〈Regular Article〉

Prescription Patterns of Antimicrobial Agents for Upper Respiratory Tract Infections in Patients Visiting the Emergency Department of Kawasaki Medical School Hospital: A Descriptive Study

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ABSTRACT Antimicrobial resistance (AMR) has become a global threat. The need for the appropriate use of antimicrobial agents has been recognized, such as in upper respiratory tract infections. This study aimed to clarify the prescription of antimicrobial agents for upper respiratory tract infections in the Emergency Department of Kawasaki Medical School Hospital. Patients who visited the department from January 1, 2014, to December 31, 2016, and were diagnosed with upper respiratory tract infection (common cold, acute upper respiratory tract infection, acute pharyngitis, acute tonsillitis, acute bronchitis, acute sinusitis) were included. Excluded were patients who visited non-emergency departments, those under 15 years of age, those transported by ambulance (ambulance, doctor car, doctor helicopter), and those who visited during office hours (8:30-15:30 on weekdays or 8:30-11:00 on Saturdays). A total of 3,920 patients were included in the study, with a median age of 34 years (interquartile range: 25-51 years), and 2007 (51%) were male. Of these, 1,023 patients (26%) were prescribed antimicrobial agents for upper respiratory tract infections. Of the antimicrobial agents prescribed, third-generation cephem antibiotics accounted for more than 40%. In terms of the appropriate use of antimicrobial agents, interventions against prescribing third-generation cephalosporins were considered.

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Key words：Antimicrobial resistance, Upper respiratory tract infection, Antibiotic, Third-generation cephalosporins, The common cold

INTRODUCTION

Antimicrobial agents play an important role in the treatment of bacterial infections[1)]. However, the development of new antimicrobial agents has been stagnant. Antimicrobial agents should be rationally used to preserve the effectivity of available antimicrobial agents. If no action is taken against their inappropriate use, drug-resistant diseases could cause 10 million deaths each year by 2050, which is more than the number of deaths due to cancer

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at present[2]. Antimicrobial agents are overused in the treatment of upper respiratory tract infections (URTIs), the majority of which are viral in origin. Although antimicrobial agents are ineffective against most URTIs, they are frequently prescribed, and many of these agents are broad spectrum[3-6].

In recent years, various societies have published guidelines for the appropriate use of antimicrobial agents for URTIs. In 2016, the American College of Physicians guidelines for respiratory tract infections were revised, and four high-value care advices were proposed[7]. In Japan, the National Action Plan on AMR was created in April 2016, and the outcome measure was to reduce the total use of antimicrobial agents (defined as daily dose per 1,000 residents) to two-thirds of the 2013 level and the use of oral cephalosporins (CPs), quinolones, and macrolides (MCs) to 50% by 2020[8]. In June 2017, the Ministry of Health, Labor and Welfare published the "Manual of Antimicrobial Stewardship, 1st edition"[9]. In September 2019, the Committee on the Appropriate Use of Antimicrobial Agents for Respiratory Tract Infections of the Japanese Association for Infectious Diseases published "Recommendations for the Appropriate Use of Antimicrobial Agents for Respiratory Tract Infections". In these guidelines, URTIs are divided into the following categories: 1) common cold, 2) rhinosinusitis, 3) acute pharyngitis, and 4) acute bronchitis.

To investigate the use of antimicrobial agents for URTIs at Kawasaki Medical School Hospital, we surveyed the use of antimicrobial agents in patients with URTIs who visited the emergency room of Kawasaki Medical School Hospital.

SUBJECTS AND METHODS

Study population, setting, and data collection

We collected a list of patients who visited the Emergency Department of Kawasaki Medical School Hospital from January 1, 2014, to December 31, 2016, from the Department of Medical Records. Of these, we excluded patients who visited non-emergency departments; pediatric patients (< 15 years old); patients who were transported to our hospital by ambulance, doctor car, or doctor helicopter; and patients who visited during office hours (8:30-15:30 on weekdays and 8:30-11:00 on Saturdays). We identified patients who visited the emergency department outside of office hours. If a patient visited the emergency room more than once, the patient was included in the study for each visit. We extracted the data of the assigned disease name and the prescribed medication from the electronic medical records of these patients. To reduce bias, this study included patients who visited the emergency room outside of office hours. In the emergency room outside of office hours, many patients with URTIs visited, new patients with less comorbidities visited, and physicians from many departments work there. Based on the above, we considered the patients who visited the emergency room outside of office hours to be appropriate as representative data for our hospital. We defined URTI-related diseases as common cold, acute upper respiratory infection, acute rhinosinusitis, acute pharyngitis, acute tonsillitis, or acute bronchitis and extracted these disease names using International Classification of Disease version 10 (ICD10) codes. The ICD10 codes for each are as follows: common cold, J00; acute URTI, J069; acute rhinosinusitis, J019; acute pharyngitis, J029; acute tonsillitis, J039; and acute bronchitis, J209. If more than one disease name was assigned to a patient in a single visit, duplicates were counted. We defined the date of a patient's visit to the emergency room as the "index date" and determined that a patient was diagnosed with URTI-related diseases if these diseases were diagnosed within 1 day of the index date. These patients were included in the study and examined for their age, gender, and whether they had antimicrobial prescriptions. We identified the antimicrobial agents using local codes in

Kawasaki Medical School Hospital. If the patient was prescribed oral antimicrobial agents within 1 day of the index date, we considered the patient to have been prescribed antimicrobial agents. The proportions of antimicrobial prescriptions for each URTIs were investigated separately in each year. Antimicrobial agents were divided into penicillins, MCs, CPs, new quinolones (NQs), and others. If more than one antimicrobial agent was prescribed in a single visit, the results were counted in duplicate.

Statistical analysis, ethics, and funding

Descriptive statistics were used to summarize the data. Results are reported as total numbers, percentages, medians, and interquartile ranges, as appropriate. Each research subject was given an anonymized ID for this study, and personally identifying information (e.g., a medical record number) was removed. The protocol for this study was approved by the Ethics Committee of Kawasaki Medical School (Approval No. 2898-03). Funding for this study was provided by the Kawasaki Medical School Project Research Fund.

RESULTS

Fig. 1 shows the process of study subject selection. The total number of patients who visited the Emergency Department of Kawasaki Medical School Hospital from January 1, 2014, to December 31, 2016, was 75,905. Of these, 30,589 patients visited the emergency department outside of office hours, excluding non-emergency department visits; pediatric patients (< 15 years old); patients transported by ambulance, doctor car, or doctor helicopter; and visits during office hours (8:30-15:30 on weekdays and 8:30-11:00 on Saturdays). The number of patients with URTI-related diseases within one day of the emergency room visit was 3,920.

Table 1 shows the characteristics of patients with

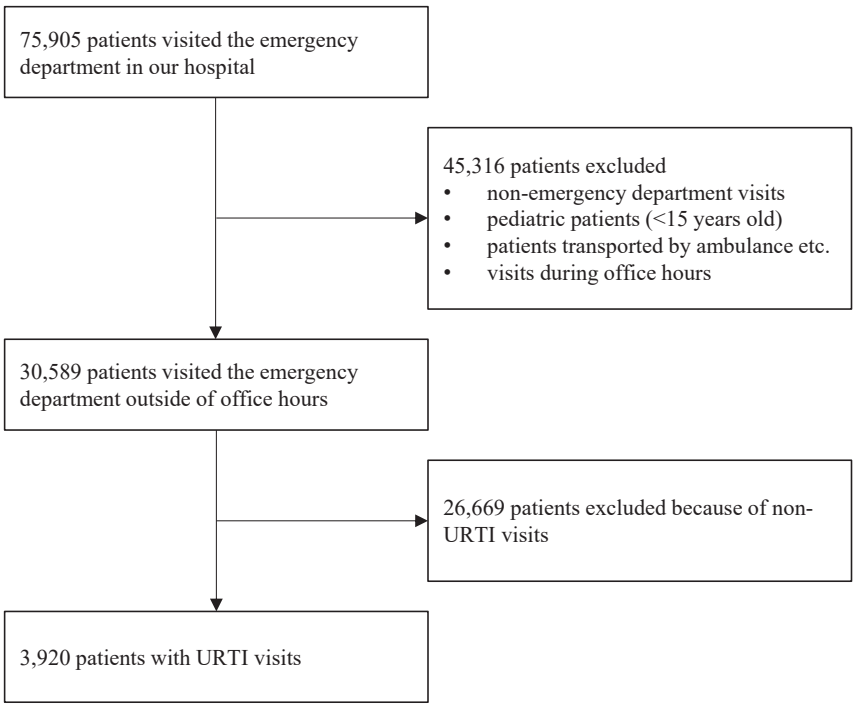

Fig. 1. Process of study subject selection.

Table 1. Characteristics of patients with upper respiratory tract infections in the study

	Patients with URTIs	With antimicrobials[a]	Without antimicrobials[a]
Number (%)	3920	1023 (26%)	2897 (74%)
Median age (IQR)	34 (25-51)	33 (24-49)	35 (25-52)
Male	2007	540	1467
Female	1913	483	1430

URTIs, upper respiratory tract infections; IQR, interquartile range
a, The number (proportion) of all patients is shown.

Table 2. Numbers and percentages of antimicrobial prescriptions for each URTI

Disease name (ICD-10)		Total	With antimicrobials	Without antimicrobials
Common cold	(J00)	752	94 (13%)	658 (88%)
Acute URTI	(J069)	1593	370 (23%)	1223 (77%)
Acute rhinosinusitis	(J019)	82	42 (51%)	40 (49%)
Acute pharyngitis	(J029)	1532	450 (29%)	1082 (71%)
Acute tonsillitis	(J039)	382	166 (43%)	216 (57%)
Acute bronchitis	(J209)	265	101 (38%)	164 (62%)

The numbers and percentages are shown by each disease name. Different diseases were counted separately if multiple diseases were diagnosed on the same day.
URTI, upper respiratory tract infection; ICD-10, international classification of disease version 10

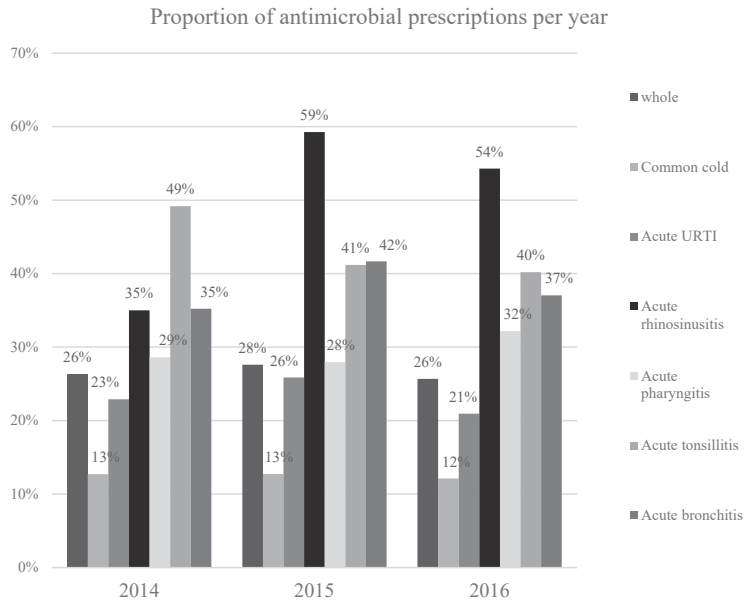

Fig. 2. Proportion of antimicrobial prescriptions per year.

URTIs in the study. The median age of patients who presented to the emergency department with URTIs was 34 (interquartile range, 25-51) years. 2007 patients (51%) were male. Antimicrobial agents were prescribed to 1,023 patients (26%).

Table 2 shows the percentages of antimicrobial prescriptions for each URTI. Antimicrobial agents were prescribed 94 counts (13%) for the common cold, 370 counts (23%) for acute URTI, 42 counts (51%) for acute rhinosinusitis, 450 counts (29%)

Table 3. Numbers and percentages of various antimicrobial prescriptions for each URTI

	Total	PC	CP	MC	NQ	Others
Common cold	95	6 (6%)	49 (52%)	18 (19%)	21 (22%)	1 (1%)
Acute URTI	376	37 (10%)	178 (47%)	76 (20%)	84 (22%)	1 (0%)
Acute rhinosinusitis	43	7 (16%)	20 (47%)	2 (5%)	13 (30%)	1 (2%)
Acute pharyngitis	460	73 (16%)	223 (48%)	57 (12%)	105 (23%)	2 (0%)
Acute tonsillitis	166	49 (30%)	70 (42%)	6 (4%)	39 (23%)	2 (1%)
Acute bronchitis	102	14 (14%)	29 (28%)	22 (22%)	36 (35%)	1 (1%)

The numbers and percentages are shown by each disease name. Different antimicrobials were counted separately if multiple antimicrobials were prescribed on the same day.
PC, penicillins; MC, macrolides; CP, third-generation cephalosporins; NQ, new quinolones; Others, tetracyclines and penems

for acute pharyngitis, 166 counts (43%) for acute tonsillitis, and 101 counts (38%) for acute bronchitis. The composite number of acute pharyngitis and acute tonsillitis cases was 616 counts (32%). Fig. 2 shows the proportion of antimicrobial prescriptions per year between 2014 and 2016. The proportions of antimicrobial prescriptions for most URTIs was remained the same or decreased, except for acute rhinosinusitis.

Table 3 shows the numbers and percentages of various antimicrobial prescriptions for each URTI. The most prescribed antimicrobial agent for URTIs, excluding acute bronchitis, was a third-generation CPs or NQs for acute bronchitis. The numbers (percentages) of prescriptions for broad-spectrum antimicrobial agents were 88 (93%) for the common cold, 338 (90%) for acute URTI, 35 (81%) for acute sinusitis, 385 (84%) for acute pharyngitis, 115 (69%) for acute tonsillitis, and 87 (85%) for acute bronchitis. Broad-spectrum antimicrobial agents accounted for 84% of all antimicrobial agents prescribed.

DISCUSSION

In this study, we investigated that how many oral antimicrobial agents, for which diseases, and what antimicrobial agents were prescribed to patients who visited the Emergency Department of Kawasaki Medical School Hospital from 2014 to 2016 and who were assigned URTI-related diseases.

The number and percentage of antimicrobial prescriptions for URTIs was 1023 patients and 26%, which was lower percentage than previously reported. In a 2005 survey on data of Japanese insurance claims, Higashi & Fukuhara found that the percentage of antimicrobial prescriptions for URTIs was 60%[10]. In a similar study of Japanese insurance claims data from 2012 to 2015, the percentage of antimicrobial agents for URTIs was 40.6% for viral URTIs, 53.9% for rhinosinusitis, 58.9% for pharyngitis, and 58.3% for bronchitis[11] Teratani *et al*. found that the percentage of antimicrobial prescriptions for URTIs was 52.7%[12]. As reported by Higashi & Fukuhara[10] and Kimura *et al*.[13], physicians will be unlikely to prescribe oral antimicrobial agents in outpatient clinics of general hospitals in contrast to clinics without inpatient beds. These results would be related that our hospital is a general hospital and provides education for medical students and residents. At our hospital, the antimicrobial stewardship team provides intervention and support for appropriate antimicrobial use, holds conferences twice a week on cases of inappropriate antimicrobial use, and the infection control team holds lectures for not only physicians but other medical professionals on the appropriate use of antimicrobials. All physicians have attended these lectures in our hospital. These various factors that cannot be identified would contribute to the lower percentage of antimicrobial prescriptions for URTIs in our hospital.

We revealed the percentage of oral antimicrobial

prescriptions for URTI-related diseases and further found that it varied from 13% to 51%. These results did not suggest that antimicrobials were appropriate prescription. "Manual of Antimicrobial Stewardship, 1st edition"[9] states the following for the appropriate use of antimicrobial agents for URTIs: 1) for patients with the common cold, not prescription of antimicrobials, 2) for patients with mild acute rhinosinusitis, not prescription of antimicrobials, 3) for patients with acute pharyngitis not confirmed group A streptococcus, not prescription of antimicrobials, 4) for patients with acute bronchitis except for the patient with pertussis or comorbidities, not prescription of antimicrobials. In our investigation, the percentage of antimicrobial use for common cold and acute URTI were 13% and 23%, respectively. The percentage of antimicrobials use for acute rhinosinusitis was 51%, and the percentage of patients with moderate to severe acute rhinosinusitis is unlikely to exceed 50%, which may indicate the inappropriate use of antimicrobials. The percentage of antimicrobial use for acute bronchitis was 38%, We did not expect that nearly 40% of patients with acute bronchitis had pertussis or comorbidities (e.g., chronic lung disease, immunocompromised conditions). Inappropriate use of antimicrobials for acute bronchitis is suggested. Similarly, inappropriate use of antimicrobials was suspected in pharyngitis, tonsillitis.

We found that third-generation CPs were frequently prescribed for URTI-related diseases, except for acute bronchitis. Kusama similarly reported that third-generation CPs were frequently prescribed in Japan[14]. The use of third-generation CPs has been associated with the occurrence of antimicrobial-resistance bacteria, such as methicillin-resistant staphylococcus aureus (MRSA)[15].

These results suggest that inappropriate use of antimicrobials exists and can be improved. Two approaches can be taken to address the issues in AMR. The first approach is to provide physicians with the percentage of antimicrobials prescribed for URTIs. In 2020, the Ministry of Health, Labor and Welfare announced that an additional medical fee would be obtained if a survey was conducted on the number of outpatients receiving oral antimicrobial prescriptions for URTIs or acute diarrhea. If these data are measured, not only can our hospital receive additional medical fees, but also physicians can reflect their own prescriptions for URTIs and acute diarrhea. The second approach is to hold effective educational programs for appropriate antimicrobial use. In our hospital, all physicians attend staff education lectures on nosocomial infection control and appropriate use of antimicrobials. However, whether they will be able to appropriately prescribe antimicrobials even if they receive education at the lectures is unclear. Yamamoto *et al*. reported the effective educational refresher course for clinicians on the appropriate use of antimicrobials for URTIs[16]. A unique feature of this course is the incorporation of active learning methods of education. These approaches are expected to promote appropriate use of antimicrobials.

The limitations of this study are as follows. First, the diagnosis of URTIs may be incorrect. In Japan, antimicrobial agents can only be prescribed by assigning an appropriate disease name to the antimicrobial agent. For example, a patient may have a common cold but be given a disease name, such as pneumonia, to be prescribed an antimicrobial agent. Second, comorbidities (underlying diseases) are not considered. Prescribing antimicrobial agents in the presence of serious comorbidity is acceptable. The Charlson comorbidity index (CCI) can be used to account for the proportion of antimicrobial prescriptions due to comorbidities[17]. However, the CCI is also difficult to obtain automatically from electronic health records. Third, which physicians are more likely to prescribe antimicrobial agents for URTIs is unclear. In addition to the diagnosis

of URTIs, the prescription of antimicrobial agents is influenced by the understanding of a patient's medical condition, the expertise of the prescribing physician, and the patient's preferences. The present study does not examine whether physicians or patients prefer to prescribe antimicrobial agents.

In conclusion, we should intervene against broad-spectrum antimicrobial agents, especially third-generation CPs, which are frequently prescribed for URTIs, as a strategy against AMR in our hospital. Antimicrobial stewardship, including the intervention of prescribing third-generation CPs, will provide high-quality medical care at our hospital.

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CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this article.

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