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

YOSHIHIRO YAMAMOTO¹, MITSUHIDE OHMICHI², AKIRA WATANABE³, YOSHITO NIKI⁴, NOBUKI AOKI⁵, SHIN KAWAI⁶, KINGO CHIDA⁷, KEICHI MIKASA⁸, MASAFUMI SEKI⁹, TADASHI ISHIDA¹⁰, JUN-ICHI KADOTA¹¹, HIROTO MATSUSE¹², JIRO FUJITA¹³ and SHIGERU KOHNO¹⁴

¹Department of Clinical Infectious Diseases, Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama
²Ohmichi Clinic of Internal and Respiratory Medicine
³Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University
⁴Department of Clinical Infectious Diseases, Showa University School of Medicine
⁵Department of Internal Medicine, Shinrakuen Hospital
⁶Department of Infectious Diseases, Division of Comprehensive Medical Care, Kyorin University School of Medicine
⁷Internal Medicine, Hamamatsu-Toyooka Hospital
⁸Center for Infectious Diseases, Nara Medical University
⁹Division of Infection Control and Prevention, Osaka University Hospital
¹⁰Department of Respiratory Medicine, Kurashiki Central Hospital
¹¹Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine
¹²Department of Respiratory Medicine, Toho University Ohashi Medical Center
¹³First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus
¹⁴Second Department of Internal Medicine, Nagasaki University Hospital

(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 20033). 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 adults3). 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>
<thead>
<tr>
<th>Participating institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obihiro Koyukikuika Naika Byouin</td>
</tr>
<tr>
<td>Medical Corporation Nomura Cardiovascular Medicine</td>
</tr>
<tr>
<td>Iida Naika Clinic</td>
</tr>
<tr>
<td>Hakusokai-Sano Hospital</td>
</tr>
<tr>
<td>Makita Hospital</td>
</tr>
<tr>
<td>Hokkaido W.F.A.C. Sapporo-Kosei General Hospital</td>
</tr>
<tr>
<td>Asohikawa Red Cross Hospital</td>
</tr>
<tr>
<td>Sapporo Minami-Sanjo Hospital</td>
</tr>
<tr>
<td>Iryushoukinkouwakai Katarihonka In</td>
</tr>
<tr>
<td>Saka General Hospital</td>
</tr>
<tr>
<td>Sendai Open Hospital</td>
</tr>
<tr>
<td>Okinawa Public General Hospital</td>
</tr>
<tr>
<td>Yamagata Saisei Hospital</td>
</tr>
<tr>
<td>Sanyudo Hospital</td>
</tr>
<tr>
<td>Jusendo General Hospital</td>
</tr>
<tr>
<td>Sukagawa Hospital</td>
</tr>
<tr>
<td>National Hospital Organization Ibarakihigashi National Hospital</td>
</tr>
<tr>
<td>Mitoh Medical Center</td>
</tr>
<tr>
<td>Iryushoujuyudansensinai Takayasu Clinic</td>
</tr>
<tr>
<td>Tanaka Naika Shionika In</td>
</tr>
<tr>
<td>Ohshin Clinics</td>
</tr>
<tr>
<td>Okano Clinic</td>
</tr>
<tr>
<td>Fujisaki Clinic</td>
</tr>
<tr>
<td>Tokyo Metropolitan Tama Medical Center</td>
</tr>
<tr>
<td>Kamada Clinic</td>
</tr>
<tr>
<td>Kikawada Clinic</td>
</tr>
<tr>
<td>Kuboyama In</td>
</tr>
<tr>
<td>Iryushoujin Koshinkai Nawa In</td>
</tr>
<tr>
<td>Sakayori Clinic</td>
</tr>
<tr>
<td>Itabashi Chuo Medical Center</td>
</tr>
<tr>
<td>Nomura Hospital</td>
</tr>
<tr>
<td>Kyorin University Hospital</td>
</tr>
<tr>
<td>Inoue Clinic</td>
</tr>
<tr>
<td>Higashiobama Medical Clinic</td>
</tr>
<tr>
<td>Shinada Respiratory and Cardiovascular Clinic</td>
</tr>
<tr>
<td>Shonandai Shiraga Clinic</td>
</tr>
<tr>
<td>Kure Clinic</td>
</tr>
<tr>
<td>Motomochi Takatsuka Naika Clinic</td>
</tr>
<tr>
<td>Sakamoto Naika Clinic</td>
</tr>
<tr>
<td>Kanagawa Cardiovascular and Respiratory Center</td>
</tr>
<tr>
<td>Yokohama Minami Kyosai Hospital</td>
</tr>
<tr>
<td>Yokohama City University Medical Center</td>
</tr>
<tr>
<td>Kanda Clinic</td>
</tr>
<tr>
<td>Ohama Medical Clinic</td>
</tr>
<tr>
<td>Olotu Yokohama Clinic</td>
</tr>
<tr>
<td>Kubota Clinic</td>
</tr>
<tr>
<td>Miyazaki Hospital</td>
</tr>
<tr>
<td>Miyagi Naika Clinic</td>
</tr>
<tr>
<td>Matsumoto Clinic</td>
</tr>
<tr>
<td>Kikko Medical Clinic</td>
</tr>
<tr>
<td>Kawasaki RM &amp; IM Clinic/Kawasaki Rheumatism &amp; Internal Medicine</td>
</tr>
<tr>
<td>Suda Medical Clinic</td>
</tr>
<tr>
<td>Shinrakuen Hospital</td>
</tr>
<tr>
<td>Saiseikai Niigata Daini Hospital</td>
</tr>
<tr>
<td>Nishi-Niigata Chuo National Hospital</td>
</tr>
<tr>
<td>Shibata Hospital - Niigata Prefectural Hospital</td>
</tr>
<tr>
<td>Kiguchi Clinic</td>
</tr>
<tr>
<td>Kofu Municipal Hospital</td>
</tr>
<tr>
<td>TENRYU HOSPITAL</td>
</tr>
<tr>
<td>Hamamatsu University School of Medicine, University Hospital</td>
</tr>
<tr>
<td>Shimada Municipal Hospital</td>
</tr>
<tr>
<td>JA Shizuoka Kosei Enshu Hospital</td>
</tr>
<tr>
<td>Hamamatsu Rosai Hospital</td>
</tr>
<tr>
<td>Iwata City Hospital</td>
</tr>
<tr>
<td>Seeri Mikatahara General Hospital</td>
</tr>
<tr>
<td>Shizuoka General Hospital</td>
</tr>
<tr>
<td>Shizuoka Hospital</td>
</tr>
<tr>
<td>Kouga Hospital</td>
</tr>
<tr>
<td>Shizuoka City Shimizu Hospital</td>
</tr>
<tr>
<td>Okanami General Hospital</td>
</tr>
<tr>
<td>Mie University Hospital</td>
</tr>
<tr>
<td>Mie Chuo Medical Center</td>
</tr>
<tr>
<td>Matsuoka City Hospital</td>
</tr>
<tr>
<td>Keiko Pure Clinic</td>
</tr>
<tr>
<td>Shiga University of Medical Science Hospital</td>
</tr>
<tr>
<td>Yamamoto Women's Hospital</td>
</tr>
<tr>
<td>Yasuda Clinic</td>
</tr>
<tr>
<td>Kubota Clinic</td>
</tr>
<tr>
<td>Osaka Hospital</td>
</tr>
<tr>
<td>Kishiwada City Hospital</td>
</tr>
<tr>
<td>Takamatsu Endocrine Clinic</td>
</tr>
<tr>
<td>Akashi Medical Center</td>
</tr>
<tr>
<td>Nara Prefectural Nara Hospital</td>
</tr>
<tr>
<td>Nara Medical University Hospital</td>
</tr>
<tr>
<td>Minami Wakayama Medical Center</td>
</tr>
<tr>
<td>Kasaoka Daichi Hospital</td>
</tr>
<tr>
<td>Kurasashi Central Hospital</td>
</tr>
<tr>
<td>Kawasaki Hospital</td>
</tr>
<tr>
<td>Kure Kyosai Hospital</td>
</tr>
<tr>
<td>Takamatsu Municipal Hospital</td>
</tr>
<tr>
<td>Fukuoka University Chikushu Hospital</td>
</tr>
<tr>
<td>Tanushimaru Central Hospital</td>
</tr>
<tr>
<td>Fukuoka University Hospital</td>
</tr>
<tr>
<td>Nippon Steel Yawata Memorial Hospital</td>
</tr>
<tr>
<td>Kokura Medical Center</td>
</tr>
<tr>
<td>Ureshino Medical Center</td>
</tr>
<tr>
<td>Sasaei, Kagoshima Hospital</td>
</tr>
<tr>
<td>Nagaoka University Hospital</td>
</tr>
<tr>
<td>Sennyo Hospital</td>
</tr>
<tr>
<td>Sasebo City General Hospital</td>
</tr>
<tr>
<td>IZUMIKAWA NAGASAKI HOSPITAL</td>
</tr>
<tr>
<td>MITSUBISHI NAGASAKI HOSPITAL</td>
</tr>
<tr>
<td>Nagaoka Municipal Hospital</td>
</tr>
<tr>
<td>Japanese Red Cross Nagaoka Genbuk Ishaya Hospital</td>
</tr>
<tr>
<td>Hokusho Central Hospital</td>
</tr>
<tr>
<td>NTT West Kyushu Hospital</td>
</tr>
<tr>
<td>Kumamoto University Hospital</td>
</tr>
<tr>
<td>Oita Nakamura Hospital</td>
</tr>
<tr>
<td>Oita University Hospital</td>
</tr>
<tr>
<td>Nishida Nouchi Memorial Hospital</td>
</tr>
<tr>
<td>Amida Memorial Hospital</td>
</tr>
<tr>
<td>Chihana Clinic</td>
</tr>
<tr>
<td>Kakazu Hospital</td>
</tr>
<tr>
<td>Yonabaru Chuo Hospital</td>
</tr>
<tr>
<td>Nakamura Clinic</td>
</tr>
<tr>
<td>Nakagami Hospital</td>
</tr>
<tr>
<td>Okinawa Red Cross Hospital</td>
</tr>
<tr>
<td>The North 5 Clinic</td>
</tr>
<tr>
<td>Kikuchi Naika Koyukikukka, Medical Corporation</td>
</tr>
<tr>
<td>Kozum, Respiratory and Internal Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Town's Toyokoro Clinic</td>
</tr>
<tr>
<td>Daido Respiratory and Internal Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Shimonoga Naika</td>
</tr>
<tr>
<td>Shikanai Naika Clinic</td>
</tr>
<tr>
<td>Matsuda Hospital, Medical Corporation</td>
</tr>
<tr>
<td>Yamamoto Kumiai General Hospital</td>
</tr>
<tr>
<td>Sato Hospital</td>
</tr>
<tr>
<td>Ishiwata Clinic</td>
</tr>
<tr>
<td>Sakai Clinic</td>
</tr>
<tr>
<td>Sasaki Naika Clinic</td>
</tr>
<tr>
<td>Ekitobu Clinic of Sengendai Station</td>
</tr>
<tr>
<td>Minamikoshigaya Medical Kemshinkai Clinic</td>
</tr>
<tr>
<td>Swing Nozaki Clinic</td>
</tr>
<tr>
<td>Tamura Clinic</td>
</tr>
<tr>
<td>Tanimoto Naika Clinic</td>
</tr>
<tr>
<td>Suzuki Clinic</td>
</tr>
<tr>
<td>Sempo Tokyo Takawa Hospital</td>
</tr>
<tr>
<td>Wakabadai Clinic</td>
</tr>
<tr>
<td>Takashima Internal Medicine, Pediatric, Orthopedics Clinic</td>
</tr>
<tr>
<td>Miyabi Clinic</td>
</tr>
<tr>
<td>Asao Clinic</td>
</tr>
<tr>
<td>Kaneko Naika</td>
</tr>
<tr>
<td>Center Kitaikumae Clinic</td>
</tr>
<tr>
<td>Yoshikawa Clinic</td>
</tr>
<tr>
<td>Higashi Oigoishima Clinic</td>
</tr>
<tr>
<td>Murohoshi Naika</td>
</tr>
<tr>
<td>Nakaoa Clinic</td>
</tr>
<tr>
<td>Nomura Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Ohe Clinic</td>
</tr>
<tr>
<td>Numata Clinic</td>
</tr>
<tr>
<td>Shishimido Naika Clinic</td>
</tr>
<tr>
<td>Kaisei In, Medical Corporation</td>
</tr>
<tr>
<td>Aoba Medical Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Yui Clinic</td>
</tr>
<tr>
<td>Sunouchi Naika</td>
</tr>
<tr>
<td>Fukushiti Naika Clinic</td>
</tr>
<tr>
<td>Nakajima In</td>
</tr>
<tr>
<td>Ogawa Int, Medical Corporation</td>
</tr>
<tr>
<td>Sado General Hospital Kousei</td>
</tr>
<tr>
<td>Kanazawa Municipal Hospital</td>
</tr>
<tr>
<td>Nishihara E.N.T. Clinic</td>
</tr>
<tr>
<td>Fujimoto Medical Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Tanaka Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Keijuku Hospital, Medical Corporation</td>
</tr>
<tr>
<td>Medical Corporation Koun Clinic</td>
</tr>
<tr>
<td>Hiroshima Prefectural Hospital</td>
</tr>
<tr>
<td>Kamei Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Omura Hospital, Independent Corporation</td>
</tr>
<tr>
<td>Iwai Surgical Clinic, Medical Corporation</td>
</tr>
<tr>
<td>Medical Corporation “Fraternity” Nishino Hospital</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th><strong>Table 2. Characteristics of the patients</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Concomitant disease</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Treatment with antimicrobials</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Hospital / Clinic</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Outpatient / Inpatient</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
(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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>on ITT analysis set</th>
<th>Treatment with antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td>203 (27.7%)</td>
<td>531 (72.3%)</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>9 (4.6%)</td>
<td>186 (95.4%)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>92 (12.9%)</td>
<td>623 (87.1%)</td>
</tr>
<tr>
<td>Others</td>
<td>29 (26.6%)</td>
<td>80 (73.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>333 (19.0%)</td>
<td>1420 (81.0%)</td>
</tr>
</tbody>
</table>

Hospital

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>on ITT analysis set</th>
<th>Treatment with antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td>114 (44.9%)</td>
<td>140 (55.1%)</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>0 (0.0%)</td>
<td>55 (100.0%)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>41 (14.8%)</td>
<td>236 (85.2%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (22.2%)</td>
<td>7 (77.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>157 (26.4%)</td>
<td>438 (73.6%)</td>
</tr>
</tbody>
</table>

Clinic

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>on ITT analysis set</th>
<th>Treatment with antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td>89 (18.5%)</td>
<td>391 (81.5%)</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>9 (6.4%)</td>
<td>131 (93.6%)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>51 (11.6%)</td>
<td>387 (88.4%)</td>
</tr>
<tr>
<td>Others</td>
<td>27 (27.0%)</td>
<td>73 (73.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (15.2%)</td>
<td>982 (84.8%)</td>
</tr>
</tbody>
</table>

*p<0.0001 by the chi-square test

Table 4. Clinical improvement and antimicrobials usage

<table>
<thead>
<tr>
<th>Day of judgment</th>
<th>Improvement or not</th>
<th>Antimicrobials</th>
<th>No antimicrobials</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 (n=1507)</td>
<td>Improved</td>
<td>1107 (92.2%)</td>
<td>255 (83.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Not improved</td>
<td>94 (7.8%)</td>
<td>51 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Day 7 (n=1753)</td>
<td>Improved</td>
<td>1349 (95.0%)</td>
<td>311 (93.4%)</td>
<td>0.2391</td>
</tr>
<tr>
<td></td>
<td>Not improved</td>
<td>71 (5.0%)</td>
<td>22 (6.6%)</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of patients</th>
<th>Antimicrobials (%)</th>
<th>No antimicrobials (%)</th>
<th>Antimicrobials improved (%)</th>
<th>No antimicrobials improved (%)</th>
<th>p value</th>
<th>Antimicrobials improved (%)</th>
<th>No antimicrobials improved (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (0 to 2)</td>
<td>623 (35.5%)</td>
<td>449 (72.1%)</td>
<td>174 (27.9%)</td>
<td>331 (92.1%)</td>
<td>149 (89.8%)</td>
<td>0.5997</td>
<td>426 (94.9%)</td>
<td>165 (94.8%)</td>
<td>0.9798</td>
</tr>
<tr>
<td>Grade 2 (3 to 4)</td>
<td>967 (55.2%)</td>
<td>824 (85.2%)</td>
<td>143 (14.8%)</td>
<td>651 (91.8%)</td>
<td>98 (76.0%)</td>
<td>&lt;0.0001</td>
<td>780 (94.7%)</td>
<td>131 (91.6%)</td>
<td>0.1492</td>
</tr>
<tr>
<td>Grade 3 (5 to 6)</td>
<td>163 (9.3%)</td>
<td>147 (90.2%)</td>
<td>16 (9.8%)</td>
<td>125 (96.9%)</td>
<td>8 (72.7%)</td>
<td>0.0004</td>
<td>143 (97.3%)</td>
<td>15 (93.8%)</td>
<td>0.4369</td>
</tr>
</tbody>
</table>
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. On the basis of the results of two clinical trials on anti-influenza drugs (double blind comparison study), Watanabe 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.

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.

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 \( \geq 3 \) 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.

**References**

6) **Watanabe, A.**: Cold syndrome—To what extent, is antibacterial drug required? Infection Front 2: 8–9, 2004
10) **Tomii, K.; Y. Matsumura, K. Maeda, et al.**: Minimal use of antibiotics for acute respiratory tract