A study on the management of acute respiratory tract infection in adults

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(Received for publication May 26, 2014)

Antimicrobials are commonly used to treat acute respiratory tract infection in adults. Furthermore, their overuse has raised concern. We conducted a field survey study that included 170 medical institutions from January 2008 to June 2010. The purpose of this study was to clarify the relationship between the rate of antimicrobial use and patient outcomes with each indication. The study included 1753 patients diagnosed with acute respiratory tract infection. Antimicrobials were used for treatment of 1420 of these patients, whereas 333 cases were not treated with antimicrobials. After 3 days of treatment, patients administered antimicrobials experienced a higher improvement rate than those who did not receive antimicrobial

treatment (92.2% vs. 83.3%, $p<0.0001$). However, after 7 days of treatment, the rates of improvement for patients in both groups were similar (95.0% and 93.4%, respectively, $p=0.2391$). In addition, according to the criteria for the usage of antimicrobials described in the Japanese Respiratory Society guidelines for the management of respiratory tract infection in adults, the patients were classified into the 3 categories (6 indication factors for antimicrobial use): Grade 1, ≤2 factors; Grade 2, 3–4 factors; Grade 3, 5–6 factors). The indication factors considered were the following: 1) temperature; 2) purulent sputum or nasal discharge; 3) tonsillar enlargement and tonsillolith/white puss; 4) middle otitis/sinusitis; 5) inflammatory reaction; and 6) high-risk patients. The results indicate that the improvement observed after 3 days of treatment in Grade 2 and Grade 3 patients was significantly higher with antimicrobial treatment than without antimicrobial treatment.

In conclusion, the administration of antimicrobials is not recommended in younger patients with no underlying disease. However, the use of antimicrobials is required in patients with a higher relative risk that corresponds to the presence of ≥3 of the 6 indication factors for antimicrobial use.

Introduction

The Japanese Respiratory Society established the committee for the preparation of a guideline (GL) for respiratory organ infection in 1998, and published the basic policy on the treatment of respiratory infection in the Japanese Respiratory Society guidelines for the management of community-acquired pneumonia in adults in March 2000[1], the Japanese Respiratory Society guidelines for the management of hospital-acquired pneumonia in adults in March 2002[2], and the Japanese Respiratory Society guidelines for the management of respiratory tract infection in adults in June 2003[3]. Thereafter, the committee performed validation studies on the first two GLs and published a revised version of the community-acquired pneumonia GL in 2005 (a pocketable condensed version, and authenticated version in 2007)[4] and hospital-acquired pneumonia GL in 2008[5] (a pocketable and authenticated version)—The GL for the management of respiratory tract infection in adults—which remains the standard GL for treatment.

Antimicrobials often have little effect on the resolution of cold syndromes, since most are caused by viruses. In addition, many studies describe the effect of facile utilization of antimicrobials in promoting the generation of resistant bacteria[6,7]. Patients with underlying diseases such as malignant tumor or diabetes, in particular, are at risk of developing serious diseases if bacterial infection is not considered. Hence, the treatment of acute respiratory tract infection by antimicrobials should not be ruled out[8,9]. Therefore, to identify an optimal therapeutic policy for the treatment of acute respiratory tract infections, we performed a field survey on a national patient base and attempted to verify the GL for acute respiratory tract infection in adults.

Patients and Methods

Subjects

Total of 170 medical institutions (Table 1) were participated from January, 2008 to June, 2010, and 2173 adult patients (aged ≥20 years) with one of following acute respiratory infections such as 1) acute pharyngitis presenting acute sore throat, 2) acute tonsillitis presenting enlarged tonsil and/or tonsillolith, or 3) acute bronchitis presenting prominent cough and/or sputum were enrolled. The diagnosis was made by each primary physician based on the definition described in the Japanese Respiratory Society guidelines for the management of respiratory tract infection in adults in June 2003[3]. Informed consent was acquired from all the patients prior to starting the research. After completion of therapeutic intervention, information related to the therapeutic process was collected for the survey. Items surveyed were as follows: patient background (body weight, height, age at start of therapy or date of birth, sex, inpatient/outpatient), disease information (underlying and complicating disease), medical agent used (therapeutic agent, prior-therapeutic agent, concomitant drugs, or concurrent medication), clinical improvement, bacteriological test results, and adverse events of clinical intervention.

The patients with the following 6 indication factors for antimicrobial use were recruited: 1) persistent high body temperature (≥3 days); 2) purulent sputum or nasal discharge; 3) tonsillar enlargement and tonsillolith/adhesion of white puss; 4) middle otitis/sinusitis; 5) severe inflammatory reaction (leukocytosis, C-reactive protein positive, or elevated erythrocyte sedimentation rate); 6) high-risk patients, as described in treatment policy of so called “cold syndromes” in “Chapter V, Acute upper respiratory inflammation” in the Japanese Respiratory Society guidelines for the management of respiratory tract infection in adults[3]. These six factors were evaluated by each primary physician. (Grade 1, ≤2 factors; Grade 2, 3–4 factors; Grade 3, 5–6 factors) Risk factors included the following: 1) older age (≥65 years); 2) underlying heart or respiratory disease; and 3) diabetes, renal disease, or immunosuppression. The final decision for treatment with antimicrobials was made by each primary physician, and the dosing period was set at 3–7 days, depending on the patient’s symptoms. In the statistical analysis, p values were calculated using a chi-square test and the significance level was set at $p=0.05$.

Evaluation of clinical improvement

Clinical improvements were assessed on days 3 and 7 after starting therapy (hereafter, abbreviated as day 3 and day 7, respectively). A primary physician judged improvement by confirming symptoms such as high temperature, sputum, nasal discharge, and tonsillar enlargement.

Exclusion criteria

The following patients were excluded from the study: patients with contraindications for an-

Table 1. Participating institutions

Obihiro Kokyuukika Naika Byouin
Medical Corporation Nomura Cardiovascular Medicine
Iida Naika Clinic
Hakushokai-Sano Hospital
Makita Hospital
Hokkaido P.W.F.A.C Sapporo-Kosei General Hospital
Asahikawa Red Cross Hospital
Sapporo Minami-Sanjo Hospital
Iryouhoujinkouwakai Kawaraginaika Iin
Saka General Hospital
Sendai Open Hospital
Okitama Public General Hospital
Yamagata Saisei Hospital
Sanyudo Hospital
Jusendo General Hospital
Sukagawa Hospital
National Hospital Organization Ibarakihigashi National Hospital
Mito Medical Center
Iryouhoujinsyadanseisinkai Takayasu Clinic
Tanaka Naika Shonika Iin
Oshima Clinic
Okano Clinic
Fujisaki Clinic
Tokyo Metropolitan Tama Medical Center
Kamada Clinic
Kikawada Clinic
Kuboyama Iin
Iryouhoujin Koushinkai Nawa Iin
Sakayori Clinic
Itabashi Chuo Medical Center
Nomura Hospital
Kyorin University Hospital
Inoue Clinic
Higashiohnuma Medical Clinic
Shinada Respiratory and Cardiovascular Clinic
Shonandai Shiraga Clinic
Kure Clinic
Motomachi Takatsuka Naika Clinic
Sakamoto Naika Clinic
Kanagawa Cardiovascular and Respiratory Center
Yokohama Minami Kyousai Hospital
Yokohama City University Medical Center
Kanda Clinic
Obana Medical Clinic
Oluto Yokohama Clinic
Kubota Clinic
Miyazaki Hospital
Miyagi Naika Clinic
Matsumoto Clinic
Kakio Medical Clinic
Kawasaki RM & IM Clinic/Kawasaki Rheumatism & Internal Medicine
Suda Medical Clinic
Shinrakuen Hospital
Saiseikai Niigata Daini Hospital
Nishi-Niigata Chuo National Hospital
Shibata Hospital - Niigata Preferctural Hospital
Kiguchi Clinic
Kofu Municipal Hospital
TENRYU HOSPITAL
Hamamatsu University School of Medicine, University Hospital
Shimada Municipal Hospital
JA Shizuoka Kohseiren Enshu Hospital
Hamamatsu Rosai Hospital
Iwata City Hospital
Seirei Mikatahara General Hospital
Shizuoka General Hospital
Shizuoka Hospital
Kouga Hospital
Shizuoka City Shimizu Hospital
Okanami General Hospital
Mie University Hospital
Mie Chuo Medical Center
Matsusaka City Hospital
Keiko Pure Clinic
Shiga University of Medical Science Hospital
Yamamoto Women's Hospital
Yasuda Clinic
Kubota Clinic
Osaka Hospital
Kishiwada City Hospital
Takamatsu Endocrine Clinic
Akashi Medical Center
Nara Prefectural Nara Hospital
Nara Medical University Hospital
Minami Wakayama Medical Center
Kasaoka Daiichi Hospital
Kurashiki Central Hospital
Kawasaki Hospital
Kure Kyosai Hospital
Takamatsu Municipal Hospital
Fukuoka University Chikushi Hospital
Tanushimaru Central Hospital
Fukuoka University Hospital
Nippon Steel Yawata Memorial Hospital
Kokura Medical Center
Ureshino Medical Center
Saiseikai Nagasaki Hospital
Nagasaki University Hospital
Senju Hospital
Sasebo City General Hospital
IZUMIKAWA HOSPITAL
MITSUBISHI NAGASAKI HOSPITAL
Nagasaki Municipal Hospital
Japanese Red Cross Nagasaki Genbaku Isahaya Hospital
Hokusho Central Hospital
NTT West Kyushu Hospital
Kumamoto University Hospital
Oita Nakamura Hospital
Oita University Hospital
Nishida Noutoku Hospital
Almeida Memorial Hospital
Chibana Clinic
Kakazu Hospital
Yonabaru Chuo Hospital
Nakamura Clinic
Nakagami Hospital
Okinawa Red Cross Hospital
The North 5 Clinic
Kikuchi Naika Kokyukika, Medical Corporation
Koizumi Respiratory and Internal Clinic, Medical Corporation
Town's Toyokoro Clinic
Daido Respiratory and Internal Clinic, Medical Corporation
Shimonaga Naika
Shikanai Naika Clinic
Matsuda Hospital, Medical Corporation
Yamamoto Kumiai General Hospital
Sato Hospital
Ishiwata Clinic
Sakai Clinic
Sasaki Naika Clinic
Ekibiru Clinic of Sengendai Station
Minamikoshigaya Medical Kenshinkai Clinic
Swing Nozaki Clinic
Tamura Clinic
Tanimoto Naika Clinic
Suzuki Clinic
Sempo Tokyo Takanawa Hospital
Wakabadai Clinic
Takahashi Internal Medicine, Pediatric, Orthopedics Clinic
Miyabi Clinic
Asao Clinic
Kaneko Naika
Center Kitaekimae Clinic
Yoshikawa Clinic
Higashi Ohgishima Clinic
Murohashi Naika
Nakaoka Clinic
Nomura Clinic, Medical Corporation
Ohe Clinic
Numata Clinic
Shishimido Naika Clinic
Kaisei Iin, Medical Corporation
Aoba Medical Clinic, Medical Corporation
Yui Clinic
Sunouchi Naika
Fukunishi Naika Clinic
Nakajima Iin
Ogiwara Iin, Medical Corporation
Sado General Hospital Kouseiren
Kanazawa Municipal Hospital
Nishihara E.N.T. Clinic
Fujimoto Medical Clinic, Medical Corporation
Tanaka Clinic, Medical Corporation
Keijukai Hospital, Medical Corporation
Medical Corporation Kouan Clinic
Hiroshima Prefectural Hospital
Kamei Clinic, Medical Corporation
Omuta Hospital, Independent Corporation
Iwai Surgical Clinic, Medical Corporation
Medical Corporation "Fraternity" Nishino Hospital

timicrobial use; patients with a medical or family history of allergy to any antimicrobial; patients with poor oral intake or intake of parenteral nutrients; patients with severe renal diseases; and patients with influenza or atypical pathogen infections.

Microbiological test

Prior to starting treatment and on days 3 and 7, test specimens including sputum were collected from the patients in each medical institution and sent to a central medical institute for (Department of Laboratory, Hokusyo-Chuo Hospital) separation/identification of bacteria and determination of colony count.

Results

Subjects

A total of 2173 patients were registered for this study. Of those patients, 420 with missing records, no clinical judgment, or other reasons were excluded. As a result, efficacy and safety of antimicrobials were analyzed in 1753 patients. Table 2 shows the characteristics of the 1753 patients on intention-to-treat basis in the study. The medical institutions (170 facilities) were classified as follows: 88 clinics with no facility to admit patients or with a facility to admit ≤19 patients (GP), and 82 hospitals with a facility to admit ≥20 patients or (HP).

The 1753 patients were classified according to the type of medical institution: 595 patients

Table 2. Characteristics of the patients

Sex	Male	829（47.3%）
	Female	924（52.7%）
Age (years)	Mean value (SD)	49.6±18.5 （Median: 47 years old）
Body weight (kg)	Mean value (SD)	59.2±13.0
Diagnosis	Acute pharyngitis	734（41.9%）
	Acute tonsillitis	195（11.1%）
	Acute bronchitis	715（40.8%）
	Others	109（6.2%）
Concomitant disease	No	984（56.1%）
	Yes	769（43.9%）
Treatment with antimicrobials	No	333（19.0%）
	Yes	1420（81.0%）
Hospital / Clinic	Hospital	595（33.9%）
	Clinic	1158（66.1%）
Outpatient / Inpatient	Outpatient	1730（98.7%）
	Inpatient	23（1.3%）

(33.9%) were in HP, and 1158 (66.1%) were in GP. The primary diagnosis was acute pharyngitis in 734 patients (41.9%), acute tonsillitis in 195 patients (11.1%), acute bronchitis in 715 (40.8%), and others in 109 (6.2%). The number of patients treated with antimicrobials was 1420 (81.0%), whereas 333 (19.0%) were not treated with antimicrobials. The use of antimicrobials is presented by medical institution and diagnosis in Table 3. The rates of the antimicrobial use were significantly different between HP and GP at 73.6% and 84.8%, respectively ($p<0.0001$). In particular, the rate of antimicrobial use in the treatment of patients with acute pharyngitis was significantly different between HP and GP at 55.1% and 81.5%, respectively ($p<0.0001$).

The number of patients with underlying disease or complicating disease was 769 (43.9%). The comorbid diseases included respiratory diseases (31%), hypertension (18%), diabetes (6%), dyslipidemia (5%), and others (40%). Concerning respiratory diseases, the proportion of patients with bronchial asthma was the highest with 64%.

Table 3. Therapy contents by diagnosis

	Diagnosis	on ITT analysis set	Treatment with antimicrobials		
			No	Yes	
Whole	Acute pharyngitis	734 (41.9%)	203 (27.7%)	531 (72.3%)	
	Acute tonsillitis	195 (11.1%)	9 (4.6%)	186 (95.4%)	
	Acute bronchitis	715 (40.8%)	92 (12.9%)	623 (87.1%)	
	Others	109 (6.2%)	29 (26.6%)	80 (73.4%)	
	Total	1753	333 (19.0%)	1420 (81.0%)	
Hospital	Acute pharyngitis	254 (42.7%)	114 (44.9%)	140 (55.1%)	※
	Acute tonsillitis	55 (9.2%)	0 (0.0%)	55 (100.0%)	
	Acute bronchitis	277 (46.6%)	41 (14.8%)	236 (85.2%)	
	Others	9 (1.5%)	2 (22.2%)	7 (77.8%)	
	Total	595	157 (26.4%)	438 (73.6%)	
Clinic	Acute pharyngitis	480 (41.5%)	89 (18.5%)	391 (81.5%)	※
	Acute tonsillitis	140 (12.1%)	9 (6.4%)	131 (93.6%)	
	Acute bronchitis	438 (37.8%)	51 (11.6%)	387 (88.4%)	
	Others	100 (8.6%)	27 (27.0%)	73 (73.0%)	
	Total	1158	176 (15.2%)	982 (84.8%)	

※ $p<0.0001$ by the chi-square test

Table 4. Clinical improvement and antimicrobials usage

Day of judgment	Improvement or not	Antimicrobials	No antimicrobials	p value
Day 3 (n=1507)	Improved	1107 (92.2%)	255 (83.3%)	<0.0001
	Not improved	94 (7.8%)	51 (16.7%)	
Day 7 (n=1753)	Improved	1349 (95.0%)	311 (93.4%)	0.2391
	Not improved	71 (5.0%)	22 (6.6%)	

Clinical improvement and antimicrobial use

Table 4 compares the relationship between clinical improvement and the use of antimicrobials between groups. The clinical improvement rate was 92.2% on day 3 in patients treated with antimicrobials, and 83.3% in patients not treated with antimicrobials ($p<0.0001$). The clinical improvement rate on day 7 was similar between the groups ($p=0.2391$). The major antimicrobials used were quinolones (43.4%), followed by cephems (36.8%) and macrolides (17.6%). The improvement rate using macrolides was predicted to be slightly lower than those of other antimicrobials on day 3 ($p=0.0173$) and day 7 ($p=0.0461$).

Clinical improvement with each grade

The patients were classified into three grades according to the number of factors related to diagnosis (6 indication factors for antimicrobial use). Table 5 presents the relative clinical improvement according to diagnosis grade.

Clinical improvement was noted in Grade 2 and Grade 3 patients treated with antimicrobials on day 3 ($p<0.0001$, $p=0.0004$). Regardless of antimicrobial use, there was no significant difference in the clinical improvement rate in Grade 1 patients on day 3 and Grade 1, 2, and 3 patients on day 7.

Bacteriological examination

Microbiological examination was performed for 92 patients, and 30 patients were completely examined. Upon final patient assessment, 27 patients were successfully treated, three patients were not successfully treated. The isolated bacterial strains included *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (including the BLNAR strain).

Table 5. Clinical improvement rate with each grade

Grade (Total number of factors)	Number of patients (Rate)	Antimicrobials (Rate)	No antimicrobials (Rate)	Day 3			Day 7		
				Antimicrobials Improved (Rate)	No antimicrobials Improved (Rate)	p value	Antimicrobials Improved (Rate)	No antimicrobials Improved (Rate)	p value
Grade 1 (0 to 2)	623 (35.5%)	449 (72.1%)	174 (27.9%)	331 (92.1%)	149 (89.8%)	0.5997	426 (94.9%)	165 (94.8%)	0.9798
Grade 2 (3 to 4)	967 (55.2%)	824 (85.2%)	143 (14.8%)	651 (91.8%)	98 (76.0%)	<0.0001	780 (94.7%)	131 (91.6%)	0.1492
Grade 3 (5 to 6)	163 (9.3%)	147 (90.2%)	16 (9.8%)	125 (96.9%)	8 (72.7%)	0.0004	143 (97.3%)	15 (93.8%)	0.4369

Adverse events

A total of 29 adverse events were reported in 24 patients (1.37%): 11 gastrointestinal symptoms (nine patients); five nervous system events (five patients); one dermatopathy (one patient); 10 abnormal clinical laboratory test values (seven patients); and two other events (two patients). There were no serious adverse events. Exception for 5 patients in whom antimicrobials were discontinued, no adverse events required special treatment.

Discussion

Most acute respiratory tract infections are caused by viruses; hence, antimicrobials are not used in treatment. Tomii *et al.* reported that the rate of antimicrobial usage was within 10% in patients aged 15–64 years with acute upper respiratory inflammation and no underlying disease. In addition, there was no difference in the satisfaction level between patients who were administered antimicrobials and those who were not[10]. On the basis of the results of two clinical trials on anti-influenza drugs (double blind comparison study), Watanabe[11] suggested that approximately 10% of healthy adults and approximately 40% of high-risk patients developed secondary bacterial infection at the time of influenza virus infection. Therefore, in such patients, the administration of antimicrobials is required at an early stage. On the other hand, the number of patients diagnosed in a medical institution is small when their symptoms are mild, which indicates that patients obtain medicines such as OTC from pharmacies for treatment at home, before consultation at a medical institution[12].

In the current study, we attempted to better elucidate issues surrounding the actual use of antimicrobials in adults with acute respiratory tract infection in medical institutions. Approximately 1420 patients (81% of the total patient population in this study) were administered antimicrobials, and this number is higher than that in previous studies. The administration rates of antimicrobials for acute tonsillitis and acute bronchitis did not differ between GP and HP. The administration rate of antimicrobials for acute pharyngitis was higher in GP than in HP, and this is similar to that reported in a previous study[13].

Significant improvement was observed on day 3 in the group using antimicrobials compared with that in those not treated with antimicrobials. In addition, no significant difference observed in clinical improvement was noted on day 3 in Grade 1 patients. However, significant differences were observed in Grade 2 and Grade 3 patients. These results indicate the possibility of bacterial infection. However, because there was no significant difference in the clinical improvement on day 7 between the groups, the bacterial infection was not very severe and patients might have recovered even if antimicrobials were not used. Other possible reasons are mild underlying diseases and a mean age of approximately 50 years.

The indication of antimicrobials administration for acute respiratory tract infection is dis-

cussed from the both sides of cost and satisfaction of the patients. The result of this study indicates that the antimicrobials use is not essential for all Grade 2 and 3 patients. However, antimicrobials are beneficial and their indication might be considered in each case. It is desired that the administration should be taken into consideration from multiple points of view and factors, which acquired from better relationship between attending physician and patient based on good communication.

In conclusion, administration of antimicrobials is not recommended for the treatment of acute respiratory tract infections in younger patients with no underlying disease. On the other hand, it is needed for treatment of patients with ≥3 of the 6 indication factors for antimicrobial use. A more detailed and proper clinical investigation using objective indices is warranted in the future.

Acknowledgements

This clinical research investigation was a multicenter study in which the medical institutes shown in Table 1 participated. The authors greatly thank the responsible physicians and physicians-in-chief at each medical institute for their collaboration.

The study was funded by the non-profit organization, Nagasaki Evaluation Organization for Clinical Interventions (NEOCI) and Shionogi & Co., Ltd.

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