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ORIGINAL ARTICLE

Recent trends in prescribing antibiotics for acute tonsillitis in pediatric ambulatory care in Taiwan, 2000—2009: A nationwide population-based study

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Abstract *Background/Purpose:* Acute tonsillitis is the leading diagnosis in pediatric ambulatory care, and group A beta-hemolytic streptococcus is the main reason for antibiotic prescriptions in patients with acute tonsillitis. The aim of this study was to analyze trends in prescribing antibiotics and to investigate the prescription patterns for acute tonsillitis in pediatric ambulatory care in Taiwan from 2000 to 2009.
Methods: Data on children younger than 18 years with a primary diagnosis of acute tonsillitis were retrieved from the National Health Insurance Research Database of Taiwan from 2000 to 2009. Concomitant bacterial infections were excluded. Sex, age, seasonality, location, level of medical institution, and physician specialty were analyzed. Annual and monthly changes in antibiotic prescriptions and classification were also evaluated.
Results: A total of 40,775 cases were enrolled, with an overall antibiotic prescription rate of 16.8%. There was a remarkable decline in the antibiotic prescription rates for tonsillitis from 28.4% in 2000 to 10.9% in 2009. Factors associated with a higher prescription rate included older age, visits from eastern Taiwan, medical centers, and nonpediatrician physicians. Otolaryngologists had higher antibiotic prescription rate, whereas pediatricians had the lowest (21.9%

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vs. 11.6%). The rates of obtaining throat cultures were low although the culture performing rate in the medical centers was significantly higher (12.3%, $p < 0.001$).
Conclusion: From 2000 to 2009, there was a remarkable decline in the antibiotic prescription rates for tonsillitis. Further studies to evaluate diagnostic tools such as rapid antigen detection tests or throat cultures to decrease antibiotic prescriptions are warranted.

Introduction

Acute tonsillitis is among the top five diagnoses of children's ambulatory visits in Taiwan,[1] and is the leading cause of antibiotic prescriptions in children globally.[2–4] Treating group A beta-hemolytic streptococcus (GABHS) infection is the main reason for prescribing antibiotics for patients with acute tonsillitis. The appropriate use of antibiotics helps to treat GABHS tonsillitis and to prevent rheumatic fever and suppurative complications such as peritonsillar or retropharyngeal abscesses.[2] Nevertheless, inappropriate antibiotic prescriptions can increase the risk of potential adverse effects, incur unnecessary medical costs, and most importantly, lead to antibiotic resistance, which is a major concern worldwide. In the treatment of GABHS tonsillitis, penicillin remains the drug of choice due to its efficacy, safety, narrow spectrum, and low cost. However, oral amoxicillin is often used in place of penicillin V in pediatric patients because of acceptance of the taste of the suspension.[5]

Although GABHS accounts for ~20–30% of all pathogens in pharyngotonsillitis in children and 5–15% in adults in previous reviews,[6] GABHS isolation rates for pediatric patients with pharyngotonsillitis in Taiwan vary widely, and had been reported to be 1.0%,[7] 1.7%,[8] and 4.1%[9] in three previous studies, respectively. However, other studies in Taiwan revealed higher GABHS isolation rates, from about 21.4%[10] to 27%[11] in pediatric patients with pharyngotonsillitis. Although there is a significant variation in the GABHS isolation rate among previous studies, so far no nationwide study has surveyed the antibiotic prescription rate for acute tonsillitis in Taiwan. Therefore, the aim of this study was to analyze trends in antibiotic prescriptions and investigate the prescription patterns for acute tonsillitis in pediatric ambulatory care in Taiwan from 2000 to 2009.

Methods

Data source

The National Health Insurance (NHI) program in Taiwan was initiated in 1995 and covered 99.9% of the population of Taiwan in 2014.[1,3,12] The National Health Insurance Research Database (NHIRD) provides population-based nationwide data on medical history and demographics. The patient information is encrypted and de-identified to prevent researchers from identifying individuals.[13]

This study was based on the NHIRD, and included data subsets of 0.2% of the ambulatory care expenditure by visit, extracted by a systemic sampling method on a monthly basis.[14] The study protocol was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital, Taipei, Taiwan (IRB number 2012-06-006A).

Study population

We enrolled patients younger than 18 years with the primary diagnosis of acute tonsillitis from 2000 to 2009 from the NHIRD. Acute tonsillitis was defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 463 (acute tonsillitis) or 034.0 (streptococcal sore throat), and we analyzed the data of these two diagnoses separately. The data were retrieved and analyzed for antibiotic prescriptions. Patients were excluded if they had concomitant bacterial infections with the possibility of antibiotic usage. The list of ICD-9-CM codes we excluded is shown in Table 1.[3,15]

Table 1 Exclusive diagnoses.

Concomitant diagnosis	ICD-9-CM codes
Sinusitis	461.xx, 473.xx
Bronchiolitis & bronchitis	466.xx, 490.xx
Pharyngitis	462.xx
Upper respiratory tract infection	465.xx
Otitis media	381.0–381.4, 382.xx
Acute laryngitis & tracheitis	464.xx
Influenza	487.xx
Pneumonia	481.xx–483.xx, 485.xx–486.xx
Urinary tract infection, cystitis	599.0, 595.0, 595.9
Cellulitis, carbuncle, furuncle	680.xx–682.xx
Prostatitis, pelvic inflammatory disease	601.xx, 614.xx
Sexual transmitted disease	090.xx–099.xx, 647.0–647.2

Note. Modified from "Antibiotic prescribing for children with nasopharyngitis (common colds), upper respiratory infections, and bronchitis who have health-professional parents," by N. Huang, L. Morlock, C.H. Lee, L.S. Chen, and Y.J. Chou, 2005, *Pediatrics, 116*, p. 826–32. Copyright 2015, N. Huang. Adapted with permission.

Data analysis

We analyzed demographic information including patient sex, age, visiting season, visiting area, level of medical institution, and physician specialty. The enrolled patients were divided into the following four age groups: 0—2 years, 3—5 years, 6—11 years, and 12—17 years. We divided the patient visiting season into spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February). The level of medical institution was classified into medical center, regional hospital, district hospital, and clinic. The visiting area included northern, central, southern, and eastern Taiwan. Physician specialty was classified as pediatrician, internal medicine doctor, family medicine doctor, otolaryngologist, and physician with another specialty.

Data on laboratory examinations including throat culture performing rate, rapid antigen detection test rate, and complete blood count examination rate were also collected. We also analyzed the antibiotic classification using the Anatomical Therapeutic Chemical classification system of the World Health Organization Collaborating Centre.

Statistical analysis

Data were retrieved from the NHIRD using Microsoft SQL Server 2008 R2 software (Microsoft, Redmond, WA, USA). SigmaPlot software (Systat Software Inc., San Jose, CA, USA) was used to create graphical drawings. The Chi-square test was used to compare differences in the antibiotic prescription rates of each demographic factor including sex, age group, seasonality, geographic location, level of medical institution, and doctor specialty. A p value < 0.05 was considered to be statistically significant.

Adjusted odds ratios (aORs) of related factors with 95% confidence intervals (CIs) were calculated using a multivariate logistic regression model, and we further analyzed statistically significant factors with multiple stepwise regression procedure.

Results

From 2000 to 2009, after excluding concomitant bacterial infections (Table 1),[3,15] there were a total of 40,775 ambulatory visits (21,669 male and 19,106 female patients) with a diagnosis of acute tonsillitis (ICD-9-CM 463) in children younger than 18 years (Table 2). Among the enrolled cases, there were 6858 antibiotic prescriptions, and the total antibiotic prescription rate was 16.8%.

The antibiotic prescription rates were then stratified according to different factors including patient-associated (sex and age), practice-associated (seasonality and geographic location), and medical-associated factors (level of medical institution and physician specialty; Tables 2 and 3).

The number of visits was highest in the patients aged 1—5 years, and then gradually decreased with age (Figure 1A); however, the antibiotic prescription rate increased with age (Figure 1B and Table 2, $p < 0.001$); in particular, the antibiotic prescription rate was higher in those residing in eastern Taiwan (aOR = 2.598, 95% CI = 2.201—3.067, and $p < 0.001$) compared with northern Taiwan. Most of the visits were to local clinics (37,016 from a total of 40,775 visits, 90.8%). Among all levels of medical institution, the antibiotic prescription rate was highest in medical centers (27.0%) and lowest in local clinics (16.3%). Among the patients who were prescribed antibiotics in medical centers, throat culture was performed in 36/176 (20.4%). After excluding those patients for whom throat culture was performed, the rate of antibiotics prescription in medical centers was 140/573 (24.4%) and 6015/37,016 (16.2%) in clinics; the rate difference between the two different medical institutions became closer after excluding patients for whom throat culture was performed, although the rate in medical centers was still significantly higher than in clinics.

With regard to physician specialty, although pediatricians and otolaryngologist saw almost the same number of patients (14,323 vs. 14,443, 35.1% vs. 35.4%, of all visits), the pediatricians had a lower rate of antibiotic prescriptions (11.6%) compared with other specialties (13.9—21.9%, $p < 0.001$).

From 2000 to 2009, there was no obvious annual change of tonsillitis patient numbers. The seasonal change of patient number was also nonsignificant (Table 2). However, there was a declining trend from 28.4% in 2000 to 10.9% in 2009 in the annual antibiotic prescription rate for acute tonsillitis (Figure 2). The antibiotic prescription patterns among the different levels of medical institutions were also analyzed. From 2000 to 2009, the antibiotic prescription rates changed from 39.7% to 20.8% in medical centers, from 21.8% to 14.6% in district hospitals, from 13.9% to 16.8% in regional hospitals, and from 29.5% to 16.3% in clinics.

The choice of antibiotics among the different medical institutions was also distinct. Extended-spectrum penicillins (including amoxicillin) were the most commonly prescribed antibiotics in medical centers (58.0% of total prescriptions) and regional hospitals, followed by first-generation cephalosporins; and in medical centers, the prescription of extended-spectrum penicillins was significantly higher than in the other three levels of medical institution ($p < 0.001$). By contrast, most antibiotics prescribed in district hospitals and clinics were first-generation cephalosporins followed by extended-spectrum penicillins. In addition, in medical centers, there were significantly more prescriptions for penicillins with beta-lactamase inhibitors (e.g., a combination of amoxicillin and clavulanic acid) than in local clinics (13.1% in medical centers, $p < 0.001$), whereas macrolides, lincosamides, and sulfonamide—trimethoprim combinations were prescribed more often in local clinics and less in medical centers.

Throat cultures were performed in 12.3% of the patients in medical centers, which was significantly higher than in other medical institutions (Table 4). The throat culture was performed in only 183 patients of the total 40,775 patients (0.4%). Complete blood count tests were also performed significantly more often in medical centers and regional hospitals (11.6% and 8.6% of all visits) than in district hospital and local clinics. The total rate of performing complete blood count test in all medical institutions was 0.8%

Table 2 Demographic characteristics and comparisons of enrolled ambulatory children with a diagnosis of tonsillitis and the antibiotic prescriptions, 2000–2009.

Variable	No. of patients with antibiotic prescriptions/ No. of total patients (%)	p*	OR (95% CI)	p	aOR (95% CI)	p**
Total	6858/40,775 (16.8)					
Sex		0.115				
Female	3154/19,106 (16.5)		0.959 (0.910–1.010)	0.115	0.959 (0.910–1.011)	0.121
Male	3704/21,669 (17.1)		1 (—)	—	1 (—)	—
Age (y)		<0.001				
0–2	1114/7816 (14.3)		0.569 (0.524–0.618)	<0.001	0.655 (0.601–0.714)	<0.001
3–5	1713/11,369 (15.1)		0.607 (0.564–0.654)	<0.001	0.685 (0.635–0.739)	<0.001
6–11	2273/13,815 (16.5)		0.674 (0.629–0.723)	<0.001	0.738 (0.687–0.792)	<0.001
12–17	1758/7775 (22.6)		1 (—)	—	1 (—)	—
Season		0.095				
Spring	1868/10,742 (17.4)		1.041 (0.968–1.118)	0.279	1.058 (0.983–1.139)	0.130
Summer	1645/9712 (16.9)		1.008 (0.936–1.086)	0.832	1.039 (0.963–1.121)	0.323
Autumn	1641/10,193 (16.1)		0.949 (0.881–1.022)	0.163	0.968 (0.898–1.044)	0.397
Winter	1704/10,128 (16.8)		1 (—)	—	1 (—)	—
Area of Taiwan		<0.001				
East	236/681 (34.7)		2.495 (2.121–2.935)	<0.001	2.598 (2.201–3.067)	<0.001
Middle	1159/9121 (12.7)		0.685 (0.637–0.736)	<0.001	0.736 (0.684–0.792)	<0.001
South	2248/12,632 (17.8)		1.019 (0.960–1.081)	0.545	0.981 (0.924–1.042)	0.536
North	3215/18,341 (17.5)		1 (—)	—	1 (—)	—
Physician specialty		<0.001				
Otolaryngology	3157/14,443 (21.9)		2.124 (1.991–2.265)	<0.001	2.199 (2.051–2.358)	<0.001
General medicine	315/1791 (17.6)		1.620 (1.420–1.849)	<0.001	1.501 (1.311–1.722)	<0.001
Family medicine	565/4059 (13.9)		1.228 (1.108–1.360)	<0.001	1.285 (1.155–1.429)	<0.001
Other specialties	1154/6159 (18.7)		1.751 (1.613–1.900)	<0.001	1.704 (1.567–1.854)	<0.001
Pediatrics	1667/14,323 (11.6)		1 (—)	—	1 (—)	—
Medical institution level		<0.001				
Clinics	6016/37,016 (16.3)		0.526 (0.441–0.627)	<0.001	0.412 (0.344–0.494)	<0.001
District hospitals	320/1335 (24.0)		0.854 (0.690–1.058)	0.149	0.849 (0.681–1.059)	0.147
Regional hospitals	346/1771 (19.5)		0.658 (0.534–0.811)	<0.001	0.752 (0.608–0.931)	0.009
Medical centers	176/653 (27.0)		1 (—)	—	1 (—)	—

* Compared by Chi square test.
** Compared by multivariate logistic regression, adjusted by all other factors.
aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio.

(314 complete blood count tests done in total 40,775 patients). However, rapid antigen detection tests were only performed in six cases in 0.2% systemic sampling of the ambulatory care visits.

Patients with a primary diagnosis of ICD-9-CM 034.0 (streptococcal sore throat) were also analyzed separately. However, as there were too few cases (303 cases during 2000–2009 in 0.2% systemic sampling of the ambulatory care visits), excluding this diagnosis did not change the result statistically.

Discussion

In this study, the overall antibiotic prescription rate for pediatric tonsillitis was 16.8% from 2000 to 2009. Moreover, our results revealed a declining trend in the antibiotic prescription rate for acute tonsillitis from 28.4% in 2000 to 10.9% in 2009. This decline is similar to a previous study, which reported a decreasing trend in antibiotics prescribed for respiratory tract infections over the past 10 years in Taiwan.[3] The antibiotic prescription rate for tonsillitis has been reported to be around 10.1%[3] and 10.3%[8] in Taiwan and up to 51–74% in the United States, and even up to 89% if the diagnosis is specifically streptococcal sore throat.[16] However, a decrease in antimicrobials prescribed for acute tonsillitis, pharyngitis, and other respiratory tract infections has also been reported in the United States in the decades before 2000.[3,16–18] Since 2001, there had been antibiotics controlling policy in Taiwan, which restricted the use of antibiotics for nonbacterial infections, and this may be the reason for decreased antibiotic prescriptions.[3,19] It has been suggested that more judicious antibiotic usage can be accomplished under public health programs and professional organization promotions, because under an NHI program, physicians must be more careful when prescribing antibiotics as the government selectively verifies their prescriptions, which could also be responsible for the remarkable decline of antibiotic prescriptions.[17]

For children with a diagnosis of acute tonsillitis, four factors were associated with a significantly higher

Table 3 Multiple stepwise regressions of statistically significant factors associated with antibiotic prescriptions for acute tonsillitis in children, 2000—2009.

Variable	aOR[a]	95% CI	*p*
Age (y)			
0—2	0.656	0.602—0.714	<0.001
3—5	0.686	0.636—0.740	<0.001
6—11	0.739	0.689—0.794	<0.001
12—17	1	—	—
Area of Taiwan			
East	2.598	2.201—3.067	<0.001
Middle	0.736	0.684—0.793	<0.001
South	0.981	0.923—1.042	0.525
North	1	—	—
Physician specialty			
Otolaryngology	2.198	2.050—2.357	<0.001
General medicine	1.503	1.312—1.723	<0.001
Family medicine	1.284	1.155—1.428	<0.001
Other specialties	1.705	1.567—1.855	<0.001
Pediatrics	1	—	—
Medical institution level			
Clinics	0.411	0.343—0.493	<0.001
District hospitals	0.850	0.681—1.059	0.148
Regional hospitals	0.753	0.609—0.932	0.009
Medical centers	1	—	—

[a] Compared by multiple stepwise regression, adjusted by all other factors.
aOR = adjusted odds ratio; CI = confidence interval.

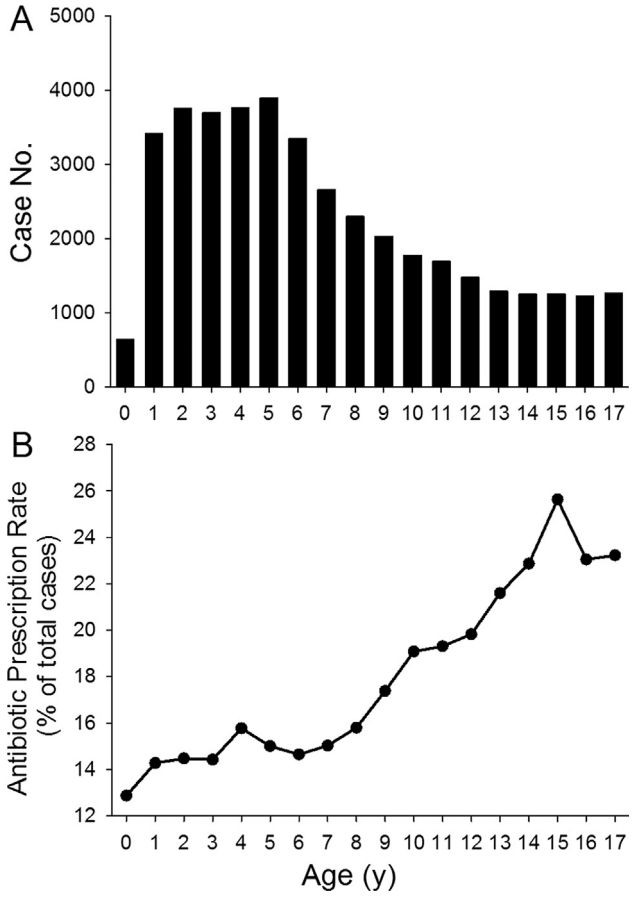

Figure 1. Antibiotic prescription rates and numbers of acute tonsillitis cases in different ages from 2000 to 2009. (A) Tonsillitis patient numbers in different ages. (B) Antibiotic prescription rate of tonsillitis among different ages.

antibiotic prescription rate in this study—older age, visits from eastern Taiwan, medical centers, and nonpediatric physicians. The higher rate in the older patients may reflect the thought that children aged 5—15 years are most susceptible to streptococcal tonsillitis[6]; and the higher antibiotic prescription rate in eastern Taiwan may be related to a deficiency in medical resources and specialists, which could result in the patients' family asking for antibiotics and the physicians being worried about not properly treating a GABHS infection because of the relative difficulty in clinical follow-up due to the remoteness of area. Parents' expectation has also been reported to be a contributing factor to inappropriate antibiotic usage.[4]

The reason for the higher antibiotic prescription rate in medical centers could reflect more complicated or severe cases. In addition, physicians in medical centers can make a diagnosis of GABHS tonsillitis more precisely according to not only clinical manifestations but also the laboratory examinations such as throat cultures or complete blood count tests, which were performed significantly more frequently in the medical centers.

Previous studies in Taiwan reported that based only on the clinical manifestations, differentiating GABHS from viruses is difficult.[11,20] The McIsaac score was developed to evaluate the necessity to perform cultures and prescribe antibiotics.[21] However, the score was shown to have poor validity in a study in Taiwan.[9] Furthermore, laboratory confirmation for GABHS before prescribing antibiotics is also the recommendation of the American Academy of Pediatrics.[16] Assuming a prevalence rate of 15—30% of GABHS in pediatric tonsillitis in the literature, and according to previously reported isolation rate of GABHS, which varied from 1.0% to 27% in Taiwan, a 12.3% culture performing rate in medical centers might be acceptable; however, a 0.4% overall culture performing rate would be rather low considering the importance of laboratory examination in making the diagnosis of GABHS. According to the literature, performance of GABHS tests (including culture or rapid antigen detection test) is significantly associated with a lower antibiotic prescription rate for children with acute tonsillitis or GABHS sore throat. GABHS tests were reportedly performed in around 51% cases in the United States,[16] which is much higher than in our results.

With regard to physician specialties, pediatricians prescribed fewer antibiotics than other specialists, which is probably because they were used to following patients with a suspected viral infection for a longer duration rather than prescribe antibiotics at the first visit, and because they are more experienced in handling children and pressure from their parents.[3] Based on previous studies, pediatricians are less likely to start antimicrobial therapy when they do not have laboratory test results, and they are more likely not to treat children with symptoms of GABHS only based on clinical findings.[4]

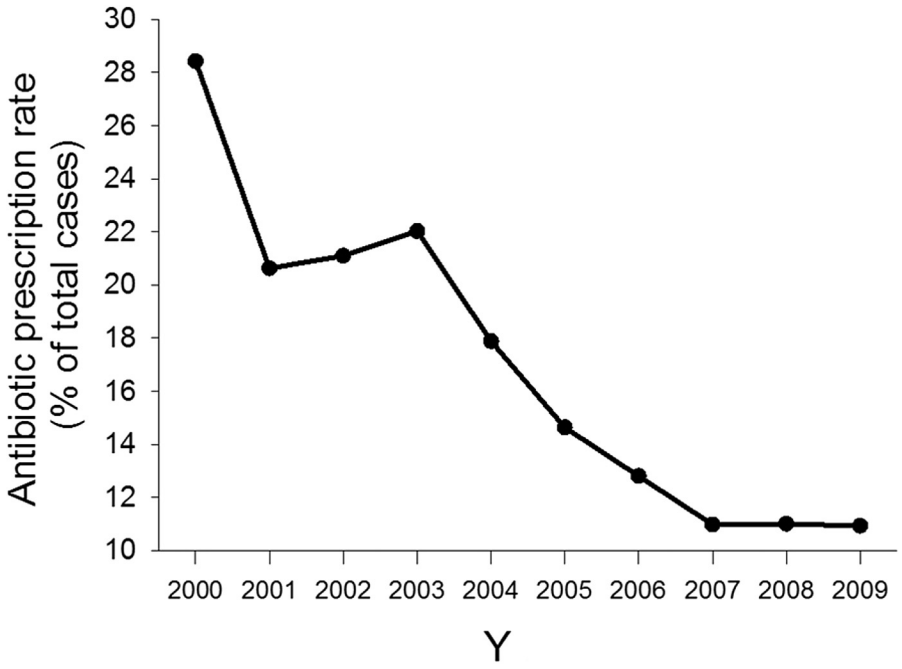

Figure 2. Annual change in the antibiotic prescription rates for children receiving ambulatory medical care and being diagnosed as having tonsillitis, 2000—2009.

With regard to the choice of antibiotics, extended-spectrum penicillins such as amoxicillin were preferred to first-generation cephalosporins in medical centers and regional hospitals, with the third option being penicillins with beta-lactamase inhibitors such as a combination of amoxicillin and clavulanic acid; the opposite situation was found in district hospitals and clinics, where first-generation cephalosporin was the most commonly prescribed antibiotics, followed by extended-spectrum penicillins. In local clinics, macrolides, lincosamides, and a combination of sulfonamide—trimethoprim were also used more often than in other medical institutions, which is probably due to their lower cost. A combination of amoxicillin and clavulanic acid was the less common option in district hospitals and local clinics. Current guidelines for the treatment of acute GABHS tonsillitis suggest that penicillin or amoxicillin should be the drug of choice considering their cost, narrow spectrum activity, and few adverse reactions; for patients who are allergic to penicillin, recommended alternatives include first-generation cephalosporins, clindamycin, or macrolides.[5,22] According to these findings, the prescription rate of recommended antibiotics for GABHS tonsillitis in our study was 85.2% in medical centers, 87.4% in regional hospitals, 93.1% in district hospitals, and 80.0% in clinics.

A previous study in Taiwan reported that acute tonsillitis is one of the six diagnoses for which antibiotics are most commonly prescribed. The authors also showed that in primary care units, cephalosporins were the most commonly prescribed antibiotic for acute tonsillitis, followed by penicillins and macrolides from 1997 to 1999.[23] Our study results are compatible with these findings.

The limitations of this study include coding errors or omissions. As we used data from NHIRD, the diagnosis relied on ICD-9-CM coding. However, a diagnosis of tonsillitis may not have been recorded as the major diagnosis if there were two or three other diagnoses concomitantly. Data concerning diagnoses of concomitant bacterial infections were also excluded. Our data were retrieved from NHIRD subsets of 0.2% sampling of the ambulatory care

Table 4 Performing rates of throat culture and CBC test in patients with acute tonsillitis among different medical institutions from 2000 to 2009.

	Total patient No.	No. of throat culture (%)	Odds ratio (95% CI)	*p*	CBC test count (%)	Odds ratio (95% CI)	*p*
All	40,775	183 (0.4)			314 (0.8)		
Clinics	37,016	1 (<0.1)	0 (0—0.001)	<0.001	14 (<0.1)	0.003 (0.002—0.005)	<0.001
District hospitals	1335	23 (1.7)	0.126 (0.078—0.202)	<0.001	71 (5.3)	0.426 (0.304—0.598)	<0.001
Regional hospitals	1771	79 (4.5)	0.334 (0.242—0.463)	<0.001	153 (8.6)	0.718 (0.537—0.960)	0.026
Medical centers	653	80 (12.3)	1	—	76 (11.6)	1	—

CBC = complete blood count; CI = confidence interval.

expenditure by visit, and therefore, even if one person had more than one medical visit in the same disease episode, it is difficult to retrieve all sequential visits of the same patient due to randomized sampling. Thus, longitudinal follow-up of particular case is difficult in our study. Moreover, the NHIRD does not include self-paid medications or laboratory examinations at any medical institutions.

In conclusion, the annual antibiotic prescription rate for pediatric tonsillitis markedly declined from 2000 to 2009 in Taiwan. The factors associated with higher antibiotic prescription rate for pediatric tonsillitis were older age, visits from eastern Taiwan, medical centers, and physicians other than pediatricians. However, the overall rates of performing throat cultures and complete blood count tests were low although the rates were significantly higher in medical centers. Further studies to evaluate diagnostic tools usage such as rapid antigen detection tests or throat cultures to reduce the number of antibiotic prescriptions in pediatric ambulatory care are warranted.

Conflicts of interest

All authors declare no conflicts of interest.

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