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상기도 감염으로 입원한 소아환자에서 항생제 사용에 대한 후향적 분석

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A Retrospective Analysis of Use in Hospitalized Children with Upper Respiratory Tract Infection

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Purpose: The inappropriate prescription of antibiotics in children with upper respiratory tract infection (URTI) is common. This study evaluated the factors that influence antibiotics use in hospitalized children with viral URTI confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay.
Methods: The medical records of admitted patients who performed RT-PCR assay for respiratory virus pathogens from January 2013 to November 2014 were examined. The demographic and clinical features were compared between patients who were administered antibiotics at admission and those who were not. We also investigated differences between children who continued antibiotics and those who stopped antibiotics after a viral pathogen was identified.
Results: In the total 393 inpatients, the median age was 23 months (interquartile range, 13 to 41.3 months). Antimicrobial agents were prescribed in 79 patients (20.1%) at admission. Patients with acute otitis media (AOM) had higher rates of antibiotics prescription than those without AOM (48.1% vs. 2.2%, $P<0.001$), with an adjusted odds ratio of 91.1 (95% confidence interval, 30.5 to 271.7). Level of high-sensitivity C-reactive protein and the proportion of acute rhinosinusitis were also significantly associated with antibiotics use ($P<0.001$). Among the 44 patients with viruses identified using the RT-PCR method during hospitalization, antibiotic use was continued in 28 patients (63.6%). AOM was statistically associated with continued antibiotic use in the patients ($P=0.002$).
Conclusions: Although the respiratory virus responsible for URTI etiology is identified, clinicians might not discontinue antibiotics if AOM is accompanying. Therefore, careful diagnosis and management of AOM could be a strategy to reduce unjustified antibiotic prescriptions for children with URTI.

Key Words: Anti-bacterial agents; Otitis media; Polymerase chain reaction; Respiratory tract infections

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Introduction

Acute respiratory tract infection is the most common illness to visit to pediatric health facilities[1]. Although it has been reported that upper respiratory tract infections (URTIs) are mostly viral in origin and are typically self-limiting in children, unnecessary antibiotics are fre-

quently prescribed[2,3]. In Korea, the overall antibiotic prescription rate in pediatric outpatients with URTIs was 55.4% in 2011[4]. Despite the recent decline in antibiotic prescription rates, this rate is still much higher than that of Western countries[5,6].

The proper use of antibiotics has been challenging due to difficulties distinguishing between bacterial and viral infections in clinical practice[7,8]. These limitations have inspired a great deal of research into methods for verifying possible viral pathogens. Prior retrospective studies have suggested that a rapid antigen test could reduce the use of antibiotics and the duration of hospitalization[9,10]. However, other studies have reported contradictory results[11]. Recently, reverse transcriptase-polymerase chain reaction (RT-PCR) analyzes have become more sensitive than traditional methods, such as viral culture, direct fluorescent assays, and rapid antigen detection tests[12].

The development of a RT-PCR test was expected to result in further increases in diagnostic yield and a reduction in antibiotic prescription[13]. However, several recent studies in pediatric populations have shown that the introduction of RT-PCR test has not reduced antibiotic use in clinical practice[8,14].

This study was conducted to evaluate the factors associated with antibiotic use in children hospitalized with URTI and to identify the clinical characteristics associated with continued use of prescription antibiotics notwithstanding the detection of a respiratory virus by RT-PCR.

Materials and Methods

1. Study population

The medical records of the Department of Pediatrics, Kosin University Gospel Hospital (Busan, Korea), a tertiary care center, were analyzed. Data were collected by reviewing the electronic medical records of all cases of admitted children <18 years of age, on whom multiplex RT-PCR using the Seeplex RV7 Detection System (Seegene Inc., Seoul, Korea) were performed between January 2013 and November 2014. Among these patients, those being initially admitted for respiratory symptoms with fever and ultimately diagnosed with an URTI at discharge were eligible for inclusion. Patients treated with chemotherapy, immunosuppressive therapy, stem cell transplantation, corticosteroid, or mechanical ventilation in the pediatric intensive care unit and those receiving antibiotic therapy due to culture-proven bacterial infections (bacterial pharyngotonsilitis, urinary tract infection, bacteremia, and meningitis) were excluded. Further excluded were all newborns that had been hospitalized since birth. This study was reviewed and approved by the Institutional Review Board of Kosin University Gospel Hospital (2015-02-020).

2. Data collection

Demographic characteristics and clinical and laboratory information were obtained from electrical medical records. Clinical information included the diagnoses made by pediatrician at admission and discharge, complications, duration of hospital stay, fever duration, whether antibiotics were used before and after the respiratory virus results being reported, and antibiotic classification. Complications of URTI at admission were classified as either acute otitis media (AOM) or acute rhinosinusitis. Pediatricians had made diagnoses using portable otoscope and if tympanic membrane did not visible, video otoscope was used. Antibiotics were categorized into three families including penicillins (ampicillin, ampicillin-sulbactam, amoxicillin, and amoxicillin-clavulanate), cephalosporins (cefotaxime, ceftriaxone, and cefpodoxime), and macrolides (clarithromycin). Macrolides were given by the oral route, other antibiotics by the intravenous injections.

We recorded laboratory variables including white blood cell (WBC) count, high-sensitivity C-reactive protein (hS-CRP), erythrocyte sedimentation rate (ESR), RT-PCR results, and report dates. The blood samples of children were obtained at admission, and results were reported within 3 hours. Respiratory virus RT-PCR assays using a nasopharyngeal swab specimen were performed at the Clinical Microbiological Laboratory at Kosin University Gospel Hospital. Seven viruses (influenza viruses A and B, respiratory syncytial virus,

adenovirus, parainfluenza virus, rhinovirus, and human metapneumovirus) were included in the panel. The assays were conducted in every Monday and Thursday.

3. Statistical analysis

All data were analyzed using SPSS version 22 (IBM Co., Armonk, NY, USA). Categorical variables were compared using the chi-square test or Fisher exact test to determine the relationships between antibiotic prescriptions and clinically informed variables. The Student t-test was used to compare continuous variables, and data without a normal distribution were analyzed with the Mann-Whitney U test. *P*-value less than 0.05 was considered to indicate statistical significance. All variables that were significant in the previous test were evaluated with the use multivariable logistic-regression models to analyze factors associated with initial antibiotics prescription.

Results

During the study period, RT-PCR assays were performed on a total of 1,277 patients upon admission. Of these, 393 inpatients met the inclusion criteria. The median (interquartile range [IQR]) age of inpatients meeting the inclusion criteria was 23 months (IQR, 13 to 41 months) (Table 1). Acute nasopharyngitis (67.4%, 265/393), acute pharyngotonsillitis (27.2%, 107/393), and acute laryngitis (5.4%. 21/393) were diagnosed in these patients. AOM was observed in 45 children (11.5%) and acute rhinosinusitis in 14 (3.6%). Four patients (1%) were diagnosed with concurrent AOM and acute rhinosinusitis.

Antibiotics were prescribed for 79 patients (20.1%) with URTI upon admission. The demographic and clinical characteristics of the patients who received antibiotics were compared with those of the 314 patients (79.9%) who did not receive antibiotics treatment (Table 2). Among those who received antibiotics, diagnoses of AOM and acute rhinosinusitis were more common (48.1% vs. 2.2%, 16.5% vs. 0.3%, respectively). The median WBC count (12,190/mm^3 vs. 10,840/mm^3, *P*=0.006), the median serum level of hS-CRP (2.1 mg/dL vs. 0.7 mg/dL, *P*<0.001) and the median ESR (23 mm/hr vs. 14 mm/hr, *P*<0.001) were higher in patients who received antibiotics than in those who did not. Risk factors for initial antibiotics use were AOM, acute rhinosinusitis, and HS-CRP. Patients having AOM, as compared with those who did not, had a relative risk of receiving antibiotics of 91.1 (95% confidence interval, 30.5 to 271.7; *P*<0.001). The odd ratio for initial antibiotics use, when level of WBC count and ESR increased, did not significantly increased on multivariate analysis.

Antibiotics were used in 18.5% (49/265) children diagnosed with acute nasopharyngitis and in 24.3% (26/107) with acute pharyngotonsilitis (Table 3). A single antibiotic agent was prescribed to 77 patients (97.5%), and combination therapy was administered to two patients. Among single-agent therapies, the penicillin family (68.3%, 54/79) was the most common agent used for each URTI, followed by cephalosporins (29.1%, 23/79).

Respiratory viruses were detected using the RT-PCR test in 223 (56.7%) of 393 patients. Of these, 43 patients (19.3%) were positive for two viruses, two pati-

Table 1. Baseline Characteristics of the Inpatients with Upper Respiratory Tract Infections

Characteristic	Total patients (n=393)
Age (mo)	23 (13–41)
Sex	
Male	234 (59.5)
Diagnosis	
Acute nasopharyngitis	265 (67.4)
Acute pharyngotonsillitis	107 (27.2)
Acute laryngitis	21 (5.4)
Complication	
AOM	45 (11.5)
Acute rhinosinusitis	14 (3.6)
Laboratory findings	
WBC count (/mm^3)	10,940 (8,035–14,475)
hS-CRP (mg/dL)	0.8 (0.25–2.2)
ESR (mm/hr)	15.0 (7.0–25.0)

Values are presented as median (interquartile range) or number (%).
Abbreviations: AOM, acute otitis media; WBC, white blood cell; hS-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation reaction.

ents (0.9%) were positive for three viruses, and one patient (0.5%) was positive for four concurrent viruses. Adenovirus (28.3%, 52/184) and rhinovirus (27.7%, 51/184) were commonly identified in acute nasopharyngitis. Adenovirus (44.6%, 29/65) was the most frequently found pathgen related to acute pharyngotonsilitis. In patient with acute laryngitis, parainfluenza was more commonly detected (50%, 12/24) (Fig. 1). In one-thirds of patients (17/52) diagnosed with AOM, viruses did not detected. Among the rest, adenovirus (21%) and rhinovirus (15.4%) was identified.

Of the 79 patients who received antibiotics, 35 patients were discharged or had discontinued antibiotics earlier. The remaining patients (n=44) have treated antibiotics when RT-PCR results had been reported. Antibiotics were continued in 28 patients (63.6%) after clinicians were informed that viruses had been identified using the RT-PCR method. A comparison of the characteristics of children who either continued or discontinued antibiotic therapy after the identification of a viral patho-

Table 2. Factors Associated with Initial Antibiotics Prescriptions in the Patients Who Diagnosed as Upper Respiratory Tract Infection

Variable	Patients who were prescribed antibiotics (n=79)	Patients who were not prescribed antibiotics (n=314)	*P*-value*	Odds ratio (95% CI)	
				Univariate model	Multivariate model†
Age (mo)	23 (13–47)	23 (14–38)	0.885	1.0 (0.99–1.01)	
Male sex	43 (54.4)	191 (60.8)	0.373	1.3 (0.77–2.01)	
Diagnosis			0.435		
Acute nasopharyngitis	49 (62.0)	216 (68.8)		Reference	
Acute pharyngotonsillitis	26 (32.9)	81 (25.8)		1.4 (0.8–2.4)	
Acute laryngitis	4 (5.1)	17 (5.4)		1.0 (0.3–3.2)	
Complication					
AOM	38 (48.1)	7 (2.2)	<0.001	40.0 (17.0–97.0)	91.1 (30.5–271.7)
Acute rhinosinusitis	13 (16.5)	1 (0.3)	<0.001	61.7 (7.9–479.5)	116.7 (12.6–1,079.7)
Laboratory findings					
WBC count (/mm^3)	12,190 (8,835–16,280)	10,840 (7,640–14,120)	0.006	1.0 (1.0–1.0)	
hS-CRP (mg/dL)	2.1 (0.5–4.9)	0.7 (0.2–1.7)	<0.001	1.4 (1.23–1.54)	1.6 (1.3–1.9)
ESR (mm/hr)	23 (11.5–34)	14 (7–22)	<0.001	1.0 (1.0–1.05)	

Values are presented as median (interquartile range) or number (%).
**P*-values are for comparisons across groups, with the use of Fisher exact test or chi-square test for categorical variables and the Mann-Whitney U test for continuous variables.
†The multivariate model included only effects with *P*-value of less than 0.05.
Abbreviations: CI, confidence interval; AOM, acute otitis media; WBC, white blood cell; hS-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation reaction.

Table 3. Prescribed Antibiotics for Hospitalized Children with Upper Respiratory Tract Infection

Variable	Total (n=393)	Acute nasopharyngitis (n=266)	Acute pharyngotonsillitis (n=107)	Acute laryngitis (n=21)	Acute otitis media* (n=45)	Acute rhinosinusitis* (n=14)
Patients prescribed antibiotics*	79 (20.1)	49 (18.5)	26 (24.3)	4 (19.0)	38 (84.4)	13 (92.9)
Antibiotic classification†						
Single						
Penicillins	54 (68.4)	29 (59.2)	22 (84.8)	3 (14.3)	22 (57.9)	12 (92.3)
Cephalosporins	23 (29.0)	20 (41.2)	2 (7.6)	1 (4.8)	15 (39.5)	1 (7.7)
Combination						
Penicillins+macrolides†	1 (1.3)	0	1 (3.8)	0	0	0
Cephalosporins+macrolides	1 (1.3)	0	1 (3.8)	0	1 (2.6)	0

Values are presented as number (%).
*Acute otitis media and acute rhinosinusitis were considered as the complications of upper respiratory tract infection.
†Macrolides were given by the oral route, other antibiotics by the intravenous injections.

gen is presented in Table 4. AOM was a statistically significant diagnosis in patients who maintained antibiotic usage (P=0.002). There were no significant differences in age, duration of fever, laboratory findings, or length of hospitalization between the two groups.

Discussion

In this study, we analyzed the factors related to use antibiotics in patients with URTI. Children who were administered antibiotics at admission had a higher prevalence of AOM compared with those who did not. Similarly, the proportion of AOM was also greater in patients who continued antibiotics therapy, even when informed of respiratory virus presence, than in patients who stopped antibiotics. Therefore, diagnosis of AOM might affect antibiotic prescription behavior in children with URTI.

AOM is a major reason for antibiotic use in children [15,16]. The rate of antibiotic prescriptions for AOM in our trial (84.4%) was consistent with rates reported in other Korean studies (86.1%)[17]. This rate varies from 56% in the Netherlands to 95% in the USA, Canada, and Australia[18]. In response to concerns about the emergence of antibiotic-resistant microorganisms and the economic burden of disease caused by antibiotic resistance, the need for accurate diagnosis of AOM to minimize unnecessary treatment has been globally agreed upon[19-21].

However, accurate diagnosis of AOM could be difficult in infants and young children because of incooperation with the examination and cerumen barrier of tympanic membrane. Recently published American Academy of Pediatrics guideline of AOM endorses strict otoscopic diagnostic criteria to differentiate AOM from otitis media with effusion[19]. Therefore, a cautious examination of the tympanic membrane and understanding the wide clinical spectrum of otitis media are required to achieve a high degree of diagnostic accuracy[22]. In addition to

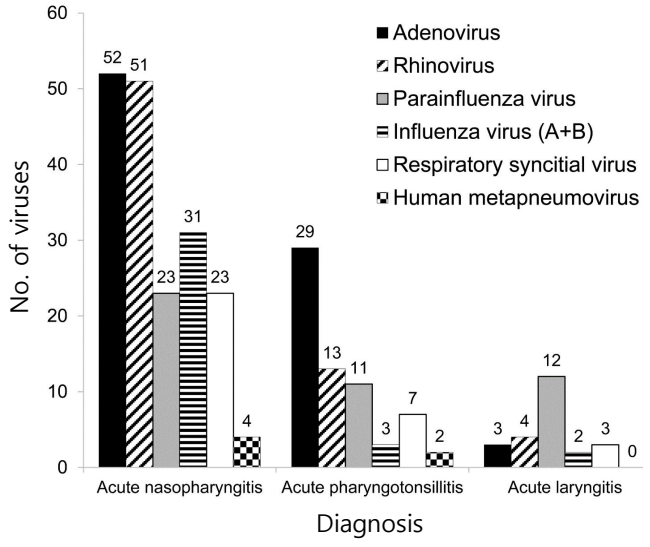

Fig. 1. Viruses identified in 393 nasopharyngeal swabs obtained from admitted children with upper respiratory tract infection. Among patients infected with viral particles, 42 patients were positive for two viruses, two patients were positive for three viruses, and one patient was positive for four concurrent viruses.

Table 4. Characteristics of Children Who Either Continued or Discontinued Antibiotic Use after Respiratory Viruses were Detected with Reverse Transcriptase-Polymerase Chain Reaction

Characteristic	Continued use of antibiotics		*P* value*
	Yes (n=28)	No (n=16)	
Age (mo)	19 (11–28)	20 (16–36)	0.916
Age group (mo)			
≤12	9 (32.1)	2 (12.5)	0.279
>12	19 (67.9)	14 (87.5)	
Male sex	16 (57.1)	9 (56.3)	1.000
Length of hospitalization (day)	3 (2–4)	3 (2–4)	0.751
Diagnosis			
Acute nasopharyngitis	17 (60.7)	9 (56.3)	0.513
Acute pharyngotonsillitis	9 (32.1)	7 (43.8)	
Acute laryngitis	2 (7.1)	0	
Complication			
AOM	21 (75.0)	4 (25.0)	0.002
Acute rhinosinusitis	4 (14.3)	1 (6.3)	0.638
Laboratory findings			
WBC count (/mm^3)	17,439±7,087	13,474±5,727	0.409
hS-CRP (mg/dL)	2.7±3.4	4.5±4.5	0.153
ESR (mm/hr)	24.3±16.3	31.5±14.2	0.167

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
*P values are for comparisons across groups, with the use of Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables.
Abbreviations: AOM, acute otitis media; WBC, white blood cell; hS-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation reaction.

this effort to accurate diagnosis of AOM, "watchful waiting" in selected children without progression of signs or symptoms within 48 to 72 hours before prescribing antibiotics for AOM has been recommended to clinicians[19,23].

Twenty percent (79/393) of inpatients with URTIs were treated with antimicrobial agents during this study period. This proportion was lower than that of tertiary hospitals analyzed in a recent study evaluating pediatric outpatients with URTI from 2009 to 2011 in Korea (49.5%)[4].

Measuring serum CRP as a means of differentiating between viral and bacterial infections is known to be helpful in making the decision whether or not to prescribe antimicrobial agents to children with acute respiratory illness[24]. A previous study of 176 children determined that serum CRP level exceeding 4 mg/dL probably implied bacterial respiratory infection[25]. Of this study's subjects, children who received antibiotics upon admission had higher level of hS-CRP than those who did not. However, the difference in the level of mean hS-CRP was not likely to impact on initial antibiotics use in the clinical setting. The lower odd ratio for hS-CRP associated with initial antibiotics prescription could explain its discrepancy.

In the present study, although a virus was detected using an RT-PCR assay, the antibiotic administration was continued in 28 patients (62.2%, 28/45). This finding corresponded with previous studies suggesting that detecting a viral respiratory pathogen using RT-PCR analysis result did not reduce antibiotic use[8,14,26]. Other randomized trials evaluating the effect of viral RT-PCR results have presumed that similar findings were explained by the clinician's concerns regarding bacterial superinfection in patients with acute respiratory illness[8]. Although it is accepted that respiratory virus infection predisposes patients to subsequent bacterial respiratory superinfection, the virtual incidence of these serious bacterial infections remains ambiguous[11,27].

Our study has several limitations. First, the diagnosis of AOM was not made precisely. The results were not deduced based on an exact diagnosis protocol but electronic medical records. Second, the RT-PCR analyses in our study were performed only twice a week, resulting in discharged patients before PCR results was reported. This fact could have decreased the advantage provided by RT-PCR as a rapid diagnostic tool, which could have an effect on antibiotic prescription rates. However, other studies have revealed that rapid communication of RT-PCR results did not reduce antibiotic use[28]. Third, it is unlikely that positive RT-PCR results always imply a true viral respiratory tract infection. In a recent study that compared viral PCR results from children with respiratory infection to asymptomatic matched controls, respiratory viruses, such as bocavirus, rhinovirus, adenovirus, coronavirus, and enterovirus, were frequently detected in asymptomatic matched controls[29]. Fourth, this trial was not performed for all inpatients who were diagnosed with an upper respiratory virus but was limited to subjects who received viral RT-PCR analysis. In addition, the performance of our study in a tertiary care center, where antibiotic use is less likely than in a primary care setting, limits the ability to extend our results to a general pediatric clinic. Despite these limitations, the strength of the present study is that it was based on an actual clinical practice.

In this study of children with URTI, antibiotic prescriptions were more frequently found among patients with AOM than among those without AOM. After respiratory viral pathogen was identified using RT-PCR, maintenance of antibiotic treatment were more common in the children with AOM than those without AOM. Therefore, accurate diagnosis of AOM could be a clue in reducing the unnecessary antibiotics use in children with viral URTIs. Well-designed education programs and studies to select patients who might benefit from antimicrobial agents are also important to improve management of AOM. Future prospective studies will be required to develop strategies that can change the prescribing behavior of physicians to minimize unjustified antibiotic use in viral infections.

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요약

목적: 상기도 감염인 소아에게 항생제를 처방하는 것은 아직도 많은 진료실에서 이루어지고 있다. 이 연구는 역전사 중합효소연쇄반응 검사로 호흡기 바이러스가 확인된 이후에도 항생제를 사용한 소아 환자들의 임상적 특징을 조사하고자 하였다.
방법: 2013년 1월부터 2014년 11월에 고신대학교 복음병원 소아청소년과에 상기도 감염으로 입원한 환자 중 역전사 중합효소연쇄반응을 시행한 환자들을 대상으로 후향적 의무기록 분석을 통해 평가하였다.
결과: 상기도 감염으로 진단받은 393명 중 전체 환자 연령의 중앙값은 23개월이었다. 입원 당시 항생제를 처방받은 환자(79명, 20.1%)와 항생제를 처방받지 않은 환자들의 임상적 요인을 비교할 때, 중이염 또는 부비동염의 동반, 높은 고감도 C-반응단백질의 수치가 항생제 처방과 의미 있게 관련 있었다(P<0.001). 입원하여 항생제를 사용하던 중 역전사 중합효소연쇄반응 방법으로 호흡기 바이러스가 확인되었지만, 항생제를 계속 사용한 환자는 44명 중 28명(63.6%)이었다. 항생제를 계속 사용한 환자는 항생제를 중단한 환자와 비교할 때 중이염 동반 비율이 유의하게 높았다(75% vs. 25%, P=0.002).
결론: 본 연구에서 상기도 감염의 원인이 바이러스임을 확인된 소아 환자에게서도 항생제를 지속한 주된 이유는 중이염이 동반되었기 때문이었다. 중이염을 정확하게 진단하고 그 중 항생제가 꼭 필요한 경우를 가려낸다면 소아 상기도 감염에서 불필요한 항생제 사용을 줄이는 데 도움이 될 것으로 생각된다.