Manual of Antimicrobial Stewardship

3rd Edition, Main Volume

Microorganisms Coming to an Issue for Infections in Inpatients

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Glossary

Antimicrobials

Classification		Classification	Name of antibacterial agent	Abbreviation
Beta-lactams	Penicillin	Injection	Ampicillin	ABPC
		Injection	Sulbactam/ Ampicillin	SBT/ABPC
		Injection	Piperacillin	PIPC
		Injection	Tazobactam/ Piperacillin	TAZ/PIPC
	1st generation cephalosporins	Injection	Cefazolin	CEZ
	3rd generation cephalosporins	Injection	Cefotaxime	CTX
		Injection	Ceftazidime	CAZ
		Injection	Ceftriaxone	CTRX
	4th generation cephalosporins	Injection	Cefepime	CFPM
	Oxacephem-type	Injection	Flomoxef	FMOX
	Cephamycin series	Injection	Cefmetazole	CMZ
	Beta-lactamase inhibitor combination cephalosporins	Injection	Tazobactam/ Ceftolozane	TAZ/CTLZ
	Carbapenem	Injection	Meropenem	MEPM
		Injection	Imipenem/ Cilastatin	IPM/CS
		Injection	Relevactam/ Imipenem/ Cilastatin	REL/IPM/CS
	Monobactam	Injection	Aztreonam	AZT
Glycopeptide-based		Injection	Teicoplanin	TEIC
		Injection	Vancomycin	VCM
Oxazolidinones		Injection	Linezolid	LZD
Lipopeptide-based		Injection	Daptomycin	DAP
Quinolones (Fluoroquinolones)		Injection	Ciprofloxacin	CPFX
		Injection	Levofloxacin	LVFX
Aminoglycoside		Injection	Amikacin	AMK
		Injection	Gentamicin	GM
		Injection	Tobramycin	TOB
Tetracycline		Injection	Tigecycline	TGC
		Injection	Minocycline	MINO

Classification		Classification	Name of antibacterial agent	Abbreviation
Lincomycin		Injection	Clindamycin	CLDM
Polypeptide		Injection	Colistin	CL
Other antibacterial agents	Sulfa drug	Injection	Sulfamethoxazole/ Trimethoprim (Co-trimoxazole)	–
	Nitroimidazole	Injection	Metronidazole	MNZ
	Fosfomycin	Injection	Phosphomycin	FOM
Antifungal agent	Polyene-macrolide	Injection	Amphotericin B	AMPH-B
		Injection	Liposomal amphotericin B	L-AMB
	Triazole	Injection	Fluconazole	FLCZ
		Injection	Fosfluconazole	F-FLCZ
		Injection	Voriconazole	VRCZ
	Echinocandin	Injection	Caspofungin	CPFG
		Injection	Micafungin	MCFG
Beta-lactams	Penicillin	Oral	Benzylpenicillin Benzathine	PCG
		Oral	Amoxicillin	AMPC
		Oral	Clavulanic acid/ Amoxicillin	CVA/AMPC
	1st generation cephalosporins	Oral	Cephalexin	CEX
	3rd generation cephalosporins	Oral	Cefcapene	CFPN-PI
		Oral	Cefditoren	CDTR-PI
		Oral	Cefteram	CFTM-PI
		Oral	Cefpodoxime	CPDX-PR
	Carbapenem	Oral	Tebipenem	TBPM-PI
	Peneme-type	Oral	Faropenem	FRPM
Oxazolidinones		Oral	Linezolid	LZD

Classification		Classification	Name of antibacterial agent	Abbreviation
Quinolones (Fluoroquinolones)		Oral	Galenoxacin	GRNX
		Oral	Ciprofloxacin	CPFX
		Oral	Moxifloxacin	MFLX
		Oral	Levofloxacin	LVFX
Tetracycline		Oral	Doxycycline	DOXY
		Oral	Minocycline	MINO
		Oral	Tetracycline	TC
Lincomycin		Oral	Clindamycin	CLDM
Macrolide		Oral	Azithromycin	AZM
		Oral	Erythromycin	EM
		Oral	Clarithromycin	CAM
		Oral	Fidaxomicin	FDX
Glycopeptide-based		Oral	Vancomycin	VCM
Other antibacterial agents	Sulfa drug	Oral	Sulfamethoxazole/ Trimethoprim (Co-trimoxazole)	–
	Nitroimidazole	Oral	Metronidazole	MNZ
	Fosfomycin series	Oral	Fosfomycin	FOM
Antifungal agent	Triazole	Oral	Fluconazole	FLCZ
		Oral	Voriconazole	VRCZ

Bacteria and viruses

Technical name (often the internationally accepted Latin, scientific, or Linnaean name of plants and animals)
Gram-negative bacillus
Acinetobacter baumannii
Haemophilus influenzae
Enterohemorrhagic *E. coli*: EHEC
Enterotoxigenic *E. coli*: ETEC
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Yersinia enterocolitica
Enterobacter spp.
Shigella spp.
Vibrio parahaemolyticus
Vibrio cholerae
Campylobacter jejuni
Bordetella pertussis
Salmonella spp.
Fusobacterium spp.
Bacteroides spp.
Providencia spp.
Proteus mirabilis
Serratia marcescens
Citrobacter freundii
Stenotrophomonas maltophilia
Salmonella enterica subsp. *enterica* serovar Typhi
Salmonella enterica subsp. *enterica* serovar Paratyphi A
Gram-positive bacillus
Clostridium perfringens
Clostridium botulinum
Clostridioides difficile
Bacillus cereus
Bacillus spp.
Propionibacterium spp.
Corynebacterium spp.
Gram-negative coccus
Moraxella catarrhalis

Technical name (often the internationally accepted Latin, scientific, or Linnaean name of plants and animals)
Gram-positive coccus
Enterococcus spp.
Streptococcus pneumoniae
Group A β-hemolytic *Streptococcus* spp.: GAS
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus lugdunensis
Coagulase-negative staphylococci: CNS
Fungus
Candida spp.
Atypical bacteria, other bacteria
Mycoplasma spp.
Chlamydophila pneumoniae
Chlamydia spp.
Legionella spp.
Entamoeba histolytica
Antimicrobial-resistant bacteria
Carbapenem-resistant *Acinetobacter baumannii*: CRAB
Multidrug-resistant *Acinetobacter* spp.: MDRA
AmpC β-lactamase producing *Enterobacterales*: AmpC
Carbapenem-resistant *Enterobacterales*: CRE
Difficult-to-treat resistance *P. aeruginosa*: DTR-PA
Extended-spectrum β-lactamase producing *Enterobacterales*: ESBL
Methicillin-Resistant [Susceptible] *Staphylococcus aureus*: MRSA [MSSA]
Multidrug-resistant *Pseudomonas aeruginosa*: MDRP
Vancomycin-resistant enterococci: VRE

List of abbreviations

Abbreviation	Name
Organization name	
ACP	American College of Physicians
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
IDSA	Infectious Diseases Society of America
JAID	Japanese Association for Infectious Diseases
Terminology	
AST	Antimicrobial Stewardship Team
CAUTI	Catheter-associated Urinary Tract Infections
CDI	*Clostridioides difficile* Infection
CLABSI	Central Line-associated Bloodstream Infection
CRBSI	Catheter-related Bloodstream Infection
SSI	Surgical Site infection
TDM	Therapeutic Drug Monitoring

1. Introduction

(1) Background

Antimicrobials[*1] 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.[1] On the other hand, antimicrobials can cause adverse effects and therefore need to be used in an appropriate manner.[1] As a result of misuse of antimicrobials, antimicrobial resistance (AMR) has been recently recognized as a major global public health threat.[1] Without appropriate measures, it is estimated that 10 million people will die annually worldwide from antimicrobial-resistant bacteria by 2050, with estimated 4.9 million deaths related to antimicrobial-resistant bacteria annually and approximately 1.2 million deaths caused by antimicrobial-resistant bacteria already in 2019.[2-4] The development of new antimicrobial agents has been stagnant since the 1980s, while AMR has posed significant threats to public health.[1] There is a concern, therefore, that without appropriate antimicrobial use today, effective antimicrobial agents may run out.[5] 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 (2016-2020) adopted by the Government of Japan in April 2016 and the National Action Plan on AMR (2023-2027) was updated in April 2023.[1] 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.[1]

A study on antimicrobial consumption in Japan based on sales data showed Japan consumed 10.22 Defined Daily Doses (DDDs)[*2] per 1,000 inhabitants per day in 2013 and oral antimicrobial agents accounted for 90.1% of the total consumption.[6] Compared to other countries, Japan consumed a relatively higher proportion of oral 3rd-generation cephalosporins, fluoroquinolones and macrolides.[1] 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.[7] And in Japan, antimicrobial agents are excessively prescribed for diarrhea in patients under 65 years old[8] and for pneumonia in children. Only a quarter of facilities prescribe antimicrobials in compliance with guidelines.[9] On the other hand, the introduction of an additional fee for the appropriate use of antimicrobials in pediatric patients reduced antimicrobial prescribing in the target age group, and in addition, the educational effect on healthcare providers reduced antimicrobial prescribing in all age

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*1 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

*2 **DDD:** DDD stands for Defined Daily Dose. It represents the average dose for an adult (70 kg body weight) when an antimicrobial agent is used for its main disease indication. The World Health Organization provides the DDD for each agent.

groups.[10] 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. The outcome indicators of Japan's Action Plan on AMR (2023-2027) include "By 2027, reduce daily antimicrobial use per 1,000 population by 15% from the level in 2020" and "By 2027, reduce daily IV carbapenem antimicrobial use per 1,000 population from the level in 2000,"[1] and it is noted that those outcome indices should be achieved through promoting appropriate infectious disease practice.

(3) Target Readers

The 2nd edition of this manual was intended primarily for healthcare professionals providing outpatient care. However, in revising the 3rd edition, a section on the proper use of antimicrobial agents in hospitalized patients was added to further enhance the content so that it is intended for a wider range of patients. 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 to fully promote antimicrobial stewardship.

(i) General outpatient edition

This manual is intended for medical professionals, particularly physicians who examine, prescribe for, and counsel patients in an outpatient setting. 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 3rd-generation cephalosporins, fluoroquinolones and macrolides are prescribed in outpatient settings. Therefore, the manual is structured to help medical professionals distinguish the outpatient clinical situations where antimicrobial agents are indicated from those where they are not.

(ii) Appropriate use of antimicrobial agents in hospitalized patients, ed.

In "Basic Approach to Infectious Diseases in Hospitalized Patients," the basic approach to the appropriate use of antimicrobial agents for hospitalized patients, who are expected to have more complicated conditions compared to outpatients, is explained. It is intended for various healthcare professionals involved in the treatment of inpatients at medical institutions. A separate volume," Microorganisms that cause problems in inpatient infections," is intended for healthcare professionals who treat infections in hospitalized patients at various medical institutions (including healthcare professionals specializing in infectious disease care and hospital Antimicrobial Stewardship Teams [ASTs]), The article provides specific information on the treatment of infections in hospitalized patients, including antimicrobial-resistant organisms.

(4) Target Patient Populations

In this manual, the following patient groups are assumed for outpatients and inpatients, respectively. For details beyond the scope of this manual, such as prescribing for patients who are allergic to penicillin, please consider consulting a medical specialist or referring to an adult medical textbook. It is recommended that consultation with in-house ASTs and infectious disease specialists should also be actively utilized with regard to the appropriate use of antimicrobial agents in hospitalized patients.

(i) Outpatients

As described below, 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 the optimal use of specific antimicrobial agents, the latter half of the manual focuses on the clinical management of ARTI and acute diarrhea because 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.[6,7] The target subjects of the manual are healthy, immunocompetent adult and pediatric patients, including infants.

(ii) In-patients

In healthcare facilities, not only patients are admitted for treatment of infectious diseases, but also patients may develop infections during hospitalization for treatment of other diseases or may develop another infectious complication during treatment of an infectious disease. The majority of these infections are healthcare-associated infections, and those related to medical device insertion or surgery are the subject of domestic surveillance.[11-13] Prevention of healthcare-associated infections is extremely important because of their enormous impact on patient length of stay, increased complication and fatality rates, and increased healthcare costs.[14] However, since this article focuses on the proper use of antimicrobial agents, it does not include a description of prevention, but rather outlines the basic concept of proper use of antimicrobial agents for “inpatient infections,” including healthcare-associated infections, and describes the specific treatment methods in a separate volume.

Healthcare facilities play an important role in the development and spread of antimicrobial resistance, and the appropriate use of antimicrobial agents for infectious diseases in healthcare facilities is essential in the fight against antimicrobial-resistance.[15] Although the principles of the concept of proper use can be applied to children, the specific prescribing examples in particular are written for adult patients with normal renal function. Therefore, it is recommended that an individual approach be taken, such as referring to the literature or consulting with a medical specialist, for pediatric use and dosage and administration adjustments for renal dysfunction.

Critically ill and immunocompromised patients in this volume are mainly those with organ dysfunction or septic shock,[16] those receiving immunosuppressive drugs or chemotherapy, and those with primary or acquired immunodeficiency syndrome.[17] However, the decision should be based on the course and current status of each patient.

The package insert 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 from January 1, 2017 to January 31, 2023. “Acute bronchitis” OR “respiratory tract infection” OR “pharyngitis” OR “rhinosinusitis” OR “the common cold” OR “bronchiolitis” OR “croup” 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.

With regard to inpatients, we added the literature of the experts in each section while taking into account the current practice guideline recommendations by expert groups such as JAID/JSC, CDC, IDSA, ESCMID, and NICE. For the inpatient section, “¶” was inserted at the end of dosage and administration and a note was added in the appendix when the indication was not included in the indications in the package insert, when the maximum recommended dose in the package insert was exceeded, or when it was mentioned in the Social Insurance Medical Fee Payment Fund Review Information Provision Case.

2. General Principles

(1) What is Antimicrobial Stewardship?

Antimicrobial stewardship[*3] is a concept involving measures and interventions taken to improve optimal antimicrobial use. 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.[18]

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. 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.[19]

(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 healthcare 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 Frequently referred to as 'Antimicrobial Stewardship'

(3) Inappropriate and Unnecessary Use of Antimicrobials

In this manual, the situations where antimicrobial use is not indicated 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' judgments can compromise the diagnosis of an infectious disease and even harm patients due to adverse events and overdose. Therefore, except in special circumstances, patients should refrain from such behavior while physicians should instruct patients not to engage such use of antimicrobials.

(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[20] and to reduce the incidence of acute diarrhea.[21] 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.[22] Soap and water are also indicated to manage acute diarrhea caused by norovirus.[23]

(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, or the triple combination vaccine [DPT] with diphtheria and tetanus), measles and rubella (MR) vaccine, coronavirus vaccine, pneumococcal vaccine and *Haemophilus influenza* 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, and rotavirus vaccine for acute diarrhea are given to children as routine vaccination, 23-valent pneumococcal polysaccharide vaccine and influenza vaccine are given to the elderly as routine vaccination, and influenza virus vaccine for the non- elderly and the triple combination vaccine [DPT] with diphtheria and tetanus are given as voluntary vaccination.[24] As of October 2023, the novel coronavirus vaccine is publicly subsidized for children aged 6 months and older.

(iii) Cough etiquette

Cough etiquette is recommended to prevent person-to-person transmission of microorganisms that cause ARTI.[24] 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) Mask

With the outbreak of novel coronavirus infection (COVID-19), studies on the effectiveness of masks have been conducted around the world. Although caution must be exercised in interpretation, as epidemic conditions and other factors vary from study to study, several studies suggest that masks are effective in preventing infection.[25]

In addition, for adults and children old enough to wear masks, wearing a mask indoors, in crowded places with many people, etc., can reduce the spread of droplets from coughing and sneezing.[26]

(v) 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 are, usual care (control), water gargling, and iodine gargling, and the water gargling group had a significantly lower incidence of ARTI than the control group.[27] 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.[28] Given these findings, the effectiveness of gargling is still being debated.

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Children of School Age to Adults

4. 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.[1,2]

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,[3] and patients report as "flu" even when they do not have respiratory tract symptoms.[4] 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 2020 estimated that there were 128 patients presenting with acute upper respiratory tract infection[*4] per 100,000 populations per day.[5] Also, a study conducted in the USA in the 1960s showed the number of ARTI episodes per year was three to seven times among the age group 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,[6] 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.[7]

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.[8] Therefore, the question, "Does this clinical presentation 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.[6,9] The pathogens are rarely bacteria, including group A *Streptococcus* spp. (GAS), a pathogen of acute pharyngitis, and *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, pathogens of acute bronchitis.[6,9]

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.[10,11]

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 "Children of school age to Adults" less applicable.

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*4 Acute upper respiratory tract infections are diseases classified as J00-J06 in the International Classification of Diseases, 10th Edition (ICD10).

Furthermore, fever among infants requires particular attention to bacteremia and urinary tract infection as important differential diagnosis.[12] Therefore, "pediatric" patients in this "Children of school age to Adults" refers to school-aged children and above unless otherwise specified. Infants over three months old are described in "Infants and Toddlers."

The epidemiology of ARTI among school-aged children and above is generally similar to that of adults,[13,14] but among pediatric patients, caution is required with respect to bacterial infections secondary to ARTI, pneumonia caused by *Mycoplasma pneumoniae*,[15,16] diagnosis of GAS (described below),[17] and age-specific adverse effects due to medications.[18]

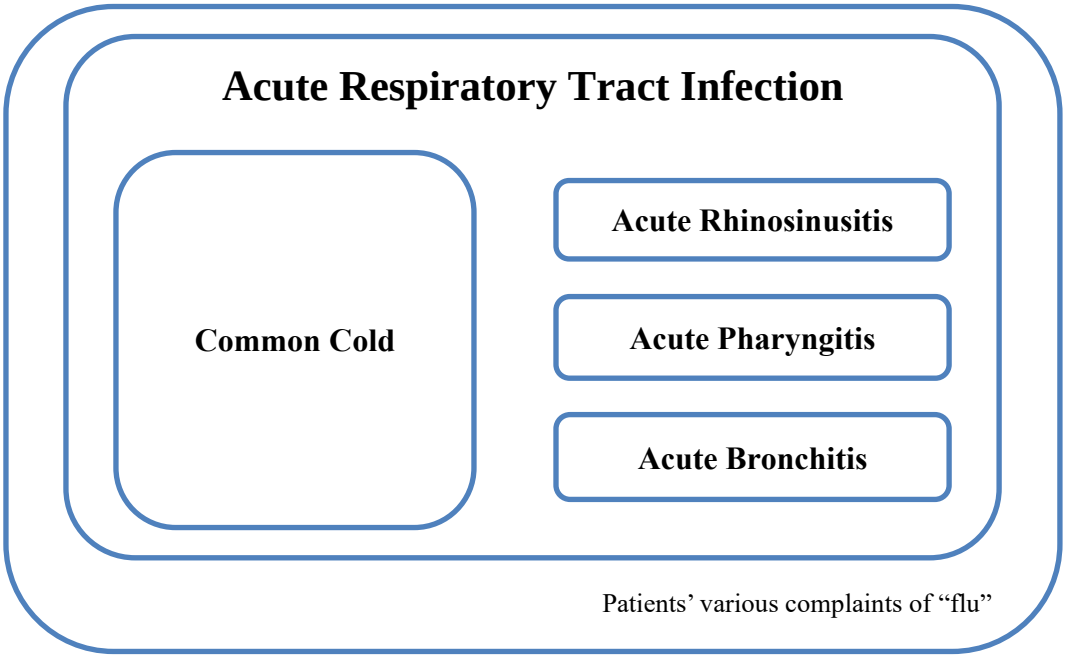

Figure 1. Concept and Classification of Acute Respiratory Tract Infection in This Manual *5

(3) Diagnosis and Differential Diagnosis 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.[3,19-21] This classifies ARTI into common cold (nonspecific upper respiratory infection), acute rhinosinusitis, acute 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.

*5 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.

Table 1. Classification of Acute Respiratory Tract Infection
– Modified from References 3 and 20

Classification	Rhinorrhea/ Nasal congestion	Sore throat	Cough/Sputum production
Common Cold	▲	▲	▲
Acute Rhinosinusitis	◎	×	×
Acute Pharyngitis	×	◎	×
Acute Bronchitis	×	×	◎

◎ as major symptoms, ▲ as concurrent but not prominent symptoms, × as mild symptoms or no symptoms

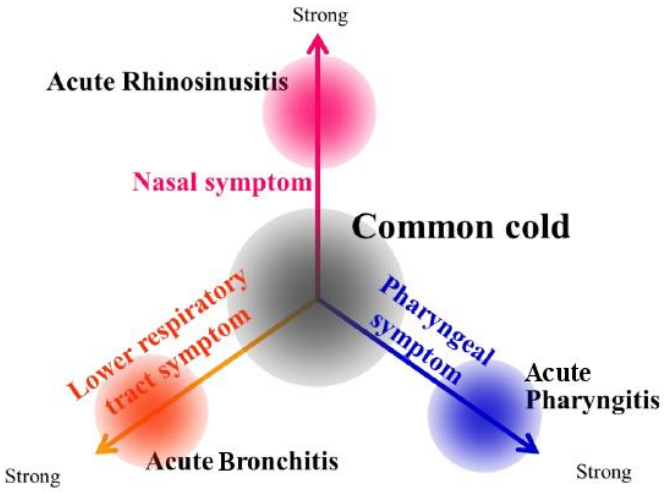

Figure 2. Visual Image of Acute Respiratory Tract Infection Classification

(i) Common cold

In this manual, the common cold is an 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 a 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 three days after the onset of the symptoms, and the illness is relieved after seven to 10 days.[23] Cough due to common cold may last for about three weeks but a prolonged cough does not necessarily suggest a secondary bacterial infection which requires antimicrobials.[23] In contrast, persistent progression of the illness beyond its natural course and the onset of worsening symptoms after initial improvement may suggest a secondary bacterial infection.[21]

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. 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.[22,24,25]

As for COVID-19, in addition to upper respiratory tract symptoms such as sore throat, nasal discharge and nasal obstruction, systemic symptoms such as fatigue, fever, and myalgia

often occur. The patient may be suspected of having COVID-19, For details on the treatment of patients suspected of having COVID-19 or diagnosed with COVID-19, please refer to the latest edition of the "Guideline for the Treatment of New-type Coronavirus Infections (COVID-19)" issued by the MHLW's Headquarters for the Promotion of Countermeasures to Combat New-type Coronavirus Infections.

(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."[26]

Less than 2% of acute viral upper respiratory infections have been reported to be complicated by acute bacterial sinusitis.[27,28] The color of nasal discharge is not helpful in differentiating between viral and bacterial infections,[29] but double-sickening (worsening symptoms following an illness that was initially improving) may be suggestive of bacterial infections.[22,30]

(iii) Acute pharyngitis

Acute 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.[17,31,32] On the other hand, researchers in Japan reported about 30% of adult cases[33] of pharyngitis in the age group of 20 to 59 years old and 17% of pediatric cases[34] tested positive for GAS. In general, pharyngitis caused by GAS is common among school aged children and above while it is relatively rare among infants,[17,31,35] 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.[36] Although group C and G *Streptococcus* spp. 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.[37-45]

The Centor score, McIsaac score, and modified Centor score with age adjustment, are known to support the diagnosis of GAS pharyngitis (Table 2).[46,47] Recommendations on the use of rapid diagnostic tests for GAS and antibacterial treatment based on the Centor score and/or McIsaac score vary.[17,21,48,49] ACP/CDC and ESCMID suggest rapid diagnostic tests may be unnecessary when the Centor score is 2 or below.[21,48] 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.[50] When antibacterial treatment was limited only to those tested positive for GAS rapid diagnostic test or culture, unnecessary antibacterial use was reduced[46] and cost- effectiveness was improved.[51]

Conversely, among pediatric patients, only 68% of those with Centor score of 4 tested positive for GAS.[52] 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 46 and 47

Fever 38°C or higher		1 point
Absence of cough		1 point
Anterior cervical lymphadenopathy with tenderness		1 point
Tonsillitis with white moss		1 point
Age	3-14 years old	1 point
	15-44 years old	0 points
	45 years old-	−1 point

Differential diagnosis of pharyngitis includes infectious mononucleosis (IM) caused by Epstein–Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), rubella virus and toxoplasma. However, IM cannot be ruled out by Centor/McIsaac scores alone as the scores are often high among patients with IM.[53] Posterior cervical and/or auricular adenopathy, and splenomegaly are specific findings among patients with IM,[54] and lymphocyte dominance in a peripheral blood test with a lymphocyte-white blood cell count ratio higher than 0.35 is also helpful to diagnose IM.[55]

Differential diagnosis of pharyngitis also includes epiglottitis, deep neck abscess (peri-tonsillar abscess, retropharyngeal abscess, and Ludwig angina, etc.) and Lemierre syndrome. Therefore, “red flag” signs and symptoms[*6] such as the worst 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.[56,57] 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.[49] 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.[56,57]

*6 “Red flag” (dangerous symptoms) refers to symptoms that should be properly diagnosed or treated without fail in medical practice.

(iv) Acute bronchitis

Acute bronchitis is classified as a type of ARTI with cough dominant, with or without fever and sputum production. It is common that post-infectious cough lasts for weeks. The mean duration of cough due to ARTI was reported to be 17.8 days.[58*7]

More than 90% of the pathogens of acute bronchitis are viruses and the remaining 5 to 10% are *Bordetella pertussis*, *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and so forth,[21,59] but purulence and color of sputum are not helpful in differentiating bacterial infection.[21] Of note, for healthy, immunocompetent adults younger than 70 years of age, an X-ray is generally not indicated when neither abnormal vital signs (body temperature ≥38°C, pulse ≥100/min and respiratory rate ≥ 24) nor abnormal lung examination is found.[21]

Pertussis, is often difficult to accurately diagnose in a clinical setting because clinical findings are generally non-specific,.[60] Vomiting after cough episodes and inspiratory whoop make a diagnosis of pertussis more likely.[60] A serum test for pertussis, that is, anti-*B. pertussis* toxin (PT) antibody, is difficult to utilize in an actual clinical setting due to the long turn-around time.[61,62] 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 a 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.[63,64] 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 diagnosis of acute bronchitis may also include tuberculosis if cough lasts for a few weeks or more, 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 two weeks,[30] and 10% of school aged children and above infected with *Mycoplasma pneumoniae* may subsequently develop pneumonia.[16] In addition, a guideline by the Japanese Society of Pediatric Pulmonology (JSPP)/JSPID describes pertussis as a differential diagnosis for pediatric patients aged one and above with cough lasting longer than a week, and defines the clinical diagnosis of pertussis for those aged one and above as at least one of the following being met: characteristic inspiratory whoop, episodic prolonged coughing spells, vomiting after coughing, and dyspnea.[65]

Therefore, follow-up over time is one of the keys to successful management.

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

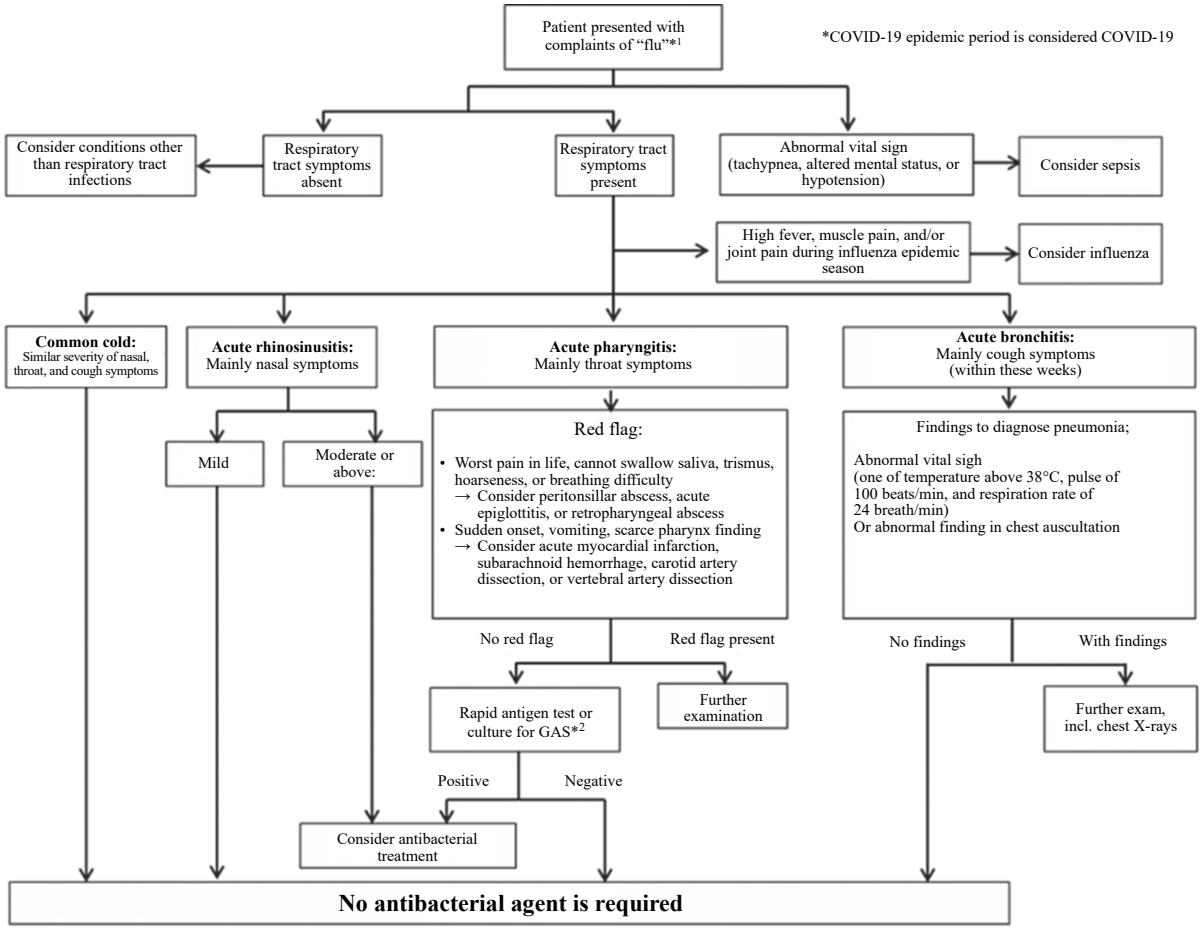

Figure 3. Flowchart of Diagnosis and Treatment of Acute Respiratory Tract Infection

*1 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.

*2 GAS: Group A β-hemolytic *Streptococcus* spp.

(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, JSPP/JSPID and ACP/CDC, the common cold is a viral illness and antimicrobial therapy is not recommended.[2,21,65] 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.[66]

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 five to seven 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 seven 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 67 and 68

		None	Mild	Moderate to more Severe
Clinical symptoms	Rhinorrhea	0	1	2
	Facial pain/ Frontal headache	0	1	2
Nasal findings	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 69

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 ≥ 39°C and purulent nasal discharge for at least three days and patients are sick-looking
3. Recurrent fever, or deterioration of daytime nasal discharge or cough one week after recovery from common cold

50% and 70% of cases of acute rhinosinusitis including possible bacterial rhinosinusitis were reported to be resolved after one week and after two weeks, respectively, regardless of antimicrobial therapy.[70] In addition, adverse events such as nausea, diarrhea and abdominal pain were observed in the antimicrobial treatment group than the placebo group, while recovery from acute rhinosinusitis in seven to 14 days was more frequent in the treatment group, suggesting that risks due to antimicrobial therapy outweigh benefits.[70] 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.[66]

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, ≥39°C and purulent nasal discharge or facial pain lasting for at least three days) and cases of double-sickening (worsening symptoms following a typical viral illness that lasted five days and was initially improving).[21] 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.[49,67,68]

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 ≥39°C and purulent nasal discharge for at least three days; (3) Worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement. Otherwise, watchful waiting without antimicrobial therapy is recommended.[69]

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,[71,72] 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.[21,72] The recommended regimen is oral amoxicillin 500 mg[*8] three times daily for five to seven days.[21] 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 500 mg and clavulanate 125 mg three times daily for five to seven days.[21]

The recommended duration of antimicrobial therapy used to be 10 to 14 days,[83] but a recent study showed short-term treatment (three to seven days) was not inferior in treatment effect to long-term treatment (six 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.[73]

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 250 mg 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.

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 five to seven days be selected as the first-line regimen. While guidelines

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

developed abroad recommend tetracyclines and fluoroquinolones as alternatives if an adult patient is allergic to β lactams,[30,72] it has been reported that resistance of *Streptococcus pneumoniae*, the major pathogen of bacterial rhinosinusitis, to tetracyclines is high in Japan,[74] 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 40 mg/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 90 mg/kg of amoxicillin hydrate." Also, a couple of guidelines recommend amoxicillin as the first-line regimen for acute rhinosinusitis.[49,67,69]

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 seven to 10 days be selected as the first-line regimen.

(iii) Acute 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.[17,21] There is yet to be consensus on whether pharyngitis with anaerobes such as *Fusobacterium*, and group C and G *Streptococcus* spp. [*9] needs to be treated or not.[57,75]

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).[76] 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) [*10] was 33, suggesting the absolute risk difference between the two groups was not substantially high.[76] Given its safety, effectiveness and narrow spectrum of antibacterial coverage, a couple of guidelines recommend penicillins as the first-line regimen.[17,21,49] The drug package insert of amoxicillin states: "The usual dosage for oral administration is 250 mg 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.[17,21] Regarding the duration of 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.[17,48]

According to the IDSA guideline, cephalexin, a 1st-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.[17]

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*9 The statement is not applicable to cases with severe invasive streptococcal infection by group C and G *Streptococcus* spp., including possible cases.

*10 The Number Needed to Treat (NNT) is the number of patients needed to treat to prevent one additional bad outcome.

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 ≥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 150 mg every six hours in usual cases and 300 mg 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 500 mg orally twice daily for those with a mild penicillin allergy and clindamycin 300 mg orally three times daily for those with a severe penicillin allergy.[17]

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 JSPP/JSPID recommends a 10-day course of oral amoxicillin for GAS pharyngitis.[65] 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 (four to six 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.[77] 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.[77] Research conducted in Japan to compare oral amoxicillin for 10 days to oral cephalosporins for five 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.[78]

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 diagnosis of pharyngitis is 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.[79] 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.[21,59] 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.[21,59]

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,[14,65,80] 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.[81,82]

For the treatment of pertussis, antimicrobial therapy after the catarrhal phase (usually two weeks after symptom onset) is ineffective in symptom resolution, but antimicrobial therapy within three weeks after the onset among those aged one year and older may contribute to lower transmission to others.[59,83] 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 three days.[59,83,84] However, the package insert includes pertussis as an indication for pediatric clarithromycin and erythromycin, while azithromycin does not include pertussis as an indication, but is acceptable for insurance review.[84] 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 25 mg/kg to 50 mg/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.[86-88] 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.[87,88]

Table 5. Important Elements in Explaining ARTI to Patients

– Created from References 86 to 88

1) Collection of information	• Elicit the patient's concerns and expectations. • Actively ask for their opinion on antimicrobials.
2) Provide appropriate information	• Provide important information. – In acute bronchitis, the cough may last up to 4 weeks. – Most acute respiratory tract infections resolve spontaneously. – The body fights against pathogens, but it takes time to get better. • Provide correct information about antimicrobial agents. • It is important to take adequate nutrition, fluids, and rest.
3) Conclusion	• Summarize the previous exchanges and confirm understanding of the information. • Provide specific instructions on symptoms to watch for and when to see the doctor again.

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.[89,90] 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 "Warm beverages will ease the nasal congestion."[91] 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.[91] 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.[91]

Recently, the scientific evidence on delayed antimicrobial prescription as a measure to decrease antibacterial consumption in ARTI management has been mounting.[*11] 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.[92-94]

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 seven to 10 days.[13] However, when double-sickening occurs with worsening symptoms following an illness that was initially improving, secondary bacterial infections need to be considered.[56,57]

*[11] Refer to 5. Appendix (2)

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.

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 three 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 three 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 two to three 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 three 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.[95-96] 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.

5. Acute Diarrhea

(1) What is Acute Diarrhea?

Acute diarrhea is defined as the passage of unusually loose or watery stools, at least three or more times above baseline in a 24-hour period, lasting less than 14 days.[97,98] 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.[99] Acute infectious diarrhea may be associated with nausea, vomiting, abdominal pain, abdominal distention, fever, bloody stool and tenesmus.[98] Acute infectious diarrhea is referred to as "gastroenteritis" and "enteritis" and vomiting may be the dominant symptom with diarrhea less prominent.[98]

(2) Epidemiology of Acute Diarrhea

A patient census report conducted by MHLW in October 2020, off-peak for diarrheal diseases, estimated that there were 16 patients presenting with intestinal infectious diseases[*12] per 100,000 populations per day.[5]

The etiology of acute diarrhea is mostly viral infections,[100] such as norovirus and rotavirus.[101] In Japan, voluntary vaccination for rotavirus started in 2011, and became a routine vaccination in 2020. After the start of voluntary vaccination, the incidence of rotavirus diarrhea has been decreasing.[103]

Bacteria that can cause acute diarrhea include non-typhoidal *Salmonella* spp., *Campylobacter* spp., enterohemorrhagic *Escherichia coli* (EHEC), and *Vibrio* spp.,[100] 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.[104] *Clostridioides difficile* is also in differential if a patient has recent exposure to antibacterial agents.[104] It is notable that typhoid fever and paratyphoid fever rarely cause diarrhea.[105]

(3) Diagnosis and Differential Diagnosis 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.[100] In particular, if vomiting is dominant, viral illness and food poisoning due to toxins are more likely.[106] 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.[106]

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.[107,108] Since a study[109] 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.

*12 "Intestinal infectious diseases" represent A00 to A09 according to ICD10.

During history taking, it is important to consider the characteristics (watery or bloody) and severity*13 of the diarrhea.[98] Particularly, returning travelers (especially from developing countries) who develop severe bloody diarrhea with total disability and body temperature of ≥38°C or watery diarrhea with resultant moderate physical disability with onset of one week after travel may have bacterial enteritis, such as typhoid fever, Non-typhoidal *Salmonella* enteritis, *Campylobacter* enteritis and ETEC, or amebic dysentery.[98,110]

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.[111] 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 diagnosis of bloody diarrhea includes EHEC, intussusception, Meckel's diverticulum and upper GI bleeding.[112,113]

(i) Acute diarrhea due to viruses

Acute diarrhea due to viral infections includes rotavirus, and norovirus in adults.[100,106] Food exposure to undercooked bivalves and contaminated with norovirus is well known as a mode of transmission of norovirus infection, but human to human transmission is possible.[114] The incubation period of norovirus infection is generally half a day to two days. The illness often starts with vomiting, followed by watery diarrhea.[115] Vomiting and diarrhea usually resolve within a day and within two to three days, respectively, but the symptoms may persist over seven days to 10 days.[116,117] Fever is often absent or, if any, resolves within two days,[116] so if fever lasts longer than two days, a different etiology other than viral infection needs to be considered.

A rapid antigen test for norovirus*14 is approved under the Pharmaceutical Affairs Law, and its sensitivity has improved up to 87.4% to 93.1% recently.[118-121] 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 three years old.

*13 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

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

(ii) Acute diarrhea due to bacteria

Those with acute diarrhea due to bacteria tend to develop severe abdominal pain, high fever (≥38°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.[116,122,123]

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.[92]

For children, it is rare to require urgent laboratory tests including stool culture, 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.[124]

Table 6. Common Food Source and Incubation Period of Acute Diarrhea and Food Poisoning – Created from References 116, 122 and 123

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

(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 symptomatic relief are ensured whether the etiology is viral or bacterial.[98,100] It is important to assess dehydration by checking vital signs and orthostatic hypotension, to recommend as much oral fluid intake as possible,[98,100] 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.[98,125]

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).[98,100] JAID/JSC suggest antibacterial therapy for the following situations[100]:

- 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.[112]

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.

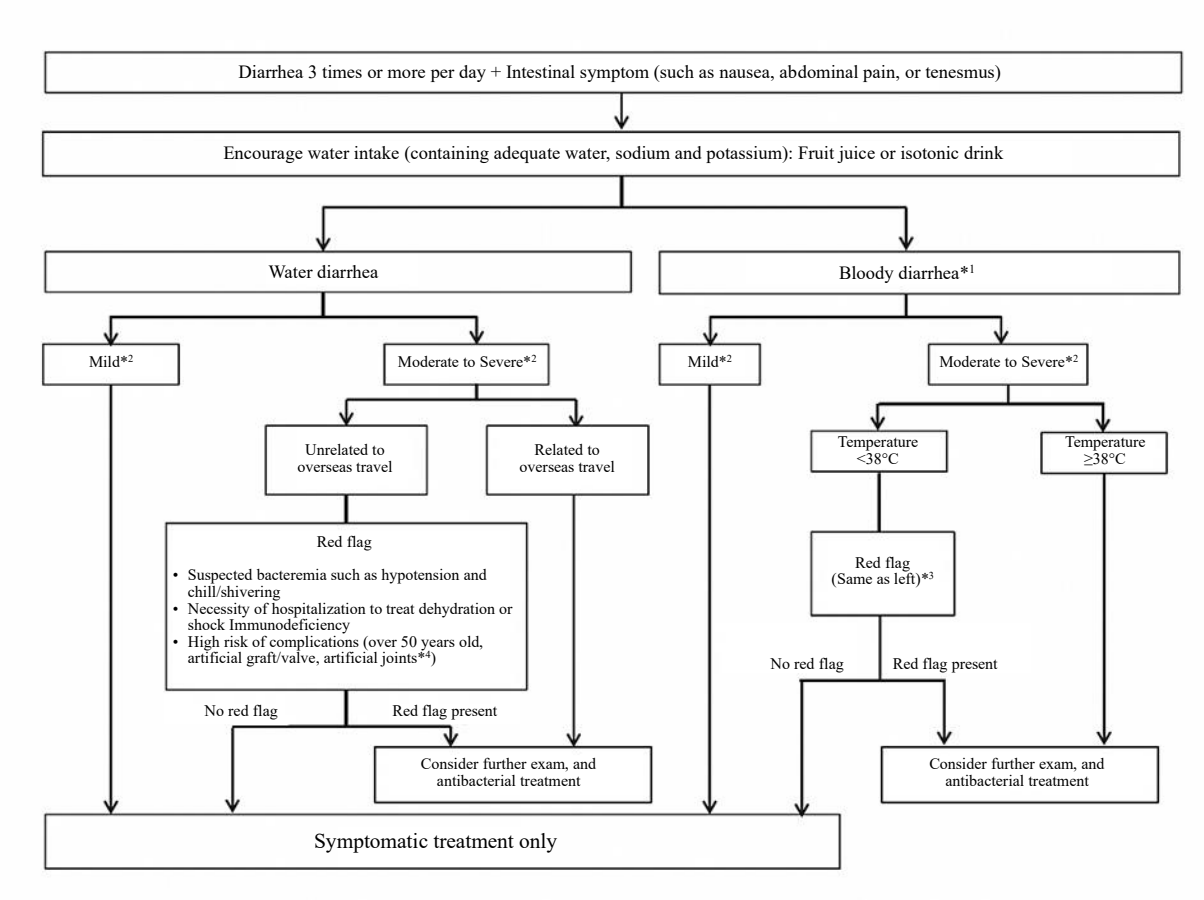

Figure 4. Flowchart of Diagnosis and Treatment of Acute Diarrhea

(Target Populations: Children of School Aged to Adults, Modified from Reference 98)

*1 Macroscopically containing blood

*2 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

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

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

(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.[112] 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 > two seconds*[15]; (2) Dry mucous membrane; (3) Absence of tears; and (4) Change in systemic condition.[126] 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.[14] ORS is a standard therapy for acute diarrhea.[97,112] In

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

addition to its effectiveness, blood access is not required, so ORS is recommended to prevent dehydration or treat mild to moderate dehydration.[97,112]

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 (50 mL/kg to 100 mL/kg for mild to moderate dehydration).[112]

Of note, evidence on anti-emesis for vomiting and antidiarrheals for diarrhea is scarce and neither is recommended.[112]

(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.[100,112] Even if the cause of acute diarrhea is considered bacterial, most are self-limiting and antibacterial therapy is not required.[100,112] 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.[112,127]

(iii) Non-typhoidal *Salmonella* gastroenteritis

- We recommend against antibacterial therapy for mild* *Campylobacter* enteritis in 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.[128] 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[129]:

- Age younger than three 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 three to seven 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 three to seven days as the second-line treatment are recommended.[100] (Ceftriaxone and azithromycin are not indicated strains on the label)

(iv) *Campylobacter* enteritis

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

* Mild = no change in functional activities

For *Campylobacter* infection, it is reported that antibacterial therapy can shorten the time to symptomatic relief by 1.32 days (95% CI 0.64 to 1.99)[130]. However, antibacterial therapy is not recommended by JAID/JSC except in severe cases.[100] Because most are self-limiting. Therefore, in this manual, we recommend against antibacterial therapy for mild *Campylobacter* enteritis in otherwise healthy patients.

It is notable that *Campylobacter* spp. resistant to fluoroquinolones have been increasing. According to the JAID/JSC guideline, oral clarithromycin 200 mg twice daily for three to five days and azithromycin 500 mg once daily for 3 days are recommended. Oral azithromycin 500 mg once daily for 3 days are recommended when antibacterial therapy is considered for severe cases.[100] (Azithromycin is not indicated for *Campylobacter* infection on the package insert)

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

Patients with EHEC often present with bloody diarrhea but fever is rare in the classic presentation.[129] Serotype O157 is the most common pathogen, but others include O26 and O111.[100] About 5% to 10% of those with EHEC infections develop hemolytic uremic syndrome (HUS) as a complication.[100]

For the management of EHEC, a review article does not recommend antimicrobial therapy as it may enhance toxin production and increase risk of HUS.[106] A meta-analysis showed antibacterial therapy is not associated with incidence of HUS (OR 1.33, 95% CI 0.89 to 1.99).[131] 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.[131] 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,[132,133] and the JAID/JSC guideline states: “At present, there is no consensus on antibacterial therapy.”[100]

Of note, antidiarrheals for the management of EHEC infections are not recommended as they increase the risk of HUS.[100,134,135]

(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 diagnosis 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) Collection of information	• Elicit the patient's concerns and expectations. • Actively ask for their opinion on antimicrobials.
2) Provide appropriate information	• Provide important information. – Diarrhea may last up to a week. – Most cases of acute diarrhea resolve spontaneously. – The body fights against pathogens, but it takes time to get better. • Provide correct information about antimicrobial agents. • It is important to take adequate nutrition, fluids, and rest.
3) Conclusion	• Summarize the previous exchanges and confirm understanding of the information. • Provide specific instructions on symptoms to watch for and when to see the doctor again.

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 "beneficial" bacteria in the gut. Therefore, management of dehydration and symptomatic relief plays the key role. Please take a sufficient amount of fluids. If you vomit, please take a small amount at a time. You have to make up for the amount lost with oral fluid intake.

Absorption of water from the gut is diminished 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, 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.[99,101] 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.

6. 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 1 mm). 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 the examples of viruses. A virus cannot 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.

	Bacteria	Viruses
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
Antibacterials (Antibiotics)	Effective	Ineffective

*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 "Multidrug 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.

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 three 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 one day after taking antibacterials, then think "Whether the antibacterials worked or not, the prescription was good because the patient improved anyway."

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.

(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.[92-94,136] 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.[137,138] 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[*16], and the third group was not given antibacterial agents (no antibacterial group), and their clinical outcomes were followed.[94]

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.[94]

In conclusion, DAP can decrease antibacterial consumption without increasing unfavorable outcomes such as complications, adverse effects and unscheduled patient visits.[92-94]

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.

*16 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 four days in principle, including the day of prescription and weekends, therefore, interventions conducted overseas may not always be applicable.

(i) Check list for clinical management of ARTI and acute diarrhea

Acute Respiratory Tract Infection 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	□ Vital sign				
	□ Temperature	(°C)		Highest temp. before consultation (°C)	
	□ Consciousness level	□ Clear	□ Abnormal	(JCS) or (GCS:)	
	□ Heart rate (pulses)	(/min)			
	□ Blood pressure	(/ mmHg)			
	□ Respiration rate □ SpO2	(breaths/min) (%)			
	□ Occupation				
	□ Surrounding people having the same symptom	□ No	□ Yes→	(Who/duration)	
	□ Past overseas trip	□ No	□ Yes→	Country:	Period: From to
	□ Underlying disease	□ No	□ Yes→	Disease name:	
	□ History of allergy to antibacterial agents	□ No	□ Yes→	Drug name:	Symptom/seriousness:

Symptom	□ Nasal	□ Mild	□ Moderate	□ Serious	(duration)
	□ Throat	□ Mild	□ Moderate	□ Serious	(duration)
	□ Cough	□ Mild	□ Moderate	□ Serious	(duration)
	□ Other symptoms	(severity and duration of symptoms)			

Diagnosis (including tentative diagnosis)	□ Cold		
	□ Acute rhinosinusitis	Seriousness	□ Mild □ Moderate □ Serious
	□ Acute pharyngitis	Red flag □ None	□ Worst pain ever; cannot swallow saliva; trismus; breathing difficulty □ Sudden onset, vomiting, scarce pharynx
		Streptococcus pyogenes test	□ No need of examination □ Negative □ Positive □ Under examination
	□ Acute bronchitis	Red flag □ None	□ Abnormal vital sign, finding in chest auscultation
		Bordetella pertussis test	□ No need of examination □ Negative □ Positive □ Under examination
	□ Others	Disease name	

Patient/family education when antibacterial agents are not prescribed	□ Worry and expectation of the patient □ Idea about antibacterial agents □ Future prognosis □ Importance of sufficient nutrition, water intake, and rest □ Confirmation of information understanding □ Symptoms to be noted and treatment

Doctor's name	

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	□ Vital sign				
	□ Temperature	(°C)		Highest temp. before consultation (°C)	
	□ Consciousness level	□ Clear	□ Abnormal	(JCS) or (GCS:)	
	□ Heart rate (pulses)	(/min)			
	□ Blood pressure	(/ mmHg)			
	□ Respiration rate □ SpO2	(breaths/min) (%)			
	□ Occupation				
	□ Surrounding people having the same symptom	□ No	□ Yes→	(Who/duration)	
	□ Past overseas trip	□ No	□ Yes→	Country:	Period: From to
	□ Past administration of antibacterial agents	□ No	□ Yes→	(Drug name/duration)	
	□ Underlying disease	□ No	□ Yes→	Disease name:	
	□ History of allergy to antibacterial agents	□ No	□ Yes→	Drug name:	Symptom/seriousness:

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

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

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

Patient education when antibacterial agents are not prescribed	□ Worry and expectation of the patient □ Idea about antibacterial agents □ Future prognosis □ Importance of sufficient nutrition, water intake, and rest □ Confirmation of information understanding □ Symptoms to be noted and treatment

Doctor's name	

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Infants and Toddlers

8. Characteristics and Precautions for Acute Respiratory Tract Infections in Children

- This manual covers the common cold/acute rhinosinusitis, acute pharyngitis, croup (laryngitis), acute bronchitis, and acute bronchiolitis, which account for most acute respiratory tract infections in children. It is intended for children (between three months old and before school age) without underlying illness, and management of severe cases is excluded.
  - Differentiate these diseases from group A hemolytic streptococcal pharyngitis, bacterial sinusitis, pertussis, and atypical pneumonia, which require antibacterial agents.
  - Secondary bacterial infections may prolong and exacerbate the clinical course and require re-examination as appropriate. However, prophylactic administration of antibacterial agents should not be performed.
- In children, age-specific risks should be considered.
  - Differentiation of respiratory tract infections in newborns and early infants under three months old includes serious illnesses and should be examined by a physician accustomed to pediatric practice.
  - For respiratory tract infections in infants over three months old, it is difficult to differentiate among the common cold, acute rhinosinusitis, and acute pharyngitis. Croup syndrome and acute bronchiolitis are characteristic syndromes in infants. Complication of otitis media should be noted. Severe bacterial infections (deep cervical abscess, bacterial epiglottitis, bacterial tracheitis, and bacterial pneumonia) should be considered at the time of diagnosis, and if the source of infection is unclear, urinary tract infection or occult bacteremia should be considered as differential diagnosis. If severe cough is observed or local spread is reported, the possibility of pertussis should be considered.
  - For children over school age, the common cold, acute rhinosinusitis, acute pharyngitis, and acute bronchitis can be differentiated and should be treated separately. (see “Children of school age to Adults”).
- Some therapeutic agents used to treat acute respiratory tract symptoms are known to have adverse reactions specific to children.

(1) Characteristics and Classification of Acute Respiratory Tract Infections in Children

Most of acute respiratory tract infections have viral etiology that resolve spontaneously.[1] In adults, the indications for treatment were determined by classifying acute respiratory tract infections into the common cold, acute rhinosinusitis, pharyngitis, or bronchitis based on the primary symptoms. The same approach can be applied to children of school age and older, since the risk of complications is low and they are able to report their symptoms. British guidelines dealing with infectious diseases in children also have a cutoff of five years of age.[2]

In contrast, it is challenging to classify acute respiratory tract infections in very young children since the inflammation of the respiratory tract due to viral infection extends from the upper to lower respiratory tract, nasal discharge and cough are often mixed, and complaints

of a sore throat are uncertain. Although the exact name of the disease is defined by the primary site of inflammation and pathogen, clinically, it is diagnosed as the common cold, acute rhinosinusitis, pharyngitis, croup syndrome, bronchitis, or bronchiolitis based on a combination of age, symptoms, and physical findings (Figure 1). COVID-19 should be considered in COVID-19 endemic areas. Although there are various notations and classifications in textbooks and literature, this manual clinically defines viral infections that do not require antibacterial agents from the viewpoint of proper use of antibacterial agents. In children, the differentiation of these viral diseases from bacterial infectious diseases and other pathological conditions is important in clinical practice.

	Predominant age (years)	Clinical features
	0 1 2 3 4 5	
Common cold/ Acute rhinosinusitis		Nasal discharge and cough to an equal extent
Acute pharyngitis		Findings and symptoms localized to the pharynx
Croup syndrome		Barking cough, inspiratory wheezing
Acute bronchitis		Symptoms mainly include cough
Acute bronchiolitis		From nasal discharge and cough to expiratory wheezing

Figure 1. Classification of Respiratory Tract Infections

(2) Relationship between Age and Infectious Diseases in Children

In children, the pathological conditions and frequency of complications differ depending on age, and medical treatment that considers the age of the child is necessary.

Infants under three months old	This manual does not apply to babies under three months old. In practice, they should be examined by a physician specializing in pediatric care.
Infants over three months old	For infants over three months old, upper respiratory tract symptoms such as nasal discharge or mild cough are broadly defined as the common cold or acute rhinosinusitis. In adults, a common cold is defined as an acute respiratory tract infection where nasal, pharyngeal, and lower respiratory tract symptoms are present simultaneously and to the same extent. However, it is difficult to clearly distinguish these symptoms in infants. Diseases specific to children include croup syndrome, characterized by a barking cough, laryngitis and bronchiolitis which causes wheezing as primary lower respiratory symptom. These diseases are generally viral in origin and do not require administration of antibacterial agents[3,4]; However, it is necessary to rule out a severe bacterial infection, and regardless of the presence of a viral disease, otitis media, occult bacteremia, and urinary tract infections should be considered. Also, even among young children, attention should be paid to group A β-hemolytic streptococcal infections, pertussis, and *Mycoplasma* pneumonia as indications for antibacterial agent administration.
Children over school age	In children over school age, it is possible to diagnose the common cold, acute rhinosinusitis, acute pharyngitis, and acute bronchitis based on symptoms and physical examination using the same disease definitions as in adults (see “Children of school age to Adults”). At the same time, attention should be paid to group A β-hemolytic streptococcal infections, pertussis, and *mycoplasma* pneumonia as indications for antibacterial agent administration.

(3) Differential Diagnosis of Acute Respiratory Tract Infections in Children

The common cold, acute rhinosinusitis, acute pharyngitis, croup syndrome, acute bronchitis, and acute bronchiolitis account for the majority of acute respiratory tract infections and, generally improve spontaneously. Bacterial infections which require antibacterial agents in daily practice include pharyngitis due to group A β-hemolytic *Streptococcus* spp. after three years of age, bacterial sinusitis caused by prolonged common cold or acute rhinosinusitis, otitis media, and pneumonia. There are diagnosed clinically and the indication for antibacterial agent is determined.

Meanwhile in children, it is necessary to exclude serious diseases or potentially serious pathological conditions (Figure 2). The first step is to exclude patients generally in poor condition. In pediatric practice, excluding severe infections from "somewhat ill" patients is often required is often required. The Pediatric Assessment Triangle (PAT) (Figure 3), which evaluates appearance, circulation to skin, and respiratory effort, is used as an objective index to prevent overlooking critically ill patients and to enable screening by nurses and paramedics.[5]

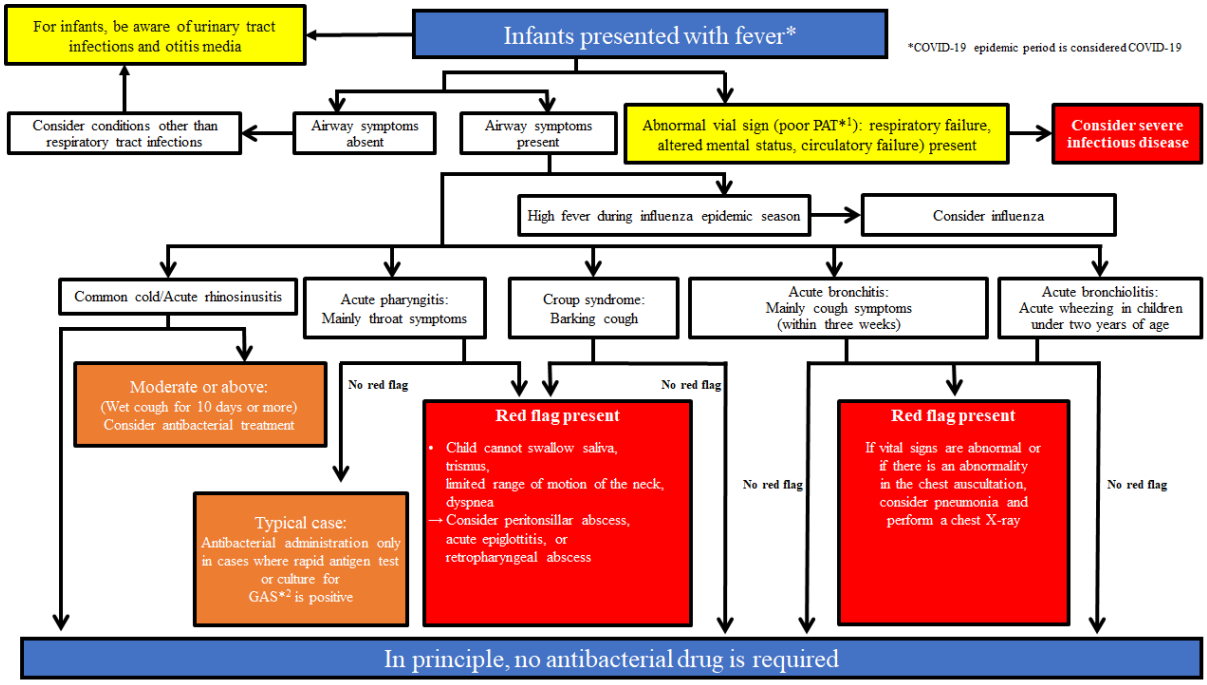

Figure 2. Medical Flow Chart for Pediatric Respiratory Tract Infections

*1 PAT; Pediatric Assessment Triangle, which evaluates appearance, circulation to skin, and respiratory effort

*2 GAS: group A β-hemolytic *Streptococcus* spp.

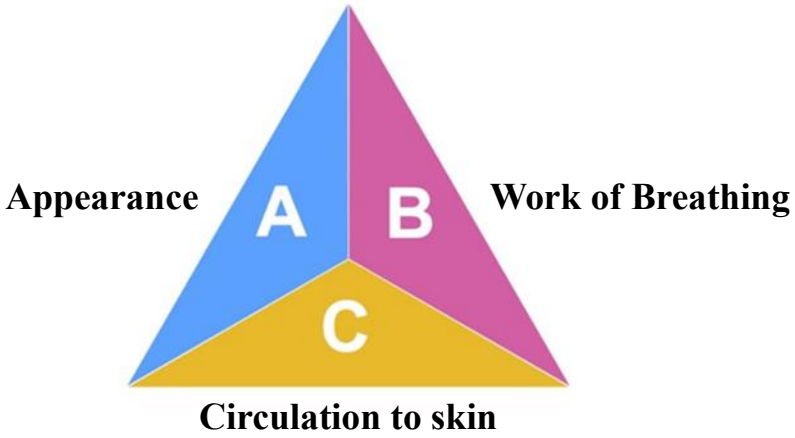

Figure 3. Pediatric Assessment Triangle (PAT)

Created with reference to Kazutaka Nishiyama, Usefulness of triage using PAT. Igaku-Shoin No. 2865. 2010.

In addition, even when an acute respiratory tract infection is diagnosed, it is highly necessary to exclude its complications and differential diagnosis from physical findings. Specifically, there are the examples of orbital cellulitis and mastoiditis as complications of bacterial sinusitis and otitis media, deep cervical abscess as a differential diagnosis of pharyngitis, acute epiglottitis and bacterial tracheitis as a differential diagnosis of croup syndrome, and complications of bacterial pneumonia in lower respiratory tract infections. Understand the normal clinical course and consider a closer examination if improvement is poor or if a bimodal course is observed. The indication for antibacterial agent treatment must be determined based on appropriate tests and diagnoses, and fever alone is not a simple indication for antibacterial agent treatment.

Furthermore, even when an acute respiratory tract infection is diagnosed, an infant may have a combination of different pathological conditions. Acute otitis media, urinary tract infections, and occult bacteremia are the most common in infants. Acute otitis media is excluded by assessing the eardrum findings as part of the physical examination. If the clinical course and findings are consistent with those febrile illnesses from other etiologies, urinary tract infection work ups examinations are not necessary. However, if high fever is present and there are no other findings, urinalysis should be considered. It has previously been reported that healthy infants aged 3–36 months presented with fever, that they develop bacteremia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, even in the absence of obvious clinical findings, and that approximately 7% develop serious infectious diseases, such as bacterial meningitis.[6] This condition is called occult bacteremia, and patients with a fever of 39.5°C or higher and hyperleukocythemia (15,000/μL) are considered to have a 5–10% risk of developing occult bacteremia. In the past, immediate antibacterial agent administration after blood cultures collection was recommended. However, the risk has been significantly reduced after the introduction of pneumococcal and *Haemophilus influenzae* type b (Hib) vaccines; thus, these procedures are not always necessary for vaccinated patients

It is important to identify bacterial infections based on careful interviews and medical examinations, to explain the medical condition and natural course of the disease to parents, and to provide information about indications of close follow up examination. Since this manual focuses on clarifying the pathological conditions that do and do not require antibacterial agents in outpatient pediatric care, it does not cover the treatment of bacterial

infections for which antibacterial agents are indicated. For that point, please refer to the guidelines provided by the academic society.

(4) Drugs to Be Cautious of Administering to Children

Among the drugs for acute respiratory tract infections, there are some that may have side effects specific to children. While most of the symptomatic drugs have no clear evidence, they are reported to have side effects. When using antibacterial agents, it is necessary to pay attention to the description in the package insert.

Table 1. Agents for which Pediatric-specific Adverse Effects are a Concern

Drug	Concerns
Co-trimoxazole	Low birth weight babies and newborns (less than 28 days old) are at risk of kernicterus and are therefore contraindicated.[7] (Generally avoid administration within two months after birth).
Ceftriaxone	Preterm infants and newborns with hyperbilirubinemia are contraindicated due to kernicterus; care should be taken due to crystallization in combination with calcium-containing infusion products.[8]
Macrolide	Oral administration during the neonatal period increases the risk of hypertrophic pyloric stenosis.[9] (Erythromycin in particular, but also reported in azithromycin).
Tetracycline	Not to be administered in children under eight years of age due to the risk of tooth discoloration, unless there are no other alternatives[10] (Tetracycline, minocycline, and doxycycline).
Antibacterial agents with a pivoxil group	Cases have also been reported in which hypoglycemia, convulsions, and encephalopathy occurred with hypocarnitinemia, leading to sequelae. (Cefcapene pivoxil [hydrochloride hydrate], cefditoren pivoxil, cefteram pivoxil, tebipenem pivoxil).
Fluoroquinolone	Joint disorders have been reported after administering to juvenile animals, and some drugs are contraindicated in children. (Ciprofloxacin, levofloxacin, and garenoxacin).
Antipyretic analgesics	These are associated with the development of acute encephalopathy in children with influenza and chickenpox. Refer to the Ministry of Health, Labour and Welfare's Manual for Management of Individual Serious Adverse Drug Reactions "Acute encephalopathy in children" (March 2011). (Acetylsalicylic acid, mefenamic acid, and diclofenac sodium, or common cold drugs)
Antihistamine	Reported to be associated with a risk of inducing febrile seizures and the development of acute encephalopathy. Refer to the Ministry of Health, Labour and Welfare's Manual for Management of Individual Serious Adverse Drug Reactions "Acute encephalopathy in children" (March 2011).
Dihydrocodeine	Contraindicated in the United States for children under 12 years of age since it metabolized to dihydromorphine, which has a strong respiratory depressant effect (Journal of the Japanese Society of Pediatrics 2018;122:1186-1190).
Theophylline preparation	Refer to the Ministry of Health, Labour and Welfare's Manual for Management of Individual Serious Adverse Drug Reactions related to the onset of acute encephalopathy, "Acute encephalopathy in children" (March 2011). http://www.info.pmda.go.jp/juutoku/file/jfm1104007.pdf There is some debate about the causal relationship with acute encephalopathy, although no conclusions have been reached.
Loperamide	Loperamide has been reported to cause intestinal obstruction in infants. It is contraindicated for children less than six months of age. Loperamide should not be administered to infants between 6 months and 2 years of age unless it is deemed unavoidable for treatment.

9. Various Theories on Acute Respiratory Tract Infections in Children

(1) Common Cold/Acute Rhinosinusitis

- Acute upper respiratory tract infection caused by a virus, characterized by nasal discharge and nasal congestion. It may also cause fever, muscle aches, headaches, coughs, sore throats, hoarseness, moodiness, sleep disorders, loss of appetite, vomiting, and diarrhea.[11]
- For common cold, rhinitis is the main symptom, it is typically accompanied by spontaneously resolving sinusitis, including acute rhinosinusitis.[11,12]
- Dehydration may be possible if patients have poor appetite or are unable to drink enough water, frequent oral rehydration is recommended (see section on acute diarrhea).

Recommendations for antibacterial agents

- Administration of antibacterial agents is not recommended for common colds and acute sinusitis and should not be administered prophylactically.
- Even if the initial diagnosis is common cold/acute sinusitis, cases in which the respiratory condition worsens, wet cough lasts for 10 days or more, or the condition re-exacerbates after remission should be differentiated from suppurative sinusitis, bacterial pneumonia, or suppurative otitis media, which would be indications for antibacterial agents. If either a respiratory tract symptom or otitis media is suspected, administration of amoxicillin hydrate should be considered as an initial treatment. If atypical pneumonia is suspected, macrolides can be administered, if necessary.

(i) What is the common cold?

In children, the common cold may cause various symptoms, including fever, hoarseness, headache, muscular pain, moodiness, sleep disturbances, loss of appetite, vomiting, and diarrhea, in addition to airway symptoms, such as cough and sore throat.[11] Since infants often develop acute rhinosinusitis, it is difficult to clearly distinguish between the common cold and acute rhinosinusitis, and clinically, there is little significance in differentiating these illnesses. It is necessary to discern the presence of secondary bacterial infections.

(ii) Epidemiology of the common cold

Children, especially infants, suffer from the common cold six to eight times a year on average, and 10–15% of children experience it at least 12 times a year, although the incidence decreases with age.[1,11] The common cold occurs throughout the year, but most often around winter. Children in group childcare are more susceptible than those being cared for at home. Transmission routes are contact and droplet infection,[13] and symptoms often appear within an incubation period of one to three days after infection.[13]

(iii) Diagnosis and differentiation

A common cold is suspected based on acute upper respiratory tract symptoms, such as runny nose and mild cough, and the clinical diagnosis is based primarily on symptoms and physical findings. The history of contact with people with symptoms of common cold is also important.[4]

Symptoms generally peak at two to three days and improve spontaneously. They often disappear within 10 days, although mild symptoms may persist for two to three weeks.[1] If

there is a trend toward improvement followed by a relapse or if fever persists for three days or longer, a secondary bacterial infection should be considered. In addition, acute bacterial sinusitis, for which antibacterial agent use is indicated, often has prolonged symptoms for 10 days or more.[13,14]

It is also important to exclude differential diagnosis.[11] Differential diagnosis include allergic rhinitis, lower respiratory tract inflammation, foreign bodies in the respiratory tract, group A β-hemolytic streptococcal infection, and pertussis.[11] In the common cold, auscultation is not accompanied by laryngeal stenosis sounds such as stridor and pulmonary breath sounds such as wheezing (wheeze) and rales (crackles), which helps in the differentiation.

Children are prone to dehydration, because of which it is important to monitor their fluid intake, check for urination, and evaluate for physical findings of dehydration.[15]

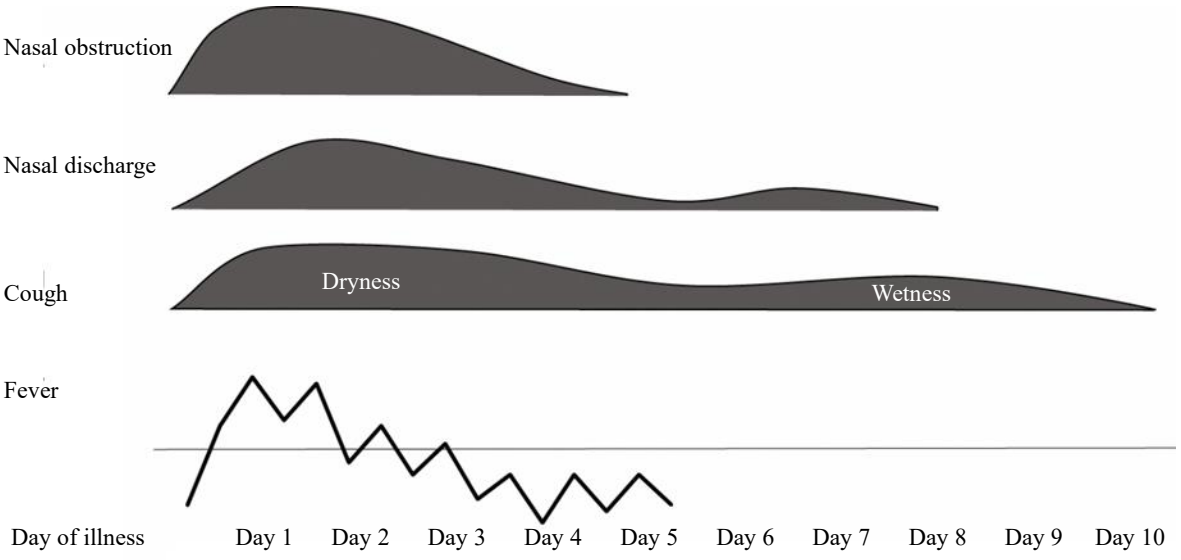

Figure 4. Natural Course of the Common Cold

(iv) Treatment

For fever, sore throat, and others, symptomatic treatment with antipyretic analgesics, such as acetaminophen, should be administered as appropriate.[12,16] In addition, parents/guardians should be advised on oral rehydration to prevent dehydration.

(v) Antibacterial treatment

It has been established that antibacterial agents are not necessary for the common cold or acute rhinosinusitis.[14,17-23] Regarding the administration of antibacterial agents to prevent complications of bacterial infections during the course of viral infections, multiple randomized controlled studies compared symptom improvement with or without antibacterial agent administration in patients with mild common cold, acute rhinosinusitis, pharyngitis, or bronchitis, and the results have shown no significant difference.[17] Moreover, a systematic review of 12 randomized controlled trials (RCTs) of children aged 0–12 years reported that antibacterial agent treatment for upper respiratory tract infection did not alleviate symptoms or reduce complications.[24] In a retrospective study of patients with mastoiditis, peritonsillar abscess, or pneumonia, it was estimated that more than 2,500 patients with nonspecific upper

respiratory infections would need to theoretically be treated with antibacterial agents to prevent a serious bacterial infection.[25] Therefore, as a general rule, it is recommended not to administer antibacterial agents for preventive purposes.

Antibacterial agents may be given to children with purulent nasal discharge. However, a systematic review[17] summarizing randomized controlled studies that examined the efficacy of antibacterial agents compared with a placebo group (placebo drug) for patients with acute upper respiratory tract infections or purulent nasal discharge found no difference in symptom improvement by day seven in the six studies on children and adults or in the two RCTs on children. In addition, the frequency of adverse events in the four RCTs in adults showed a higher relative risk of 2.62 (95% confidence interval [CI], 1.32–5.18) in the antibacterial agent-treated group.[17] In two RCTs in children, the relative risk was 0.91 (95% CI, 0.51–1.63), showing no difference.[17] Furthermore, four RCTs showed no significant difference in the purulent nasal discharge, with a relative risk of 1.46 (95% CI, 1.10–1.94). [17] The most recent randomized controlled trial in children aged 2-11 years also reported no difference in the usefulness of antimicrobial agents in the presence or absence of yellow or green nasal discharge. Therefore, the presence of purulent nasal discharge does not, in principle, require antibacterial agents.[26,27]

Criteria by which antibacterial agent administration is considered inappropriate

Patients who meet all of the following do not need antibacterial agents at that point in time:

- Nasal discharge
- Nasal congestion ± fever ± mild cough
- No respiratory problems
- Good general condition
- The duration of the fever is within three days
- The duration of nasal discharge is within 10 days
- The duration of a wet cough is within 10 days (two weeks)

It is important to recognize that the common cold and acute rhinosinusitis may be prolonged and can cause purulent complications. Acute rhinosinusitis is usually observed in school aged children and above with developed sinuses and is accompanied by redness of the cheeks, pain, and nasal congestion.[28] Moreover, in studies including patients with a wet cough for 10 days or longer (i.e., pediatric patients with rhinosinusitis or persistent bronchitis), improvement of symptoms by the administration of antibacterial agents was observed.[29] In two studies involving 140 patients, the odds ratio for clinical treatment failure in the antibacterial agent-treated group compared with that in the non-treated group was 0.13 (95% CI, 0.06–0.31).

Conditions for which antibacterial agent administration should be considered

If any of the following applies, the patient's condition is determined to be persistent or severe:

1. Nasal discharge, post-nasal drip, or cough during the day that lasts for 10 days or longer.
2. ever of 39°C or higher and purulent nasal discharge for at least three days with serious illness.
3. common cold, followed one week later by a re-occurring fever or worsening of nasal discharge and cough during the day.

The guidelines of the Japanese Rhinologic Society indicate amoxicillin hydrate 40 mg/kg/day in three divided doses for 7–10 days as an example of a prescription for acute rhinosinusitis.

4. Patients with complications (purulent otitis media, bacterial pneumonia, urinary tract infection, bacteremia, and others) for which other antibacterial agents are appropriate. In principle, amoxicillin hydrate is often the first choice, although in cases of atypical pneumonia, if necessary, macrolides can be considered.

(vi) Explanation to patients and parents

International literature has shown that the satisfaction of patients who have a cold and their parents/guardians is more dependent on the reassurance they receive from the explanation of the condition than on the prescription of any antibacterial agents.[30] The key point of the explanation is to provide specific guidance. This includes providing an explanation that in many cases, the condition will heal spontaneously and providing guidance on symptomatic treatment, which can be performed at home. Tachypnea, orthopnea, labored breathing, decreased consciousness, an inability to drink water, no urination for more than half a day, and sluggishness are all indicators that should prompt another visit to a medical institution.

Example of explanation from doctor to patient: In the case of a common cold

- This is a “cold” caused by a virus. Symptoms of a “cold” will improve spontaneously but may last for one week or two until they disappear completely. If your child is relatively healthy, hydrated, and urinates sufficiently, he/she should rest at home until the fever subsides and his/her symptoms improve.
- Antibacterial agents do not work against viruses. If a child is administered the drug even though he/she does not need it, he/she may develop a problem in the future by creating antimicrobial resistant bacteria which antibacterial agents do not work against, or he/she may develop diarrhea as a side effect of the drug and may become sick.
- If your child has a fever, he/she should rest and wear light clothing such that heat does not build up. However, if your child’s limbs are cold or he/she has chills, he/she should be kept warm. If your child has a high fever and feels sluggish, you may use an antipyretic, such as acetaminophen. Lowering the fever may help your child to have a better appetite and to drink more fluids. Give him/her water that contains salt. If your child has a stuffy nose, he/she can blow his/her nose, or if he/she cannot, wipe it off and use a pillow to raise the upper body.
- Occasionally, a child may have otitis media, sinusitis, or pneumonia. If your child continues to have a fever for three days or longer and feels sick or if his/her symptoms worsen, please see the doctor again.
- If your child’s breathing is particularly labored (breathing on his/her shoulders or breathing is difficult and he/she cannot lie down), if he/she is unconscious, if he/she has not been able to get enough water and not peed for more than half a day, or has been sluggish, please visit a doctor immediately.

<Literature Search Method>

For information on the common cold and acute rhinosinusitis in children, see Nelson Textbook of Pediatrics (20th ed), Feigin and Cherry's Textbook of Pediatric Infectious Diseases (7th ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (8th ed), the Japanese Society for Pediatric Infectious Diseases (JSPID), the Japanese Association for Infectious Diseases/Japanese Society for Chemotherapy (JAID/JSC), the Infectious Diseases Society of America (IDSA), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), and other expert groups, we conducted a literature search for the second and subsequent editions to reflect the latest evidence while taking into account the recommendations of current practice guidelines.

<Search formula in MEDLINE>

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Results 42 hits. (September 4, 2018 - January 31, 2023)

rhinosinusitis[All Fields] AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2018/09/04"[PDat] : "2023/01/31"[PDat] AND (English[lang] OR Japanese[lang]) AND ("infant"[MeSH Terms] OR "child, preschool"[MeSH Terms]))
Results 20 hits. (September 4, 2018 - January 31, 2023)

<How to search for Japanese-language articles in Medical Journal>

Common Cold, 2008-2018, excluding case reports, original papers, excluding conference proceedings, meta-analyses, randomized controlled trials, quasi-randomized controlled trials. Comparative Trials, Pediatric
Results 10 hits. (September 4, 2018 - January 31, 2023)
Acute Rhinosinusitis, 2008-2018, excluding case reports, original articles, excluding conference proceedings, meta-analyses, randomized controlled trials, quasi-randomized controlled trials. Comparative Trials, Pediatric
Results 3 hits. (September 4, 2018 - January 31, 2023)

(2) Acute Pharyngitis

- Acute pharyngitis is an acute inflammation of the pharynx due to infectious and non-infectious factors.
- In acute pharyngitis, it is important to determine whether the infectious etiology is group A β-hemolytic *Streptococcus* spp. (GAS) by combining clinical findings and test results.
- It is recommended that no antibacterial agents be administered for acute pharyngitis in which GAS is not detected by a rapid antigen or culture test.
- When administering antibacterial agents for acute pharyngitis in which GAS is detected by a rapid antigen or culture test, the following antibacterial agents are recommended.

Recommended antibacterial agents

- Amoxicillin hydrate, oral administration for 10 days

(i) What is acute pharyngitis?

Acute pharyngitis is an acute inflammation of the pharynx with redness, swelling, exudates, ulcers, and blisters. Factors contributing to inflammation of the pharynx include non-infectious and infectious factors. Non-infectious factors include environmental (e.g., tobacco, pollutants, and allergens) and dietary (e.g., hot foods and irritants) factors. The pharynx is also a site for inflammation caused by auto-inflammatory diseases, such as periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome and inflammatory bowel disease. A history of illness and physical examination are used to distinguish between infectious and non-infectious factors. The most common infectious etiology is a virus, in both children and adults.[31,32] The most common bacterial factor is GAS.

In the treatment of acute pharyngitis, it is important not to overlook acute upper respiratory tract obstructive diseases, such as acute epiglottitis, cervical abscess, and peritonsillar abscess. Spontaneously resolving viral pharyngitis and treatable bacterial infectious diseases (e.g., GAS pharyngitis) should be differentiated and a followed up appropriately.

(ii) Epidemiology of acute pharyngitis

Among pediatric patients diagnosed with acute pharyngitis, GAS-positive cases are reported in 16.3%[32] of cases in Japan and 27% of cases in other countries.[31] In contrast, not all GAS detected in pharyngeal cultures are the causative organisms of acute pharyngitis, and 10–30% of asymptomatic infants are carriers of GAS.[33] Acute pharyngitis due to GAS is more common in children between the age of 5–12 years and rare in children under the age of three years.

(iii) Diagnosis and differentiation

The purpose of diagnosing acute pharyngitis is to determine if GAS is the causative organism. It is difficult for children to accurately complain of a sore throat or pain upon swallowing; thus, it is important to suspect pharyngitis when there are nonspecific symptoms, such as fever with a headache and vomiting. A clinical study evaluating the likelihood ratios of GAS pharyngitis symptoms in children (3–18 years old) reported a relatively high positive likelihood ratio for scarlet fever-like rashes and petechiae on the soft palate.[32] The

differentiating points between viral pharyngitis and GAS pharyngitis are shown in the table below.

Table 2. Group A β-hemolytic Streptococcal Pharyngitis and Viral Pharyngitis

GAS pharyngitis	• Sudden onset • Fever • Headache • Nausea/vomiting • Abdominal pain • Anterior cervical lymphadenopathy with tenderness • Scarlet fever-like rash
Viral pharyngitis	• Conjunctivitis • Cough • Hoarseness • Nasal discharge • Muscle pain • Diarrhea

The Centor criteria are also used in children, although the positivity rate at the absolute highest score (4 points) is 68%.[35] Determining that GAS is the cause of acute pharyngitis based on the score alone leads to overdiagnosis and overtreatment. Therefore, laboratory diagnosis is useful for more accurate diagnosis.

Table 3. Centor Criteria

Temperature ≥38°C	1 point
Absence of cough	1 point
Swollen, tender anterior cervical nodes	1 point
Tonsillar swelling or exudate	1 point

It is important to avoid antimicrobial treatment for non-GAS pharyngitis for GAS carriers due to over-testing and non-GAS pharyngitis caused by viruses with a similar clinical picture. For that purpose, it is important to make a comprehensive diagnosis (i.e., to examine the patient and to perform appropriate tests only in cases in which the prior probability of GAS pharyngitis is judged to be high). In addition, since GAS pharyngitis is rare in children under three years of age and the complications of secondary acute rheumatic fever (ARF) are uncommon, it is recommended not to examine these children, except when they are in close contact with GAS pharyngitis patients.[36]

The basic principles of the GAS test are 1) review the test indications (as seen in the table below), 2) test for children with indications, and 3) no culture is required if the rapid test is positive. If the test is performed on children for whom the test is not indicated, carriers will be detected and will consequently lead to excessive use of antibacterial agents. It is also recommended not to test if the clinical probability of viral infection is high (i.e., if the child has a cough or runny nose with which the prior probability of GAS pharyngitis is evaluated to be low).

Table 4. Indications for GAS Rapid Antigen Test

Those that satisfy 1), 2), and 3) below. 1) There are symptoms and signs of acute pharyngitis, and acute GAS pharyngitis is suspected. 2) There are physical findings of acute GAS pharyngitis. 3) In principle, the child is three years of age or older (this does not apply in cases where it is prevalent in the surrounding area).

The test characteristics of the GAS rapid antigen test are 70–90% sensitivity and 95% specificity.[37] The sensitivity varies from study to study, while the specificity is almost consistent. Owing to the high specificity, it can be said that no additional culture test is necessary if the test result is positive. In contrast, if the test result is negative, the positivity rate does not improve even if the test is repeated, and thus, it is impractical to repeat the test.[38]

Culture tests are the standard method for the diagnosis of GAS pharyngitis.[37] However, during an epidemic, GAS is found to be detected in approximately 20% of people, and since the situation lasts for more than six months, it is difficult to distinguish viral pharyngitis in GAS carriers. For this reason, the culture test should be performed only when the rapid antigen test is negative but the actual clinical likelihood of GAS is high.

Important differential diagnosis (red flag)

- Acute upper respiratory tract obstructive diseases, such as acute epiglottitis, cervical abscess, and peritonsillar abscess.
  The patient's general condition deteriorates rapidly, and wheezing, abnormal posture (sniffing or tripod position), and hypersalivation are conspicuous. In these diseases, suffocation can occur in a short time, and thus it is important to keep the child in a comfortable position to avoid subjecting him/her in stressful conditions during blood sampling, X-ray examinations, and oral examinations, as well as to promptly transfer the child to a facility that can safely secure his or her airway.

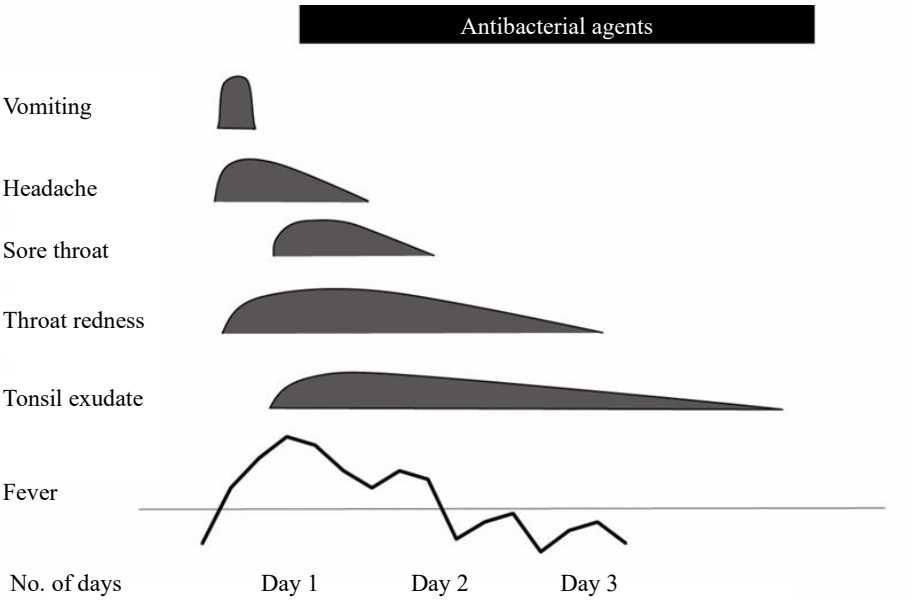

Figure 5. Natural Course of Acute Streptococcal Pharyngitis

(iv) Antibacterial agents treatment

As previously mentioned, most cases of acute pharyngitis are viral and do not require antibacterial agents. On the other hand, there are reports that unnecessary use of antibacterial agents can be reduced by limiting antibiotic prescriptions to only cases where GAS is detected by rapid diagnostic or culture tests.[39]

Therefore, this manual recommends that antibacterial agent therapy should be considered only when GAS pharyngitis is strongly suspected and a rapid antigen test or culture test is positive.

The treatment of GAS pharyngitis is described below.

1) GAS pharyngitis treatment objectives

There are three objectives of antibacterial agent use for acute pharyngitis caused by GAS.

The primary objective is the prevention of ARF by GAS eradication. Initiation of antibacterial agents within nine days of GAS pharyngitis onset has proven effective in preventing ARF.[40]

The second objective is rapid symptom relief. Generally, symptoms due to GAS pharyngitis resolve in three to four days, although antibacterial agents shorten the duration of symptoms by half a day to one day.[41]

The third objective is to prevent transmission of infection to the surrounding people. Early antibacterial agent initiation can reduce transmission to the surrounding people.[42] As a result, social losses can be avoided because parents can return to work earlier.

2) First-line antibacterial agents for GAS pharyngitis

GAS is susceptible to all penicillins. Penicillins are recommended in the guidelines of the IDSA.[43] In the 2022 Japanese Guidelines for Pediatric Respiratory Infectious Diseases, amoxicillin hydrate or benzathin benzylpenicillin are recommended as the first-line antimicrobial agent for GAS pharyngitis.[44]

3) Antimicrobial dose and dosing interval for GAS pharyngitis

Japan's Guidelines for the Treatment of Pediatric Respiratory Infectious Diseases from 2017 states that the pediatric dose of amoxicillin hydrate is 30–50 mg/kg/day in two or three divided doses.[44,45]

Adherence is important in pediatric outpatient antibacterial agent therapy. In the United States, 50 mg/kg (maximum 1 g) once daily for 10 days is also recommended. A single-center RCT study of 353 children aged 5–12 years in New Zealand found amoxicillin hydrate once daily to be non-inferior to penicillin V twice daily.[46] A non-inferiority study comparing amoxicillin hydrate twice daily with once daily has also demonstrated non-inferiority of the once daily treatment.[47] Once daily amoxicillin hydrate appears favorable in terms of adherence. However, since only 10% or 20% amoxicillin hydrate products are available in Japan to realistically administer 1,000 mg of amoxicillin hydrate once daily, 10 g of the 10% product (5 g if it is the 20% product) would need to be administered, which is a large amount. Therefore, since it is practically difficult, the above-mentioned dosing method is recommended in this manual.

4) Duration of antibacterial agent therapy for GAS pharyngitis

The recommended duration of treatment with penicillins for GAS pharyngitis is 10 days. A 2012 Cochrane review of antibacterial agent therapy for GAS pharyngitis in children comparing 10 days of treatment with penicillins with four to six days of treatment with non-penicillin antibacterial agents found a significantly faster rate of symptom resolution but higher relapse rates in the short-term treatment group. Side effects were less frequent in the penicillin group, and the rate of complication with rheumatic fever and nephritis was not significantly different.[48] In a retrospective cohort study comparing the eradication and recurrence rates after GAS pharyngitis was treated with amoxicillin hydrate for 10 days or cephalosporin antibacterial agents for five days, the eradication rate was significantly higher in the amoxicillin hydrate group (91.7%, but 82.0% in the cephalosporin antibacterial agents group, p=0.01) and there was no difference in the recurrence rate.[49]

5) Alternative to antibacterial agents for GAS pharyngitis

Clindamycin is recommended in cases of severe penicillin allergies (e.g., anaphylactic shock). [43] However, in Japan, clindamycin resistance of GAS is as high as 24% (the resistance rate to macrolides is also as high as 61%),[50] and when it is administered, it should be used with caution, referring to susceptibility test results and others. Other alternatives are being investigated, but they do not clearly outperform penicillins in efficacy.[51]

In summary, antibacterial agent treatment for acute pharyngitis is as follows:

- Do not administer antibacterial agents for acute pharyngitis with the exclusion of GAS
- If acute pharyngitis due to GAS is diagnosed:

  <u>First choice</u>

  Amoxicillin hydrate 30–50 mg/kg/day (maximum 1000 mg/day),
  orally administered twice or three times daily for 10 days

  Benzylpenicillin Benzathine 50,000 units/kg/day (maximum 1.6 million units/day),
  orally administered three or four times daily Oral for 10 days

  <u>If there is a severe penicillin allergy</u>

  Clindamycin 15 mg/kg/day (20 mg/kg/day for severe infections; up to 900 mg/day),
  orally administered three times daily for 10 days

  Clarithromycin 15 mg/kg/day (up to 400 mg/day),
  orally administered twice daily for 10 days.

(v) Explanation to patients and parents

Example of explanation from doctor to patient: Acute pharyngitis

If acute pharyngitis is diagnosed and GAS rapid antigen test results are positive, antibiotics must be taken for 10 days as prescribed by your doctor to prevent the serious complications of rheumatic fever. Do not discontinue this medicine at your own discretion even after the child's fever has subsided.

In acute pharyngitis caused by GAS if 24 h have passed since starting antibacterial agents and if the patient's general condition is good, he/she can go to school or preschool.

If acute pharyngitis is diagnosed as not being caused by GAS: most of the causes are viral, because of which it is important to pay attention to the following signs of serious illness, to use antipyretic analgesics and other drugs to relieve symptoms, and to rest well. Symptoms usually improve within 2–3 days to 10 days.

If the child has symptoms, such as severe sore throat or drooling, the respiratory tract (airway) may be narrowed; please take the child for a visit to the emergency room.

<Literature search methods>

With regard to acute pharyngitis in children, we conducted a literature search to reflect the latest evidence based meta-analyses, statistical reviews, and randomized comparative controlled studies while considering the recommendations of current medical guidelines by groups of experts, such as the JSPID, JAID/JSC, IDSA, and ESCMID.

<Search formula on MEDLINE>

"Pharyngitis"[Mesh] AND ((Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Clinical Study[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2018/08/14"[PDat]: "2023/01/31"[PDat] AND (English[lang] OR Japanese[lang]))
The result was 334 hits. Filtering this by CHILDREN (birth-18 years) resulted in 132 hits.
(August 14, 2018 - January 31, 2023)

<How to search for Japanese-language articles in Medical Journal>

Pharyngitis, 2007-2018, excluding case reports, excluding conference proceedings, meta-analyses, randomized controlled trials, quasi-randomized controlled trials. Comparative trials, pediatric
The result was 38 hits.
(August 14, 2018 - January 31, 2023)

(3) Croup Syndrome

- A disease that cause inspiratory wheezing (stridor), elevated cough (barking cough cough), and hoarseness, primarily due to laryngeal obstruction caused by a viral infection.[52]
- It is often accompanied by rhinitis or pharyngitis, which often worsen rapidly at night and resolve spontaneously in a few days to a week.[52]
- It is important to exclude acute epiglottitis, bacterial tracheitis, foreign body in the larynx, or allergic laryngeal edema, which can lead to impending airway obstruction.[4]
- Adrenaline inhalation and dexamethasone are indicated for children with inspiratory wheezing at rest.

Recommendations for antibacterial agents

- It is recommended not to administer antibacterial agents for croup syndrome.

(i) What is croup syndrome?

Croup syndrome is a disease caused by inflammation of the larynx due to acute viral infection and presents with symptoms and findings, such as a characteristic barking cough and inspiratory wheezing due to acute laryngeal stenosis.

(ii) Epidemiology of croup syndrome

Historically, diphtheria was the cause of croup syndrome, although it has been eliminated due to widespread vaccination.[53] Currently, the major causative agents are viruses, mainly parainfluenza viruses, which are common in the age group between three months and five years of age and are prevalent in the fall and winter when viruses are widespread.[52,54] SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) is a SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) may be a factor. Annually, it manifests in 2–6% of infants and repeatedly affects 5%[54] of them. The routes of infection are contact and droplet infection. The major cause of acute epiglottitis, an important differential diagnosis, was *H. influenzae* type b, which has been dramatically reduced with the widespread use of the Hib vaccine.[4]

(iii) Diagnosis and differentiation

Croup syndrome is clinically diagnosed based on symptoms and physical findings. Preceding symptoms, such as nasal discharge, cough and fever, often occur within the first 12–48 h.[54] It is accompanied by a characteristic, high-pitched cough (barking cough). Hoarseness is common, and when the symptoms progress, inspiratory wheezing is heard even when the patient is at rest.[4]

Important differential diagnosis (red flag)

In addition to acute epiglottitis, it is important to exclude other diseases that cause impending upper airway obstruction, such as bacterial tracheitis, foreign body in the larynx, and allergic laryngeal edema.

Strong obstruction may be accompanied by tachypnea, orthopnea, respiratory depression, and decreased oxygenation, and the child may be placed in a sniffing or tripod position (see Pharyngitis) to avoid airway obstruction. Examination should be avoided as

much as possible because symptoms of airway obstruction may be exacerbated by crying of the infant or irritating the larynx with tongue pressors. In principle, it is a clinical diagnosis, and checking pencil signs on the frontal and lateral radiographs of the neck is not mandatory.[2]

For the differential diagnosis, inspect for episodes of accidental ingestion of a foreign body. Lateral radiographs may be helpful in the differentiation of acute epiglottitis, although airway management should be prioritized over testing.[52]

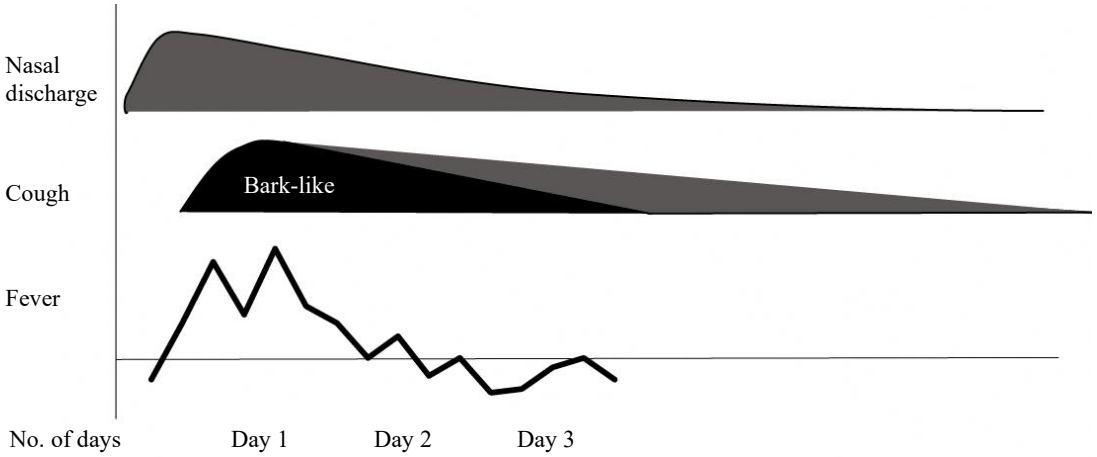

Figure 6. Natural Course of Croup Syndrome

(iv) Treatment methods

Mild disease does not require treatment. If inspiratory wheezing is heard at rest, adrenaline inhalation or oral dexamethasone (0.15–0.6 mg/kg/dose) can be administered to improve laryngeal edema.[23,55-57]

Antipyretic analgesics, such as acetaminophen, should be used as appropriate for fever, pharyngeal pain, and others. Inhalation of humidified air is ineffective.[58,59] Even though respiratory failure due to airway obstruction is rare in patients with croup syndrome, the airway should be protected quickly when there are symptoms of impending airway blockage.

(v) Antibacterial agent treatment

Most cases of croup syndrome are viral infections and not indicated for antibacterial agents.[23,52,58] It generally resolves spontaneously within three days. However, if acute epiglottitis is suspected, the patient should be hospitalized and treated with an intravenous administration of antibacterial agents. For more details, please refer to the manuals and guidelines of academic society.[23,28]

(vi) Explanation to patients and parents

Instruct the parent and/or patient on oral fluid replacement to avoid dehydration, and if labored respiration or orthopnea appear, the parents should be instructed to bring the child toa medical institution immediately.

Example of explanation from doctor to patient: Croup syndrome

> Croup syndrome is caused by a narrowing of the airway in the throat due to viral infection. Antibacterial agents are not effective because the symptoms are caused by viruses. Allow the child to rest as much as possible, because crying or fussing may worsen the symptoms.
>
> In most cases, this disease resolves spontaneously, however hospitalization may be required if the airway becomes too narrow. Croup syndrome gets often worse at night, so please keep a close eye on your child at home and take him/her to the hospital as soon as possible when his/her difficulty breathing gets worse.

<Literature search methods>

Regarding croup syndrome in children, we conducted a literature search to reflect the latest evidence, while considering the recommendations of the current medical guidelines by groups of experts, such as Nelson Textbook of Pediatrics (20th ed), Feigin and Cherry's Textbook of Pediatric Infectious Diseases (7th ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (8th ed), the JSPID, the JAID/JSC, the IDSA, and the ESCMID.

<Search formula on MEDLINE>

"Laryngitis"[Mesh] AND ((Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Clinical Study[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR Systematic Reviews[sb]) AND "2018/08/20"[PDat]: "2023/01/31"[PDat] AND (English[lang] OR Japanese[lang]))
The result was 30 hits. Filtering this by CHILDREN (birth-18 years) resulted in 27 hits.
(August 19, 2018 - January 31, 2023)

<How to search for Japanese-language articles in Medical Journal>

Croup, 2006-2018, excluding case reports, excluding conference proceedings, meta-analyses, randomized controlled trials, quasi-randomized controlled trials. Comparative trials, pediatric
Two results were found. (August 19, 2018 - January 31, 2023)

(4) Acute Bronchitis

- Acute bronchitis is inflammation of the lower respiratory tract with coughing as the main symptom, many cases of which are viral in origin and will spontaneously resolve.
- Diagnostic tests are essentially unnecessary, although if pneumonia or pertussis is suspected based on an epidemic or clinical findings, exclusion tests should be performed to rule out the diagnosis.

Recommendations on antibacterial agent use

- It is recommended not to administer antibacterial agents for acute bronchitis.

(i) What is acute bronchitis?

Acute bronchitis is inflammation of the lower respiratory tract with cough as the main symptom, with or without fever and sputum. Although it is often difficult to clearly distinguish acute bronchitis from upper respiratory tract inflammation or acute rhinosinusitis, in this manual, acute bronchitis is defined as an acute respiratory tract infection where cough is the main symptom. Among children, acute bronchiolitis in infants and toddlers with wheezing warrants particular attention. This is described in the next section.

(ii) Epidemiology of acute bronchitis

Most causative organisms are considered to be viruses,[60] although other organisms, such as *Mycoplasma* spp., *Chlamydia* spp., and *Bordetella pertussis* should be considered. In addition, the disease concept of "persistent bacterial bronchitis" due to bacterial infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, has been proposed in infants and toddlers with a cough persisting for more than three weeks.[41,61,62] On the other hand, it is often difficult to distinguish it from acute rhinosinusitis in children, who may present with similar symptoms.

(iii) Diagnosis and differentiation

There are no clear diagnostic criteria for acute bronchitis; when an acute respiratory tract infection is accompanied by lower respiratory tract symptoms (mainly cough) and auscultatory rales and pneumonia is ruled out based on respiratory status and imaging findings, it falls into this category.[23] The Guidelines of the Japanese Society of Pediatric Pulmonology and Japanese Society for Pediatric Infectious Diseases define acute bronchitis as a state in which rales are heard in lower respiratory airway auscultation, but with no apparent abnormal findings on chest radiography.[23]

Because clinical diagnosis is predominant, testing is generally not necessary for the purpose of diagnosing acute bronchitis. Thus, testing is performed to exclude other differential diagnosis.[63]

For cases with a prolonged cough for more than 10 days, rhinosinusitis, prolonged bacterial bronchitis, or atypical pneumonia should be considered if they are accompanied by a productive cough. Though it is rare, tuberculosis should also be considered. In addition, there are a variety of other differential diagnosis, including acute bronchitis, airway foreign body, and gastroesophageal reflux.

The Guidelines for the Diagnosis and Treatment of Pediatric Respiratory Infections 2022 (Pediatric Respiratory Infections Guidelines Development Committee) defines clinical

pertussis when it meets one or more of the following criteria as one of the differential diagnosis of cough in children younger than one year of age: “inspiratory whistle,” “paroxysmal continuous cough,” “vomiting after coughing,” and “apnea attack with or without cyanosis.”

In case of children older than one year of age, they should have a cough of at least one week in addition to the above criteria. Definitive diagnosis requires positive cultures of *B. pertussis* isolation, nucleic acid amplification (polymerase chain reaction or loop-mediated isothermal amplification) tests, or serological confirmation of *B. pertussis* IgM/IgA and IgG antibodies.[23]

Important differential diagnosis (red flag)

Pneumonia, empyema, and airway foreign bodies can be listed as differential diagnosis. In cases with persistent fever or respiratory disturbance, tests are considered according to vital signs and chest examination findings to rule out pneumonia and empyema. It is also important to differentiate non-infectious respiratory diseases, such as bronchial asthma, and noninfectious diseases, such as airway foreign bodies.

(iv) Treatment methods

Generally, the diseases are treated symptomatically. According to the results of a systematic review, bronchodilators were ineffective for an acute cough in children without obstructive airway disease.[64]

(v) Antibacterial agent therapy

Antibacterial agents are, in general, not required for acute bronchitis.[65] Domestic and international guidelines on pediatric respiratory diseases also state that antibacterial agents are not required for acute bronchitis with cough that persists for less than three weeks as the main symptom.[19,44,67-70] If pertussis is suspected or diagnosed, macrolide antibiotics are recommended. On the other hand, the use of macrolides is considered when the causative organisms are diagnosed as *Mycoplasma* spp. or *Chlamydia* spp., although the usefulness of macrolides in bronchitis has not been established.[71]

When treated as pertussis either is applicable:

Erythromycin	25–50 mg/kg/day, divided four times daily for 14 days
Clarithromycin	10–15 mg/kg/day, divided twice daily for seven days
Azithromycin	10 mg/kg/day once daily for 5 days*
	(Not an indicated organism on the package insert)[72]

If a productive cough persists for more than 10 days with no remission and if prolonged bacterial bronchitis or sinusitis is suspected, the administration of amoxicillin hydrate should be considered.[62,73]

(vi) Explanation to patients and parents

Explanation from doctor to patient: Acute bronchitis

Acute bronchitis is an illness caused by a virus that resolves spontaneously, so there should be no need for concern. However, coughing may persist for one to two weeks. When the symptom is improving slowly, there is often no need for concern.

In most cases, antibacterial agents are ineffective, but sometimes children are infected with bacteria such as *B. pertussis* or *Mycoplasma* spp., or they may develop pneumonia due to secondary bacterial infections. If the symptom does not improve after several days, or there is high fever or breathing difficulty, please visit a medical institution again.

<Literature search method>

With regard to bronchitis in children, we conducted a literature search to reflect the latest evidence, taking into account the recommendations of current medical guidelines by groups of experts, such as Nelson Textbook of Pediatrics (20th ed), Feigin and Cherry's Textbook of Pediatric Infectious Diseases (7th ed), Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (8th ed), the JSPID, the JAID/JSC, the IDSA, and the ESCMID.

<Search formula on MEDLINE>

("bronchitis"[MeSH Terms] OR "bronchitis"[All Fields]) NOT ("bronchiolitis"[MeSH Terms] OR "bronchiolitis"[All Fields]) AND ((Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND ("2018/08/19"[PDAT]: "2023/01/31"[PDAT]) AND (English[lang] OR Japanese[lang]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))
Results 20 hits. (08/19/2018 - 01/31/2023)

<How to search for Japanese-language articles in Medical Journal>

#1 ((bronchiolitis/TH or bronchiolitis/AL)) and (DT=2019:2023 PT=original paper, excluding conference proceedings RD=meta-analysis, randomized controlled trial, quasi-randomized controlled trial, controlled study, practice guideline (CK=human) AND (CK=newborn, infant (1-23 months), toddler (2-5), child (13-18)) 5), Child (6-12), Adolescent (13-18))))
#2 (bronchiolitis/TH or bronchiolitis/AL)
#1 not #2
The above resulted in 17 hits; no papers examined the need for antimicrobials in RCTs.
(August 20, 2018 - January 31, 2023)

(5) Acute Bronchiolitis

- Acute bronchiolitis is a viral infection that causes nasal discharge and obstruction and subsequent coughing, wheezing, and forced respiration in children below two years of age.
- It is clinically diagnosed and generally does not require specific diagnostic testing for acute bronchiolitis.
- Vital signs and oxygen saturation should be measured to assess general condition, and respiratory status should be evaluated. Additionally, it is important to examine the presence of complications.
- Systemic management depending on respiratory and general condition is critical. Pay attention to the fluid balance and perform fluid replacement as necessary. Nasal aspiration with saline should be performed if there is excessive secretion in the upper respiratory tract.
- The disease may progress during its natural course, and complications such as otitis media and bacterial sinusitis may occur; it is important to assess the patient's condition.

Recommendations on antibacterial agent use

- It is recommended not to administer antibacterial agents for acute bronchiolitis.

(i) What is acute bronchiolitis?

Acute bronchiolitis in infants and toddlers is a lower respiratory tract infection caused by viruses and is a disease which causes respiratory disturbance, characterized by inflammation and edema of bronchiole epithelium and obstructive lesions due to mucus production. In general, it refers to a condition in children below two years of age in which upper respiratory tract inflammatory symptoms, such as nasal discharge and nasal obstruction, are followed by cough, expiratory wheezing, and labored breathing with lower respiratory tract infection. Fever may or may not be present.

(ii) Epidemiology of acute bronchiolitis

Respiratory syncytial (RS) virus is the most important causative organism. It is estimated that over 90% of children are infected with the RS virus by two years of age, and 40% of those infected for the first time develop a lower respiratory tract infection. Other infectious agents include human metapneumovirus, parainfluenza type 3, and bocavirus.

Bronchiolitis is the most common cause of hospitalization in infants, and patients in early infancy or with an underlying disease are at increased risk for respiratory disturbances.

(iii) Diagnosis and differentiation

Diagnosis is clinical and generally does not require blood tests, chest radiography, or rapid antigen testing.[70] It is important to measure vital signs and oxygen saturation to assess the patient's condition, respiratory status, and complications.[74]

Important differential diagnosis (red flag)

Differential diagnosis include pneumonia, bronchial asthma, airway foreign bodies, and various diseases that can cause respiratory disturbance in infants and toddlers. Although not the age group covered by this manual, RS viral infections during the neonatal period (within 28 days of birth) may cause apnea during the illness, even if the clinical presentation is limited to upper respiratory tract inflammation, and hospital admission should be

considered for monitoring and treatment. In infants, usually nasal discharge and cough are the primary manifestations, and worsening of the symptoms characterized by wheezing is often recognized around three to six days after infection. Especially patients in early infancy, patients with prematurity, congenital heart disease, chronic pulmonary disease, and immunodeficiency often have severe respiratory disturbance and require hospitalization; watch for signs of severe illness such as tachypnea, labored breathing and hypoxemia, and consider referral to a secondary medical institution, if necessary.

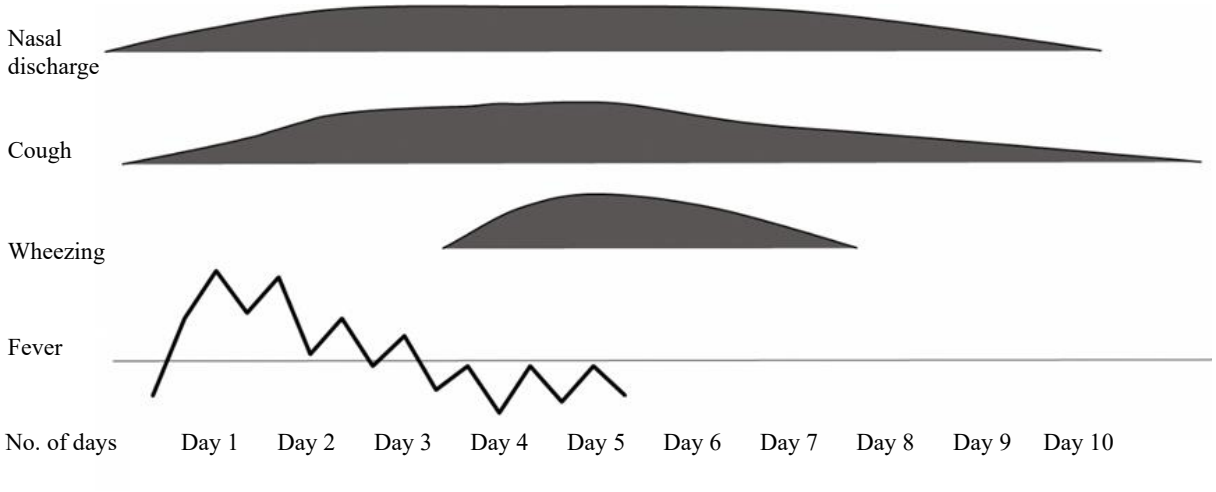

Figure 7. Spontaneous Progress of Acute Bronchiolitis

(iv) Treatment methods

There is no effective therapeutics, although systemic management according to respiratory and general condition is important.[75] It is essential to pay attention to dehydration and to perform fluid replacement as necessary. Nasal aspiration is also recommended for patients with excessive upper respiratory tract secretions.[76] There is a possibility that the disease condition may progress, and complications may arise during the disease course; therefore, risk assessment and identification of the condition are important.

(v) Antibacterial agent treatment

Antibacterial agents are not required for acute bronchiolitis. A systematic review based on a number of papers ruled out the efficacy of antibacterial agents,[77] and this is also the consensus of national and international practice guidelines.[44,63,74] However, since bacterial pneumonia and otitis media may occur, caution should be exercised when the fever is prolonged or when patients with signs of remission experienced repeat exacerbation.[78] Otitis media concurrent rates are reported to be at 30–60%.[79,80]

The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines do not recommend that nasal aspiration be performed in all cases, although it is recommended for cases with poor respiratory status or oral intake due to hypersecretion of the upper respiratory tract.[63] Both the efficacy of pharmacotherapy with bronchodilators and corticosteroids and usefulness of physical therapy have been ruled out through systematic review[81-83] and are not recommended in various guidelines.[74] Adrenaline Inhalation has been considered in the emergency department, and inhalation therapy with hypertonic saline[84] has

been reported to be of certain efficacy.[85] However, these treatments should be adequately monitored and are not recommended for general pediatric outpatient settings.

(vi) Explanation to patients and parents

Example of explanation from doctor to patient: Acute bronchiolitis

> Acute bronchiolitis is a viral infection. The bronchioles may become narrow and can cause coughing or gasping for breath.
>
> Most cases of acute bronchitis resolve spontaneously. However, breathing may be difficult, and caution is needed. Antibacterial agents are not effective. However, if a fever persists, complications such as otitis media and sinusitis may occur. In addition, adequate hydration is required to prevent dehydration. If breathing is labored, fever persists, or hydration with fluids such as milk is not possible, please see a doctor.

<Literature search method>

Existing domestic and international guidelines for Bronchiolitis (the Japanese Society for Pediatric Infectious Diseases Guidelines,[44] UK NICE Guidelines,[63] and American Pediatric Society Guidelines[74]) and systematic reviews[77] were primarily referenced. Literature in the past five years was examined, and resources related to outpatient care was referenced.

<Search formula on MEDLINE>

"Bronchiolitis"[Mesh] AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2018/08/21"[PDat]: "2023/01/31"["2023/01/31" PDat] AND "humans"[MeSH Terms] AND (English[lang] OR Japanese[lang]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))
Results 93 hits. (August 20, 2018 - January 31, 2023)

10. Acute Diarrhea

- Acute diarrhea is an abnormality in fecal characteristics and stool volume. It may be accompanied by abdominal symptoms, such as vomiting, abdominal pain, and fever.
- Most of the pathogens responsible for acute diarrhea in children in Japan are viruses.
- In pediatric acute diarrhea, evaluating the severity of the disease is more important than diagnosing the cause. The urgency should be rapidly assessed, and in case of dehydration oral rehydration therapy should be initiated immediately.

Recommendations for antibacterial agent use

- If acute diarrhea is caused by viral agents, antibacterial agents are not needed.
- It is recommended that antibacterial agents not be given to suspected cases of mild bacterial enteritis in healthy patients.
- Antibacterial agents may be considered for cases of bacterial enteritis in children under three months old, immunocompromised individuals, and in cases with severe septic complications.

(1) What is Acute Diarrhea?

Acute diarrhea is defined as fecal abnormalities, such as loose or watery stools three or more times within 24 h,[86] more than twice the normal frequency,[87] or more than twice the normal volume (10 mL/kg/day or more in infants and 200 g/24 h or more in toddlers and older children).[88] Vomiting often precedes diarrhea, although in some cases diarrhea can be the sole symptom, and vomiting can be dominate specially in young children. Complications of abdominal pain and fever may be noted. Although progression of symptom is faster in younger children, the degree of symptom severity may vary among individuals. Pathogens could be both viral and bacterial, but overwhelming majority of cases in industrialized countries, such as Japan, are viral.

(2) Epidemiology of Acute Diarrhea

In Japan it is prevalent in winter, and most cases are presumed to be caused by viruses, such as noroviruses.[89] Noroviruses are the leading (or second leading) cause of infectious gastroenteritis in children (12%).[90] Before the introduction of vaccines, rotaviruses affect 90% of children up to three years of age, in both developed and developing countries. Rotavirus vaccines prevent severe diarrhea approximately 90% in rotavirus cases in developed countries. In Japan, voluntary vaccination against rotavirus gastroenteritis began in January, 2011, and has become a routine vaccination from 2020; notification of rotavirus gastroenteritis patients from the key fixed sites began in October, 2013. A rotavirus gastroenteritis patient surveillance reported a downward trend in the number of patients with rotavirus gastroenteritis in the 2013/2014 and 2014/2015 seasons compared with that in the 2010/2011-2012/2013 seasons.[91] Since the introduction of routine vaccination in 2020, the disease has further declined sharply and become rare.[92]

(3) Diagnosis and Differentiation

In acute diarrhea in children, it is necessary to determine whether the cause is viral or not. Signs and symptoms that are typical of viral gastroenteritis include initial vomiting, mild to moderate periumbilical abdominal pain or tenderness, watery diarrhea without bloody stool, absence of fever (or just a low-grade fever), absence of severe abdominal pain, and the presence of similar symptoms in the family or surrounding populations.[93] On the other hand, consider bacterial enteritis in the presence of fever, tenesmus, and bloody stools. The presence of bloody stools is associated with bacterial enteritis such as enterohemorrhagic *Escherichia coli* infection, as well as a number of another differential diagnosis such as intussusception, Meckel's diverticulum, and upper gastrointestinal ulcers.[93] Many of the diseases presenting with bloody stools, especially in young children, are severe and may suddenly change for the worse, and in principle, hospitalization and close examination are required.[94]

Rapid antigen testing (for rotavirus, norovirus, and intestinal adenovirus) makes no difference in the treatment or handling of the symptoms and is generally not meaningful in pediatric outpatient practice. In certain cases, it is indicated in hospital or group-care settings that testing can be performed for infection control awareness or when a reliable diagnosis is necessary because rotaviruses and noroviral gastroenteritis rarely present with high fever.[95]

Few cases require urgent stool cultures, and tests are indicated for children with severe abdominal pain or bloody stools due to suspected bacterial enterocolitis, with suspected hemolytic-uremic syndrome (HUS) due to enterohemorrhagic *E. coli* infection, and with compromised immune system.

Important differential diagnosis (red flag)

The following are important differential diagnosis of vomiting:

Findings	Disease
Observe symptoms and signs suggestive of acute abdominal disease	Intussusception, appendicitis, testicular torsion, strangulated ileus, and others
Observe symptoms and signs suggestive of increased intracranial pressure	Meningitis, intracranial hemorrhage
Others	Sepsis (including toxic shock syndrome), diabetic ketoacidosis, urinary tract infection

Since these diseases can worsen in an hourly basis, transfer of the patient to a high-level medical institution should be considered immediately.

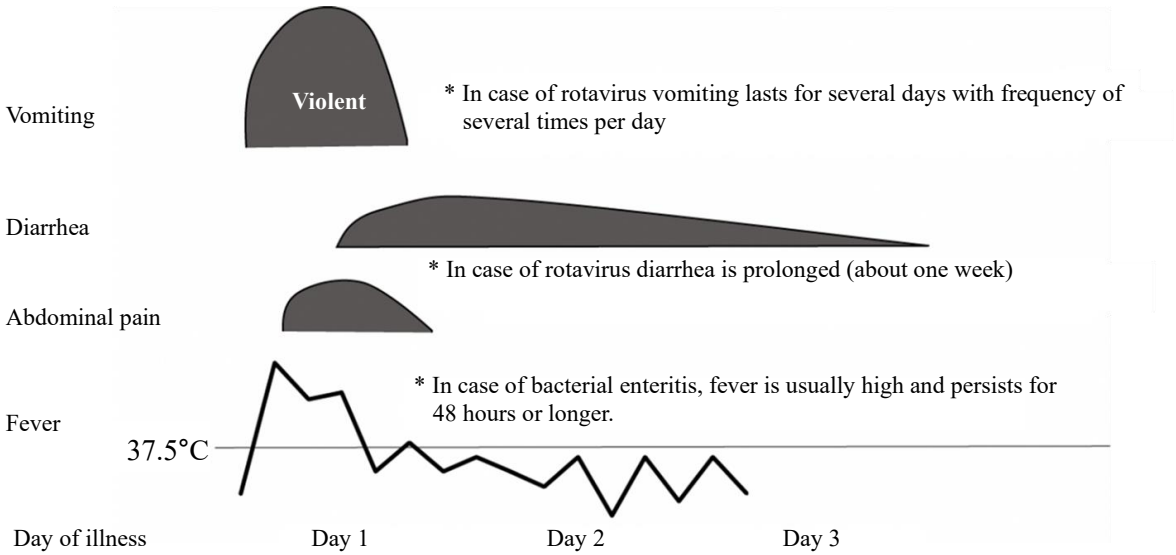

Figure 8. Natural Course of Acute Viral Diarrhea

(4) Treatment Method

Treatment for acute diarrhea include: 1) response to dehydration (i.e., oral rehydration therapy and intravenous fluids), 2) probiotics, and 3) avoiding unnecessary use of antibacterial agents.[93,94]

(i) Response to dehydration

Upon diagnosis of acute diarrhea, assessment of disease severity is of primary importance, and the severity is most affected by the presence of dehydration.

Care for dehydration is important especially in children because their fluid requirements per body weight is high, and they are reliant on others (notably their guardians) due to their inability to self-support fluid and diet intake.[93,95] Thus, dehydration must be assessed and addressed promptly.

It is important not to overlook dehydration (weight loss) of more than 5% of body weight and more severe dehydration, which often requires fluid therapy.[96] The presence of two of any of the following four items are considered evidence of dehydration of 5% or more: 1) the capillary refill time (the time for the nail bed to return to its original color following compression of the nail bed of the finger for five seconds) is two seconds or more, 2) dry mucous membranes, 3) no tears, and 4) changes in general condition (likelihood ratio [LR] + 6.1; 95% CI, 3.8–9.7).[96]

Individuals at high risk of requiring intravenous fluids are infants of six months of age or younger, of low birth weight, with chronic illness, aged three months or younger and presenting with fever (38°C or more), aged three months to three years and presenting with high fever (39°C or more), and those with bloody stools, persistent vomiting, decreased urine output, orbital depression, or decreased level of consciousness.[93]

Oral rehydration solution is a global standard treatment for acute diarrhea.[95] It is effective and has the advantage of not requiring vascular access, and thus, the burden on the child is minimal.[95] It is recommended for the preemptive prevention of dehydration and for the treatment of mild to moderate dehydration.[95]

Specifically, it is important to initiate rehydration as soon as possible (within 3–4 hours of the signs of dehydration), gradually increasing the dosage from a small amount (about one teaspoon) to a volume equal to lost fluid (50–100 mL/kg for mild to moderate dehydration) over the course of 3–4 hours.

(ii) Probiotics

The UK practice guideline[94] and the 2014 guideline of the European Society for Paediatric Nutrition, Gastroenterology and Hepatology[95] recommended its use for acute diarrhea as reducing the duration and frequency of diarrhea in children. Subsequently, however, the European Society for Pediatric Nutrition, Gastroenterology, and Hepatology lowered the recommendation level in 2020 after multiple studies showed no benefit. However, there are national differences in the formulations used, and the evidence is not strong enough to immediately deny their use. Thus, this manual does not recommend uniform use of probiotics.[96-100]

(5) Antibacterial Agent Therapy

When viral enteritis is diagnosed, antibacterial agents are not only ineffective but also are considered harmful as they disrupt the intestinal flora and cause bacterial alternation.[86]

If bacterial enteritis is diagnosed, timely and appropriate antibacterial agent therapy can improve the severity of diarrhea and shorten the duration of disease. In contrast, antibacterial agents prolong bacterial colonization and the extensive use of antibacterial agents for diarrhea causes antimicrobial resistance.

Even diarrhea caused by bacterial enteritis often spontaneously resolves. Therefore, in the case of mild disease in a healthy child, after collecting stool cultures, symptomatic treatment should be administered first, and antibacterial agent treatment should be considered depending on disease progression and stool culture results. If symptoms of bacterial enteritis (e.g., severe abdominal pain, tenesmus, bloody stools, high fever) are present, fecal cultures should be obtained first and antibacterial agent therapy should be considered. Meanwhile, in high-risk patients, such as those with poor general condition, those under three months old, and immunocompromised individuals, it is practical to apply systemic management and antibacterial agent treatment under hospitalization in principle.

(i) Initial treatment

- When there are severe symptoms due to bacterial enteritis and antibacterial agent therapy is considered appropriate;
- When *Campylobacter enteritis* is suspected based on history and Gram stain of stool samples;
  Clarithromycin 15 mg/kg/day divided twice daily for three to five days
  Azithromycin 10 mg/kg/day once daily for 3 days
- In cases where infectious enteritis caused by bacteria other than *Campylobacter* spp. is strongly suggested and there is an increased risk of severe illness, such as bacteremia, there is no clear evidence on the effectiveness of drugs covered by insurance in Japan. Refer to the guidelines of the Japanese Society for Infectious Diseases and the Japanese Society for Chemotherapy (JAID/JSC Infectious Diseases Treatment Guidelines 2019 - Intestinal Infectious Diseases).

(ii) Definitive treatment

- *Campylobacter* enteritis
  Antibacterial agents are not essential because spontaneous healing can be expected. Antibacterial agent administration is considered for severe cases, such as those with high fever, strong abdominal pain, and bloody stool.
  Clarithromycin 15 mg/kg/day divided twice daily for three to five days
  Azithromycin 10 mg/kg/day once daily for 3 days

- Non-typhoidal *Salmonella* enteritis
  Because antibacterial agents prolong the duration of shedding, they should not be administered to asymptomatic carriers or patients with mild disease. High-risk cases (young children, especially infants under three months old, immunosuppressed, and with inflammatory bowel disease) are candidates for treatment. Severe cases or those with complications will require hospitalization.
  Since bacteremia is often complicated at this time, blood cultures should be collected. If infectious enteritis caused by non-typhoidal *Salmonella* is strongly suggested and there is a high risk of severe disease, such as bacteremia, there is no clear evidence on the effectiveness of drugs covered by insurance in Japan. Refer to the guidelines from academic societies (e.g., JAID/JAS Guidelines 2019 - Intestinal Infectious Diseases -).

- Diarrheagenic *E. coli* infection
  Other enterocolitis caused by diarrheagenic *E. coli,* with the exception of enterohemorrhagic *E. coli* (EHEC), tends to resolve spontaneously. In enteritis in which the involvement of EHEC is suspected, there is still no unified opinion on antibacterial agent administration in Japan. Guidelines in Europe and North America often have negative opinions about antibacterial agents (mostly Sulfamethoxazole and Trimethoprim and beta-lactams) because they increase the risk of developing HUS (Hemolytic Uremic Syndrome). In contrast, a meta-analysis reported that antibacterial agents do not affect the risk of HUS.[101] Furthermore, although the number of cases in Japan is limited, it has been reported that the use of antibacterial agents, mainly fosfomycin, was effective in previous outbreaks.[102-104]

According to the guidelines of the JAID and JSC, “there are no unified recommendations for antibacterial agent treatments at this time.” Concomitantly, this manual follows the above guideline and does not recommend administration of antibacterial agents, but does recommend supportive care, and recommends that follow-ups be performed frequently to maximize early detection of HUS with thorough explanation of occurrence rate (3-10% of EHEC-infected patients are said to develop HUS).

(6) Other Concepts Concerning Pharmacotherapy

Antiemetic agents for vomiting and antidiarrheal agents for diarrhea are poorly documented and not recommended.[94] Loperamide has been reported to cause intestinal obstruction in infants and is contraindicated for children less than six months of age and, in principle, contraindicated for children under two years of age.[94]

(7) Explanation to Patients and Parents

Example of explanation from doctor to patient: Acute gastroenteritis

This is described as a “stomach flu.” Most are caused by viruses, and there are no special treatments (= special drugs). This heals spontaneously depending on one’s own immune system.

There is no reason to run bacterial or viral tests, except for young children with fever, severe cases, or immunodeficiency.

Treatment is based on prevention of dehydration. It is important to frequently consume fluids similar to bodily fluid contents. First, give a small amount (initially about a teaspoon) every 10–15 minutes.

Giving too much too suddenly may induce vomiting, which will further aggravate dehydration. Please be patient and give it in small quantities. Continue for about an hour and gradually increase the amount if you observe no worsening of the symptoms. Consult your doctor about how much you should give.

If your child is unable to take fluids or if he/she vomits more or experience more diarrhea, further dehydration may occur, and intravenous fluids (fluid therapy) may be needed. Moreover, if your child does not urinate, is cranky, has a worsening state of consciousness (feeling groggy and tending to wander off and sleep), has severe abdominal pain, or a parent/guardian feels that the child is “acting differently than usual,” please consult a medical institution again.

<Literature search method>

Regarding the acute diarrhea in children, we conducted a literature search to reflect the latest evidence based meta-analyses, statistical reviews, and randomized controlled studies, taking into account recommendations of current medical guidelines by the groups of experts such as the Japanese Society of Emergency Pediatrics, JAID/JSC, World Health Organization, medical care guidelines (NICE) in the UK, and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

<Search formula on MEDLINE>

(((“Diarrhea”[Mesh] AND “Acute Disease”[Mesh]) OR “infectious diarrhea”[All Fields]) OR ((“dysentery”[MeSH Terms] OR “dysentery”[All Fields])) OR “acute gastroenteritis”[All Fields] AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Guideline[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND “8/14/2018”[PDat] : “1/31/2023”[PDat] AND (English[lang] OR Japanese[lang]))
The result was 261 hits. Filtering this by CHILDREN (birth-18 years) resulted in 179 hits.
(August 14, 2018 - January 31, 2023)

<How to search for Japanese-language articles in Medical Journal>

Acute Diarrhea, 2019-2023, excluding case reports, excluding conference proceedings, and 7 results were found.
(Aug. 14, 2018)

7 references that were considered appropriate for the AMR Action Plan after reviewing the contents of the above references (references).
In addition to the above, we referred to the Japanese guidelines for the treatment of pediatric acute gastroenteritis, 2017 edition (Japanese Society of Pediatric Emergency Medicine Guidelines for the Treatment of Acute Gastroenteritis, ed

11. Acute Otitis Media

- To diagnose acute otitis media in children, it is important not to rely solely on complaints of ear pain or ear discharge, but to obtain tympanic membrane findings in patients complaining of fever, moodiness, or cold symptoms.
- If there is only tympanic membrane redness and no bulging, as a rule, acute otitis media is not diagnosed.
- Antibacterial agent therapy is recommended for acute otitis media with ear discharge of middle ear origin.
- Consider antibacterial agent therapy in the presence of fever, moodiness, or earache and if there are tympanic findings with redness and swelling.
- Even with tympanic membrane findings, acute otitis media may resolve spontaneously; consider a 2–3 day follow-up period without antibacterial agents for patients with mild disease that has a low risk of becoming severe, taking into consideration patient risks such as age, underlying disease, local inflammatory findings in the middle ear, and general condition.

Recommendations on antibacterial agents use

- The first-line drug for acute otitis media is amoxicillin hydrate.
- Cooperation with an otorhinolaryngologist is important in this disease.

* This manual describes the criteria and initial drug of choice for general practitioners to determine the need for antibacterial agent therapy in children with suspected otitis media. For more complex cases, such as refractory cases or infections caused by resistant bacteria, please refer to the guidelines of academic societies.

(1) What is acute otitis media?

It is defined as an acute onset of middle ear infection that may be accompanied by ear pain, fever, and ear discharge.[105] Acute otitis media occurs when inflammation or infection spreads to the middle ear cavity via the Eustachian tube. The main causative organisms are *S. pneumoniae*, *H. influenzae,* and *Moraxella catarrhalis*.

Exudative otitis media is defined as the cause of hearing loss with fluid in the middle ear cavity without acute inflammatory symptoms (ear pain or fever) and without perforation of the tympanic membrane and is different from acute otitis media.[106] There is no indication for administration of antibacterial agents for exudative otitis media.

(2) Epidemiology of Acute Otitis Media

Acute otitis media is a common infection that affects up to 75% of children under age of one, and up to 40% of children aged seven years on four or more occasions.[107,108]

Anatomic and immunologic factors both explains well the high prevalence of this condition in infants. As for anatomical factor, the Eustachian tube in adults is long and slender with a high slope of approximately 45 degrees, while the Eustachian tube in children is short and wide with a low slope of approximately 10 degrees, making it easy for inflammation to spread from the nasopharynx (nasal cavity) and cause acute otitis media. As for immunologic factor, children particularly those aged six months to two years are immunologically susceptible to infection due to low specific antibodies against *S. pneumoniae* and *H. influenzae*.[108-111] Moreover, infants are unable to blow their nose on their own and are prone to poor drainage. Other factors, such as secondhand smoking and non-breastfeeding, are said to increase the risk of developing the disease.

(3) Diagnosis

The diagnosis of acute otitis media is based on accurate local findings on examination of the tympanic membrane using an otoscope. National otitis media guidelines emphasize the importance of local findings and recommend a diagnosis based on detailed inspections.[105] The American Academy of Pediatrics Guidelines[112] also list the following three criteria for the diagnosis of acute otitis media based on tympanic membrane findings: (1) acute otitis media is diagnosed when there is moderate to severe eardrum distention or ear leakage that is not due to acute otitis externa; (2) acute otitis media is diagnosed when there is acute (within 48 h) onset of otalgia (touching, pulling, or rubbing of the ear) along with mild swelling of the tympanic membrane and intense tympanic membrane redness; and (3) tympanic membrane erythema without fluid retention in the middle ear cavity should not be diagnosed as acute otitis media. Overall, the most important finding of otitis media is a bulging tympanic membrane. Tympanic membrane erythema may be caused by fever or crying alone.

Since infants cannot accurately describe otalgia, there is the possibility that fever and grumpiness may be the only complaints, and because otitis media does not accompany fever in 40% of cases,[113-116] the tympanic membrane findings are important. In contrast, there is a need to identify other local infections and systemic severe bacterial infections as a differential for otalgia, fever, and grumpiness. Oral lesions, for instance, can also cause otalgia. If cerumen is present and cannot be removed and the tympanic membrane is difficult to assess, consider referral to an otolaryngologist.

Table 5. Differentiation of Otalgia

Differential diagnosis of otalgia	
1) Otitis media	8) Meningitis
2) Tympanitis	9) Pyogenic sialadenitis
3) Otitis externa	10) Herpes zoster
4) Foreign body in the ear canal	11) Mastoiditis
5) Infectious parotitis (mumps)	12) Trauma
6) Preauricular and postauricular lymphadenitis	13) Cellulitis
7) Dental eruption, gingivitis	

Table 6. Findings (Red Flag) to Watch Out for and to Consider during Treatment of Otalgia and Otitis Media

Findings	Considerations and differential diagnosis
No improvement in both local and systemic findings after two to three days of observation without antibacterial agents	Consider administering antibacterial agents as otitis media treatment Determine the presence or absence of other infection foci and re-examine the diagnosis
Neither local nor systemic findings improve within two to three days of starting antibacterial agent therapy	Determine the presence or absence of other infection foci and re-examine the diagnosis Determine indications for surgical drainage (tympanostomy) Consider changing antibacterial agents with resistant bacteria in mind
Redness, swelling, and tenderness in the posterior part of the auricle, and auricular rises	Mastoiditis
Stiff neck, impaired consciousness, convulsions, and “not doing well”	Meningitis
Swelling and pain around the mandibular angle, redness around the salivary gland orifice	Pyogenic sialadenitis, mumps

(4) Antibacterial Agent Therapy

(i) Objectives and indications for treatment of otitis media with antibacterial agents

The goal of antibacterial agent therapy is to achieve early improvement of symptoms associated with acute otitis media (fever, otalgia, and others) and to reduce complications secondary to acute otitis media. A Cochrane review published in 2015 found that antibacterial agent therapy has certain efficacy in preventing abnormal tympanometry (poor tympanic membrane mobility), tympanic membrane perforation, and the development of contralateral acute otitis media.[117] In contrast, more than three-quarters of cases of acute otitis media heal spontaneously within a week without antibacterial agent prescriptions; 70% of cases in children over two years of age improve within three days, and about half of cases in children under two years of age heal within 10 days. More than half of acute otitis media cases do not require antibacterial agents.[118-122] In addition, antibacterial agent therapy can cause side effects such as diarrhea and lead to drug resistance in bacteria. Thus, it is important to determine whether it is necessary and, if so, to select an appropriate antibacterial agent treatment.

The American Academy of Pediatrics guidelines recommend antibacterial agents be administered (1) in the presence of ear discharge, (2) in severe cases (toxic, ear pain lasting more than 48 h, and fever of 39°C or higher), and (3) in bilateral cases among patients aged six months to two years.[112] The Japanese guidelines also suggests that a period of two to three days without antibacterial agents is reasonable after evaluation of clinical symptoms and tympanic membrane findings, considering age and risk factors, given the expectation of spontaneous remission.[105]

(ii) Criteria for administration of antibacterial agents

The criteria for the administration of antibacterial agents for otitis media are defined as follows:

- If there is ear leakage of middle ear origin, antibacterial agent administration should be considered. The diagnosis is most accurate if the tympanic membrane can be visualized by aspiration or other means and a pulsatile ear leak can be confirmed at the site of the perforation.
- Consider antibacterial agent therapy in the presence of fever, grumpiness, or ear pain and if there are tympanic findings with redness and swelling.
- If the patient is in good general condition and there is no ear leakage of middle ear origin, explain that the condition often improves spontaneously; that the use of antibacterial agents has side effects and has the disadvantage of creating resistant bacteria; and that antibacterial therapy should be considered if there is no improvement with follow-up. After obtaining consent (see instructions below), provide symptomatic treatment, mainly with antipyretic and analgesic agents, without antibacterial agents for two to three days.
- When assessing indications for antibacterial administration, the following risk factors for developing severe otitis media should be considered: young children below two years of age; presence of underlying medical conditions, such as immunodeficiency; unvaccinated against pneumococcal disease; a history of otitis media; and poor access to medical care.

(iii) First-line drugs

Amoxicillin hydrate is recommended as the first-line drug. Bacteria targeted for treatment are *S. pneumoniae* and non-typable *H. influenzae* (NTHi). After the introduction of the pneumococcal vaccine (PCV), there has been an increase in the number of infections caused by serotypes other than the 13-valent contained in the vaccine, and *S. pneumoniae* and NTHi are now equally frequent with a slight dominance of *H. influenzae*.[96] In Japan, penicillin resistant *S. pneumoniae* (PRSP) and β -lactamase negative ampicillin-resistant (BLNAR) NTHi are causing problems. In the case of *S. pneumoniae*, non-invasive infections can often be treated with high-dose amoxicillin hydrate, making it the initial choice.[122]

In the case of otitis media caused by BLNAR, there are many highly resistant strains that are difficult to treat. Treatment selection should be made based on guidelines and other factors, with the presence of resistant strains taken into account.[105] For *M. catarrhalis* and β-lactamase positive ampicillin-resistant (BLPAR) *H. influenzae*, which produce β-lactamase, amoxicillin hydrate is not a good option; a fixed-dose combination with a β-lactamase inhibitor-amoxicillin-clavulanic acid is the drug of choice. However, *M. catarrhalis* alone has almost no pathogenicity, and BLPAR *H. influenzae* also appears infrequently in Japan.[123] Therefore, the use of amoxicillin-clavulanic acid or other drugs should be considered only in cases with children that do not respond adequately to treatment with amoxicillin hydrate. In addition, a randomized controlled trial in children in Japan reported fewer treatment failures with clarithromycin than with amoxicillin alone for otitis media.[124]

(iv) Dosage and administration interval

Amoxicillin hydrate: 60–90 mg/kg/day, divided three times daily (not exceeding 90 mg [potency]/kg)

(v) Treatment period

The American Academy of Pediatrics guidelines call for the duration of treatment to be 10 days for children under two years of age, 7–10 days for children two to five years of age, and 5–7 days for children six years of age and older, according to age.[112] Japanese guidelines recommend starting treatment initially for five days, followed by observation of disease progression on day three and four.[123] In a non-inferiority RCT restricted to children under two years of age, 5-day dosing was reported to have a higher failure rate than 10-day dosing.[125]

In this manual, 10 days is recommended for children under two years of age, and five days is the basic recommendation for later ages. On the other hand, if the patient's general condition remains unchanged or deteriorates, it is recommended that the patient be re-evaluated within two to three days, and if the patient is cured before the recommended treatment period, a decision to shorten or extend the treatment period should be made according to the individual case.

(vi) Alternative medicine

If no penicillin can be used due to β-lactam allergy and others, the drug of choice should be considered in accordance with guidelines from academic societies.[105] Macrolides are not recommended based on domestic causative organism susceptibility results.

(vii) Disease course after treatment

Symptoms may worsen during the first 24 hours of treatment, but mostly begin to improve within 24 hours and are ameliorated within 72 hours.[121]

(viii) Ear drops (antibacterial agents)

If ear drops (antibacterial agents) enter the middle ear cavity, theoretically high concentrations of antibacterial agents could be expected to reach the middle ear. In the absence of tympanic perforation, it is ineffective and not recommended. In addition, there are no well-researched reports of ear drops after tympanostomy. In patients with implanted tympanic ventilation tubes, several RCTs have demonstrated efficacy, including a shorter time to healing, and administration in select cases should be considered.[105]

(ix) Indication for tympanostomy

Whether or not tympanostomy accelerates the healing of acute otitis media has not been fully proven, although it has been shown to improve severe otalgia, fever, and hearing loss at an early stage. The indication should be considered in the presence of severe systemic symptoms, such as severe ear pain, fever, and grumpiness, as well as localized findings and generalized bulging of the tympanic membrane.

(x) Analgesics

Acetaminophen as needed 10–15 mg/kg/dose (at least four to six hours apart)

(5) Explanation to Patients and Parents

Example of explanation from doctor to patient: Acute otitis media

The middle ear is connected to the innermost part of the nose by a tube called the Eustachian tube. Children's Eustachian tubes are wider, shorter, and relatively more horizontal than those of adults, because of which viral infections such as the common cold and allergies can easily spread inflammation through the Eustachian tubes to the middle ear. Inflammation of the middle ear results in painful and irritated ears, fever, and swollen and red eardrums. At this time, antibacterial agents are not particularly necessary, and the fever and pain can often be treated simply with antipyretic painkillers. Antibacterial agents can be helpful, although they can be bad if used when they are not needed and can cause side effects such as diarrhea or create resistant strains of bacteria that can be very difficult to treat in the future.

Small children catch colds easily, are unable to blow their noses by themselves, and have low resistance to the bacteria that cause otitis media; thus, the amount of bacteria in the middle ear (behind the eardrum) can grow too high. If your child becomes irritable or has severely swollen eardrums, antibacterial agents will be needed to alleviate the symptoms. In rare cases, an eardrum incision may be made to drain the pus. Your child should be followed up on an outpatient basis to determine until when to wait and when antibacterial agents are needed.

<Policies for adopting scientific evidence (search formulas, among others)>

Regarding acute otitis in children, we conducted a literature search to reflect the latest evidence based meta-analyses, statistical reviews, and randomized controlled studies, while considering the recommendations of the current medical guidelines by groups of experts, such as the JSPID, JAID/JSC, IDSA, and ESCMID.

<Search formula on MEDLINE>

"otitis media"[Mesh] AND ((Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Clinical Study[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2019/5/17"[PDat]: "2023/1/31"[PDat] AND (English[lang] OR Japanese[lang]))
The result was 220 hits.
Filtering this by CHILD (birth-18 years) resulted in 154 cases.
(May 16, 2019)

<How to search for Japanese-language articles in Medical Journal>

Acute otitis media, 2019-2023, excluding case reports, excluding conference proceedings, meta-analysis, randomized controlled trial, quasi-randomized controlled trial, controlled trial
Two results were found.
(May 17, 2019)

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Antimicrobial Stewardship in Inpatients

13. Basic Principles for Infections in Inpatients

(1) Diagnostic and Therapeutic Processes

(i) Approach to treat pyrexia in inpatients

Summary

- If an inpatient has pyrexia, the possibility of infection should first be assessed.
- Identification of the causative microorganism requires culture tests corresponding to organ-specific clinical findings.
- If *Clostridioides difficile* infection (CDI) is suspected, a specimen for CD toxin/glutamate dehydrogenase (GDH) test should be submitted instead of that for stool culture (see the section on CDI).
- If an infected organ is not successfully identified, 2 sets of blood cultures should be obtained.
- If the search for infection fails to obtain findings suggestive of infection, potential non-infectious diseases such as pseudogout and drug fever should be considered.

1) Epidemiology

Pyrexia in an inpatient is defined as a new event of pyrexia that started 48 hours or more after admission. Since pyrexia in inpatients is mostly caused by infections (Figure 1),[1] the possibility of infection should be considered first. Infections commonly causing pyrexia are pneumonia, surgical site infection (SSI), intestinal infection, urinary tract infection (UTI), and bloodstream infection.[2] Non-infectious diseases accompanied by pyrexia are drug fever, pseudogout, procedure-related pyrexia, hematoma, etc.[1]

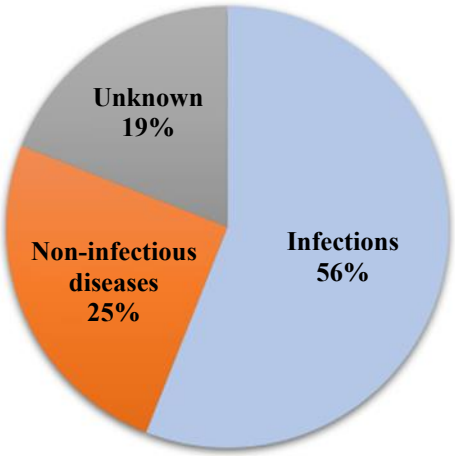

Figure 1. Breakdown of Pyrexia in Inpatients by Cause[1]

2) Points when making a diagnosis

Pneumonia

- Clinical findings: Cough/sputum, abnormal respiratory sounds, increased respiratory rate, decreased partial pressure of oxygen in the arterial blood (PaO_2), and decrease in percutaneous arterial oxygen saturation (SpO_2)
- Examinations necessary for organ-based diagnosis: Chest X-ray and chest CT scan (if necessary)
- Examinations necessary for microbial-based diagnosis: Sputum Gram staining and sputum culture
- A diagnosis of ventilator-associated pneumonia (VAP) may be made in a similar manner.

UTI

- Clinical findings: Acute pyelonephritis is suspected if the patient has back pain or costovertebral angle (CVA) or percussion tenderness. However, these symptoms are often subclinical. The patient, if male, should be checked for tenderness of the prostate gland or epididymis and enlarged scrotum.
- Examinations necessary for organ-based diagnosis: Qualitative urine white blood cells and urinary sediment.
- Examinations necessary for microbial-based diagnosis: Urine Gram staining and urine culture.
- If catheter-associated urinary tract infection (CAUTI) is suspected, the urethral catheter should be replaced before submission of a specimen for urine culture.

Intestinal infection

- Diarrhea newly occurring after 72 hours of hospitalization is reported to be caused by infections in 29.4% of the affected inpatients (CDI in 24.6% and others in 4.8%), non-infectious diseases in 45.3%, and unknown factors in 25.3%.[3] Here, the points for a diagnosis of CDI are described.
- Clinical findings: Anorexia, abdominal pain, and diarrhea (diarrhea may not occur at an early stage)
- Examinations necessary for organ-based diagnosis: Not particular. A diagnosis should be made based on clinical symptoms.
- Examinations necessary for microbial-based diagnosis: See the section for CDI. In principle, stool culture is not required for a diagnosis of CDI.

Catheter—related bloodstream infection

- Any catheter, such as peripheral venous, central venous, or arterial indwelling catheter, can cause catheter-related bloodstream infection (CRBSI).
- Clinical findings: Infection should be suspected if redness at the catheter insertion site is observed. However, this finding is rarely observed in central venous catheters and central venous ports infection. The frequency is approximately 60% with peripheral venous catheters[4] and approximately 3% with central venous catheters.[5]
- Examinations necessary for organ-based diagnosis: Specimens for 2 sets of blood culture.

  *If a central venous catheter is inserted, a specimen for 1 set of blood culture should be collected from backflow blood in the catheter and that for the other set should be collected from peripheral blood. If the same microbial species are detected in both sets, central line-associated bloodstream infection (CLABSI) should be diagnosed.

- CRBSI can also be diagnosed when the same microbial species are detected in both cultures of catheter tip and peripheral blood.[5] According to a report,[6] if the backflow blood culture tests positive at least 2 hours before the peripheral blood culture does, a diagnosis of CRBSI can be made with the sensitivity of 85% and specificity of 91%.
- Examinations necessary for microbial-based diagnosis: Specimens for 2 sets of blood culture.

Wound infection

- Pressure ulcer infection and postoperative SSI mainly represent wound infections. SSI is classified into superficial incisional SSI, deep incisional SSI, and organ/space SSI according to the site of infection.[7]
- Clinical findings: Drainage from the wound as well as redness, swelling, feeling hot, and pain of the wound.
- Superficial incisional SSI: Drainage from the surface of the incision site as well as redness, swelling, feeling hot, and pain of the wound.
- Deep incisional SSI: Drainage from the deep incision site as well as redness, swelling, feeling hot, and pain of the wound.
- Organ/space SSI: Drainage from a drain placed in the organ/space.
- Examinations necessary for organ-based diagnosis: An organ-based diagnosis of superficial incisional SSI can be made with macroscopic findings, but a diagnosis of deep incisional or organ/space SSI should be made by echography, CT scan, etc.
- Examinations necessary for microbial-based diagnosis: Gram staining/culture of wound exudate and pus. Gram staining/culture of fluid or tissue aseptically collected from an organ/space.

(ii) Implementation of appropriate culture

Summary

- Cultures should not be performed with specimens collected from asymptomatic patients.
- Stool culture is not performed for diarrhea that occurs 72 hours or longer after hospitalization.
- A blood specimen for culture must always be submitted before the administration of antibacterial agents and before switching to broad-spectrum antibacterial agents.
- In principle, culture tests are not repeated to assess the treatment effectiveness on infection.

1) Precautions for collection of specimens for culture

Culture should not be performed with specimens collected from asymptomatic patients (sputum culture in patients without respiratory symptoms, etc.). Before using antibacterial agents in patients with suspected infection, a specimen should be submitted for culture. A specimen should be submitted for culture if currently used antibacterial agents are changed because of poor improvement of the clinical symptoms.

Sputum that is less salivary but rather purulent is suitable for culture. A salivary specimen should not be submitted for culture.

Collection of midstream urine or urine collected by catheterization is recommended. If a patient with an indwelling urethral catheter is suspected to have UTI, the catheter should be replaced if possible, before collecting a urine specimen. If urine sediment is also negative for white blood cells, the urine specimen may not be submitted for culture.

Only diarrheal stool should be submitted for culture. No stool solids should be submitted for other purposes than resistant strain screening. Since diarrhea occurring 72 hours or longer after hospitalization is most likely due to CDI, the specimen should be submitted for the CDI test, but not for regular stool culture (see the section for *C. difficile*).[3]

Pus can be divided into open pus already exposed to air and closed pus not exposed to air. Closed pus, if applicable, may involve anaerobic microorganisms, and thus the specimen should also be submitted for anaerobic culture. A specimen from the wound of a gangrenous diabetic foot, etc. to be submitted for culture should consist of fluid or tissue collected from the depth of the site after debridement of necrotic tissues, and not from the wound surface.[8] Culture of a specimen collected from the wound surface can provide results that are difficult to interpret because indigenous microorganisms may be detected.

2) When to collect a blood specimen for culture

A blood specimen for culture must always be collected before the start of antibacterial agents and before switching currently used antibacterial agents to broad-spectrum agents. A blood specimen for culture should be collected from patients who have pyrexia, chills and shivering, unexplained hypothermia, unexplained shock, unexplained disturbed consciousness, unexplained stimulation of an inflammatory response, etc. For each culture set, 20 mL blood (10 mL each in an aerobic bottle and an anaerobic bottle) should be collected. In principle, at least 2 sets (2 replicates) should be subjected to the culture test. In a study in adult inpatients, the positive rate was 73.1%, 89.7%, and 98.2% when blood culture of 1, 2, and 3 sets, respectively,[9] was performed.

3) Others

In principle, culture tests are not repeated to assess the treatment effectiveness on infection. Exceptions are cases of intravascular infection, such as infective endocarditis, and those in which *Staphylococcus aureus* or *Candida* spp. Is detected in the blood. In these cases, blood culture should always be repeated to assess the treatment effectiveness after the start of the treatment (see the sections of "*Staphylococcus aureus*" and "*Candida* spp."). The treatment effectiveness may be assessed based on a decrease in microbial count or disappearance of microorganisms observed in Gram-stained preparations of sputum in case of pneumonia and urine in case of UTI.

(iii) Empiric treatment

Summary

- Consider whether empiric treatment is immediately necessary based on the vital sign and symptoms specific for bacteremia before the start of antibacterial agents.
- If you determined that empiric treatment is required for infection, the infected organs and causative pathogens should be evaluated before the start of antibacterial agents, and antibacterial agents that are effective against the presumed causative pathogens should be selected.
- After starting the antibacterial agents, the patient's symptoms and condition should be assessed with the clinical course and culture results, and then the antibacterial regimen should be adjusted.

Antibacterial agents are usually administered empirically. In other words, treatment is often started when the causative pathogen of the infection in the patient remain to be non-identified or even the presence or absence of actual bacterial infection in the patient remains to be not accurately determined.[11] In routine practice, treatment is usually started after the diagnosis has been confirmed, but for infections, empirical treatment is often started before the diagnosis is confirmed because the results of clinical microbiology tests take several days. Therefore, the potential causative organs and microorganisms should be assumed to some extent before the start of treatment.

1) Evaluate whether the situation requires empiric treatment for the infection.

"Bacterial infection immediately requires empirical treatment" is not always true, and the treatment may be started after the results become available if the situation allows. On the other hand, bacterial infection in immunocompromised patients and sepsis require prompt administration of antibacterial agents. Risk assessment regarding how sepsis can be detected early is critical. In actual clinical settings, Quick Sequential Organ Failure Assessment (qSOFA), which is easy to remember, and SOFA score, etc. in the field of intensive care may be used. However, it is important to make overall judgments, not only based on a single index. The table summarizes points to assess vital signs and other indicators. Particularly, comparison between data before onset of pyrexia and those after the treatment is useful for assessing the severity and predicting the course.

Table 1. Items Used to Assess the Infection and Points

Vital signs	Point
Body temperature	➢ Body temperature does not necessarily reflect severity. The positive rate of blood culture also does not change according to the body temperature,[11] and some patients with a low body temperature may actually have a serious infection.
Respiratory rate	➢ Tachypnea is a sensitive indicator of sepsis. ➢ According to qSOFA, **22 beats/min or above** is considered as one criterion.[12] ➢ In elderly patients with chronic diseases, however, a rate of 16 to 25 beats/min is deemed normal, and the rate of 30 beats/min or higher requires caution.[13] ➢ In the intensive care unit, blood pressure and pulse rate are controlled with drugs, etc., but the respiratory rate remains high.
Blood pressure	➢ Even if the patient does not experience obvious hypotension, blood pressure lower than usual should be considered as a potential sign of shock. ➢ Attention should be paid especially when pulse and systolic blood pressure are reversed. ➢ According to qSOFA, **systolic blood pressure of 100 mmHg or lower** is considered as one criterion.[12]
Pulse rate	➢ Pulse rate increases in association with pyrexia but is unlikely to increase in elderly patients and patients taking drugs such as β-blockers.
Consciousness level	➢ In case the level is worse than usual, delirium suddenly manifests, and the mood is worse than usual are all considered as disturbed consciousness, which is recognized as a symptom that occurs at an early stage of sepsis. ➢ According to qSOFA, a **change in consciousness level** is also considered as one criterion.[12]
Useful indicators in inpatients	**Point**
Dietary intake	➢ Pyrexia accompanied by decreased dietary intake is a criterion for bacteraemia.[14]
Chills and shivering	➢ Patients who experience mild chills (wanting to put on a jacket), chills (wanting to drape a blanket over oneself), and shivering (shaking despite use of a thick blanket) are reported to have bacteremia at the odds ratios of 1.8, 4.1, and 12.1, respectively.[15]
Blood glucose level	➢ Unexplained hypoglycemia in inpatients in whom blood glucose level is measured may also be a premonitory sign of sepsis.[16]

White blood cell count (WBC) and C-reactive protein (CRP), which are conventionally used in daily clinical practice, are not recommended as primary indicators of empirical treatment because they vary depending on various other factors.[17] Procalcitonin level is considered a specific indicator of bacterial infection, but is reported to have inadequate sensitivity to bacteremia in inpatients.[1] A positive result for procalcitonin does not contribute to the assessment of causative organs or microorganisms and thus has no impact on the decision as to which antibacterial agents should be chosen. Physicians, therefore, should not make judgment based only on a single value and must pay careful attention to the patient for any premonitory signs of sepsis such as a change in vital signs other than pyrexia, shivering, reduced dietary intake, and hypoglycemia without overlooking anything. In addition to the above signs, the presence of organ disorder indicates severe disease, increasing the importance of the choice of the initial treatment. The previously described SOFA score is one of the organ disorder assessment measures.[18]

2) Reality of empiric treatment for pyrexia in inpatients

Pyrexia occurring within 48 hours of hospitalization should be treated as a symptom of community-acquired infection, while the symptom occurring after that should be considered attributable to nosocomial infection. For pyrexia occurring immediately after admission, however, the possibility of nosocomial infection should still be assumed if the inpatient has been transferred from a care facility or has a history of hospitalization within the last 90 days.

Antibacterial agents used in empiric treatment should have a limited spectrum covering only potential causative microorganisms suggested by the differential diagnosis.[19] That is, severe disease may not have to be treated with broad-spectrum antibacterial agents, and carriers of resistant strains may not have to be treated with antibacterial agents that cover these strains. The incidence of infections caused by a resistant strain in patients carrying the resistant strain is reported to be 8% to 14%, which is not so high.[20]

Patients with severe disease should immediately be treated with antibacterial agents.[10] "Surviving Sepsis Campaign Guidelines 2021" recommends that patients with sepsis accompanied by shock be treated within 1 hour after collection of a specimen for culture.[17]

For patients who experience pyrexia but are considered unlikely to have severe sepsis, on the other hand, broad-spectrum antibacterial agents may not always have to be chosen as the initial empiric treatment. For such cases, the option of a wait-and-see approach without antibacterial agents after collection of a specimen for culture and a treatment strategy starting with narrow-spectrum antibacterial agents followed by a change of antibacterial agents based on the later obtained culture results are also available.[21]

Once treatment with antibacterial agents is initiated, optimization of the treatment must be implemented. Choice of antibacterial agents for empiric treatment greatly vary among regions or institutions because of the prevalence of resistant strains. For this reason, institutional guidelines recommended by the antimicrobial stewardship team (AST) in the hospital, if available, should be referred to.

There are relatively limited cases that require differentiation of bacteria causing problematic infections in hospital, and common ones are CRBSI (peripheral venous line, central venous line, arterial line, dialysis catheter, etc.), UTI (including CAUTI), pneumonia (including VAP), CDI, and SSI. The other cases include biliary tract infections and skin and soft tissue infections originating from pressure ulcer lesions. Table 2 summarizes the representative causative microorganisms that are problematic with each infection.

Table 2. Representative Causative Microorganisms That Are Problematic in Common Nosocomial Infections

Infections	Possible causative microorganisms
CRBSI	➢ *Staphylococcus epidermidis*, *Staphylococcus aureus*, Gram-negative bacilli, *Candida* spp.
UTI	➢ Gram-negative bacilli, *Enterococcus* spp. ➢ Detection of *S. aureus* indicates bacteremia precedes UTI.
Pneumonia (including VAP)	➢ Gram-positive cocci, *S. aureus*, Gram-negative bacilli in the mouth
SSI	➢ Superficial layer: *S. aureus* (methicillin-susceptible *Staphylococcus aureus* [MSSA], methicillin-resistant *Staphylococcus aureus* [MRSA]), *S. epidermidis* ➢ Deep sites: *S. aureus*, Gram-negative bacilli ➢ Organ/space: Gram-negative bacilli, anaerobes, *Enterococcus* spp., *Candida* spp.

Finally, when treatment with antibacterial agents is initiated, it should subsequently be optimized, not only as far as the type of antibacterial agents, but also concerning the regimen, including dosages, dosing intervals, and timing. Treatment that is not adequate in any of the above conditions would have the increased risk of poor outcome as well as adverse drug reactions and development of resistant strains. Patients should be instructed to adhere to these conditions for improved outcome.[22]

The treatment plan should be based on the patient's renal functions but revised through the orders which are issued in response to inquiries from ward pharmacists or AST.

(iv) Interpretation of culture results

Summary

- Culture results do not necessarily reflect the true causative microorganism.
- Since the prevalence of causative microorganisms differs among organs, attention should be paid not only to the type of the detected microorganism, but also to the nature of the culture specimens in which the microorganisms were detected.
- If *S. aureus* is detected in urine culture, the infection is unlikely to be UTI, and the possibility of bloodstream infection should be considered.
- If bacteria prone to contamination (contaminating bacteria) are detected in 1 of 2 sets of blood culture, the result is likely to be affected by contamination. If these bacteria are detected in both of 2 sets, they should be deemed as true causative bacteria.

1) Interpretation of culture results

Microorganisms detected in culture may be colonized (carried) organisms depending on the specimen and are thus not necessarily the target of treatment. This principle is also applicable to "microorganisms that are problematic in infections in inpatients" described later. Even if antimicrobial-resistant strains are detected, they may not have to be set as the target of treatment as long as they are colonized. Whether the detected bacteria are actually the cause of the infection should always be determined taking clinical and Gram staining findings into account.

Microorganisms causing pneumonia in hospitals often include resistant Gram-negative bacilli and *S. aureus*. *S. epidermidis*, *Candida* spp., and *Enterococcus* spp., even if detected in culture of a specimen from the respiratory tract, are not usually considered as causative bacteria. In hospitals, UTI is commonly caused by resistant Gram-negative bacilli and *Enterococcus* spp., *Candida* spp., *S. aureus*, and *S. epidermidis* are not usually considered as causative bacteria. However, if *S. aureus* is detected in urine culture, bloodstream infection is reported to coexist in approximately 27% of patients positive for this organism, and thus a blood specimen for culture should be collected from those with increased inflammatory reaction where applicable.[23] A specimen collected by scratching a diabetic foot gangrene lesion is highly likely to contain contaminating bacteria but not true causative ones.

2) Blood culture results

A judgment about whether the microorganism detected in blood culture is a true causative bacterium or a contaminating one can differ depending on the microbial species.

If *Streptococcus pneumoniae*, group A β-hemolytic *streptococcus* spp., *S. aureus*, Gram-negative bacilli, or *Candida* spp. is detected even in 1 cultured set, the detected bacteria should be considered as a true causative one. On the other hand, if coagulase negative *Staphylococcus* (CNS), *Cutibacterium* (formerly *Propionibacterium*) spp. (*Propionibacterium acnes* is reclassified into *Cutibacterium*), *Corynebacterium* spp., or *Bacillus* spp. is detected only in 1 cultured set, the detected microorganism may be deemed as a contaminating one (Tables 3 and 4). However, if any of these strains are detected in 2 or more cultured sets, the detected bacteria should be deemed as a true causative one, and appropriate treatment should be considered.[24]

If it is difficult to judge whether the blood culture results, including detection of CNS, are affected by contamination, blood culture should be performed again. If the patient's clinical symptoms do not improve, start of treatment with antibacterial agents should be considered in addition to the repeated blood culture.

If only 1 set of blood cultures is available, it is difficult to judge whether contamination has occurred.

Table 3. Proportion of True Causative Bacteria and Contaminating Ones Detected in Blood Culture[25]

Microbial name	Truly causative	Contaminating	Unknown clinical meaning
Streptococcus pneumoniae	100%	0%	0%
Candida glabrata	100%	0%	0%
Candida albicans	98%	0%	2%
β-hemolytic streptococci	97%	0%	3%
Bacteroides spp.	97%	0%	3%
Escherichia coli	97%	1%	2%
Klebsiella pneumoniae	95%	1%	4%
Staphylococcus aureus	93%	1%	6%
Clostridium spp.	64%	24%	12%
Enterococcus	63%	11%	26%
Viridans streptococci	30%	55%	15%
CNS	10%	82%	7%
Corynebacterium spp.	8%	88%	3%
Bacillus spp.*	0%	100%	0%

*There is a report that *Bacillus* spp. was identified as the true causative bacteria in 8.3% of infection cases.[24]

Table 4. Proportions of True Causative Bacteria and Contaminating Ones When CNS (*Staphylococcus epidermidis*) is Positive in Blood Culture[24]

Number of positive sets	Truly causative	Contaminating	Not determined
1/1	0	97%	3%
1/2	2%	95%	3%
2/2	60%	3%	37%
1/3	0	100%	0%
2/3	75%	0	25%
3/3	100%	0	0%

(v) Optimization of choice of antibacterial agents

Summary

- Once the treatment is initiated, the effectiveness must be evaluated. If there is no evidence of bacterial infection at 72 hours of the treatment, discontinuation of antibacterial agents should be considered.
- Of bacteria detected in culture, potentially causative bacteria should be identified, and a switch to narrow-spectrum antibacterial agents should be made to cover the identified bacteria (de-escalation, narrowing).
- If the patient's condition deteriorates even within 72 hours after starting the treatment, the causative organs, causative microorganisms, and choice of antibacterial agents should be reconsidered.

1) Timing of assessment of treatment effectiveness and culture results

Choosing appropriate antibacterial agents for the initial treatment is difficult, and inappropriate and/or unnecessary antibacterial agents are often used (see Appendix, p. 1).

Once treatment with antibacterial agents is initiated, the treatment must be optimized by evaluating the treatment effectiveness appropriately and based on culture results. The recommended timing of evaluating the empiric treatment with antibacterial agents and optimization of the antibacterial treatment in inpatients is at 72 hours after the start of the treatment.[26-29]

According to a report,[30] in case of blood cultures that remained negative after incubation for 48 hours or longer, 99.8% finally provided a negative result. According to another report,[31] of blood cultures of bacteremia specimens from patients with neutropenic fever, 90% or more provided a positive result within 24 hours of incubation. Although *Candida* spp. requires longer growth time than general bacteria, most fungi that potentially cause problematic pyrexia among inpatients provide a positive result within 72 hours of incubation.

Sputum culture and urine culture have not been fully characterized, leaving the susceptibility of some microorganisms still unknown, but at least predominant causative bacteria are specified. If the treatment with antibacterial agents is effective, Gram-stained preparations can indicate a decrease in microbial count or disappearance of microorganisms before the culture results become available. If UTI responds to antibacterial agents, a decrease in microbial count can be found within several hours after the start of treatment. For pneumonia and UTI, recommended timing of assessment of the treatment effectiveness is 72 hours after start of the treatment; at this timing, whether the response is observed should be checked.[29,32]

If the bacterial test is outsourced to an external institution, the assessment may be delayed by the transportation time.

The above recommended timing was determined based on aspects described below. At 72 hours after the start of the treatment in clinical settings:

A) Most of the culture results are available and the diagnosis of the infection and causative microorganisms can be confirmed (or suspected microorganisms are ruled out); and
B) The treatment effectiveness with antibacterial agents can be confirmed.

Last but not least, it is still important to assess patients every day.[33] Of note, when information that enables optimization earlier than the above timing becomes available, the optimization should be implemented immediately.

2) Evaluation of appropriateness

Even if broad-spectrum antibacterial agents used in the initial empiric treatment are safe and effective for the disease, the current broad-spectrum antibacterial agents are considered inappropriate as long as the disease can respond to narrow-spectrum antibacterial agents and evidence of the treatment is available. One reason for considering the broad-spectrum antibacterial agents inappropriate is that the above empiric treatment leads to overuse of broad-spectrum antibacterial agents and thereby increases the risk for the development of resistant strains in the concerned patient and population in which he or she is included. Another reason is related to the fact that first-line antibacterial agents are specified for each term of infection and most of them have a narrow spectrum; continued use of non-first-line broad-spectrum antibacterial agents increases the risk for treatment failure (inappropriate).

If infection is not reasonably proven by the culture results, imaging examinations, etc., the continued use of the initially used antibacterial agents is considered unnecessary. In addition, antibacterial agents continued beyond the standard therapy duration are considered unnecessary as well (unnecessary).

If the dose, dosing interval or regimen does not meet the recommendations based on the patient's renal function, such treatment is also considered inappropriate (suboptimal).

Emphasis has been placed on the above uses of antibacterial agents leading to increasing resistant strains,[34] the emergence of adverse reactions,[35] and the development of CDI.[36] According to a publication,[35] the incidence of adverse reactions to antibacterial agents in inpatients at the internal medicine department is approximately 20%, and unnecessary antibacterial agents are responsible for approximately 20% of the adverse reactions.

3) The reality of the optimization of choice of antibacterial agents for pyrexia in inpatients

At 72 hours after the start of treatment (no need to wait if earlier judgment can be made),

A) If bacterial infection to be treated is not reasonably proven based on the course of treatment and the test results, the initially used antibacterial agents should be discontinued.
B) The disease duration of bacterial infection is determined based on the course of treatment and the test results.
C) If no bacteria requiring anti-MRSA drugs, such as MRSA, are detected, anti-MRSA drugs should be discontinued.
D) If empirical treatment with carbapenems is initiated, switching to more narrow-spectrum antibacterial agents should be implemented, except in case of bacteremia caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria, infections susceptible only to carbapenems, and severe diseases with unknown focus owing to neutropenic pyrexia in patients with hematological malignancy.
E) If there is no infection involving multiple microorganisms including obligate anaerobes, switching to antibacterial agents other than combination antibacterial agents containing a β-lactamase inhibitor should be implemented.
F) If appropriate antibacterial agents are used and the patient's condition is stable,

switching to broad-spectrum antibacterial agents at the middle of treatment has no merit.[37]

G) If the patient has a severe disease or strong concern about discontinuation of antibacterial agents, the therapy duration should be specified according to the disease duration of the diagnosed infection. Uncertainty of the diagnosed term has been pointed out as a factor for use of unnecessary antibacterial agents, and thus giving the definite diagnosis leads to antimicrobial stewardship.[38]

4) Optimization in specific situations

A) Fluoroquinolones should be used only for infections for which the first-line drugs are fluoroquinolones or for which alternative drugs other than fluoroquinolones are not available. Serious adverse reactions have been reported in elderly patients although the incidence is low.[39]

B) *Candida* spp. should be specified as the target of treatment if it is detected in a specimen of severe community-acquired gastrointestinal perforation or nosocomial intraabdominal infection (organ/space SSI).[40]

C) *S. aureus* or Gram-negative bacillus should be specified as the target of treatment in principle, if it is detected even in 1 set of blood culture. If the infection is not polymicrobial, antibacterial agents should be optimized only to cover the detected microorganism.[41]

D) In patients with neutropenic pyrexia, antipseudomonal antibacterial agents should be continued in principle, but if vital signs are stable, antibacterial agents may be optimized based on culture results.[42] Similar treatment is reported to lead to no clinical deterioration in patients with underlying hematological malignancies (acute myeloid leukemia, etc.).[43,44]

Switching from broad-spectrum antibacterial agents to narrow-spectrum ones is reported to be safe.[45-49] The same is true for antifungal drugs.[50,51] The narrowing strategy is reported to decrease the risk for CDI.[52] The goal of antimicrobial stewardship is to maximize outcomes and minimize the risk for the development of antimicrobial-resistant strains, adverse drug reactions, and CDI in patients.

Post prescription review and feedback for of broad-spectrum antibacterial agents and AST recommendations such as feedback are shown to reduce the amount of broad-spectrum antibacterial agents used without affecting mortality or hospital stay.[53-56] The knowledge of the choice of regimens and appropriate therapy duration for infections is updated every day. Optimization of choice of antibacterial agents should be implemented or supported by not only attending physicians but also the entire hospital staff including AST and infectious disease specialists because it is effective for improving the outcome of the patients and preventing the development of antimicrobial-resistant strains.

(vi) Duration of antimicrobial therapy

Summary

- The duration of antimicrobial therapy should be determined by taking all relevant factors into account, including the patient background, infected organs, and causative microorganisms.
- Short-term antimicrobial therapy can be considered if there are no complications such as abscess and the clinical course is favorable.
- If it is difficult to remove a catheter, prosthesis, or device, or if there is an abscess

without drainage, consider prolonged duration of antimicrobial therapy.

1) Recent trends of the duration of antimicrobial therapy for the common infections during hospitalization

The duration of antibacterial therapy has largely been determined by common practice based on expert opinions, rules of thumb, and the like, and in reality, there is little good quality evidence from randomized controlled trials (RCTs), etc.[57] It has recently been recognized that administration of antibacterial agents has significant repercussions in the form of problems with drug resistance and disruption of the normal flora.[58-60] Considering these concerns of excess use of antimicrobial agents, much clinical research assessing the efficacy and safety of short-course of antimicrobial therapy have been conducted, and the evidence supporting short-course therapy has been accumulated. Consequently, the short-course of therapy for several infections are commonly accepted and guidelines have adopted them.[61] On the other hand, there are major concerns about shortening the therapy duration, including treatment failure, relapse, and associated increase in mortality.[62-65]

Table 5. Examples of Duration of Antimicrobial Therapy Commonly Encountered During Hospitalization, and Recent Trends

Infections	Standard therapy duration*	Shortened therapy duration*
Hospital-acquired pneumonia, including VAP	14-15 days	7-8 days
Uncomplicated cystitis in women	3 (−7) days	—
Uncomplicated pyelonephritis in women	10-14 days	5-7 days
Febrile UTI in men	14 days	—
CAUTI	7-14 days	・ 5 days for non-severe cases treated with levofloxacin ・ 7-day course is considered for treatment with intravenous β-lactams or oral antibacterial agents with excellent bioavailability, even if complicated by bacteremia.
Cellulitis	10 days	5-6 days
Uncomplicated CRBSI	・ CNS: 5-7 days ・ *Enterococcus* spp., Gram-negative bacteria: 7-14 days ・ *Staphylococcus aureus*, *Candida* spp.: For at least 14 days following negative conversion of blood culture (Catheter must be removed. For details, see individual chapters)	—
Acute cholecystitis	7-14 days	・ Mild to moderate: 24 hours after cholecystectomy ・ Severe: 4-7 days after cholecystectomy
Acute suppurative cholangitis	4-7 days	3-5 days
Perforative peritonitis	10-15 days	4-8 days
Postoperative intraabdominal infection with adequate drainage	10-15 days	4-8 days
Postoperative intraabdominal infection with inadequate drainage	Must be considered on a case-by-case basis	Not clear
Uncomplicated *S. aureus* bacteremia**	28-42 days after negative conversion of the blood culture	14 days after negative conversion of the blood culture
Uncomplicated Gram-negative bacteremia (*Enterobacterales*)	10-14 days	7 days
Uncomplicated Gram-negative bacteremia (glucose non-fermenting bacteria [e.g., *Pseudomonas aeruginosa*, *Acinetobacter* spp., etc.])	11-15 days or 11-21 days	6-11 days

*See pages 2-4 of the Appendix for points to consider and reference literature on the therapy duration.

**See the section on *Staphylococcus aureus*.

2) Essential concepts of determining the duration of antimicrobial therapy and some pitfalls

A) Factors involved in the determination of therapy duration

It is crucial to grasp the pathophysiological conditions of the patients for determining the duration of antimicrobial therapy.[66] The points that must be ascertained before the determination of therapy durations are summarized in Table 6.

The first point is to assess background factors such as underlying diseases. If severe immunodeficiency is present, short-term therapy may not be indicated. In addition, if solid organ tumors are present in the background, intractable infections associated with anatomical abnormalities such as narrowing or obstruction of the airway or biliary tract by tumors or anatomical changes due to surgery or radiotherapy are likely to occur.[67,68]

Second, every effort should be made for the identification of the specific organ involved. For example, in male patients, the UTIs that are most commonly accompanied by high fever are pyelonephritis and prostatitis,[69] but in the latter case, some experts will recommend a therapy duration of 2 to 4 weeks because of poor drug penetration into the prostate gland.[70] In a recent RCT, it was even reported that 7 days of therapy was inferior to 14 days of therapy in male patients with febrile UTIs (including prostatitis).[63]

Causative microorganisms and their antimicrobial susceptibility are also important. For VAP, most guidelines recommend therapy for 7 days.[71] However, in an RCT on VAP caused by *P. aeruginosa*, it was reported that short-term therapy (8 days) was not shown to be non-inferior to long-term therapy (15 days).[72] With highly antimicrobial-resistant bacteria, therapy duration should be carefully considered when non-first-line antibacterial agents are used. It is also important to evaluate for the presence of local infectious complications such as abscess and remote infectious complications, including intravascular infections such as infective endocarditis, because surgical intervention or prolongation of the therapy duration may become necessary. Moreover, if the infection involving a catheter, prosthesis, or device, whether or not it is possible to remove the object becomes an important consideration when deciding upon the duration of antimicrobial therapy.

For the blood stream infections caused by *S. aureus* and *Candida* spp. or the intravascular infections, the negative blood cultures need to be confirmed for setting the start point of the duration of antimicrobial therapy.[6,73,74]

While fever resolution and hemodynamic stabilization (vital signs) are important indicators in the evaluation of response to therapy, attention should also be paid to changes in general condition (dietary intake, etc.), blood test findings, and symptoms specific to infected organs. Short-term therapy may not be indicated in cases with a slow response to therapy.[75]

Table 6. Points That Must Be Grasped When Determining the Therapy Duration

- Patient background factors such as underlying diseases: in particular, immunodeficiency and anatomical changes/abnormalities
- Infected organs
- Causative microorganisms and their antimicrobial susceptibility
- Are there any local infectious complications such as an abscess, pyothorax, or a purulent thrombus?
- Are there any remote infectious complications (arthritis, vertebral discitis, infective endocarditis, etc.)?
- Has the infection involved a catheter, prosthesis, or device, and if it has, can the object be removed?
- In patients with bloodstream infections, especially those due to *S. aureus* or *Candida*, as well as in patients with intravascular infections, including CRBSI, has the negative conversion of the blood culture been confirmed?
- Has the response to therapy with antimicrobial agents been favorable? (Generally evaluated at about 72 hours)

B) Conditions for indication of short-term therapy

In many cases, there are conditions for the indication of short-term therapy. For example, the therapy duration for *S. aureus* bacteremia is generally 4 to 6 weeks after negative conversion of blood culture,[76] but in cases of "uncomplicated" bacteremia that meet certain conditions, it may be possible to select short-term therapy as an exception (See section on *Staphylococcus aureus*).[77]

Moreover, while the therapy duration for bacteremia caused by Gram-negative bacteria has traditionally been 14 days, RCTs have demonstrated the non-inferiority of 7 days of therapy, particularly for "uncomplicated" bacteremia caused by *Enterobacterales*,[78-80] and a meta-analysis also showed no significant differences in outcomes between the 7-day and 14-day therapy groups[81] (see Appendix, p 5). In a study that used the Delphi method to attempt to define "uncomplicated" bacteremia caused by Gram-negative bacteria, cases that met all of the conditions in Table 7 were defined as "uncomplicated" bacteremia.[82] When determining whether short-term therapy is indicated for a patient, clinicians should carefully consider whether these conditions generally apply to the case.

Table 7. Example of the Expert Definition of Uncomplicated Bacteremia Caused by Gram-negative Bacteria[82]

・ **The infection focus that caused the bacteremia is one of the following:** (1) UTI, (2) intraabdominal/biliary tract infection, (3) CRBSI, (4) pneumonia (excluding cases with organic lung disease, complication of pyothorax/abscess, and cases with cystic fibrosis), (5) skin or soft tissue infection
・ **Source control** – Removal of any infected hardware and catheter devices and near complete drainage of infected fluid collections, as well as image assurance of no residual or metastatic sites of infection, if necessary.
・ **Patients without immunocompromise and risk for opportunistic infections (e.g., recent solid organ transplant recipients; expected prolonged neutropenia with ANC <500 cells/mL during the GN-BSI treatment course; recent CD4 cell count <200 cells/mL; chronic corticosteroids and/or immunomodulator therapy)** – Select immunocompromised patients such as those on stable immunomodulatory therapy may be considered on a case-by-case basis
・ **Clinical improvement within 72 hours of effective antibiotic treatment—at a minimum includes defervescence and hemodynamic stability** – A short-term therapy is not impossible even if this condition is not met, but if this condition is met, the patient is an active reasonable candidate for short-term therapy.

(2) Management

(i) Principles for confronting the cases with insufficient response to antimicrobial therapy

Summary

- The choice of parameters of and timing of assessing the response to antimicrobial therapy are crucial.
- The causes of insufficient response to antimicrobial therapy vary, so the assessment for the causes should be taken prior over the change of antimicrobial agents.
- It is important to consider what the causative microorganisms might be evoking from the patient background, and to make a thorough investigation of which microorganisms are not covered by the antimicrobial agents currently being administered.

A) Timing of response assessment and importance of parameters used for response assessment

For the appropriate timing for assessing the response to antimicrobial therapy, see the previous section ((v) Optimization of choice of antibacterial agents, (1) Timing of assessment of treatment and culture result). If this timing is too early, the response might be underrated and unnecessary addition or change of antimicrobials might be performed.

The appropriate choice of parameters for assessing the response to therapy is also important. Parameters used for assessment of the response to therapy can be roughly divided into 2 types: non-organ-specific parameters such as pyrexia, dietary intake, white blood cell count, and CRP level, and parameters with relatively high specificity for infected organs, for example, in the case with pyelonephritis, this type of parameter includes lower back pain, tenderness of costovertebral angle (CVA), laboratory data like pyuria and bacteriuria. (Table 8). When assessing the response to the antimicrobial therapy, consideration for these two types of parameters should be taken. And in the case with insufficient response, it is important to grasp that what kind of parameter is not improved.

One of the shortcomings of the parameters nonspecific to the organs is that this kind of parameters are likely to be affected by the new infections in other organs or non-infectious inflammatory diseases. For example, in the case with pneumonia, prolonged fever during the therapy may be observed despite of the improvement of the organ-specific parameters like respiration rate, oxygen saturation, symptoms like difficulty of breath, and the auscultation findings of lungs. In this case, the differential diagnosis of prolonged fever includes a variety of causes; local infective complications like lung abscess formation, remote complications like infective endocarditis or vertebral osteomyelitis, newly occurred infections other than pneumonia such as CAUTI and CRBSI, and non-infection causes of fever like pseudogout and drug fever, as well as the worsened pneumonia.[83]

On the other hand, some parameters, such as improvement in chest imaging findings in pneumonia, are organ-specific but may lag behind the clinical improvement.[84] In such cases, assessing the response of pneumonia to treatment based on the chest imaging findings alone may lead to unnecessarily use of broad-spectrum antimicrobial agents and prolonged treatment. Furthermore, particularly in nosocomial infections, there may be a paucity of clinical parameters other than non-organ-specific symptoms such as pyrexia and increased CRP to begin with (Typically, this applies to some cases of CRBSI and CAUTI). In infections with few organ-specific findings, repeating the blood culture or repeating Gram staining of samples collected from an infected organ to compare findings over time may help with response assessment.

Table 8. Classification of Parameters Used in Infection Response Assessment and Representative Examples

<table>
<tr><th>Type of parameter</th><th>Characteristics</th><th colspan="2">Representative examples</th></tr>
<tr><td>Non-organ-specific parameters</td><td>・ Easy to monitor
・ Tend to reflect severity
・ Evaluation does not vary much depending on the evaluator
・ Variability due to various factors may make disease assessment of infections difficult
・ Certain parameters do not reflect disease activity in real time</td><td colspan="2">・ Pyrexia, chills, shivering
・ General malaise
・ Consciousness (especially in the elderly)
・ Blood pressure, pulse rate, respiratory rate
・ Dietary intake
・ Hematological findings (white blood cell count, CRP, procalcitonin, and lactic acid)
・ Arterial blood gas analysis findings</td></tr>
<tr><td rowspan="5">Parameters with relatively high specificity to infected organs</td><td rowspan="5">・ Factors affecting disease assessment are narrowed down, making it easier to judge exacerbation/improvement of infection being treated.
・ Evaluation of parameters such as physical findings and Gram staining findings is likely to be subject to examiner variability.
・ Certain parameters may be less sensitive depending on the patient population (e.g., children, elderly, immunocompromised).
・ Certain parameters may be easily affected by non-infectious factors (For example, in the case of lung parameters, respiratory discomfort, oxygen saturation, and chest image findings may change in the presence of pulmonary edema, etc.)
・ Certain parameters may improve more slowly than the infection itself.
・ Depending on which organ is infected, there may be few such organ-specific parameters.</td><td>Infected organs</td><td>Representative parameters</td></tr>
<tr><td>Lung (pneumonia)</td><td>・ Difficulty of breathing, amount and nature of sputum, chest pain or back pain (if inflammation develops in the pleura)
・ Respiratory rate, oxygen saturation
・ Chest auscultation findings
・ Sputum Gram staining findings
・ Chest imaging findings</td></tr>
<tr><td>Kidney (Pyelonephritis)</td><td>・ Low back pain/flank pain
・ CVA percussion tenderness, bilateral renal tenderness
・ Pyuria/bacteriuria
・ Urine Gram staining findings</td></tr>
<tr><td>Prostate (Prostatitis)</td><td>・ Dysuria, painful urination
・ Prostatic tenderness on digital rectal exam</td></tr>
<tr><td>Intravascular (infective endocarditis, CRBSI)</td><td>・ Negative conversion of blood culture
・ Imaging findings (infective endocarditis, infected aneurysm, etc.)</td></tr>
<tr><td>Meninges/brain (meningitis/ encephalitis)</td><td>・ Headache, nausea and vomiting
・ Consciousness
・ Signs of meningeal irritation such as nuchal rigidity, neurological findings
・ Cerebrospinal fluid findings
・ Cerebrospinal fluid Gram staining findings, negative conversion of cerebrospinal fluid culture</td></tr>
</table>

B) The process to differentiate the causes for insufficient response to the antimicrobial therapy

In the hemodynamically collapsed cases due to infections, even after administration of antimicrobials, considering the change to broad-spectrum antimicrobials is reasonable.' However, even in these cases, the thorough list of the potential causative pathogens should be made, because the causative pathogens are different according to the patient's background, such as underlying illness, or history of medical exposure, animal exposure, and foreign travel. For example, when making a differential diagnosis of treatment-refractory pneumonia in the elderly or immunocompromised patients, tuberculosis and nontuberculous mycobacteriosis should be considered. In another instance, *Candida* spp. should be considered as the cause of sepsis in patients with long ICU stay and exposure to broad-spectrum antimicrobial agent after abdominal surgery.[85] Thus, it is important to list the potential causative pathogens assumed from the patient's conditions and to consider whether each potential pathogen is covered by the currently administered antimicrobials.

If the patient's general condition is not bad but the infection does not seem to be improved, consider making a differential diagnosis of the cause as shown in the table.[83,86,87]

When an infection does not seem to have responded to treatment, the clinician will often consider switching antibacterial agents, bearing in mind the possibility of antimicrobial-resistant bacteria, but in many cases, the spectrum of the antimicrobial agent is not the reason why it is not effective (See Appendix, p. 5).

If the therapeutic effect seems to be insufficient, it is important to consider the differential diagnosis in Table 9 and investigate the cause by adding microbiological tests and imaging tests as necessary. At the same time, adding or switching antimicrobial agents should be considered, taking into account the possibility of infection caused by microorganisms that are not covered by the spectrum of the antimicrobial agent being administered.

Table 9. Main Causes of Insufficient Response to Treatment

Classification	Differential diagnosis
Problem with response assessment	➢ Timing of response assessment was too early (See main text) ➢ Problem with parameters used in response assessment (See main text) ➢ Problem with setting therapeutic parameters: deciding whether to make colonized bacteria an object of treatment, etc.
Problem with antimicrobial spectrum	➢ Drug-resistant bacteria: MRSA, ESBL-producing bacteria, multidrug-resistant *P. aeruginosa*, etc. ➢ Microorganisms' clinicians are less likely to consider: *Legionella*, fungi, mycobacteria (particularly tuberculosis), parasites, etc.
Problems related to the method of administration of antimicrobial agents	➢ Method of administration that disregards pharmacokinetics (PK) and pharmacodynamics (PD): dosing interval too long, dose too low, failure to take into account the effects of renal function or dialysis ➢ Problem with organ penetration: particularly in meningitis and prostatitis ➢ Decreased effect owing to drug interactions
Presence of immunodeficiency	➢ Neutropenia, use of immunosuppressants, HIV infection, etc.
Infection accompanied by focal anatomical changes	➢ Empyema, abscess, formation of a purulent thrombus ➢ Obstruction by tumor or stone
Remote site infection	➢ Complication with infective endocarditis, arthritis or osteomyelitis
Complication of new infection	➢ Infections of organs not targeted for treatment: pneumonia, CRBSI, CAUTI, decubitus infection, sinusitis, etc. ➢ CDI
Causes other than infection	➢ Drug fever/drug eruption, phlebitis, deep vein thrombosis, pseudogout, etc.

(ii) Intravenous and oral administration of antibacterial agents

Summary

- There are many advantages of switching from intravenous to oral antibacterial agents, and if possible, this should be considered proactively.
- When switching to oral antibacterial agents, it is necessary to meet certain conditions.
- If drugs with excellent bioavailability are selected, oral antibacterial agents can be expected to be as effective as intravenous antibacterial agents in many cases.

Introduction

The routes of administration for antibacterial agents are intravenous and oral. For inpatients, intravenous administration of antibacterial agents is often selected as the initial treatment for reasons such as severity and difficulties with oral intake. Although intravenous administration can be used throughout the entire therapy duration in some cases, switching from intravenous to oral administration has various advantages. For example, it makes it possible to reduce drug costs and the time involved in the dispensing of intravenous antibacterial agents. It can also shorten the hospitalization period, improve patient comfort, and reduce infusion-related complications such as infection and thrombosis.[88-90] For this reason, from the standpoint of antimicrobial stewardship, it is desirable to proactively consider switching in cases where it is possible.

Switching from intravenous antibacterials to oral antibacterials

When considering switching from intravenous to oral antibacterial agents, it is recommended that all of the following criteria be met (Table 10).[89-91]

Table 10. Recommended Criteria for Switching from Intravenous Antibacterial Agents to Oral Antibacterial Agents

- Improvement of clinical symptoms
- Maintenance of fever resolution (below 38°C) for 24 hours; stable respiration and hemodynamics.
- Not an infection requiring continuous treatment with intravenous antibacterial agents (e.g., meningitis, febrile neutropenia, infective endocarditis, etc.)
- Can be administered orally or via nasogastric tube, and sufficient absorption is expected.
- Appropriate oral antibacterial options are available.
- Patients can be expected to continue taking the antibacterial agent without self-interruption (for outpatients, etc.)

As shown below, there are several possible patterns for switching from intravenous antibacterial agents to oral antibacterial agents,[92] but the selection of a drug from among the possibilities should depend on the symptoms of the infection, antimicrobial susceptibility, and patient characteristics (renal function, history of allergy, etc.).

i) Replacing the intravenous form of a drug with the oral form of the same compound (e.g., switching from an intravenous infusion of levofloxacin to oral levofloxacin)
ii) Switching from an intravenous antibacterial agent to the oral form of an equivalent antibacterial agent that is of the same class and same indication but consists of a different compound (e.g., switching from cefazolin IV to cephalexin oral).

iii) Switching from an intravenous antibacterial agent to an oral antibacterial agent that is of another class (e.g., switching from vancomycin IV to oral sulfamethoxazole/trimethoprim [Co-trimoxazole])

Bioavailability of oral antibacterial agents

Bioavailability differs among oral antibacterial agents. An oral antibacterial agent with excellent bioavailability can be expected to be as effective as an intravenous antibacterial agent in many cases. Examples of oral antibacterial agents with good bioavailability (≥ 60%) are listed in Table 11.[90,92,93] For actual administration, it is necessary to determine the duration of microbial therapy according to the infection focus and to adjust the dosage and administration according to the renal function. For voriconazole, blood concentration measurement and dose adjustment by therapeutic drug monitoring (TDM) is recommended.[21,94]

Table 11. Examples of Oral Antibacterial Agents with Good Bioavailability

Antibacterial agent	
Penicillins	Amoxicillin
	Clavulanic acid/Amoxicillin*
Cephalosporins	Cephalexin
Fluoroquinolones	Ciprofloxacin
	Levofloxacin
	Moxifloxacin
Tetracyclines	Doxycycline
	Minocycline
Lincomycins	Clindamycin
Nitroimidazoles	Metronidazole
Oxazolidinones	Linezolid
Co-trimoxazole	Sulfamethoxazole/trimethoprim
Antifungals	
Azoles	Fluconazole
	Voriconazole

*Clavulanic acid bioavailability may be less than 60%[95]

(iii) Antibacterial therapy for terminally ill patients

Summary

- "No administration of antibacterial agents" is also an option at the end of life.

When considering the treatment of a patient at the end of life, it is very important to ask, "What is the goal of treatment?" Given the patient's situation, do we aim to alleviate symptoms or to prolong the patient's life? It is firstly necessary to discuss this with the patient and the family to confirm their intentions and determine the goal. Whether antibacterial agents are necessary and how useful they will be should be judged based on this therapeutic goal (Figure 2).[96] Routine ethical procedures may be required.

Administration of antibacterial agents is not everything in the treatment of infections. A diagnosis is required for appropriate antibacterial administration. In addition to

administration of antibacterial agents, there are other important factors, such as control of the infection focus and improvement of the host immunity. For this reason, invasive tests or treatment may be required in some cases. If antibacterial agents are administered aimlessly without controlling the infection focus, the patient's suffering may actually be unnecessarily prolonged, depending on the patient's condition.

Administration of antibacterial agents cannot alter the natural course of the background conditions such as advanced dementia or cancer. It is important to understand that while it may be possible to prolong survival, the period of suffering may also be prolonged. Moreover, pyrexia is not necessarily caused by infection, and non-infectious types of pyrexia such as tumor fever, drug fever, and thrombus formation must be considered in the differential diagnosis. This being the case, we must carefully deliberate the necessity of choosing to administer antibacterial agents that may disadvantage the patient in multiple ways, including matters like securing of an intravenous infusion route, physical restraints, blood collection, phlebitis, drug eruption, diarrhea, CDI, and the emergence of multidrug-resistant bacteria.

On the other hand, administration of antibacterial agents may be beneficial even in cases where symptom relief is the therapeutic goal. For example, treatment of a UTI may relieve painful urination, and treatment of oral candidiasis may alleviate dysphagia.[97]

The most important thing is to ascertain the treatment goal by thoroughly discussing it with the patient. This should be the basis for judging whether or not administration of antibacterial agents will be beneficial for the patient.

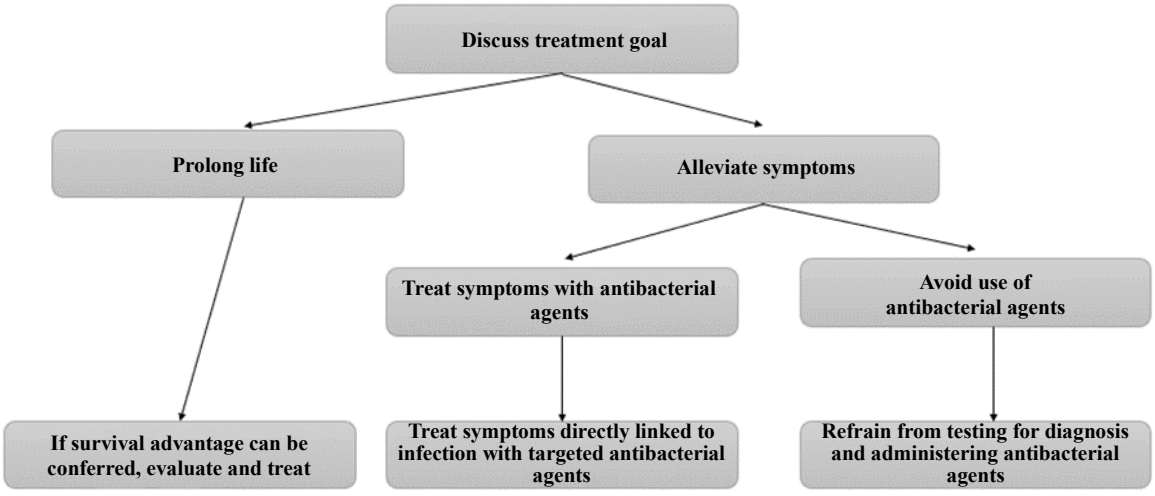

Figure 2. Algorithm for Beginning the Discussion of Antibacterial Use in the Therapeutic Goal Discussion[96]

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Background of Preparation of "Manual of Antimicrobial Stewardship, 3rd Edition"

This manual is the revised 3rd edition of "Manual of Antimicrobial Stewardship, 1st Edition," published on June 1, 2017. The 2nd Edition, published on December 5, 2019, added information on antimicrobial stewardship in infants, and this 3rd Edition has newly added information on antimicrobial stewardship in inpatients. "Manual of Antimicrobial Stewardship, 3rd Edition" was prepared based on the discussion conducted at the 5th Meeting of the Working Group on Antimicrobial Stewardship (AMS), Etc. (Norio Ohmagari, Chairperson) held on September 28, 2023. It was published on November 16, 2023 after being reviewed at the 8th Meeting of the Subcommittee on Antimicrobial Resistance (AMR) (Norio Ohmagari, Chairperson, October 10, 2023 [date decided by round-robin meeting]) and the 80th Meeting of the Health Sciences Council Working Group on Infectious Diseases (Takaji Wakita, Chairperson, October 27, 2023).

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