitis Study Group: PhaTONS) in Japan during 2004–2005. The aims of this prospective study were to evaluate the causative pathogens of adult acute

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pharyngo-tonsillitis in comparison with clinical features. An appropriate scoring system was also developed and applied for evaluating severities and clinical course of acute pharyngo-tonsillitis.

2. Methods

2.1. Population

Adult outpatients with acute pharyngo-tonsillitis between ages of 15 and 80 years old, irrespective of gender, were eligible and were enrolled in this prospective study. The diagnostic criteria for acute pharyngo-tonsillitis included sore throat, histories of fever, erythema of pharyngo-tonsillar mucosa, and, if any, tonsillar exudates. Exclusion criteria included cases with complications that reduce antimicrobial treatments, antibiotics in preceding month, pregnancy, and immune deficiency including immunosuppressive medications.

2.2. General design

We designed the study as a prospective trial organized by a nationwide study groups (Pharyngo-Tonsillitis Study Group: PhaTONS) during May 2004–June 2005. Adult patients with pharyngo-tonsillitis were prospectively enrolled in this study. The severity and clinical courses of the disease were evaluated by a clinical scoring system (Table 1). Swabs from tonsillar crypts for identifying pathogens and blood examinations were performed at the first visit (day 0). The patients were treated with or without antibiotics according to the severity of illness. Briefly, the mild cases were treated with oral antibiotics or symptomatic management without antibiotics, the moderate cases were treated with oral antibiotics, and the severe cases were treated with oral or parenteral antibiotics. For the evaluation of relationship between doctors' habit of using and selecting antimicrobial agents and the severity of illness, antimicrobial agents were selected and used by physician's own decision. Informed consent approved by the Institutional Review Board was obtained from the patients at the time of enrollment in the study.

2.3. A clinical scoring system

We assessed the severity and clinical course of the disease using a scoring system consisting of symptoms and pharyngo-tonsillar findings (Table 1). We evaluated difficulties in a daily life, sore throat, and fever as symptoms and scored erythema and swelling of pharyngo-tonsillar mucosa and the presence of exudates or plugs in tonsils grading from 0 (none) to 2 (marked). Severities of the disease were classified into three groups according to total scores. Patients with total scores ≥ 9 , 4–8, and ≤ 3 were assigned into severe group, moderate group and mild group, respectively.

2.4. Identification of bacteria

Standard laboratory methods were performed to identify pathogenic bacteria according to the Manual of Clinical Microbiology (8th edition). Briefly, swabs from tonsillar crypts were cultured on sheep blood agar, chocolate agar and MacConkey agar plates overnight at 37 °C in 5% CO₂. *Haemophilus influenzae* (*H. influenzae*) were determined by growth in chocolate but not in blood agar plates, catalase test, and requirement of X and V factor. *Haemophilus haemolyticus* (*H. haemolyticus*) were differentiated from *H. influenzae* by haemolysis on blood agar plates. *Streptococcus pneumoniae* (*S. pneumoniae*) were identified by optochin susceptibility and bile solubility. *S. pyogenes* were confirmed by latex agglutination with commercially available latex reagen (BioMerieux, Marcy l'Etoile, France) and bacitracin susceptibility. Suspected *Staphylococcus aureus* (*S. aureus*) were identified by use of DNase testing and a Staphaurex latex test (Remel, Lenexa, USA). The growth of bacteria was graded from 0 to +4.

2.5. Detection of virus by PCR

We applied PCR to identify adenovirus and RT-PCR to identify human metapneumo virus (hMPV), influenza virus A and B, and respiratory syncytial (RS) virus A and B. Swabs from tonsillar crypts were suspended into minimum essential medium (MEM) with penicillin and streptomycin. Nucleic acid including RNA and DNA were purified using high pure viral nucleic acid purification kit (Roche, Basel,

Table 1
A clinical scoring system for acute pharyngo-tonsillitis

	Clinical scores		
	0	1	2
Symptoms			
Difficulties in a daily	Not so annoying	Annoying, but can work	Absence from work
Life sore throat/swallowing pain	Discomfort	Sore, but can swallow	Difficult to swallow
Fever	<37.5 °C	37.6–38.5 °C	<38.6 °C
Pharyngo-tonsillar findings			
Pharyngeal erythema or swelling	Mild	Moderate	Marked
Tonsillar erythema or swelling	Mild	Moderate	Marked
Presence of exudates or plugs in tonsils	None	Scattered	Whole tonsil

Switzerland). The final amplified products were separated by electrophoresis on 2% agarose gels and visualized by ethidium bromide.

2.6. Statistical analysis

Statistical analysis of data was performed using non-parametric test. Comparisons between two groups were assessed by Tukey–Kramer analysis. Comparisons of clinical outcomes of the disease were assessed by Wilcoxon signed-rank test. Correlation between clinical scores and numbers of WBC or levels of CRP were assessed Pearson regression analysis. Statistical tests were based on a level of significance of p -value less than 0.05. Calculations were performed using the statistical software package JMP6.0.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Populations

A total 236 adult patients with pharyngo-tonsillitis were enrolled in this study. During a study 22 patients were dropped out for incomplete follow-up and 214 patients (89.4%) were finally evaluated for causative pathogens and clinical outcomes of the disease. They were 114 males and 100 females, ranging in ages between 16 and 79 years old (mean 33.9 years old). Acute pharyngitis is a painful inflammation of the mucosa of the pharynx. Acute pharyngitis includes a sore throat and is characterized by signs of erythema of pharyngeal mucosa. Acute tonsillitis is an infectious inflammation of the pharyngeal tonsils. Acute tonsillitis accompanying acute pharyngitis includes a severe sore throat, painful and difficult swallowing, fever and chills and is characterized by signs of red, swollen tonsils which have a purulent exudative coating of white pus. The characteristics of illness in this study were classified in 165 cases with acute tonsillitis and 49 cases with acute pharyngitis (Table 2).

3.2. Pathogens

A total 234 pathogenic bacteria were identified in 157 (73.4%) out of a total 214 patients. The organisms were *S. pyogenes* (29 isolates, 13.6%), hemolytic streptococci (35 isolates, 16.4%), *H. influenzae* (52 isolates, 24.3%), *H. haemolyticus* (23 isolates, 10.7%), *S. aureus* (71 isolates, 33.2%), *S. pneumoniae* (11 isolates, 5.1%), *M. catarrhalis* (8 isolates, 3.7%), and others (13 isolates, 6.1%) (Table 3). There were no significant differences in distribution of bacteria between acute tonsillitis and pharyngitis.

Thirty-one viruses were identified by PCR. They were adenovirus (10 out of 205 cases, 4.8%), influenza virus (6 out of 205 cases, 2.9%), RS virus (2 out of 191 cases, 1.0%), and hMPV (13 out of 206 cases, 6.3%) (Table 3). Among 206 cases in which both bacterial culture and virus PCR

Table 2

Demography and disease of patients in this study

Populations	Numbers	Ratio (%)
Sex (male:female)	114:100	53.3:46.7
Age (y.o.)		
16–19	12	5.6
20–29	86	40.2
30–39	68	31.8
40–49	17	7.9
50–59	16	7.5
60–69	10	4.7
70–79	5	2.3
Diagnosis		
Acute tonsillitis	165	77.1
Acute pharyngitis	49	22.9
Severity		
Mild	33	15.4
Moderate	121	56.5
Severe	60	28.0

were performed, bacteria alone were identified in 128 cases (62.1%), virus alone were identified in 7 cases (3.4%), both bacteria and virus were identified in 23 cases (11.2%). In 48 cases (23.3%) neither bacteria nor virus was identified.

3.3. Correlations among clinical features and pathogens

Both severities of disease and inflammatory parameters were compared with pathogens. Although *S. pyogenes* together with *Hemolytic streptococci*, *H. influenzae*, *H. haemolyticus*, *S. aureus*, *S. pneumoniae*, *M. catarrhalis* were frequently identified among patients with acute pharyngo-tonsillitis, the clinical scores were not different among those

Table 3

Pathogens identified in this study

Pathogens	Numbers of isolates/cases	%
Bacteria		
<i>S. pyogenes</i>	29/214	13.6
Haemolytic streptococci	35/214	16.4
β-Hemolytic streptococcus	6/214	
Group C streptococcus	8/214	
Group G streptococcus	6/214	
<i>S. agalactiae</i>	11/214	
<i>H. influenzae</i>	52/214	24.3
<i>H. haemolyticus</i>	23/214	10.7
<i>S. pneumoniae</i>	11/214	5.1
<i>M. catarrhalis</i>	8/214	3.7
<i>S. aureus</i>	71/214	33.2
Others	13/214	6.1
Virus		
Adenovirus	10/205	4.9
Influenza virus	6/205	2.9
RS virus	2/191	1.0
Human metapneumo virus	13/206	6.3

pathogens (Fig. 1A). On the other hands, the numbers of total WBC at the first visit were significantly higher in cases with *S. pyogenes* than cases with other pathogens (Fig. 1B). The levels of CRP were significantly higher in cases with *S.*

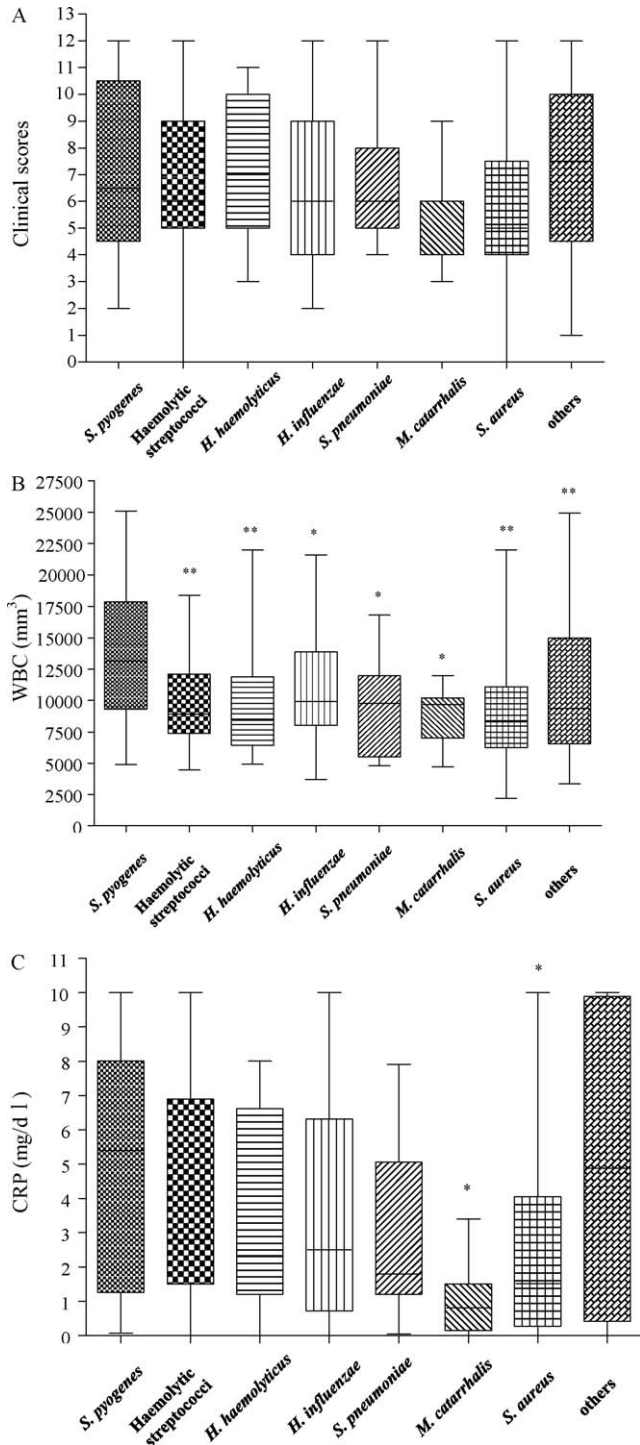


Fig. 1. Distributions of clinical scores, total WBC counts, and serum levels of CRP in patients with *S. pyogenes* or other pathogens. Figures show maximum, 75% value, median, 25% value and minimum. The *p*-values are analyzed by Tukey–Kramer analysis.

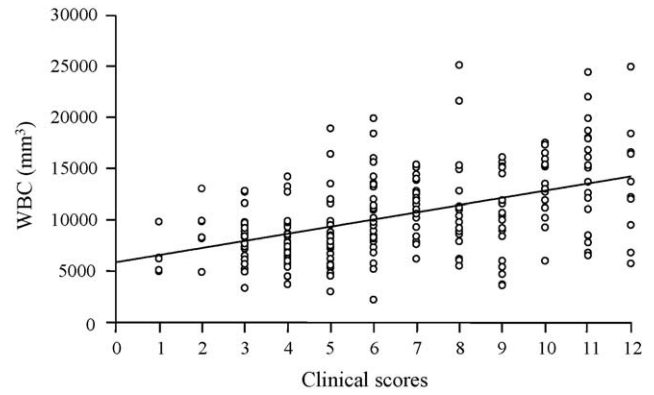


Fig. 2. Correlation between clinical scores and total WBC counts. Each circle shows cases. $r = 0.482$, $y = 695.6x + 5734.6$, $p < 0.001$.

pyogenes than in cases with *S. aureus* and *M. catarrhalis* ($p < 0.05$) (Fig. 1C).

3.4. The severity classification of acute tonsillitis by clinical scoring system

Patients were classified into 33 (15.4%) mild cases, 121 (56.5%) moderate cases, and 60 (28.0%) severe cases according to the criteria by clinical scores. The ratio of acute tonsillitis and pharyngitis according to the severities were 51.4% and 48.6% in mild cases, 73.7% and 26.3% in moderate cases, and 98.4% and 1.6% in severe cases, respectively. Total numbers of WBC at the first visit showed a positive correlation with clinical scores ($r = 0.482$, $p < 0.001$) (Fig. 2). The mean \pm S.D. of WBC in mild cases, moderate cases, and severe cases were 7937 ± 2585 cells/mm³, 9578 ± 3790 cells/mm³, and $12,727 \pm 4082$ cells/mm³, respectively. The levels of CRP at the first visit were also showed a positive correlation with clinical scores ($r = 0.571$, $p < 0.001$) (Fig. 3). The mean \pm S.D. of CRP in mild cases, moderate cases, and severe cases were 0.6 ± 0.8 mg/dl, 3.6 ± 4.1 mg/dl, and 8.5 ± 7.0 mg/dl, respectively. The frequencies of isolations of pathogenic microorganisms did not differ regarding the severities of the disease.

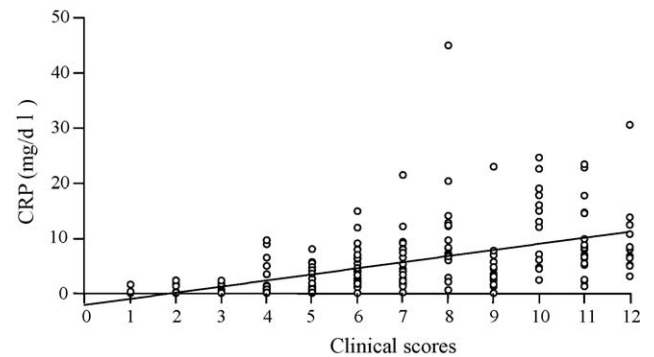


Fig. 3. Correlation between clinical scores and serum levels of CRP. Each circle shows cases. $r = 0.571$, $y = 1.1x \pm 2.4$, $p < 0.001$.

3.5. Treatments and clinical outcomes

The clinical outcomes were evaluated by a scoring system according to the severities of the disease (Fig. 4a and b). In 33 mild cases, 21 (63.6%) patients followed up without antibiotics and improved scores gradually whereas 12 (36.4%) patients were treated with oral antibiotics (AMPC: 12.1%, LVFX: 15.2%, CFPN: 9.1%). In 121 moderate cases, 120 (99.2%) patients were treated with antibiotics and 87 patients (71.9%) were treated with AMPC (66 patients, 54.5%) or LVFX (21 patients, 17.4%). All severe cases were treated with antibiotics. Seven patients (11.7%) were treated with AMPC and 14 patients (23.3%) were treated with

LVFX. In the severe cases, 22 patients (36.7%) were treated with parenteral antibiotics. Among those 22 patients, 12 patients (20.0%) were treated with CTRX. The clinical scores of moderate and severe cases were significantly improved after antimicrobial treatments ($p < 0.01$).

4. Discussion

Because of a wide range of illness with sore throat, diagnosis of acute pharyngitis is still troublesome for primary care physicians. In the current study, we defined causative pathogens and the severity of acute pharyngo-

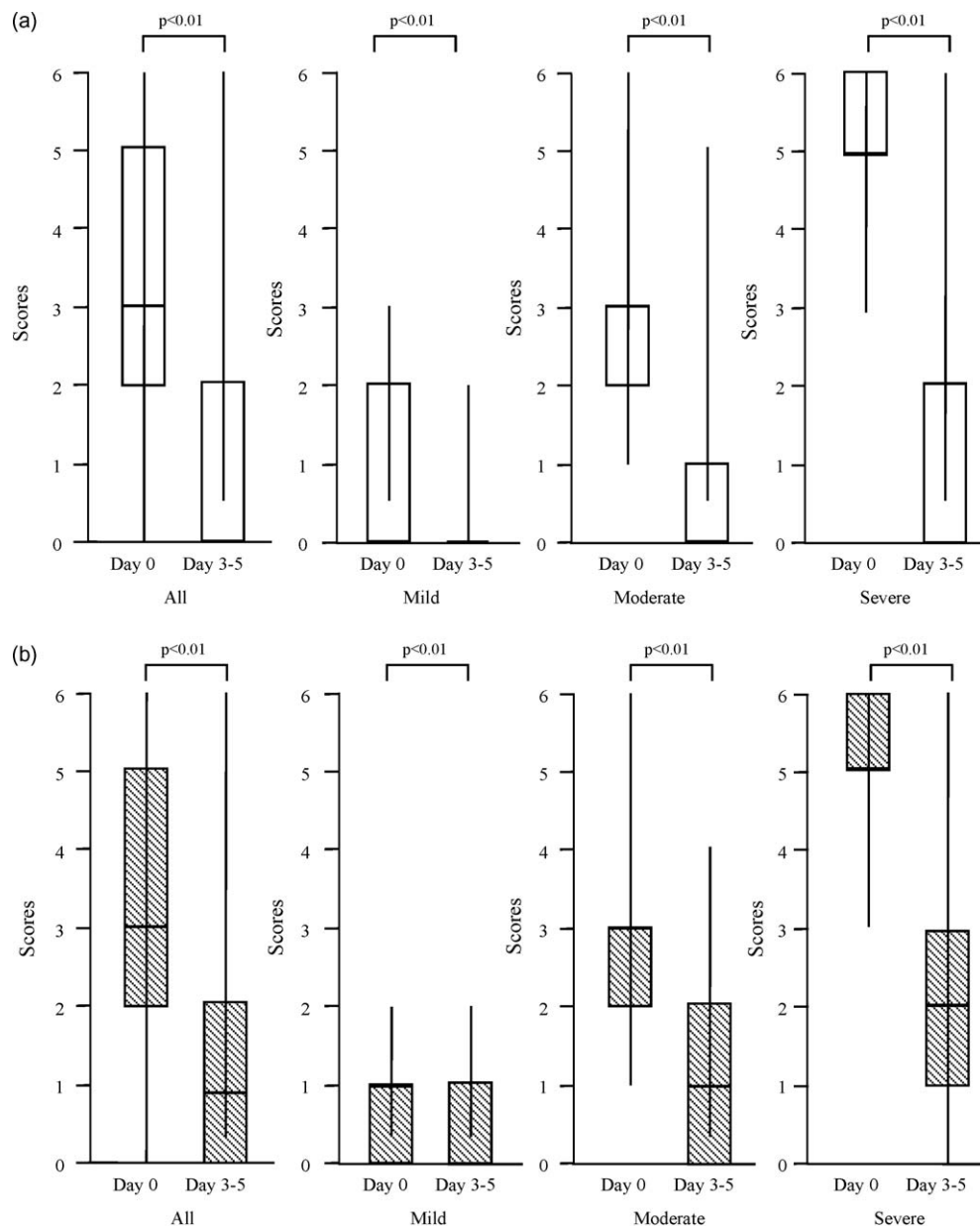


Fig. 4. Clinical outcomes of acute pharyngo-tonsillitis depending on the severity of the disease: (a) clinical symptoms and (b) pharyngo-tonsillar findings, figures show maximum, 75% value, median, 25% value and minimum. The p -values are analyzed by Wilcoxon signed-rank test.

tonsillitis by a clinical scoring system in adult patients. Most of acute pharyngo-tonsillitis were reported to be caused by viruses such as adenovirus, rhinovirus, corona virus, parainfluenza virus, coxackie virus, influenza virus, herpes virus, and cytomegalovirus and were considered to be self-limiting [4,19]. In this study, the frequencies of viruses in adult acute pharyngo-tonsillitis were lower rather than those reported in children, when we applied PCR/RT-PCR to identify four important viruses such as RS virus, adenovirus, influenza virus, and hMPV from pharyngeal swab. The implication of viral infections might be low in adult acute pharyngo-tonsillitis [29,31]. Bacteria were identified in 73.3% of patients studied herein. *S. pyogenes* that had been reported as an important causative pathogen responsible for acute pharyngo-tonsillitis were identified at 13.6% [15,28,32]. Other hemolytic streptococci were also frequently identified from the patients with acute pharyngo-tonsillitis. However, the pathogenic roles of group C or G streptococci in the upper respiratory tract infections have not been completely studied. The *Haemophilus* spp. and *Staphylococcus* spp. are more controversial. Isolation of *S. pyogenes* was closely related with the high value of inflammatory parameters such as white blood cells and C-reactive protein compared to isolation of other pathogens.

Determinations of infections due to *S. pyogenes* have been an important issue for studying acute pharyngo-tonsillitis [2,14,17,22]. Several clinical findings have the discriminative value in distinguishing *S. pyogenes* from other causes of acute pharyngo-tonsillitis. The ability of experienced physicians to predict positive throat cultures of *S. pyogenes* is moderate with estimated sensitivity and specificity ranging from 55 to 74% and 58 to 76%, respectively. In an attempt to improve clinical sensitivity and specificity, investigators have developed clinical decision rules based on constellation of physical signs and symptoms [13,30,33]. The Centor score has been the most reliable predictors for estimating the likelihood of infections of *S. pyogenes* in a patients presenting with a sore throat [9]. The score is calculated by determining how many of the following four clinical features are present: history of fever, tonsillar exudates, anterior cervical adenopathy, and absence of cough. At the usual clinical setting, the majority of primary care physicians prescribe antimicrobial agents and pain-killers based on the severity of illness [18]. Although the Center score is useful to infer *S. pyogenes*, the score is not valuable for diagnosis of the severity of the illness. A rapid antigen detection kit for *S. pyogenes* using a latex agglutination method also applied to determine infections with *S. pyogenes*. The test showed negative predicting value at 95% and relatively lower positive predicting value at 62% [37]. There has been a general consensus that negative rapid antigen tests for *S. pyogenes* should be confirmed by the culture test [17]. However, recent guidelines have suggested that confirmation of negative rapid antigen test results for *S. pyogenes* in adults is either not necessary at all or only if the sensitivity of the

rapid antigen test is <80% [11,28]. The rapid antigen tests has the lower sensitivity compared to a well-performed culture. Therefore, the importance of rapid identification of *S. pyogenes* is still controversial.

We applied a scoring system based on symptoms and clinical findings to diagnose the severity of acute pharyngo-tonsillitis in this study. The scoring system reflected severities of the illness correlated well with numbers of WBC and levels of CRP. Although we could not found any correlations between identification of *S. pyogenes* and severity of the disease, identification of *S. pyogenes* clearly correlated with numbers of WBC and levels of CRP. Regarding to antibiotic treatment, it is important to discriminate causative agents such as bacterial and/or virus infection in acute pharyngo-tonsillitis. However, it is sometimes difficult to discriminate them in the usual clinical setting. The current study was also designed to evaluate correlation among clinical parameters such as clinical scores, WBC, and CRP. Viruses were identified in only 21 (9.8%) patients and there were no correlation between identification of viruses and numbers of WBC or levels of CRP. In contrast, the numbers of total WBC and the levels of CRP at the first visit were significantly higher in cases with *S. pyogenes* indicating the importance of *S. pyogenes* as the causative pathogen for acute pharyngo-tonsillitis. Thus, the clinical scoring system together with blood test could discriminate the possible bacterial infections from virus infections.

We further confirmed the usefulness of the clinical scoring system to evaluate the efficacy of antimicrobial treatments on acute pharyngo-tonsillitis. The study on the difference of treatment outcomes among various age groups reported that group A β -hemolytic streptococcus required antibiotic therapy [35,36]. In this study, a marked reduction of clinical scores after antimicrobial treatments in severe and moderate cases indicated high efficacy of them for the illness with higher severity. On the other hand, mild cases showed decrease of scores regardless of antimicrobial treatments. Thus, the current study strongly suggested that the clinical scoring system reflected disease severity well and would be very useful for evaluating clinical course and decision making for the antimicrobial treatment of acute pharyngo-tonsillitis.

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References

- [1] Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002;35:113–25.
- [2] Bisno AL, Gerber MA, Gwaltney Jr JM, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Disease Society of America. *Clin Infect Dis* 1997;25:574–83.
- [3] Bisno AL, Kaplan EL. Appropriate use of antibiotics: pharyngitis. *Ann Intern Med* 2002;136:489–90.
- [4] Bisno AL, Peter GS, Kaplan EL. Diagnosis of strep throat in adults: are clinical criteria really good enough? *Clin Infect Dis* 2002;35:126–9.
- [5] Bisno AL. Acute pharyngitis. *N Engl J Med* 2001;344:205–11.
- [6] Bourbeau PP. Roles of the microbiology laboratory in diagnosis and management of pharyngitis. *J Clin Microbiol* 2003;41:3467–72.
- [7] Breese BB. A simple scorecard for the tentative diagnosis of streptococcal pharyngitis. *Am J Dis Child* 1977;131:514–7.
- [8] Bulter CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throat. *BMJ* 1998;317:637–42.
- [9] Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making* 1981;1:239–49.
- [10] Cooper RJ, Hoffman JR, Bartlett JG, Besser RE, Gonzales R, Hickner JM, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Ann Intern Med* 2001;134:509–17.
- [11] Dagnelie CF, van der Graaf Y, De Melker RA. Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. *Br J Gen Pract* 1996;46:589–93.
- [12] De Meyere M, Mervielde Y, Verchraegen G, Bogaert M. Effect of penicillin on the clinical course of streptococcal pharyngitis in general practice. *Eur J Clin Pharmacol* 1992;43:581–5.
- [13] Dobbs F. A scoring system for predicting group A streptococcal throat infection. *Br J Gen Pract* 1996;46:461–4.
- [14] Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? *JAMA* 2000;284:2912–8.
- [15] Fox K, Turner J, Fox A. Role of beta-hemolytic group C streptococci in pharyngitis: incidence and biochemical characteristics of *Streptococcus equisimilis* and *Streptococcus anginosus* in patients and healthy controls. *J Clin Microbiol* 1993;31:804–7.
- [16] Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman JR, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. *Ann Intern Med* 2001;134:479–86.
- [17] Gunnarsson RK, Holm SE, Soderstrom M. The prevalence of β -haemolytic streptococci in throat specimens from healthy children and adults, Implications for the clinical value of throat cultures. *Scand J Prim Health Care* 1997;15:149–55.
- [18] Howe RW, Millar MR, Coast J, Whitfield M, Peters TJ, Brookes S. A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat. *Br J Gen Pract* 1997;47:280–4.
- [19] Huovinen P, Lahtonen R, Ziegler T, Meurman O, Hakkarainen K, Miettinen A, et al. Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. *Ann Intern Med* 1989;110:612–6.
- [20] Kaplan EL, Johnson DR, Del Rosario MC, Horn DL. Susceptibility of group A beta-hemolytic streptococci to thirteen antibiotics: examination of 301 strains isolated in the United States between 1994 and 1997. *Pediatr Infect Dis J* 1999;18:1069–72.
- [21] Kellogg JA, Manzella JP. Detection of group A streptococci in the laboratory or physician's office. Culture vs antibody methods. *JAMA* 1986;255:2638–42.
- [22] Kellogg JA. Suitability of throat culture procedures for detection of group A streptococci and as reference standards for evaluation of streptococcal antigen detection kits. *J Clin Microbiol* 1990;28:165–9.
- [23] Krober MS, Bass JW, Michels GN. *Streptococcal pharyngitis*. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA* 1985;253:1271–4.
- [24] Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey. 1989–1999. *JAMA* 2001;286:1181–6.
- [25] Little P, Gould G, Williamson I, Warner G, Gantley M, Kinmonth AL. Clinical and psychosocial predictors of illness duration from randomized controlled trial of prescribing strategies for sore throat. *BMJ* 1999;319:736–7.
- [26] Little P, Gould G, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomized trial of prescribing strategies for sore throat; the medicalizing effect of prescribing antibiotics. *BMJ* 1997;315:350–2.
- [27] Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomized trial of prescribing strategies in managing sore throat. *BMJ* 1997;314:722–7.
- [28] Little P, Williamson I. Sore throat management in general practice 1996;13:317–21.
- [29] Mackay IM, Jacob KC, Woolhouse D, Waller K, Syrmiss MW, Whitley DM, et al. Molecular Assays for detection of human Metapneumovirus. *J Clin Microbiol* 2003;41:100–5.
- [30] McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ* 1998;158:75–83.
- [31] Ordas J, Boga JA, Alvarez-Arguelles M, Villa L, Villa L, Rodriguez-Dehli C, et al. Role of metapneumovirus in viral respiratory infections in young children. *J Clin Microbiol* 2006;44:2739–42.
- [32] Poses RM, Cebul RD, Collins M, Fager SS. The accuracy of experienced physicians' probability estimates for patients with sore throat. Implications for decision making. *JAMA* 1985;254:925–9.
- [33] Singh S, Dolan JG, Centor RM. Optimal management of adults with pharyngitis—a multi-criteria decision analysis. *BMC Med Inf Decis Making* 2006;6:14.
- [34] Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *Ann Intern Med* 2001;134:506–8.
- [35] Wannamaker LW. Diagnosis of pharyngitis: clinical and epidemiological features. In: Shulman Praeger S, editor. *Pharyngitis: management in an era of declining rheumatic fever*. 1984.
- [36] Wannamaker LW. Perplexity and precision in the diagnosis of *Streptococcal pharyngitis*. *Am J Dis Child* 1972;124:352–8.
- [37] Webb KH, Needham CA, Kurtz SR. Use of a high-sensitivity rapid strep test without culture confirmation of negative results: 2 years' experience. *J Fam Pract* 2000;49:34–8.