

**Manual of Antimicrobial Stewardship  
(1st Edition)**

**The Government of Japan  
Ministry of Health, Labour and Welfare  
Health Service Bureau  
Tuberculosis and Infectious Diseases Control Division**



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## 1. Introduction

### (1) Background

Antimicrobials<sup>\*1</sup> are of paramount importance in today's health care and have contributed greatly to the treatment of infectious diseases and reduction in morbidity and mortality.<sup>1</sup> On the other hand, antimicrobials can cause adverse effects and therefore need to be used in an appropriate manner.<sup>1</sup> As a result of misuse of antimicrobials, antimicrobial resistance (AMR) has been recently recognized as a major global public health threat.<sup>1</sup> Without appropriate measures, it is estimated that there will be 10 million deaths per year due to organisms with AMR in 2050.<sup>2,3</sup> The development of new antimicrobial agents has been stagnant since the 1980s, while AMR has posed significant threats to public health.<sup>1</sup> There is a concern, therefore, that without appropriate antimicrobial use today, effective antimicrobial agents may run out in the future.<sup>4</sup> This situation must be averted; and antimicrobial stewardship is an important strategy to combat AMR.

A global action plan on AMR was adopted at the World Health Assembly in May 2015, and was followed by a national action plan on AMR adopted by the Government of Japan in April 2016.<sup>1</sup> Antimicrobial stewardship has been set as one of the important strategies and needs to be promoted among all stakeholders including medical professionals and patients in everyday practice.<sup>1</sup>

A study on antimicrobial consumption in Japan based on sales data showed Japan consumed 15.8 Defined Daily Doses (DDDs)<sup>\*2</sup> per 1,000 inhabitants per day in 2013 and oral antimicrobial agents accounted for 92.4% of the total consumption.<sup>5</sup> Compared to other countries, Japan consumed a relatively higher proportion of oral third-generation cephalosporins, fluoroquinolones and macrolides.<sup>1,5</sup> Little is known about the misuse of antimicrobials in Japan, but for example, a report from the USA showed about 30% of total antimicrobial use was inappropriate.<sup>6</sup> Therefore, it is reasonably assumed that a certain proportion of antimicrobial use in Japan is also not appropriate and this needs to be addressed in Japan.

This manual aims to promote antimicrobial stewardship by providing clear guidance to improve the clinical management of selected infectious diseases.

### (2) Purpose of the Manual

The purpose of this manual is to improve the clinical management of infectious diseases, leading to a reduction in inappropriate and unnecessary use of antimicrobial agents without causing harm to patients. Japan's national plan on AMR sets "Reduce antimicrobial use per day per 1,000 inhabitants in 2020 to two-thirds of the level in 2013" as one of the outcome indices,<sup>1</sup> and it is noted that those outcome indices should be achieved through promoting appropriate infectious disease practice.

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<sup>\*1</sup> There are multiple relevant terminologies with different definitions. However, in reality, the following terms are often used interchangeably by the general public in Japan to mean drugs effective against bacteria:  
**antimicrobial agents, antimicrobials:** antimicrobial agents, or antimicrobials, are active against microorganisms, which are generally categorized into bacteria, fungi, viruses and parasites. These are the general term for drugs to treat and prevent infectious diseases. They contain antibacterial agents, antifungal agents, antiviral agents and antiparasitic agents.

**antibacterial agents:** antimicrobial agents that are active against bacteria.

**antibiotics:** informally defined as an agent that is derived from bacterial sources to inhibit and control cell activities of microorganisms

**antibiotic agents:** another term for drugs that use the antibacterial action of antibiotics

<sup>\*2</sup> **DDD:** DDD stands for Defined Daily Dose. It represents the average dose for an adult when an antimicrobial agent is used for its main disease indication. The World Health Organization provides the DDD for each agent.

### **(3) Target Readers**

This manual is intended for medical professionals, particularly physicians who examine, prescribe for, and counsel patients in an outpatient setting. The manual does not provide appropriate antimicrobial use in an inpatient setting. Topics that are controversial even among experts were excluded from the manual. Seeking expert consultation and referring to academic literatures are encouraged for topics beyond the scope of the manual, such as alternative recommendations for those with a penicillin allergy.

As noted above, a large proportion of antimicrobial consumption in Japan is explained by oral antimicrobial agents and, presumably, a substantial share of the oral third-generation cephalosporins, fluoroquinolones and macrolides are prescribed in outpatient settings. Therefore, the manual is structured so as to help medical professionals distinguish the outpatient clinical situations where antimicrobial agents are indicated from those where they are not. Moreover, the manual is expected to be helpful to other medical professionals who are not directly involved with antimicrobial prescription, and it is highly recommended that all who are involved in health care including patients read the manual in order to fully promote antimicrobial stewardship.

### **(4) Target Patient Populations**

The indications for antimicrobial use in outpatient settings are relatively limited since many clinical entities such as acute respiratory tract infections (ARTI) and acute diarrhea do not require antimicrobials. In order to promote optimal use of specific antimicrobial agents, the latter half of the manual focuses on the clinical management of ARTI and acute diarrhea because it is believed that antimicrobials are often unnecessarily prescribed for these two common conditions based on the available evidence regarding misuse of antimicrobials and the type of antimicrobial agents commonly prescribed in Japan.<sup>5,6</sup> The target subjects of the manual are healthy, immunocompetent adult and pediatric (school aged children and above) patients. Infants are excluded as particular attention to the age-specific pathophysiology is often required for infants.

The Summary of Product Characteristics (SPC) of each medication needs to be referred to for appropriate prescription with the right dose and frequency.

In the appendix, the manual contains relevant documents to support clinical practice according to the recommendations given within.

### **(5) Manual Development Processes**

While major clinical guidelines developed by the Japanese Association for Infectious Diseases (JAID), Japanese Society of Chemotherapy (JSC), Japanese Society for Pediatric Infectious Diseases (JSPID), Oto-Rhino-Laryngological Society of Japan, Japanese Rhinologic Society, the US Centers for Disease Control and Prevention (CDC), American College of Physicians (ACP), Infectious Diseases Society of America (IDSA), American Academy of Pediatrics (AAP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), National Institute for Health and Care Excellence (NICE) and others were referred to, a review of the literature on ARTI was made for meta-analyses, systematic reviews and randomized clinical trials in order to formulate recommendations based on the latest

scientific evidence. Cochrane Library, PubMed and Ichushi (Japan Medical Abstracts Society) were used as search websites for articles published as of December 31, 2016. “Acute bronchitis” OR “respiratory tract infection” OR “pharyngitis” OR “rhinosinusitis” OR “the common cold” as Medical Subject Headings (MeSH) terms were used for English articles while “acute bronchitis” OR “respiratory tract infection” OR “pharyngitis” OR “rhinosinusitis” OR “common cold” were used for Japanese articles.

For acute diarrhea, while major clinical guidelines developed by JAID/JSC, IDSA, the American College of Gastroenterology (ACG), World Gastroenterology Organization (WGO) and others were referred to, a similar search strategy was adopted with the search terms of “diarrhea” and (“acute disease” OR “infectious diarrhea” OR “dysentery” OR “acute gastroenteritis”) as MeSH terms for English articles, and “gastroenteritis” OR “acute diarrhea” for Japanese articles.

Of note, the patient population of the literature review was limited to immunocompetent adult or pediatric patients without chronic lung disease for ARTI, and immunocompetent adult or pediatric patients without chronic bowel disease for acute diarrhea.

## **2. General Principles**

### **(1) What is Antimicrobial Stewardship?**

Antimicrobial stewardship<sup>\*3</sup> is a concept involving measures and interventions taken in order to improve optimal antimicrobial use.<sup>7</sup> Antimicrobial stewardship aims to help determine indications for antimicrobials and optimal antimicrobial regimens with the right route, dose, frequency and duration, leading to improving patients' outcomes and the minimization of adverse events caused by antimicrobials.

The activities reported in the literature include prospective audits with direct feedback to those who prescribe antimicrobials, limited access to particular antimicrobial agents with preauthorization, education and promotion for optimal antimicrobial use, facility-specific guideline development for de-escalation of antimicrobials and treatment guidance, change from intravenous to oral regimens, use of rapid diagnostics, and interventions to delay antimicrobial use.<sup>7-9</sup> In actual clinical settings, the above activities are utilized singly or in combination. Which activities are chosen should be determined by the clinical setting (inpatient vs. outpatient) and resources available at individual health care facilities.<sup>10</sup>

### **(2) Indications for Antimicrobials**

In general, antimicrobial use is indicated when an infectious disease for which antimicrobial use is the standard treatment has been diagnosed or is strongly suspected. Antimicrobial use needs to be minimized for other situations, and every physician should know the indications for antimicrobials depending on his or her clinical setting, as even a bacterial infection may not necessarily require antimicrobials and may be self-limiting.

Patients should adhere to prescriptions of antimicrobials given by physicians. The remaining antimicrobials should be discarded when a physician gives an instruction to stop taking them before the originally intended duration is up.

Also, patients should be referred to an appropriate health care facility in a timely manner in case it is difficult to manage them in an outpatient setting. While preparing for patient referral, physicians are encouraged to obtain appropriate microbiological work-ups such as multiple sets of blood cultures and a gram stain and culture of sputum and/or urine prior to empiric antimicrobial treatment in order to diagnose an infectious disease without compromising the culture results.

### **(3) Inappropriate and Unnecessary Use of Antimicrobials**

In this manual, the situations where antimicrobial use is not appropriate are divided into "unnecessary use" and "inappropriate use." "Unnecessary use" is when antimicrobials are used when they are unnecessary. "Inappropriate use" is when antimicrobial selection, dosage and/or duration are not within the standardized usage.

It is noted that saving and taking antimicrobials from prior prescriptions based on patients' own judgements can compromise the diagnosis of an infectious disease and even harm patients due to adverse events and overdose. Therefore, patients should refrain from such behavior while physicians should instruct patients not to engage such use of antimicrobials.

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<sup>\*3</sup> Frequently referred to as 'Antimicrobial Stewardship'

**(4) Miscellaneous**

Prevention of infectious diseases contributes to a reduction in antimicrobial use through reduced infectious disease burden with antimicrobial indications. The following are considered preventive against ARTI and acute diarrhea.

**(i) Hand hygiene**

Hand hygiene is proven to prevent the spread of microorganisms including viruses that cause ARTI and acute diarrhea, and, in particular, is reported to be effective against the spread of ARTI from pediatric patients<sup>11</sup> and to reduce the incidence of acute diarrhea.<sup>12</sup> Alcohol-based hand rub, and soap and water are the two major ways of performing hand hygiene, and soap and water is recommended when hands are (visibly) contaminated with nasal discharge, sputum, vomitus or stools.<sup>13</sup> Soap and water is also indicated to manage acute diarrhea caused by norovirus.<sup>14</sup>

**(ii) Vaccination**

There are several vaccines available to prevent ARTI and acute diarrhea in Japan. They include influenza vaccine, pertussis-containing vaccine (given as combination DPT-IPV vaccines including diphtheria, pertussis, tetanus and inactivated polio vaccine components), measles and rubella (MR) vaccine, pneumococcal vaccine and *Haemophilus influenzae* type b (Hib) vaccine for ARTI, and rotavirus vaccine for acute diarrhea. In Japan, DPT-IPV vaccines, MR vaccine, 13-valent pneumococcal conjugate vaccine and Hib vaccine are given to children as routine vaccination, 23-valent pneumococcal polysaccharide vaccine and influenza vaccine are given to the elderly as routine vaccination, and rotavirus and influenza virus vaccine for the non-elderly are given as voluntary vaccination.<sup>15</sup>

**(iii) Cough etiquette**

Cough etiquette is recommended to prevent person-to-person transmission of microorganisms that cause ARTI.<sup>16</sup> The following are specifically recommended:

- Wear a mask when coughing and sneezing
- If a mask is not worn, use a tissue or upper arm to cover coughs and sneezes, and turn face away from others
- Discard tissues contaminated with nasal discharge and/or sputum, and clean hands immediately

**(iv) Gargling**

Evidence of throat gargling is scarce in the literature. In a randomized controlled trial conducted in Japan, comparisons were made among three groups, that is, usual care (control), water gargling, and iodine gargling, and the water gargling group had significantly lower incidence of ARTI than the control group.<sup>17</sup> However, the study was non-blind and the external validity of the study was difficult to assess. Additionally, a randomized controlled trial to assess the effectiveness of vitamin D and gargling to prevent ARTI showed no apparent effectiveness of gargling.<sup>18</sup> Given these findings, the effectiveness of gargling is still being debated.



### 3. Acute Respiratory Tract Infection (ARTI)

#### (1) What is acute respiratory tract infection?

Acute respiratory tract infection (ARTI) includes acute upper respiratory tract infection and acute lower respiratory tract infection (acute uncomplicated bronchitis). Terminologies such as “flu,” “flu-like syndrome” and “common cold” are commonly used.<sup>19,20</sup>

The word “flu” is used in many ways, referring to “acute upper respiratory infection” in a narrow sense and “acute upper and lower respiratory infection” in a wide sense,<sup>21</sup> and patients report as “flu” even when they do not have respiratory tract symptoms.<sup>22,23</sup> It is important to determine whether a patient’s clinical presentation suggests ARTI or not when he or she complains, “I’ve got the flu.”

#### (2) Epidemiology of ARTI

A patient census report conducted by the Ministry of Health, Labour and Welfare (MHLW) in October 2014 estimated that there were 195 patients presenting with acute upper respiratory tract infection per 100,000 populations per day.<sup>24</sup> Also, a study conducted in the USA in the 1960s showed the numbers of ARTI episodes per year were three to seven times among the age group of below 10 years, two to three times among the age group of 10 to 39, and one to two times among the age group of 40 and above,<sup>25</sup> and a recent nation-wide report in Australia showed there was a linear correlation between age and predicted incidence of ARTI and the predicted incidence decreased as age increased.<sup>26</sup>

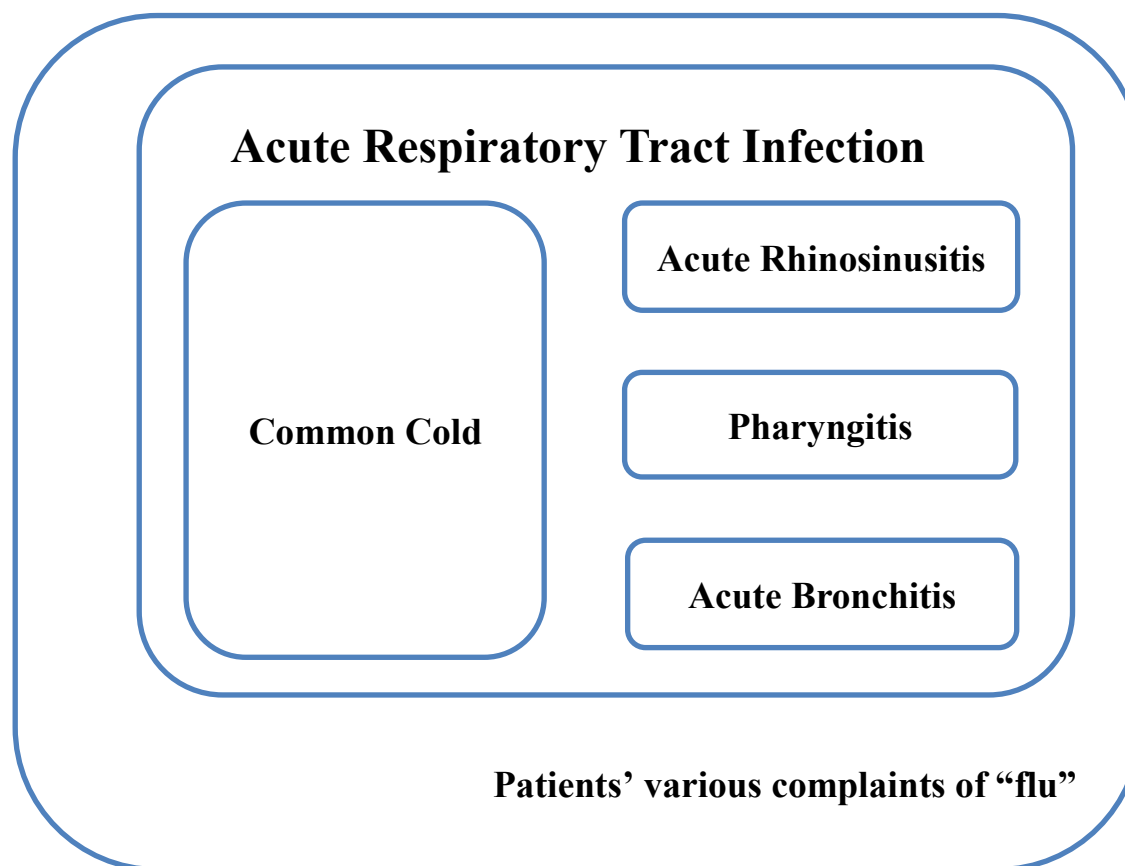
A cohort study following 419 people aged 65 and above who received home health care in Japan showed there were 13 cases diagnosed as “common cold” among 229 fever episodes in a year.<sup>27</sup> Therefore, the question, “Does this clinical presentation really constitute ARTI?” must be carefully assessed when an elderly patient complains of “common cold.” About 90% of the pathogens involved in ARTI are viruses such as rhinovirus and coronavirus.<sup>25,28</sup> The pathogens are rarely bacteria, including group A streptococcus (GAS), a pathogen of acute pharyngitis, and *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, pathogens of acute bronchitis.<sup>25,28</sup>

When elderly patients with chronic cardiac and/or respiratory illness are infected with viruses of ARTI pathogens, dyspnea is more commonly seen among them, leading to more frequent hospitalizations.<sup>29,30</sup>

It is noted that among infants, symptoms and signs of ARTI are difficult to assess and age-specific conditions such as croup syndrome and bronchiolitis are included in ARTI, making the categorization suggested in this manual less applicable. Furthermore, fever among infants requires particular attention to bacteremia and urinary tract infection as important differential diagnoses.<sup>31</sup> Therefore, “pediatric” patients in this manual refers to school aged children and above unless otherwise specified.

The epidemiology of ARTI among school aged children and above is generally similar to that of adults,<sup>32,33</sup> but among pediatric patients caution is required with respect to bacterial infections secondary to ARTI, pneumonia caused by *Mycoplasma pneumoniae*,<sup>34,35</sup> diagnosis of GAS (described below),<sup>36</sup> and age-specific adverse effects due to medications.<sup>37</sup>

**Figure 1. Concept and classification of acute respiratory tract infection in this manual**<sup>\*4</sup>



### (3) Diagnosis and Differential Diagnoses of ARTI

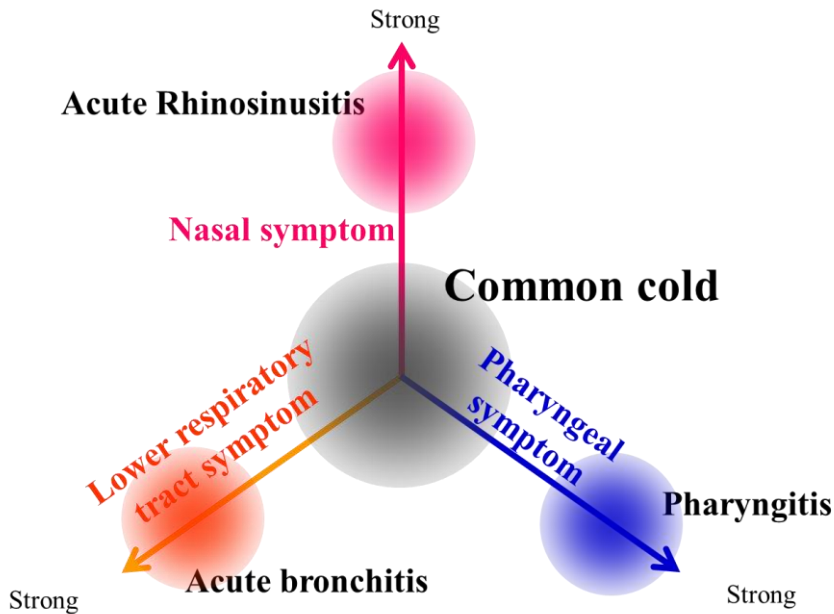
ACP provides a classification of ARTI and can be used as a tool to differentiate between those who require antimicrobials and those who don't.<sup>21,38–40</sup> This classifies ARTI into common cold (nonspecific upper respiratory infection), acute rhinosinusitis, pharyngitis and acute bronchitis, according to nasal symptoms (rhinorrhea and nasal congestion), throat symptoms (sore throat) and lower respiratory symptoms (cough and sputum production) as the three major types of symptoms (Table 1). This manual follows this classification. Of note, management of pneumonia is beyond the scope of this manual.

**Table 1. Classification of acute respiratory tract infection – modified from References 21 and 39**

<b>Classification</b>	<b>Rhinorrhea/ Nasal Congestion</b>	<b>Sore Throat</b>	<b>Cough/Sputum Production</b>
<b>Common Cold</b>	Δ	Δ	Δ
<b>Acute Rhinosinusitis</b>	⊙	×	×
<b>Pharyngitis</b>	×	⊙	×
<b>Acute Bronchitis</b>	×	×	⊙

⊙ as major symptoms, Δ as concurrent but not prominent symptoms, × as mild symptoms or no symptoms

<sup>\*4</sup> The definitions of “Common Cold,” “Acute Rhinosinusitis,” “Pharyngitis” and “Acute Bronchitis” from *Ann Intern Med.* 2016;164:425-34 are applied to four different classifications of ARTI in this manual.

**Figure 2. Visual image of acute respiratory tract infection classification****(i) Common cold**

In this manual, the common cold is acute upper respiratory viral illness with three major types of symptoms co-existent “simultaneously” and “to the same extent” regardless of fever (Table 1). Nonspecific upper respiratory infection is classified as common cold in this manual.

Patients with the common cold typically present with mild fever, malaise and sore throat, followed by rhinorrhea and nasal congestion, and further followed by cough and sputum production. The peak of the symptoms occurs around 3 days after the onset of the symptoms, and the illness is relieved after 7 to 10 days.<sup>41</sup> Cough due to common cold may last for about 3 weeks but a prolonged cough does not necessarily suggest a secondary bacterial infection which requires antimicrobials.<sup>41</sup> In contrast, persistent progression of the illness beyond its natural course and onset of worsening symptoms after initial improvement may suggest a secondary bacterial infection.<sup>40</sup>

It is noted that influenza, for which an anti-viral agent may be indicated, causes relatively severe constitutional symptoms such as high fever, muscle ache and joint pain, and cough is more frequently observed and its onset is earlier compared to the common cold. A rapid influenza diagnostic test is also available if the diagnosis is in question.<sup>42-44</sup>

**(ii) Acute rhinosinusitis**

In this manual, acute rhinosinusitis is classified as a type of ARTI with sneezing, rhinorrhea and nasal congestion dominant, with or without fever. Sinusitis is mostly accompanied by inflammation of nasal cavities and is preceded by rhinitis. The term “rhinosinusitis” has lately replaced “sinusitis.”<sup>45</sup>

Less than 2% of acute viral upper respiratory infections have been reported to be complicated by acute bacterial sinusitis.<sup>46,47</sup> Color of nasal discharge is not helpful to differentiate between viral and bacterial infections,<sup>48</sup> but double-sickening (worsening symptoms following an illness that was initially improving) may be suggestive of bacterial infections.<sup>40,49</sup>

**(iii) Pharyngitis**

Pharyngitis is classified in this manual as a type of ARTI with sore throat dominant. For the sake of the manual, tonsillitis is included in pharyngitis. Most of the pathogens are viruses, and GAS, an indication for antibacterial agents, constitutes 10% of the pathogens among adult cases of pharyngitis.<sup>36,50,51</sup> On the other hand, researchers in Japan reported about 30% of adult cases of pharyngitis in the age group of 20 to 59 years old and 17% of pediatric cases tested positive for GAS.<sup>52,53</sup> In general, pharyngitis caused by GAS is common among school aged children and above while it is relatively rare among infants,<sup>36,50,54</sup> but GAS growth from throat culture does not necessarily represent a true pathogen, and more than 20% of asymptomatic children may be carriers of GAS.<sup>55</sup> Although group C and G streptococci and *Fusobacterium* have been recently identified as a possible pathogen for pharyngitis in Europe and America, little data exists for the epidemiology of those organisms in Japan.<sup>56-64</sup>

The Centor score and McIsaac score, a modified Centor score with age adjustment, are known to support diagnosis of GAS pharyngitis (Table 2).<sup>65,66</sup> Recommendations on the use of rapid diagnostic tests for GAS and antibacterial treatment based on Centor and/or McIsaac scores vary.<sup>36,40,67,68</sup> ACP/CDC and ESCMID suggest rapid diagnostic tests may be unnecessary when the Centor score is 2 or below.<sup>40,67</sup> Rapid diagnostic tests, however, may be considered for high-risk populations for GAS infection such as those with recent and close exposure to GAS patients, even if the Centor score is 2 or below.<sup>69</sup> When antibacterial treatment was limited only to those tested positive for GAS rapid diagnostic test or culture, unnecessary antibacterial use was reduced<sup>65</sup> and cost effectiveness was improved.<sup>70</sup>

Conversely, among pediatric patients, only 68% of those with a Centor score of 4 tested positive for GAS.<sup>71</sup> Therefore, over-diagnosis may occur if only the Centor score or McIsaac score is used to diagnose GAS pharyngitis among children: laboratory tests are required for more accurate diagnoses.

**Table 2. McIsaac score** – created from References 65 and 66

- **Fever of 38°C or above: 1**
- **Absence of cough: 1**
- **Swollen, tender anterior cervical nodes: 1**
- **Tonsillar swelling or exudate: 1**
- **Age of 3 to 14: 1, 15 to 44: 0, 45 and above : -1**

Differential diagnoses of pharyngitis include infectious mononucleosis (IM) caused by Epstein–Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), rubella virus and toxoplasma, but IM can't be ruled out by Centor/McIsaac scores alone as the scores are often high among patients with IM.<sup>72</sup> Posterior cervical and/or auricular adenopathy, and splenomegaly are specific findings among patients with IM,<sup>73</sup> and lymphocyte dominance in peripheral blood test with a lymphocyte-white blood cell count ratio higher than 0.35 is also helpful to diagnose IM.<sup>74</sup>

Differential diagnoses of pharyngitis also include epiglottitis, deep neck abscess (peri-tonsillar abscess, retropharyngeal abscess and Ludwig angina, etc.) and Lemierre syndrome. Therefore, “red flag” signs and symptoms<sup>\*5</sup> such as the worst

\*5 “Red flag” (dangerous symptoms) refers to symptoms that should be properly diagnosed or treated without fail

throat pain ever, trismus, drooling, tripod position and stridor should be taken seriously as possible indications of these high-risk illnesses, and arrangements for emergency airway management should be made.<sup>75,76</sup> In particular, pediatric patients with these conditions may cry as a result of medical examination of oral cavity, blood test and X-rays, which may lead to airway obstruction. Therefore, when these conditions are suspected, such stressful examinations and tests should be avoided and urgent transfer to a higher level of care is required for potential emergency airway management.<sup>68</sup>

Furthermore, “sore throat” without odynophagia or abnormal clinical findings in the pharynx and tonsils may suggest referred pain to the neck as well as acute myocardial infarction, sub-arachnoid hemorrhage, cervical artery dissection or vertebral artery dissection.<sup>75,76</sup>

#### (iv) Acute bronchitis

Acute bronchitis is classified as a type of ARTI with cough dominant, with or without fever and sputum production. It is not unusual that cough due to ARTI lasts for 2 to 3 weeks. The mean duration of cough due to ARTI was reported to be 17.8 days.<sup>77</sup> \*6

More than 90% of the pathogens of acute bronchitis are viruses and the remaining 5 to 10% are *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, and so forth,<sup>40,78</sup> but purulence and color of sputum are not helpful in differentiating bacterial infection.<sup>40</sup> Of note, for healthy, immunocompetent adults less than 70 years of age, X-ray is generally not indicated when neither abnormal vital signs (body temperature  $\geq 38^{\circ}\text{C}$ , pulse  $\geq 100/\text{min}$  and respiratory rate  $\geq 24$ ) nor abnormal lung examination is found.<sup>40</sup>

Pertussis, because of few specific clinical findings, is difficult to accurately diagnose in a clinical setting.<sup>79</sup> Vomiting after cough episodes and inspiratory whoop make diagnosis of pertussis a little more likely.<sup>79</sup> A serum test for pertussis, that is, anti-Bordetella pertussis toxin (PT) antibody, is difficult to utilize in an actual clinical setting due to the long turn-around time.<sup>80,81</sup> However, polymerase chain reaction (PCR) utilizing loop-mediated isothermal amplification (LAMP) to detect *B. pertussis* from a posterior pharynx swab, which was approved to be covered by insurance in November 2016 in Japan, had the sensitivity and specificity of 76.2% to 96.6% and 94.1% to 99.5%, respectively, compared to real-time PCR as a reference standard.<sup>82,83</sup> Thus, during epidemics of pertussis cases, laboratory tests may be considered for diagnosis of pertussis if severe cough persists or respiratory symptoms develop after exposure to patients with pertussis.

Differential diagnoses of acute bronchitis also include tuberculosis. If cough lasts for 2 to 3 weeks, tuberculosis needs to be ruled out as the incidence remains high in Japan.

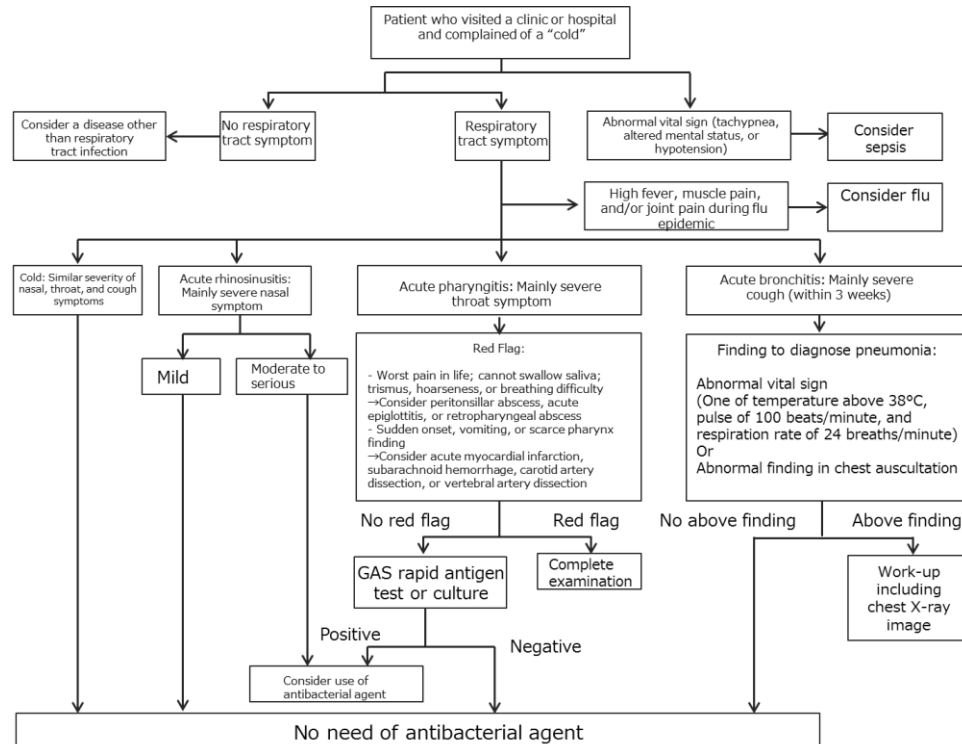
Among pediatric patients, acute rhinosinusitis is a differential diagnosis when productive cough persists for longer than 2 weeks,<sup>49</sup> and 10% of school aged children and above infected with *Mycoplasma pneumoniae* may subsequently develop pneumonia.<sup>35</sup> In addition, a guideline by the Japanese Society of Pediatric Pulmonology (JSPPP)/JSPID describes pertussis as a differential diagnosis for pediatric patients aged 1 and above with cough lasting longer than a week, and defines the clinical diagnosis of pertussis for those aged 1 and above as at least one of the following being met: characteristic inspiratory whoop, episodic prolonged coughing

in medical practice.

\*6 It varies between 15.3 and 28.6 days, depending on the study.

spells, vomiting after coughing, and dyspnea.<sup>84</sup> Therefore, follow-up over time is one of the keys to successful management.

**Figure 3. Flowchart of diagnosis and treatment of acute respiratory tract infection**



※ This flowchart was created as a support tool for clinical management, but the physician's clinical judgment should be prioritized for the decision-making process.

#### (4) Treatment of ARTI

##### (i) Common cold

- Clinicians should not prescribe antibiotics for patients with the common cold.

According to the guidelines by the Japanese Respiratory Society, JSP/JSPID and ACP/CDC, the common cold is a viral illness and antimicrobial therapy is not recommended.<sup>20,40,84</sup> Antimicrobial therapy for the common cold did not shorten time to recovery, and the risk ratio (RR) of adverse events such as nausea, diarrhea and skin rash due to antimicrobial therapy among adult patients was 2.62 (95% confidence interval [CI] 1.32 to 5.18) compared to the placebo group.<sup>85</sup>

Therefore, we recommend against antimicrobial therapy for patients with the common cold.



**(ii) Acute rhinosinusitis**

- Clinicians should not prescribe antibiotics for adult patients with mild (※1) acute rhinosinusitis.
- Clinicians should consider prescribing antibiotics for adult patients with moderate to severe (※1) acute rhinosinusitis:  
Basic regimen for adult patients: Amoxicillin orally for 5 to 7 days
- Clinicians should not prescribe antibiotics for adolescent and older pediatric patients with acute rhinosinusitis except for persistent or severe cases (※2).
- Clinicians should consider prescribing the following antibiotics for adolescent and older pediatric patients with persistent or severe (※2) rhinosinusitis:  
Basic regimen for pediatric patients): Amoxicillin orally for 7 to 10 days

※1: Severity is determined by Table 3.

※2: Please refer to Table 4.

**Table 3. Classification of severity of acute rhinosinusitis among adult patients – created from References 86 and 87**

		None	Mild	Moderate to more Severe
<b>Clinical Symptoms</b>	Rhinorrhea	0	1	2
	Facial pain/ Frontal headache	0	1	2
<b>Nasal Findings</b>	Nasal secretions/ Postnasal discharge	0 (serous)	2 (mucopurulent/ small amount)	4 (intermediate or large amount)

Total score: mild rhinosinusitis 1-3, moderate 4-6, severe 7-8

**Table 4. Criteria of persistent or severe rhinosinusitis among pediatric patients – created from Reference 88**

When one of the following is met, rhinosinusitis is determined as persistent or severe.

1. Rhinorrhea, post-nasal drip or daytime cough for 10 days or longer
2. Fever  $\geq 39^{\circ}\text{C}$  and purulent nasal discharge for at least 3 days and patients are sick-looking
3. Recurrent fever, or deterioration of daytime nasal discharge or cough 1 week after recovery from common cold

Half and 70% of cases of acute rhinosinusitis including possible bacterial rhinosinusitis were reported to be resolved after 1 week and after 2 weeks, respectively, regardless of antimicrobial therapy.<sup>89</sup> In addition, more adverse events such as nausea, diarrhea and abdominal pain were observed in the treatment group on antimicrobial therapy than the placebo group, while recovery from acute rhinosinusitis in 7 to 14 days was more frequent in the treatment group, suggesting that risks due to antimicrobial therapy outweigh benefits.<sup>89</sup> Similarly, for the treatment

of acute rhinorrhea with symptoms shorter than 10 days, no clear benefit of antimicrobial therapy was observed over the placebo group, regardless of gross appearance of nasal discharge, and the risk ratio of adverse events for acute purulent rhinitis on antimicrobial therapy was 1.46 (95% CI 1.10 to 1.94) compared to the placebo group.<sup>85</sup>

According to the ACP/CDC guideline, indications of antimicrobial therapy for acute rhinosinusitis are limited to cases with symptoms lasting longer than 10 days, severe cases (fever,  $\geq 39^{\circ}\text{C}$  and purulent nasal discharge or facial pain lasting for at least 3 days) and cases of double-sickening (worsening symptoms following a typical viral illness that lasted 5 days and was initially improving).<sup>40</sup> In addition, JAID/JSC and the guidelines by the Japanese Rhinologic Society recommend watchful waiting without antimicrobial therapy rather than antimicrobial therapy for mild cases of acute rhinosinusitis with a score of 1 to 3 as shown in Table 3.<sup>68,86,87</sup>

Accordingly, we recommend against antimicrobial therapy for adult patients with mild acute rhinosinusitis.

For pediatric patients, a guideline by AAP lists the following as indications of antimicrobial therapy for acute rhinosinusitis: (1) Nasal discharge or daytime cough or both  $> 10$  days; (2) Fever  $\geq 39^{\circ}\text{C}$  and purulent nasal discharge for at least 3 days; (3) Worsening or new onset of nasal discharge, daytime cough or fever after initial improvement. Otherwise, watchful waiting without antimicrobial therapy is recommended.<sup>88</sup>

Therefore, we recommend against antimicrobial therapy for pediatric patients with acute rhinosinusitis except in persistent, severe and worsening cases as mentioned above.

No systematic review or randomized control trial has proven that cephalosporins or macrolides are more effective in treatment of acute rhinosinusitis than amoxicillin or amoxicillin/clavulanate,<sup>90,91</sup> and guidelines by the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) and ACP/CDC recommend amoxicillin as a first-line option when a decision is made to treat moderate to severe acute rhinosinusitis with antimicrobial therapy.<sup>40,91</sup> The recommended regimen is oral amoxicillin 500mg\*<sup>7</sup> three times daily for 5 to 7 days.<sup>40</sup> AAO-HNS also suggests amoxicillin/clavulanate if concern for bacterial resistance is high or the first-line treatment response is poor. The regimen recommended by ACP/CDC is oral amoxicillin 500mg and clavulanate 125mg three times daily for 5 to 7 days.<sup>40</sup>

The recommended duration of antimicrobial therapy used to be 10 to 14 days<sup>83</sup>, but a recent study showed short-term treatment (3 to 7 days) was not inferior in treatment effect to long-term treatment (6 to 10 days). Rather, the treatment effect between the 5-day treatment group and the 10-day treatment group was similar, and fewer adverse events were observed in the 5-day treatment group.<sup>92</sup>

In Japan, amoxicillin is not approved to treat rhinosinusitis under the Pharmaceutical Affairs Law, but according to a reference by the Health Insurance Claims Review and Reimbursement Services, in general, “claims can be accepted when amoxicillin is prescribed for acute sinusitis.” The drug package insert of amoxicillin states, for infections other than *Helicobacter pylori* infection, “The usual dosage for oral administration is 250mg of amoxicillin hydrate three or four times daily. The dosage may be adjusted according to the patient’s age and symptoms,” though the description is not specific to acute rhinosinusitis.

\*7 In this manual, the dosages are described by ingredient amount (titer), not by formulation amount.



Thus, we recommend antimicrobial therapy for adult patients with moderate to severe acute rhinosinusitis and, if a decision is made to treat with an antimicrobial agent, we suggest oral amoxicillin for 5 to 7 days be selected as the first-line regimen.

While guidelines developed abroad recommend tetracyclines and fluoroquinolones as alternatives if an adult patient is allergic to  $\beta$  lactams,<sup>49,91</sup> it has been reported that resistance of *Streptococcus pneumoniae*, the major pathogen of bacterial rhinosinusitis, to tetracyclines is high in Japan,<sup>93</sup> and referral to a specialist may be considered.

For pediatric patients, the drug package insert of amoxicillin states: “The usual dosage for oral administration is 20 to 40mg/kg daily in three to four divided doses. The dosage may be adjusted according to the patient’s age and symptoms provided that the daily dosage should not exceed 90mg/kg of amoxicillin hydrate.” Also, a couple of guidelines recommend amoxicillin as the first-line regimen for acute rhinosinusitis.<sup>68,86,88</sup>

Thus, we recommend antimicrobial therapy for pediatric patients with acute rhinosinusitis only when the illness is severe or persistent as shown in Table 4, and if a decision is made to treat with an antimicrobial agent, we suggest oral amoxicillin for 7 to 10 days be selected as the first-line regimen.

### (iii) Pharyngitis

- Clinicians should not prescribe antibiotics for patients without confirmed streptococcal pharyngitis with a rapid antigen test or throat swab culture.
- When GAS is detected by a rapid antigen test or throat swab culture, the following antibiotic therapy for pharyngitis is recommended.  
Basic regimen for both adult and pediatric patients: Amoxicillin orally for 10 days

Guidelines by ACP/CDC and IDSA recommend against antimicrobial therapy for pharyngitis except where GAS tests positive by a rapid antigen test or throat swab culture.<sup>36,40</sup> There is yet to be consensus on whether pharyngitis with anaerobes such as *Fusobacterium*, and group C and G streptococci<sup>\*8</sup> needs to be treated or not.<sup>76, 94</sup>

Thus, we recommend against antimicrobial therapy for pharyngitis except where GAS tests positive either by a rapid antigen test or throat swab culture.

For the treatment of adult GAS pharyngitis, a study showed there was no statistical significance in symptom resolution between a group treated with penicillins and a group treated with cephalosporins (odds ratio [OR] 0.78, 95% CI 0.60 to 1.01).<sup>95</sup> Clinical relapse was lower among the cephalosporins group (OR 0.42, 95% CI 0.20 to 0.88), but the number needed to treat (NNT) was 33, suggesting the absolute risk difference between the two groups was not substantially high.<sup>95</sup> Given its safety, effectiveness and narrow spectrum of antibacterial coverage, a couple of guidelines recommend penicillins as the first-line regimen.<sup>36,40,68</sup> The drug package insert of amoxicillin states: “The usual dosage for oral administration is 250mg of amoxicillin hydrate three or four times daily. The dosage may be adjusted according to the patient’s age and symptoms.” Of note, some guidelines recommend oral amoxicillin 1,000 mg daily or 500 mg twice daily.<sup>36,40</sup> Regarding the duration of

\*8 The statement is not applicable to cases with severe invasive streptococcal infection by group C and G streptococci, including possible cases.

antimicrobial therapy, the evidence to support short-term therapy has been scarce and the guidelines in the USA and Europe recommend a 10-day course.<sup>36,67</sup>

According to the IDSA guideline, cephalexin, a first-generation cephalosporin is recommended for those with mild penicillin allergy, and clindamycin is recommended for those with severe penicillin allergy: history of anaphylaxis and severe drug rash.<sup>36</sup>

In Japan, cephalexin and clindamycin are approved to treat pharyngitis under the Pharmaceutical Affairs Law. The drug package insert of cephalexin states: “For adults and children with a body weight of  $\geq 20$  kg, the usual dosage for oral administration is 250 mg of cephalexin every six hours. For severe cases, or cases with bacteria growth of low susceptibility, the dosage is given as 500 mg orally every six hours. The dosage may be adjusted according to the patient’s age, body weight and symptoms.” That of clindamycin states: “For adults, the dosages for oral administration are 150mg every six hours in usual cases and 300mg every eight hours in severe cases. For children, the dosages for oral administration are 15 mg/kg daily in three to four divided doses in usual cases and 20 mg/kg daily in three to four divided doses in severe cases. The dosage may be adjusted according to the patient’s age, body weight and symptoms.” The IDSA guideline recommends cephalexin 500mg orally twice daily for those with a mild penicillin allergy and clindamycin 300mg orally three times daily for those with a severe penicillin allergy.<sup>36</sup>

Thus, for adults, we recommend antimicrobial therapy for pharyngitis with a positive result for GAS by a rapid antigen test or throat swab culture, and when a decision is made to treat with an antimicrobial agent, we suggest oral amoxicillin for 10 days.

For pediatric patients with pharyngitis, the guideline by JSP/JPID recommends a 10-day course of oral amoxicillin for GAS pharyngitis.<sup>84</sup> A review article on the treatment of pediatric patients with GAS pharyngitis showed time to symptom resolution was shorter in a group given short-term (4 to 6 days) treatment with late generation antibacterial agents other than penicillin than in a group given long-term (10 days) treatment with penicillin, but late bacteriological recurrence occurred more frequently among the short-term treatment group.<sup>96</sup> The study also found fewer adverse effects were observed among the long-term treatment group with penicillin, and no statistically significant difference was observed in long-term complications such as acute glomerulonephritis and acute rheumatic fever.<sup>96</sup> Research conducted in Japan to compare oral amoxicillin for 10 days to oral cephalosporins for 5 days to treat GAS pharyngitis showed that the rate of bacterial eradication was higher in the amoxicillin group (91.7% in the amoxicillin group vs. 82.0% in the cephalosporins group,  $p=0.01$ ), and that there was no difference in clinical relapse between the groups.<sup>97</sup>

Accordingly, for children, we recommend antimicrobial therapy for pharyngitis with a positive result for GAS by a rapid antigen test or throat swab culture, and when a decision is made to treat with an antimicrobial agent, we suggest oral amoxicillin for 10 days.

It is noted that differential diagnoses of pharyngitis are broad, including the severe illnesses as mentioned above, and when pharyngitis is suspected, GAS pharyngitis should not be the only illness to be ruled out. Furthermore, referral to a specialist needs to be considered for persistent cases.

**(iv) Acute bronchitis**

- Clinicians should not prescribe antibiotics for patients with acute bronchitis, except for the case of pertussis, among healthy, immunocompetent adults without underlying health conditions such as chronic lung disease.

For the treatment of acute bronchitis, antimicrobial therapy, in general, is rarely beneficial and the risk of adverse events outweighs the benefits of antimicrobial therapy.<sup>98</sup> The guidelines by JAID/JSC and ACP/CDC recommend against antimicrobial therapy for acute bronchitis among healthy, immunocompetent adults without underlying comorbidities such as chronic lung disease.<sup>40,78</sup> For the treatment of adult patients with acute bronchitis due to *Mycoplasma pneumoniae* in the absence of pneumonia, evidence to support antimicrobial therapy has been scarce.<sup>40,78</sup>

Thus, except in the case of pertussis, we recommend against antimicrobial therapy for acute bronchitis among healthy, immunocompetent adults without underlying comorbidities such as chronic lung disease. Of note, as mentioned above, pneumonia as a consequence of acute bronchitis should be considered among school aged children and above, and patients need to be assessed in an ongoing manner. In particular, macrolides are recommended to treat *Mycoplasma pneumoniae* infection among children,<sup>33,84,99</sup> and macrolides to treat chronic or recurrent cough over a few weeks due to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections have been reported to be effective among children.<sup>100,101</sup>

For the treatment of pertussis, antimicrobial therapy after the catarrhal phase (usually 2 weeks after symptom onset) is not effective in symptom resolution, but antimicrobial therapy within 3 weeks after the onset among those aged 1 year and older may contribute to lower transmission to others.<sup>78,102</sup> The guidelines by JAID/JSC and CDC recommend macrolides as the first-line regimen, and the standard regimen for adults is azithromycin 500 mg once on day one followed by 250 mg daily from day two to day five, or 500 mg once daily for 3 days.<sup>78,102,103</sup> However, in Japan, azithromycin is not approved to treat pertussis under the Pharmaceutical Affairs Law while pediatric clarithromycin and erythromycin are approved. The drug package insert of erythromycin states: “For adults, the usual dosage for oral administration is 800 mg to 1200 mg of erythromycin daily in four to six divided doses. For children, the dosage for oral administration is 25mg/kg to 50mg/kg daily in four to six divided doses. The dosage may be adjusted according to the patient’s age and symptoms. The pediatric dose must not exceed the adult dose.”

**(5) Explanations to Patient and Family Education**

Important elements in explaining the clinical management of ARTI to patients and family are shown in Table 5.<sup>104-106</sup> Physicians who received training on how to instruct patients based on these elements reduced antibacterial prescription by 30 to 50% compared to those without the training, without any increase in adverse events.<sup>105,106</sup>

**Table 5. Important elements in explaining ARTI to patients**

<p>1) Information Gathering</p> <ul style="list-style-type: none"> <li>▪ Ask about the patient’s concerns and expectations</li> <li>▪ Ask about their thoughts on antibacterial agents</li> </ul> <p>2) Provision of Appropriate Information</p> <ul style="list-style-type: none"> <li>▪ Provide important information <ul style="list-style-type: none"> <li>– In case of acute bronchitis, cough may last up to 4 weeks or so</li> <li>– Most cases of ARTI are self-limiting</li> <li>– The patient’s body fights against the germs but it may take time</li> </ul> </li> <li>▪ Provide accurate information on antibacterial agents</li> <li>▪ Advise rest with adequate nutrition and fluid intake</li> </ul> <p>3) Summary</p> <ul style="list-style-type: none"> <li>▪ Summarize the information exchanged and confirm the patient’s understanding</li> <li>▪ Provide detailed instructions about alarming symptoms and the timing of reconsultations</li> </ul>
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Created from References 104 to 106

When a patient and/or family member receives an explanation consisting solely of negative statements such as “This is a viral infection. There is no effective treatment available” and “There is no need for an antibacterial agent,” they tend to feel dissatisfied.<sup>107,108</sup>

On the other hand, for example, it is indicated that a patient and/or family member readily accepts positive statements such as “We can prescribe drugs to alleviate your symptoms” or “Hot beverages will ease the nasal congestion.”<sup>109</sup>

When the three situations of only positive statements provided, only negative statements provided and both provided are compared, the situation of both positive and negative statements provided lead to fewer antibacterial prescriptions and higher patient satisfaction.<sup>109</sup> Positive statements in addition to negative statements lead to a decrease in antibacterial prescriptions without compromising the patient’s satisfaction, and help maintain and strengthen a good physician-patient relationship.<sup>109</sup>

Recently, the scientific evidence on delayed antimicrobial prescription as a measure to decrease antibacterial consumption in ARTI management has been mounting.<sup>\*9</sup> When antimicrobial therapy was not clearly indicated for patients with ARTI on the first patient encounter, instead of prescribing antibacterial agents immediately, prescribing them only when the clinical course was not improving led to a decrease in antibacterial prescriptions without any increase in complications, adverse events or unscheduled consultations.<sup>114-116</sup>

For example, the common cold, as per its natural course, presents with mild fever, malaise and sore throat, followed by rhinorrhea, nasal obstruction, cough and sputum production on day one or two. Then the symptoms peak around day three and resolve slowly over 7 to 10 days.<sup>32</sup> However, when double-sickening occurs with worsening symptoms following an illness that was initially improving, secondary bacterial infections need to be considered.<sup>75,76</sup>

Thus, when antibacterial therapy is not clearly indicated on the first consultation, it is important to give detailed instructions on return consultations in case of an unfavorable clinical course.

\*9 Refer to 5. Appendix (2)

**[Example of patient education: Common Cold]**

From what I see, your current “flu” is likely to be a common cold caused by viral infection. Antibiotics won’t work for this type of “cold”. I will prescribe medications to relieve your symptoms. Getting lots of rest is the best medicine in this situation.

In general, symptoms peak on day two to three after onset, and they get better slowly over a week to 10 days.

However, there are some other diseases that look like “flu” at the beginning. And in one in a few hundreds of patients, bacterial infections such as pneumonia and sinusitis may occur secondary to a common cold.

If your symptoms don’t improve after 3 days or if they get worse, or you are unable to take foods or fluids, please come back to see me as you may need blood tests and X-rays.

**[Example of patient education: Acute Rhinosinusitis]**

Your current “flu” is likely to be acute rhinosinusitis with mainly nasal symptoms, but you don’t have clear indications for antibacterial agents at this moment. Antibiotics may cause nausea, diarrhea and allergic reactions. The risk of side effects outweighs the benefits of antibacterial use at present, and therefore I don’t recommend antibacterial therapy for now. I will prescribe medications to relieve your symptoms.

In general, symptoms peak on day two to three after onset, and they get better slowly over a week to 10 days.

If the pain below your eyes or around your forehead gets worse, you develop high fever, or your symptoms get worse after a temporary improvement, please come back to see me as you may need antibacterial therapy.

**[Example of patient education: Viral Pharyngitis]**

Your current “flu” is likely to be pharyngitis with mainly sore throat, but your current symptoms/signs suggest a viral infection, for which antibacterial therapy is not helpful. Antibiotic may cause nausea, diarrhea and allergic reactions. The risk of side effects outweighs the benefits of antibacterial use at present, and therefore

I don’t recommend antibiotics for now. I will prescribe medications to relieve your pain.

In general, symptoms peak on day two to three after onset, and they get better slowly over a week to 10 days. If you don’t feel better after 3 days, please come back to see me again.

It is unlikely, but if your sore throat becomes so severe that you can’t swallow fluids, please come and see me immediately as a different diagnosis may need to be considered.

**[Example of patient education: Acute Bronchitis]**

Your current “flu” is likely to be acute bronchitis with mainly cough. You don’t have a fever or any symptoms/signs suggestive of pneumonia. Antibiotic don’t work for acute bronchitis. Antibacterial agents may cause nausea, diarrhea and allergic reactions. The risk of side effects outweighs the benefits of antibacterial use at present, and therefore I don’t recommend antibacterial therapy for now.

I will prescribe medications to relieve your cough.

Unfortunately, this type of cough lasts 2 to 3 weeks and doesn't dramatically improve in a single day. I understand you feel bad because of your cough, but let's try to relieve it. Please come back and see me in a week.

If you can't sleep due to severe coughing, you have shortness of breath, you are coughing up increased amount of phlegm, or you develop a high fever, please come back to see me again as a different diagnosis may need to be considered, and an X-ray may be required to rule out pneumonia.

**[Example of patient education by a pharmacist: When no antibacterial agents are prescribed]**

Based on your physician's assessment, antibacterial agents are not necessary for your current "flu." Antibacterial agents may cause side effects such as diarrhea, and are not recommended at this moment. Instead, I will give you medications to relieve your symptoms as prescribed by your physician.

However, there are some other diseases that look like "flu" at the beginning.

If your symptoms don't improve after 3 days or if they get worse, or you can't take foods or fluids, please go back and see your physician.

※Whether antibacterial agents are prescribed or not, physicians clearly communicating with pharmacists ensures patient education by pharmacists, and improves patients' compliance.<sup>117-118</sup> Therefore, it is better to have physicians write a diagnosis and relevant information on the prescription sheet or in the personal medication log in order to convey the physician's thoughts to the pharmacist.



## 4. Acute Diarrhea

### (1) What is Acute Diarrhea?

Acute diarrhea is defined as the passage of unusually loose or watery stools, usually at least three or more times above baseline in a 24-hour period, lasting less than 14 days.<sup>119-120</sup> More than 90% of acute diarrhea is caused by infections while the remaining 10% results from drug-induced, toxic, ischemic or other non-infectious causes, and diarrhea may be one of multiple symptoms of these systemic illness.<sup>121</sup> Acute infectious diarrhea may be associated with nausea, vomiting, abdominal pain, abdominal distention, fever, bloody stool and tenesmus.<sup>120</sup> Acute infectious diarrhea is referred to as “gastroenteritis” and “enteritis” and vomiting may be the dominant symptom with diarrhea less prominent.<sup>120</sup>

### (2) Epidemiology of Acute Diarrhea

A patient census report conducted by MHLW in October 2014, when it was not the peak season for diarrheal diseases, estimated that there were 24 patients presenting with intestinal infectious diseases<sup>\*10</sup> per 100,000 populations per day.<sup>24</sup>

The etiology of acute diarrhea is mostly viral infections,<sup>120</sup> such as norovirus and rotavirus.<sup>122</sup> In Japan, voluntary vaccination for rotavirus started in 2011, and the incidence of rotavirus diarrhea has been decreasing.<sup>123</sup>

Bacteria that can cause acute diarrhea include non-typhoidal *Salmonella* spp., *Campylobacter* spp., enterohemorrhagic *Escherichia coli* (EHEC), and *Vibrio* spp.,<sup>124</sup> while enterotoxigenic *E. coli* (ETEC), *Campylobacter* spp. and, rarely, *Shigella* spp. and *V. cholerae* are pathogens that can be found in travelers returning from abroad.<sup>125</sup> *Clostridium difficile* is also in differential if a patient has recent exposure to antibacterial agents.<sup>126</sup> It is notable that typhoid fever and paratyphoid fever rarely cause diarrhea.<sup>127</sup>

### (3) Diagnosis and Differential Diagnoses of Acute Diarrhea

Information needed to identify the etiology of acute diarrhea includes onset, associated symptoms such as fever, abdominal pain and presence of bloody diarrhea, history of food/fluid intake, travel history, antimicrobial use, immune status and sick contact.<sup>124</sup> In particular, if vomiting is dominant, viral illness and food poisoning due to toxins are more likely.<sup>128</sup> In an outbreak, incubation periods of 14 hours and longer (typically, 24 to 48 hours) suggest viral illness, and incubation periods of two to seven hours suggests food poisoning. The difference may be useful to differential diagnosis.<sup>128</sup>

Nausea and vomiting may occur when an illness is not associated with the gastrointestinal system such as with acute myocardial infarction, intracranial pathology, sepsis, electrolyte imbalance and drug-induced illness.<sup>129,130</sup> Since a study showed about 30% of those who were hospitalized under diagnosis of “acute gastroenteritis” had etiologies outside the gastrointestinal (GI) system, diagnosing “acute gastroenteritis” only relying on patients’ symptoms without ruling out critical conditions should be avoided.

During history taking, it is important to consider the characteristics (watery or bloody) and severity of the diarrhea. Particularly, returning travelers (especially from developing countries) who develop severe bloody diarrhea with total disability and

\*10 “Intestinal infectious diseases” represent A00 to A09 according to ICD10.

body temperature of  $\geq 38^{\circ}\text{C}$  or watery diarrhea with resultant moderate physical disability with onset of 1 week after travel may have bacterial enteritis, such as typhoid fever, Non-typhoidal *Salmonella* enteritis, *Campylobacter* enteritis and ETEC, or amebic dysentery.<sup>120,132</sup> Therefore, laboratory tests and antibacterial therapy need to be considered in consultation with experts in travel medicine and infectious diseases.

Among children, acute diarrhea is mostly caused by viral infections.<sup>133</sup> Viral acute diarrhea often starts with vomiting, followed by mild to moderate peri-umbilical pain and tenderness, watery diarrhea without blood, no fever (or mild fever), no severe abdominal pain, and sick contact. On the other hand, differential diagnoses of bloody diarrhea include EHEC, intussusception, Meckel's diverticulum and upper GI bleeding.<sup>134,135</sup>

### (i) Acute diarrhea due to viruses

Acute diarrhea due to viral infections includes rotavirus, and norovirus in adults.<sup>124,128</sup> Food exposure to bivalves that are poorly cooked and contaminated with norovirus is well known as a mode of transmission of norovirus infection, but human to human transmission is not rare.<sup>136</sup> The incubation period of norovirus infection is generally half a day to 2 days. The illness often starts with vomiting, followed by watery diarrhea.<sup>137</sup> Vomiting and diarrhea usually resolve within a day and within 2 to 3 days, respectively, but the symptoms may persist over 7 days to 10 days.<sup>138,139</sup> Fever is often absent or, if any, resolves within 2 days,<sup>138</sup> so if fever lasts longer than 2 days, a different etiology other than viral infection needs to be considered.

A rapid antigen test for norovirus<sup>\*11</sup> is approved under the Pharmaceutical Affairs Law, and its sensitivity has improved up to 87.4 to 93.1% recently.<sup>140-143</sup> However, during the peak season of norovirus infections, a negative rapid antigen test does not rule out norovirus for those with typical acute diarrhea because of high pre-test probability and the routine test for every diarrheal patient is therefore not considered useful. From an infection control standpoint, regardless of the etiology, vomit and excreta must be handled as infectious materials, and a stand-alone result of negative antigen testing should not result in negligence of the control measures.

Of note, for children, the rapid antigen test for norovirus is approved for those aged less than 3 years old.

### (ii) Acute diarrhea due to bacteria

Those with acute diarrhea due to bacteria tend to develop severe abdominal pain, high fever ( $\geq 38^{\circ}\text{C}$ ), bloody stool, bloody mucous stool and tenesmus more often than those with acute diarrhea due to viruses. Patients' signs and symptoms, however, are not always helpful in identifying the etiology, and food/fluid consumption history and incubation period may be useful to some extent as shown in Table 6.<sup>138,144,145</sup>

Acute diarrhea due to bacteria among adults is often self-limiting, and therefore the benefit of identifying the etiology through routine laboratory tests for all adult patients including mild cases may be limited. On the other hand, for moderate to severe cases, cases involving persistent diarrhea, and cases where antimicrobial therapy is going to be given, laboratory tests such as stool culture may be preferable in order to identify the etiology.<sup>110</sup>

For children, it is rare to require urgent laboratory tests including stool culture,

\*11 As of March 2016, the approval is limited to those aged 3 and younger, those aged 65 and older, those with malignancies, post-transplant patients and those on antineoplastic agents and immunosuppressants.



and indications for such tests include cases involving severe abdominal pain or bloody stool, cases of possible EHEC complicated by hemolytic uremic syndrome (HUS), and immunocompromised patients.<sup>146</sup>

**Table 6. Common food source and incubation period of acute diarrhea and food poisoning**

Pathogen	Common Food Source Reported in Japan	Incubation Period
<b>Toxigenic</b>		
<i>Bacillus cereus</i>	Grains and their products (fried rice, rice products, noodles, etc.), food products with mixed ingredients (Japanese bento, sandwiches, etc.)	1-2 hours
<i>Staphylococcus aureus</i>	Rice balls, sushi, products or snacks made from meat, eggs or milk	2-6 hours
<i>Clostridium botulinum</i>	Canned products, bottled products, vacuum-packed products, ready-to-eat foods, etc.	18-36 hours
Enterotoxigenic <i>E. coli</i>	No specific foods (Main pathogen among travelers returning from developing countries)	12-72 hours
<b>Non-toxigenic</b>		
Norovirus	Bivalves such as oysters	12-48 hours
<i>Vibrio parahaemolyticus</i>	Fish (sashimi, sushi and fish products)	2-48 hours
<i>Yersinia enterocolitica</i>	Processed milk, contaminated water, foods contaminated with pork	2-144 hours
<i>Clostridium perfringens</i>	Curry, stew, foods provided at parties or hotels	8-22 hours
Non-typhoidal <i>Salmonella</i> spp.	Egg, meat (beef liver sashimi, chicken), eel, turtle, etc.	12-48 hours
Enterohemorrhagic <i>E. coli</i>	Raw or undercooked beef	1-7 days
<i>Campylobacter jejuni</i>	Raw or undercooked chicken, BBQ, beef liver sashimi	2-7 days

Created from References 138, 144 and 145

#### (4) Treatment of Acute Diarrhea

- For the management of acute diarrhea, we first recommend encouraging oral fluid intake and providing care for symptomatic relief.

Acute diarrhea among adults is usually self-limiting, and oral fluid intake and symptom relief are ensured whether the etiology is viral or bacterial.<sup>120,124</sup> It is important to assess dehydration by checking vital signs and orthostatic hypotension, to recommend as much oral fluid intake as possible,<sup>120,124</sup> and to recommend oral

fluid containing sugar, sodium and potassium. For severely dehydrated infants and the elderly, oral rehydration solution (ORS) is recommended, but for adults fruit juice and sports drinks are mostly sufficient, though fluids with little sodium may necessitate additional sodium intake.<sup>120,147</sup>

According to the guidelines by JAID/JSC and ACG, antibacterial therapy is not recommended except in severe cases and those involving travelers returning from abroad (traveler's diarrhea).<sup>120,124</sup> JAID/JSC suggest antibacterial therapy for the following situations:<sup>124</sup>

- Suspected bacteremia such as hypotension and shivering
- Cases with severe diarrhea and/or shock that require hospitalization for rehydration
- High risk of bacteremia (HIV with low CD4 count, cell-mediated immunosuppression due to steroids and immunosuppressants)
- High risk of complications (age of 50 years and older, artificial graft/valve, artificial joints)
- Return travelers

Caring for dehydration is also crucial for the management of acute diarrhea among children.<sup>134</sup>

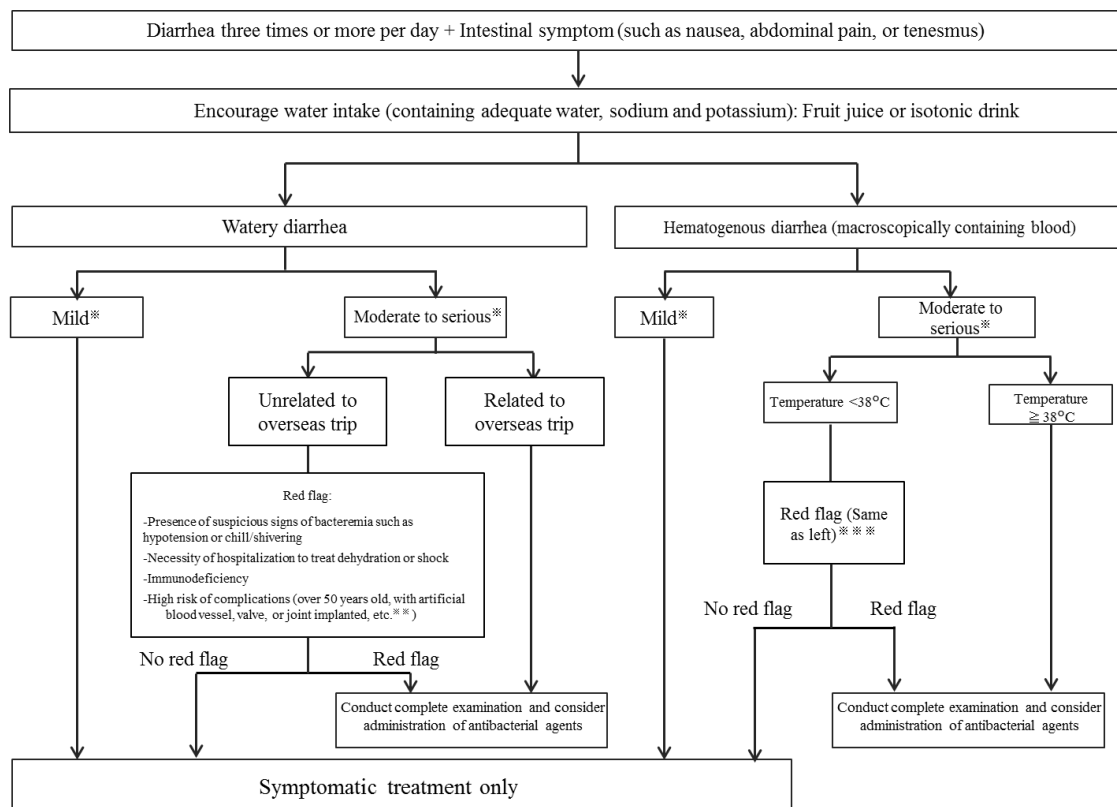
Thus, for the management of acute diarrhea, we first recommend encouraging oral fluid intake and providing care for symptomatic relief.

We suggest referring to the academic literatures for guidance on the detailed management of severe cases and traveler's diarrhea.

The process of the diagnosis and management of acute diarrhea is shown in Figure 4.

**Figure 4. Flowchart of diagnosis and treatment of acute diarrhea**

(Target populations : school aged children and above and adults, modified from Reference 120)



※Severity of diarrhea: Mild = no change in functional activities, Moderate = able to function but with forced change in activities due to illness, Severe = total disability due to diarrhea

※※Other high-risk populations include those with inflammatory bowel disease, those on dialysis and those with aortic aneurysm

※※※ Caution required for EHEC (enterohemorrhagic *E. coli*) and stool culture needs to be considered

※※※※ This was created as a support tool for clinical management, but physicians' clinical judgment should be prioritized for the decision-making process.

### (i) Management of dehydration among children

When acute diarrhea is diagnosed, it is important to determine whether the situation is urgent or not, and the urgency is mostly determined by the presence and severity of the dehydration.<sup>134</sup> Especially for children, the proportion of body water to body weight is relatively high, and their oral food and fluid intake is dependent on others (mostly parents), therefore the management of dehydration plays a significant role.

Identifying those who are dehydrated by more than 5% of body weight (body weight loss) is critical as they often require rehydration, and having at least two of the four following criteria met suggests dehydration of > 5% body weight: (1) Capillary Refill Time > 2 seconds<sup>\*12</sup>; (2) Dry mucous membrane; (3) Absence of tears; and (4) Change in systemic condition.<sup>148</sup> In addition, those who are likely to require intravenous rehydration often present with the following: bloody diarrhea, persistent vomiting, decreased urine output, sunken eyes and altered level of consciousness.<sup>33</sup>

ORS is a standard therapy for acute diarrhea.<sup>119,134</sup> In addition to its effectiveness, blood access is not required, so ORS is recommended to prevent dehydration or treat mild to moderate dehydration.<sup>119,134</sup>

\*12 Time taken for the tip of a finger to become red again after releasing pressure against it

In practice, ORS should be given at an early stage (within three to four hours after the onset of dehydration), and the amount given should be increased gradually from one full teaspoon and adjusted every two to four hours until it equals the amount lost (50ml/kg to 100ml/kg for mild to moderate dehydration).<sup>134</sup>

Of note, evidence on anti-emesis for vomiting and antidiarrheals for diarrhea is scarce and neither is recommended.<sup>134</sup>

### **(ii) Indications of antibacterial therapy for children with acute diarrhea**

Most of the pathogens causing acute diarrhea in children are viruses. Therefore, antibacterial therapy is not only ineffective, but also disrupts gut flora, leading to microbial substitution, and its use is not recommended.<sup>124,134</sup> Even if the cause of acute diarrhea is considered bacterial, most are self-limiting and antibacterial therapy is not required.<sup>124,134</sup> Of note, the guidelines developed in other countries limit indications of stool culture and antibacterial therapy to situations where the systemic illness is severe, Non-typhoidal *Salmonella* spp. or *Campylobacter* spp. is suspected among immunocompromised patients, and so forth.<sup>134,149</sup>

### **(iii) Non-typhoidal *Salmonella* gastroenteritis**

- We recommend against antibacterial therapy for mild\* non-typhoidal *Salmonella* gastroenteritis among otherwise healthy patients.

\* Mild = no change in functional activities

Even if non-typhoidal *Salmonella* spp. is identified as a pathogen, antibacterial therapy for non-typhoidal *Salmonella* spp. among healthy adults without comorbidities does not shorten time to relief of symptoms such as diarrhea and fever, but rather prolongs colonization.<sup>150</sup> Therefore, in this manual, we recommend against antibacterial therapy for mild non-typhoidal *Salmonella* infection in otherwise healthy patients.

It is noted that the following are risk factors of severe non-typhoidal *Salmonella* infection, and therefore are indications of antibacterial therapy:<sup>151</sup>

- Age younger than 3 months or 65 years and older
- Use of steroids or immunosuppressants
- Inflammatory bowel disease
- Hemodialysis
- Hemoglobinopathy such as sickle cell disease
- Abdominal aneurysm
- Prosthetic heart valve

According to the JAID/JSC guideline, when antibacterial therapy is considered for non-typhoidal *Salmonella* infections, oral levofloxacin for 3 to 7 days as the first-line treatment and, in the setting of low susceptibility to fluoroquinolones or allergy to fluoroquinolones, intravenous ceftriaxone or oral azithromycin for 3 to 7 days as the second-line treatment are recommended.<sup>124</sup>

### **(iv) *Campylobacter* enteritis**

- We recommend against antibacterial therapy for mild\* *Campylobacter* enteritis in otherwise healthy patients.

\* Mild = no change in functional activities

For *Campylobacter* treatment, antibacterial therapy is not recommended by JAID/JSC except in severe cases.<sup>124</sup> It is reported that antibacterial therapy can shorten the time to symptomatic relief by 1.32 days (95% CI 0.64 to 1.99)<sup>152</sup> but most are self-limiting and antimicrobial resistance in *Campylobacter* strains has been rising recently. Therefore, in this manual, we recommend against antibacterial therapy for mild *Campylobacter* enteritis in otherwise healthy patients.

It is notable that *Campylobacter* strains resistant to fluoroquinolones have been increasing. According the JAID/JSC guideline, oral clarithromycin 200mg twice daily for 3 to 5 days is recommended when antibacterial therapy is considered for severe cases.<sup>124</sup>

#### (v) Enterohemorrhagic *E. coli* (EHEC) infection

Patients with EHEC often present with bloody diarrhea but fever is rare in the classic presentation.<sup>151</sup> Serotype O157 is the most common pathogen, but others include O26 and O111.<sup>124</sup> About 5 to 10% of those with EHEC infections develop hemolytic uremic syndrome (HUS) as a complication.<sup>124</sup>

For the management of EHEC, a review article does not recommend antimicrobial therapy as it may enhance toxin production and increase risk of HUS.<sup>128</sup> A meta-analysis showed antibacterial therapy is not associated with incidence of HUS (OR 1.33, 95% CI 0.89 to 1.99).<sup>153</sup> However, when the data only from studies with a more restrictive definition of HUS were analyzed, OR was 2.24 (95% CI 1.45 to 3.46), suggesting antibacterial therapy is associated with increased risk of HUS.<sup>153</sup> On the other hand, research targeting pediatric patients in Japan showed fosfomycin given at an early stage of EHEC infections was not associated with subsequent HUS incidence,<sup>154,155</sup> and the JAID/JSC guideline states: “At present, there is no consensus on antibacterial therapy.”

Of note, antidiarrheals for the management of EHEC infections are not recommended as they increase the risk of HUS.<sup>124,156</sup>

#### (5) Patient and Family Education

Most cases involving acute diarrhea are self-limiting, so the management of dehydration through fluid intake is the most important concern. However, since the differential diagnoses of diarrhea and/or abdominal pain are broad, if the clinical course is not favorable, instructions for a return consultation should be given.

**Table 7. Important factors in explaining acute diarrhea to patients**

1) Information Gathering
<ul style="list-style-type: none"> <li>▪ Ask about the patient’s concerns and expectations</li> <li>▪ Ask about their thoughts on antibacterial agents</li> </ul>
2) Provision of Appropriate Information
<ul style="list-style-type: none"> <li>▪ Provide important information               <ul style="list-style-type: none"> <li>– Diarrhea may last for a week or so</li> <li>– Most cases of acute diarrhea are self-limiting</li> <li>– The patient’s body fights against the germs but it may take time</li> </ul> </li> <li>▪ Provide accurate information on antibacterial agents</li> <li>▪ Advise rest with adequate nutrition and fluid intake</li> </ul>
3) Summary
<ul style="list-style-type: none"> <li>▪ Summarize the information exchanged and confirm the patient’s understanding</li> </ul>

- Provide detailed instruction about alarming symptoms and the timing of future consultations

**[Example of patient education: Adults patients with Acute Diarrhea]**

Your illness is likely to be a viral infection in the gut. In this situation, antibacterial agents don't work, but rather may prolong the diarrhea as a result of killing the "nice" bacteria in the gut. Therefore, management of dehydration and symptomatic relief plays the central role. Please ingest a sufficient amount of fluids. If you take too much at once, you may vomit, so please take a small amount at a time. The idea is that you will make up for the amount lost with oral fluid intake.

Absorption of water from the gut is lower during the illness, but improves when you take water with sugar and salt, rather than simply taking water or tea alone. If you can eat, I suggest you eat rice porridge with *umeboshi* (pickled Japanese plum).

In general, nausea will get better in a few days. Diarrhea is worst for the first few days, but will improve over a week or so.

Please wash your hands after going to the bathroom, and don't share your towel with others to prevent the spread of the illness.

If the stool becomes tinged with blood, or you develop severe abdominal pain or high fever, other diseases such as a bacterial infection and appendicitis must be considered, so please come back to see me again. If you can't take fluids orally, please come back as you will need intravenous hydration.

**[Example of patient (caregiver) education: Pediatric patients with Acute Diarrhea]**

Your (your child's) illness is likely to be a viral infection in the gut (stomach flu). There is no specific medicine to cure the infection, but rather the body fights against it and you (your child) will get better.

Prevention of dehydration is very important for children. Please take (give) a small amount of fluids similar to bodily fluids repeatedly. At the beginning, take (give) one full teaspoon every 10 to 15 minutes. If you take (give) a lot and you (s/he) vomit(s), dehydration may worsen, so please be patient. If you (s/he) can tolerate more after an hour, please increase the amount taken (given) per time.

If you (s/he) still can't take fluids or you (s/he) lose(s) more due to vomiting or diarrhea, intravenous hydration may be indicated. If you (s/he) don't (doesn't) urinate for longer than half a day, you feel (s/he looks) irritated, tired or sleepy, or you (s/he) develop(s) severe abdominal pain, or anything unusual occurs, please come back to see me immediately, even at night.

If the stool becomes tinged with blood, or you (s/he) develop(s) severe abdominal pain or high fever, other diseases such as a bacterial infection and appendicitis must be considered, so please come back and see me again.

**[Example of patient education by a pharmacist: Acute Diarrhea]**

Based on your physician's assessment, your diarrhea is likely due to a condition called gastroenteritis (stomach flu). Antibacterial agents don't work in this situation, but rather may prolong the diarrhea. Therefore, antibacterial agents are not recommended at this moment.

Taking sufficient fluids is the most important management strategy. Please take a small amount repeatedly. It is better to take water with sugar and salt than to simply take water or tea alone.

If your stool becomes tinged with blood, you develop severe abdominal pain or high fever, or you can't take fluids orally, please go back and see your physician again.

※ Whether antibacterial agents are prescribed or not, physicians clearly communicating with pharmacists ensures patient education by pharmacists, and improves patients' compliance.<sup>117-118</sup> Therefore, it is better to have physicians write a diagnosis and relevant information on the prescription sheet or in the personal medication log in order to convey the physician's thoughts to the pharmacist.

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## 5. Appendix

### (1) To Better Understand Antimicrobial Stewardship

**Q1.** What is the difference between a virus and a bacterium?

**A1.** A bacterium is composed of a single cell. Examples include *Escherichia coli* and *Staphylococcus aureus*. The size is several micrometers (1/1000 of 1mm). A bacterium consists of organelles and genes surrounded by a cell wall, and can grow on its own. A virus, on the other hand, is not a bacterium. It is composed of genes and proteins and its size is on the scale of nanometers, making it about 1/10,000 the size of a bacterium. The influenza virus and norovirus are examples of viruses. A virus can't create or metabolize materials inside itself due to a lack of the necessary apparatus. Instead, it enters the cell of a human or animal and grows with the help of the human or animal cell. Please refer to the table shown in A2.

**Q2.** What are the differences among antimicrobials, antibacterials, antibiotics and antibiotic agents?

**A2.** The term “microorganism” is used as a general term to refer to bacteria, viruses, fungi, and protozoa. That is, antimicrobials include many types of medications that work against bacteria, viruses and fungi, etc. In particular, medicines that work against bacteria are referred to as antibacterials, antibiotics and antibiotic agents. Strictly speaking, antibacterials and antibiotics have slight differences, but are generally interchangeable.

Below is a table showing the differences between a bacterium and a virus. The point here is that antibacterials (antibiotics) don't work on viruses.

	<b>Bacteria</b>	<b>Viruses</b>
Size	Approx. one-thousandth of a millimeter	Approx. one-ten millionth of a millimeter
Cell wall	+	-
Protein synthesis	+	-
Energy production/metabolism	+	-
Proliferating capacity	Can proliferate without the help of other cells	Can only proliferate in human or animal cells
<b>Antibacterials (Antibiotics)</b>	<b>Effective</b>	<b>Ineffective</b>

※We frequently use the term “germ” instead of “bacteria” in ordinary conversation. The former generally refers to all microorganisms (including bacteria, viruses, molds and protozoa).

**Q3.** What is antimicrobial resistance (AMR)? Why does it matter to me?

**A3.** Since bacteria grow rapidly, compared to human or animal cells, their genes mutate rapidly. When they are exposed to an antibacterial, bacteria that are resistant to the antibacterial may survive. Thus, antimicrobial resistance (AMR) occurs when bacteria become resistant to antibacterials and antibacterials don't work to kill the bacteria or inhibit their growth. “MRSA” or “Multi-drug resistant *Pseudomonas*” are types of bacteria that are resistant to antibacterials. AMR can also occur among viruses. When antibacterials are given to humans, resistant bacteria may survive and continue to grow on the surface of the body or in the gut. Even for an otherwise healthy person, an infection with resistant bacteria is difficult to treat because an antibacterial, which should work, is no longer effective. To make matters worse, this type of resistant bacteria is emerging all over the world. If antibacterials are not used prudently, many will die because of infections involving resistant bacteria. AMR is the result of everybody using antibacterials. We as medical professionals want to examine you carefully and prescribe antibacterials more prudently. Please note that we will explain clearly whether antibacterials are indicated or not.



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**Q4.** Will I no longer receive antimicrobials when I get the flu or diarrhea?

**A4.** Physicians always work for the benefit of patients, seeking their quick recovery from illness, and this will never change. It is true that there are some infections for which antibacterials are effective against what appears to be flu or diarrhea caused by viruses. However, most cases involving flu and diarrhea are genuine viral infections, for which antibacterials are not effective, or are self-limiting infections. It is important to differentiate whether antibacterials are effective or not, and we make such assessment according to this manual.

**Q5.** What happens if antibacterials are used for a viral infection, which is self-limiting? Does anything bad happen?

**A5.** Antibacterials inhibit the functions of a bacterial cell and are effective against bacteria. On the other hand, a virus doesn't have a cell so antibacterials are not effective. Antibacterials don't affect human cells so they rarely do direct harm to humans, but medicine is a foreign object for humans and can cause allergies or damage organs such as the liver and kidneys. In addition, there are non-harmful or "good" bacteria (so called "colonizers") in the mouth and gut and on the skin. Antibacterials kill colonizers, and can cause diarrhea and/or abdominal pain. When colonizers are killed, bacteria or fungi resistant to antibacterials may over-grow. Those who have taken antibacterials may develop infections due to such resistant bacteria or fungi, or spread the infections to others. That is, antibacterials only do harm to those who don't need them. The more people take antibacterials, the more people carry resistant bacteria in their bodies, whether they take antibacterials or not. Then, antibacterials may not work for an infection for which they should work. This issue has been pointed out for a long time and has recently become a significant threat to global public health. To tackle AMR, antibacterials should be used only when needed (should not be used when not needed).

**Q6.** Why did I get antibacterials when I had flu or diarrhea before?

**A6.** You may wonder why you received antibacterials previously when you had similar symptoms. Physicians used to prescribe antibacterials for those symptoms, and there are some reasons for this:

- (i) Based on careful assessment, a bacterial infection, rather than a simple viral infection or diarrhea, was diagnosed, requiring antibacterials.
- (ii) The assessment to differentiate a bacterial infection with antibacterial indication from a viral infection without the indication was not thorough.
- (iii) From experiences where patients improved once antibacterials were prescribed, physicians misunderstood such improvement as a result of the antibacterials.
- (iv) Patients strongly requested antibacterials (or physicians thought patients would expect to receive antibacterials), and physicians tried to live up to their requests or expectations.

This manual is not intended to restrict antibacterial use. It aims to help differentiate whether antibacterials are indicated or not. Based on our assessment, if the scenario fits (i), we will prescribe antibacterials. We use this manual and try to differentiate whether you have an infection where antibacterials are indicated or not, and reduce the amount of antibacterial use due to scenario (ii). We assess patients carefully and don't prescribe antibacterials when they are not indicated. However, it is said that antibacterials might have been prescribed for reasons (iii) or (iv). The common cold and most diarrhea are self-limiting even without antibacterials. Assume your "flu" was a common cold, a self-limiting infection with a fever and respiratory symptoms that would be followed by recovery in 3 days. You may take OTC medications on day one and two, but would go to see a physician. You would take antibacterials and on the following day, you would feel better with no fever.

Then, you and your physician may think that the prescribed antibacterials worked. However, this is just a sequence wherein you took the antibacterials and then your symptoms improved, and doesn't imply that the antibiotics relieved your symptoms. Physicians know "antibacterials don't work for a viral infection" but patients may think "the antibiotics worked." Physicians observe such patients who improve 1 day after taking antibacterials, then think "Whether the antibacterials worked or not, the prescription was good because the patient improved anyway."

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These repeated experiences may have led physicians to think patients would be happy with antibacterials. On rare occasions, patients say “Please give me antibiotics this time because I felt better quickly with them last time.” Physicians value patients’ satisfaction and therefore might have prescribed antibacterials because the patient expressed or the physician intuited such expectations.

**Q7.** Will you not prescribe antibacterials for the flu or diarrhea?

**A7.** This manual does not instruct physicians to either prescribe or not prescribe antibacterials for the flu or diarrhea. When you have the flu or diarrhea, this manual helps physicians assess if antibacterials are indicated or not, and, if not indicated, this manual recommends against antibacterial therapy. Please ask us if you feel concerned about not having antibacterials prescribed. We will explain how we have assessed you and how we have reached a diagnosis.

As a result of a series of experiences and behaviors enacted between physicians and patients, antimicrobials have been misused and AMR has become a public threat. Previously, physicians might have prescribed antibacterials based on the idea that “antibacterials can be prescribed because at least they do no harm.” However, this is not the case. Using this manual, we try to differentiate whether antibacterials are indicated or not, and prescribe them only when really needed. Otherwise, AMR will continue to be a threat, and antibacterials may not work when they are supposed to work. In fact, we are already experiencing this to a certain extent.

As physicians, we always wish our patients a quick recovery. We will prescribe antibacterials for a bacterial infection for which they are indicated. We will try not to miss those infections. On the other hand, we will not prescribe antibacterials when we are certain that they are not indicated. We hope you understand that this approach will eventually help when you get a bacterial infection and you have effective antibacterials available.

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## (2) What is Delayed Antibiotics Prescription?

Recently, scientific evidence on delayed antibiotics prescription (DAP) as a measure to reduce antibacterial consumption in ARTI management has been mounting.<sup>114-116</sup> DAP means prescribing antibacterial agents only when the clinical course is not improving, instead of prescribing them immediately for those without clear indications for antibacterial agents. DAP is effective in reducing unnecessary antibacterial consumption and, in the UK, is recommended in the national guidelines on ARTI.<sup>157,158</sup> When applied in Japan, instead of prescribing antibacterial agents on the first encounter, patients can be advised to come back and see their physician again in case of worsening or persistent illnesses, so that they can reassess if antibacterial agents are indicated or not.

For example, a multi-center, randomized control trial in Spain recruited patients aged 18 years and older who developed ARTI (pharyngitis, acute rhinosinusitis, acute bronchitis or mild to moderate acute exacerbation of chronic obstructive pulmonary disease [COPD]) and for whom antibacterial agents were not clearly indicated. The patients were divided into three groups, where one group was given antibacterial agents on the first encounter (immediate prescription group), the second group was a DAP group<sup>\*13</sup>, and the third group was not given antibacterial agents (no antibacterial group), and their clinical outcomes were followed.<sup>116</sup>

The research showed that those who actually took antibacterial agents accounted for 91.1% in the immediate prescription group, 23.0 to 32.6% in the DAP group, and 12.1% in the no antibacterial group. The duration of moderate and severe symptoms was shorter in the immediate prescription group, but the differences compared to the DAP group and the no antibacterial group were 0.5 to 1.3 days, and 0.4 to 1.5 days, respectively, and the clinical significance of these differences is minimal. On the other hand, no differences were observed regarding complications, adverse effects, the need for unscheduled care and general health status at 30 days.<sup>116</sup>

In conclusion, DAP can decrease antibacterial consumption without increasing unfavorable outcomes such as complications, adverse effects and unscheduled patient visits.<sup>114-116</sup>

The point is, physicians should follow patients' progress on an ongoing basis. Access to health care facilities is relatively good in Japan, so if symptoms persist or don't improve after a few days, patients can be instructed to revisit the same health care facility so that the indications for antibacterial agents can be reassessed. It is important to recognize that it is difficult to make a diagnosis when seeing the patient at only "a single point" during the natural course of an illness. Physicians should see patients at "a sequence of points" along the timeline of the illness, and should know what the natural course of an illness such as ARTI is, what symptoms patients need to follow-up on, when they should come back, and when antibacterial agents are indicated so that they can provide appropriate instructions to patients. In the outpatient setting, this idea of "time sequence" is useful for the appropriate management of infectious diseases, and contributes to antimicrobial stewardship.

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<sup>\*13</sup> In the actual paper, the DAP group was further divided into two groups as "delayed patient-led prescription" and "delayed prescription collection" but for the purpose of this manual, these two groups are referred to as the DAP group.

Also, in Japan, according to Article 20 of the Rules for Health Insurance-covered Medical Facilities and Medical Care (Ministerial Ordinance No.15 of the [then] MHW enacted in 1957), a prescription is effective for 4 days in principle, including the day of prescription and weekends, therefore, interventions conducted overseas may not always be applicable.



## Acute Diarrhea Check List

(Subject: Children of school age to adults)

Entered on: MM/DD/YYYY

Patient name:	(M/F)	Height: cm
Date of birth: MM/DD/YYYY (    years old)		Weight: kg

Point to be checked in examination/ interview	<input type="checkbox"/> Vital signs	
	<input type="checkbox"/> Temperature	(    °C) Highest temp. before consultation (    °C)
	<input type="checkbox"/> Consciousness level	<input type="checkbox"/> Clear <input type="checkbox"/> Abnormal → (JCS    ) or (GCS:    )
	<input type="checkbox"/> Heart rate (pulses)	(    /min)
	<input type="checkbox"/> Blood pressure	(    /    mmHg)
	<input type="checkbox"/> Respiration rate <input type="checkbox"/> SpO2	(    breaths/min) (    %)
	<input type="checkbox"/> Occupation	
	<input type="checkbox"/> Surrounding people having the same symptom	<input type="checkbox"/> No <input type="checkbox"/> Yes → (Who/duration)
	<input type="checkbox"/> Past overseas trip	<input type="checkbox"/> No <input type="checkbox"/> Yes → Country:    Period: From    To
	<input type="checkbox"/> Past administration of antibacterial agents	<input type="checkbox"/> No <input type="checkbox"/> Yes → (Drug name/duration)
<input type="checkbox"/> Underlying disease	<input type="checkbox"/> No <input type="checkbox"/> Yes → Disease name:	
<input type="checkbox"/> History of allergy to antibacterial agents	<input type="checkbox"/> No <input type="checkbox"/> Yes → Drug name:    Symptom/seriousness:	

Symptom	<input type="checkbox"/> Seriousness of diarrhea	<input type="checkbox"/> Mild (No problem in daily life)	
		<input type="checkbox"/> Moderate (Can move but activities are limited)	(duration)
		<input type="checkbox"/> Serious (Major problem in daily life)	
	<input type="checkbox"/> Bloody feces/mucous and bloody feces	<input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Serious	(duration)
	<input type="checkbox"/> Nausea/vomiting	<input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Serious	(duration)
	<input type="checkbox"/> Abdominal pain	<input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Serious	(duration)
	<input type="checkbox"/> Tenesmus (bowel pain)	<input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Serious	(duration)
<input type="checkbox"/> Other symptoms	(degree and duration of the symptoms)		

Systemic seriousness	<input type="checkbox"/> Presence of suspicious signs of bacteremia, such as hypotension or chill/shivering
	<input type="checkbox"/> Necessity of hospitalization to treat dehydration or shock
	<input type="checkbox"/> Cellular immunodeficiency, steroid, or HIV infection with low CD4 count
	<input type="checkbox"/> 50 years old or older, implantation of artificial blood vessel, valve, or joint
	<input type="checkbox"/> None of the above

Necessity of fecal examination or treatment with antibacterial agents	<input type="checkbox"/> Moderate to serious diarrhea
	<input type="checkbox"/> Hematogenous diarrhea
	<input type="checkbox"/> Fever (≥38° C)
	<input type="checkbox"/> Past trip to overseas
	<input type="checkbox"/> Systemic serious condition
<input type="checkbox"/> One or less of the above → Administer no antibacterial agent and conduct symptomatic treatment	

Patient education when antibacterial agents are not prescribed	<input type="checkbox"/> Worry and expectation of the patient
	<input type="checkbox"/> Idea about antibacterial agents
	<input type="checkbox"/> Future prognosis
	<input type="checkbox"/> Importance of sufficient nutrition, water intake, and rest
	<input type="checkbox"/> Confirmation of information understanding
	<input type="checkbox"/> Symptoms to be noted and treatment

Doctor's name	
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### Administrative background of this manual

Following the national action plan on AMR adopted on April 5, 2016, the first meeting of a committee on AMR discussed the need for a working group on antimicrobial stewardship (chaired by Haruo Watanabe, December 5, 2016). This led to the establishment of the working group, and the group made a draft of this manual after a series of meetings (chaired by Norio Ohmagari, first time on December 19, 2016, second time on January 30, 2017, third time on February 21, 2017). Later, the draft was further discussed and approved at the second meeting of the committee (March 6, 2017) and at the 20th meeting of an advisory board of infectious diseases (chaired by Ichiro Kurane, March 27, 2017). The manual was officially published on June 1, 2017.

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