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Guidelines for the Antibiotic Use in Adults with Acute Upper Respiratory Tract Infections

Young Kyung Yoon[1,2], Chan-Soon Park[3,4], Jae Wook Kim[3,5], Kyurin Hwang[3,5], Sei Young Lee[3,6], Tae Hoon Kim[3,7], Do-Yang Park[3,8], Hyun Jun Kim[3,8], Dong-Young Kim[3,9], Hyun Jong Lee[10], Hyun-Young Shin[11,12], Yong Kyu You[13,14], Dong-Ah Park[15], and Shin-Woo Kim[1,16,17]

[1]Korean Society of Infectious Diseases; [2]Department of Internal Medicine, Korea University College of Medicine, Seoul; [3]Korean Society of Otorhinolaryngology-Head and Neck Surgery; [4]Department of Otolaryngology-Head and Neck Surgery, The Catholic University of Korea, College of Medicine, Seoul; [5]Department of Otolaryngology-Head and Neck Surgery, Soonchunhyang University Hospital Seoul, Seoul; [6]Department of Otorhinolaryngology-Head and Neck Surgery, Chung-Ang University College of Medicine, Seoul; [7]Department of Otorhinolaryngology-Head and Neck Surgery, Korea University College of Medicine, Seoul; [8]Department of Otorhinolaryngology, Ajou University, School of Medicine, Suwon; [9]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University, College of Medicine, Seoul; [10]Korean Association of Otorhinolaryngologists, [11]Korean Association of Family Medicine; [12]Department of Family Medicine, Myongji Hospital, Seonam University, College of Medicine, Goyang; [13]Korean Medical Practitioners Association; [14]Department of Internal Medicine, Nammoon Medical Clinic, Seoul; [15]Division of Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul; [16]Korean Society for Chemotherapy; [17]Department of Internal Medicine, Kungpook National University, School of Medicine, Daegu, Korea

These guidelines were developed as part of the 2016 Policy Research Servicing Project by the Korea Centers for Disease Control and Prevention. A multidisciplinary approach was taken to formulate this guideline to provide practical information about the diagnosis and treatment of adults with acute upper respiratory tract infection, with the ultimate aim to promote the appropriate use of antibiotics. The formulation of this guideline was based on a systematic literature review and analysis of the latest research findings to facilitate evidence-based practice, and focused on key questions to help clinicians obtain solutions to clinical questions that may arise during the care of a patient. These guidelines mainly cover the subjects on the assessment of antibiotic indications and appropriate selection of antibiotics for adult patients with acute pharyngotonsillitis or acute sinusitis.

Key Words: Guideline; Antibiotics; Pharyngitis; Tonsillitis; Rhinosinusitis

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Corresponding Author : Shin Woo Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Kyungpook National University Hospital, 130 Dongdoek-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-6525; Fax: +82-53-426-2046; E-mail: ksw2kms@knu.ac.kr

Use of this guideline

This guideline presents the basic principles of antibiotic use for acute upper respiratory infections in adults aged 19 years or older, in consideration of South Korea's current state of affairs as of March 2017. Physicians should use this guideline as a reference while providing individualized care to patients, and not as a basis for universal application to all adult patients. This guideline cannot be used as a standard criterion to determine the adequacy of a clinician's final decision. Further, while this guideline may be used for personal care and educational purposes, it may not be used for commercial or care evaluation purposes. In cases where parties wish to use this guideline for purposes other than providing care and education, a written request should be submitted to the Committee to obtain written approval.

I. Preface

1. Background and aim

Acute upper respiratory infection (URI) is the most common disease among adults, who generally experience an acute URI two to five times a year [1]. According to data from the United States (US), acute URI is associated with a high disease burden, accounting for 40% of work absence among adult workers and 10% of outpatient and emergency department visits [2,3]. Acute URI refers to acute infection of the nose, sinus, pharynx, middle ear, larynx and epiglottis, airway, and bronchus. The common cold is the most frequent URI. However, these infections are clinically diagnosed based on the predominant symptoms, according to the anatomical location with the most severe infiltration. In other words, URIs are classified into pharyngitis and tonsillitis (characterized by sore throat), laryngitis or epiglottitis (characterized by hoarseness), and rhinosinusitis (characterized by sinus-related symptoms) [4]. In some cases, otitis media, tracheitis, and bronchitis are also classified as acute URI.

The common cold may be caused by various pathogenic viruses. Symptoms include mild fever, nasal discharge, nasal congestion, sneezing, sore throat, cough, and muscle ache. Common cold usually resolves naturally, requiring only symptomatic therapy in certain cases; antibiotic use is not warranted [1-3]. It is well known that use of antibiotics for the common cold is not only ineffective in reducing complications such as bacterial infection but also increases medical costs by inducing side effects and resistance to antibiotics [1-3]. Avoidance of antibiotic use for the common cold is an important national healthcare issue that must be stressed to prevent antibiotic abuse; it is also used as a quality index for health care institutions.

About 5–15% of tonsillitis in adults is caused by bacteria, such as *Streptococcus pyogenes* (Group A beta-hemolytic streptococci) [5, 6], and 0.5–2% of patients may develop acute bacterial rhinosinusitis after a viral respiratory infection [7]. About 10% of acute bronchitis may be caused by bacteria such as *Bordetella pertussis, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*. Therefore, appropriate use of antibiotics is required for some cases of acute URI.

Randomized controlled trials (RCTs) are rare for upper respiratory infectious diseases, and study findings are controversial in many cases, hampering evidence-based care that references a standardized care guideline. Even existing evidence-based guidelines in other countries feature varying stances [8].

In this context, the Korean Society for Chemotherapy, Korean Society of Infectious Diseases, Korean Society of Otorhinolaryngology-Head and Neck Surgery, Korean Association of Otorhinolaryngologists, Korean Association of Family Medicine, Korean Medical Practitioners Association, and National Evidence-Based Healthcare Collaborating Agency have developed a guideline for antibiotic use in adults with upper respiratory infection. This guideline aims to promote the appropriate use of antibiotics by primary care physicians for the care of upper respiratory infection.

2. Scope

This guideline presents the basic principles of antibiotic use in adult patients with suspected URI, in consideration of the current situation in Korea as of March 2017. In particular, we focus on bacterial pharyngotonsillitis and bacterial sinusitis, which both require antibiotics. We plan to regularly revise the guideline according to future changes in Korea.

3. Clinical guideline development committee

In January 2017, a committee was established for the development of an antibiotics guideline for URI in adults. Twelve experts recommended by the Korean Society for Chemotherapy, Korean Society of Infectious Diseases, Korean Society of Otorhinolaryngology-Head and Neck Surgery, Korean Association of Otorhinolaryngologists, Korean Association of Family Medicine, Korean Medical Practitioners Association, and National Evidence-Based Healthcare Collaborating Agency participated in the development of an evidence-based and multi-

Table 1. Recommendation and evidence rating (GRADE system)

Assessment of evidence level					Strength of recommendation
Study design	Initial quality of evidence	Factors that downgrade quality of evidence	Factors that upgrade quality of evidence	Quality of evidence	
Randomized study	High →	Risk of bias Serious: -1 Very serious: -2 Inconsistency Serious: -1 Very serious: -2	Effect size Large: +1 Very large: +2 Positive relation Present: +1	High: 4 Moderate: 3 Low: 2 Very low: 1	Strong: Benefits clearly outweigh harm, or vice versa Weak: All cases other than "strong" recommendation
Observational study	Low →	Indirectness Serious: -1 Very serious: -2 Imprecision Serious: -1 Very serious: -2 Publication bias Strongly suspected: -1	Confounding variables Increased confidence of effect estimation: +1		

disciplinary clinical care guideline.

4. Literature search

Systematic literature searches were performed in PubMed (www.pubmed.gov), EMBASE (www.embase.com), KMbase (kmbase.medric.or.kr), and KoreaMed (www.koreamed.org). A literature search expert performed the searches on March 14, 2017, with date range set to January 1, 2006 through March 14, 2017. In addition, treatment guidelines published worldwide and relevant references were reviewed. From a primary search of 2,117 references, 403 were reviewed and 156 are cited in the present clinical care guideline (Appendix).

5. Key questions and consensus reaching

This clinical care guideline is designed with a focus on key questions (KQ) to help clinicians find solutions to clinical questions they face while treating patients with acute pharyngotonsillitis and sinusitis. A total of 10 key questions (five for acute pharyngotonsillitis and five for acute sinusitis) were chosen under the context of domestic situation through a meeting among the members of the guideline development committee. The nominal group technique was generally used to reach a consensus.

6. Recommendation and evidence rating

Per the GRADE (Grading of Recommendations Assessment, Development and Evaluation; http://www.gradeworkinggroup.org) approach, the quality of evidence was classified into high, moderate, low, and very low, whereas the strength of recommendation was classified into strong and weak (Table 1).

7. External expert assessment

A guideline developed by the guideline development committee was presented at the Korean Society of Chemotherapy in April 2017, and expert opinions were collected. Based on the discussion, revisions were made to the guideline in a meeting among the members of the development committee. Opinions from other expert groups were additionally collected, based on which the guideline was finalized.

8. Terms and abbreviations

This guideline presents technical terms in Korean language according to the Fifth Revision of Medical Terminology (Korean Medical Association, revised in November 2008). Corresponding English terms have been added in parentheses if the meaning is not clearly conveyed using the Korean term. Terms that cannot be presented in Korean, such as names of pathogens, proper nouns, names of drugs, and units, are written in English.

First-line treatment refers to the first round of antibiotic therapy. Second-line treatment refers to a change of antibiotics after first-line treatment is deemed to have failed.

II. Summary of recommendations

Recommendation	Strength of recommendation	Quality of evidence
KQ 1. When should empiric antimicrobial therapy be initiated in patients with signs and symptoms suggestive of acute pharyngotonsillitis?		
1-1. Antimicrobial therapy is recommended for patients with acute pharyngotonsillitis when they have complications.	Strong	High
1-2. Antimicrobial therapy is recommended when the patient's modified Centor score (McIsaac score), which reflects the severity of clinical symptoms of acute pharyngotonsillitis, is three or higher, and the patient tests positive on the rapid antigen test. In cases in which a rapid antigen test is not an option, antimicrobial therapy may be initiated according to the modified Centor score (McIsaac score). Antibiotic therapy may promptly improve and prevent complications of bacterial pharyngotonsillitis.	Strong	High
KQ 2. Which antibiotics should be used for initial empiric antimicrobial therapy in patients with acute bacterial pharyngotonsillitis?		
2-1. Ten-day amoxicillin therapy may be used; however, amoxicillin may not be used when infectious mononucleosis is suspected.	Strong	High
2-2. Five-day cefdinir or azithromycin therapy may be used in cases with poor patient compliance or in cases where 10-day antimicrobial therapy may be difficult for the patient.	Strong	Moderate
2-3. A single intramuscular (IM) injection of benzathine penicillin G (adults: 1,200,000 units IM) may be used. However, this is not recommended as first-line treatment in Korea.	Strong	High
2-4. For patients who are allergic to penicillin: for type 4 hypersensitivity (*e.g.*, rash), 10-day first-generation cephalosporin (cephalexin, cefadroxil) therapy, clindamycin, 10-day clarithromycin therapy, 5-day azithromycin therapy, or 5-day cefdinir or cefpodoxime therapy may be used.	Strong	Moderate
2-5. All beta-lactam antibiotics (*e.g.*, cephalosporin) should not be used for type 1 sensitivity (*e.g.*, anaphylaxis).	Strong	Moderate
KQ 3. When should second-line antibiotic therapy be prescribed for acute bacterial pharyngotonsillitis?		
3-1. When first-line antibiotic therapy fails for *S. pyogenes*-induced acute pharyngotonsillitis, ampicillin/sulbactam, amoxicillin/clavulanate, and narrow-spectrum cephalosporins or clindamycin may be considered as second-line therapy.	Weak	Moderate
3-2. Second-line antibiotic therapy may be considered when *S. pyogenes* continues to be identified from culture or for recurrent infections.	Weak	Moderate
3-3. A change of antibiotics may be considered when the patient develops acute suppurative complications, such as otitis media or peritonsillar abscess, and nonsuppurative complications, such as rheumatic fever and acute glomerulonephritis.	Strong	Moderate
KQ 4. What is the recommended antibiotic therapy in patients with frequent recurrent episodes of apparent bacterial pharyngotonsillitis?		
4-1. Prophylactic antibiotic therapy is not recommended for recurrent bacterial pharyngotonsillitis.	Weak	High
4-2. Recurrent bacterial pharyngotonsillitis may be treated more than once with first-line antibiotics and narrow-spectrum cephalosporin (cephradine, cefadroxil), clindamycin, amoxicillin/clavulanate, or combined penicillin and rifampin therapy may be considered as second-line therapy.	Weak	High
KQ 5. When is referral to a specialist indicated in a patient with presumed acute bacterial pharyngotonsillitis, for suppurative complications of pharyngotonsillitis?		
5-1. Acute complications of pharyngotonsillitis should be considered when the patient shows severe and persistent symptoms, has difficulty swallowing, and has "hot potato voice" along with other clinical symptoms implying airway obstruction. In such cases, the patient should be referred to a specialist to determine whether surgical treatment is indicated.	Strong	Very low

Recommendation	Strength of recommendation	Quality of evidence
KQ 6. When should empiric antimicrobial therapy be initiated in patients with signs and symptoms suggestive of acute rhinosinusitis?		
6-1. Antibiotics may be prescribed early after diagnosis of acute bacterial sinusitis.	Strong	High
6-2. Empiric antimicrobial therapy should be initiated when the patient shows no improvement of symptoms within 7 days of diagnosis of acute bacterial sinusitis or shows exacerbation of symptoms.	Strong	High
6-3. Antimicrobial therapy should be initiated when the patient shows the following severe symptoms or examination findings: high fever of greater than 39°C, facial pain, or purulent nasal discharge lasting 3–4 days.	Strong	High
KQ 7. Which antibiotics should be used for initial empiric antimicrobial therapy of acute bacterial rhinosinusitis?		
7-1. Amoxicillin or amoxicillin/clavulanate are recommended for initial empirical antimicrobial therapy for acute bacterial sinusitis in adults.	Strong	High
7-2. High doses of amoxicillin or amoxicillin/clavulanate should be considered for patients in areas with high prevalence of penicillin-resistant *S. pneumoniae,* patients with severe symptoms, older patients, patients with recent hospital admission, patients with a history of antimicrobial therapy within the past month, and immunocompromised patients.	Strong	Moderate
7-3. Patients allergic to penicillin: for patients with type 4 hypersensitivity (*e.g.*, rash), doxycycline or fluoroquinolones and third-generation cephalosporins or clindamycin may be considered. For type 1 hypersensitivity (*e.g.*, anaphylaxis), all beta-lactam antibiotics (*e.g.*, cephalosporin) should not be used. Non-beta-lactam antibiotics should be used.	Strong	High
7-4. Empirical antibiotics should be used for a short period (within 5–10 days or 4–7 days of symptom/sign improvement) unless the patient has severe acute sinusitis.	Strong	High
KQ 8. When should second-line therapy be prescribed in patients with acute bacterial rhinosinusitis?		
8-1. Second-line therapy should be considered when patients' symptoms worsen within 72 hours of initial empirical antimicrobial therapy or when patients show no improvement even after 3–5 days of treatment.	Strong	Moderate
8-2. Reassess the patient based on imaging, microbial cultures, and antibiotic susceptibility tests. Respiratory fluoroquinolone is recommended as an empirical antibiotic.	Strong	Very low
8-3. If microbial culture and susceptibility tests for the causative pathogens are difficult, use antibiotics that treat multidrug-resistant *S. pneumoniae* and *Haemophilus influenzae*, *Moraxella catarrhalis*, which produce beta-lactamase (*e.g.*, high-dose amoxicillin/clavulanate, fluoroquinolones, doxycycline, clindamycin, and third-generation cephalosporins combination therapy).	Strong	Moderate
8-4. Drugs such as ampicillin/sulbactam, ceftriaxone, cefotaxime, levofloxacin, and moxifloxacin may be used for severe conditions that require hospitalization.	Strong	Moderate
8-5. Second-line antibiotics to treat acute bacterial rhinosinusitis should be chosen in consideration of the following: prevalence of the causative pathogen of acute bacterial rhinosinusitis in Korea, prevalence of antibiotic-resistant bacteria in Korea, antibacterial effects against three representative pathogens of acute bacterial rhinosinusitis (*i.e.*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*), properties of individual antibiotics (*e.g.*, dose, duration of effects, side effects).	Strong	Very low
KQ 9. What is the recommended management strategy in patients who clinically worsen within 72 hours or fail to improve after 3–5 days of initial empirical antimicrobial therapy with first- or second-line regimens?		
9-1. For patients who show no improvement despite appropriate first-line or second-line antimicrobial therapy or patients with recurrent acute sinusitis, additional diagnosis should be performed in consideration of the patient's hypersensitivity, immune abnormalities, and tooth infections.	Strong	Very low

Recommendation	Strength of recommendation	Quality of evidence
9-2. When a related comorbidity is diagnosed, provide treatment according to the guideline for each morbidity. Consider environmental therapy, immune therapy, and drug therapy for patients with hypersensitivity.	Strong	Very low
9-3. Surgical treatment may be considered when recurrent acute sinusitis is nonresponsive to appropriate drug therapy.	Strong	Moderate
KQ 10. When is referral to a specialist indicated in a patient with presumed acute bacterial sinusitis?		
10-1. Cases in which the patient fails to show improvement or has recurrent inflammation despite appropriate treatment require additional tests, such as nasal endoscopy and radiological imaging, and referral to a corresponding specialist.	Weak	Very low
10-2. Patients with suspected orbital or intracranial complications of acute rhinosinusitis should be immediately referred to a specialist.	Strong	Very low

III. Recommendations

1. Recommendations for each key question

1) When should empiric antimicrobial therapy be initiated in patients with signs and symptoms suggestive of acute pharyngotonsillitis?

1. Antimicrobial therapy is recommended for patients with acute pharyngotonsillitis when they have complications. (Quality of evidence: High, Strength of recommendation: Strong)
2. Antimicrobial therapy is recommended when the patient's modified Centor score (McIsaac score), which reflects the severity of clinical symptoms of acute pharyngotonsillitis, is three or higher, and the patient tests positive on the rapid antigen test. In cases where a rapid antigen test is not available, antimicrobial therapy may be initiated according to the modified Centor score (McIsaac score). Antibiotic therapy may promptly improve and prevent complications of bacterial pharyngotonsillitis. (Quality of evidence: High, Strength of recommendation: Strong)

Most cases of acute pharyngotonsillitis are viral. Currently known respiratory viruses include rhinovirus, adenovirus, influenza virus, parainfluenza virus, coxsackievirus, coronavirus, echovirus, respiratory syncytial virus, and metapneumovirus. These conditions should be differentiated from infectious mononucleosis, which is caused by Epstein–Barr virus (EBV) generally among young adults, acute human immunodeficiency virus (HIV) infection, cytomegalovirus infection, and herpes simplex virus infection [9-11]. Universal use of antibiotics for patients with sore throat is beneficial in terms of shortening the length of acute pharyngotonsillitis symptoms and reducing the frequency of bacterial complications; however, such use may heighten the prevalence of side effects and facilitate the spread of antimicrobial-resistant bacteria, thereby increasing medical costs [10]. Therefore, antibiotic prescription should be avoided for acute viral pharyngotonsillitis and appropriate antimicrobial therapy should be administered for acute bacterial pharyngotonsillitis based on aggressive differentiation of the causative pathogen in the clinical setting [11, 12].

The most common cause of acute bacterial pharyngotonsillitis is *S. pyogenes*, which accounts for 5–15% of all cases of acute bacterial pharyngotonsillitis in adults [5, 6, 13]. *S. pyogenes*-induced acute pharyngotonsillitis may lead to acute suppurative complications, such as otitis media and peritonsillar abscess, as well as non-suppurative complications, such as rheumatic fever and acute glomerulonephritis; therefore, prompt diagnosis and appropriate antimicrobial therapy are necessary [5, 14]. Although acute rheumatic fever is considerably less prevalent today, its clinical significance is substantial. Group C or G beta-hemolytic streptococci, *C. pneumoniae, M. pneumoniae, Arcanobacterium haemolyticum, Corynebacterium diphtheriae, Fusobacterium necrophorum, Neisseria gonorrheae, Treponema pallidum,* and *Francisella tularensis* are also rare pathogens of acute pharyngotonsillitis.

History-taking and physical examination, throat swab culture, and rapid antigen tests are helpful in differentiation of the causative pathogen for acute pharyngotonsillitis. Symptoms such as nasal drainage, nasal congestion, cough, conjunctivitis, hoarseness, diarrhea, oral ulcer, or bullous oral lesions are more suggestive of viral than bacterial acute pharyngotonsillitis [15]. On the other hand, symptoms such as swallowing difficulty (dysphagia), sore throat, fever, headache,

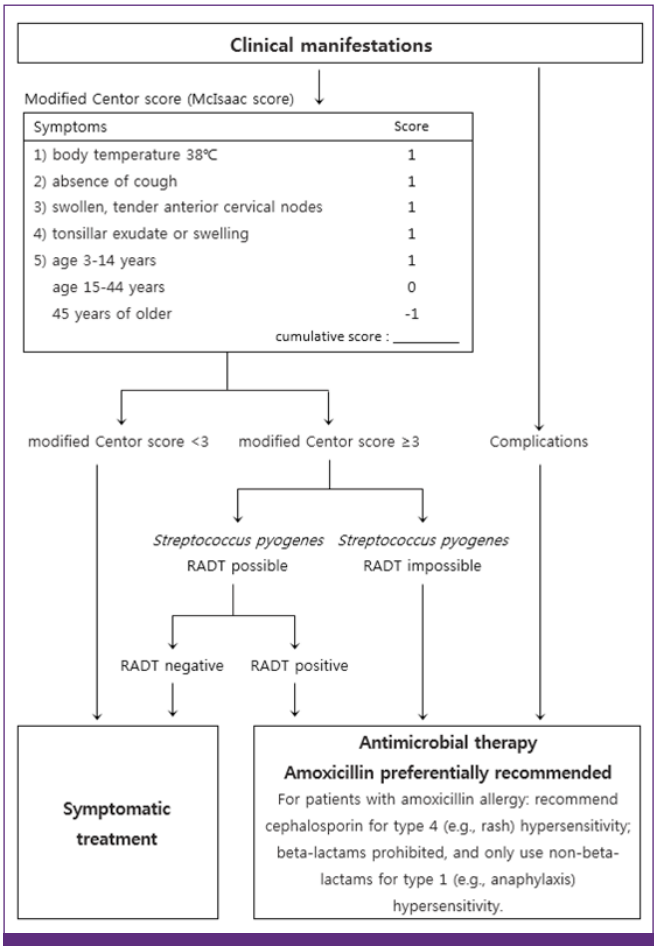

Figure 1. Flowchart for use of antibiotics for acute pharyngotonsillitis.
RADT, rapid antigen detection test.

Table 2. Risk of *Streptococcus pyogenes* infection based on the modified Centor score (McIsaac score) (McIsaac WJ, JAMA 2004;291:1587-95)

Total score	Risk of *Streptococcus pyogenes* infection (%)
≥4	51–53
3	28–35
2	11–17
1	5–10
≤0	1–2.5

abdominal pain, nausea, vomiting or petechial hemorrhage of the soft palate, enlarged lymph nodes in the neck, and scarlet fever rash suggest acute bacterial pharyngotonsillitis, especially caused by *S. pyogenes* infection [15]. Although differentiation of the pathogen based on clinical symptoms and signs produces high concordance among physicians [16, 17], the sensitivity and specificity of predicting positivity in a throat swab culture test ranges from 55–74% and 58–76%, respectively, even among highly experienced physicians [6, 18, 19].

A variety of clinical prediction tools have been proposed, although these have been associated with limited diagnostic accuracy [6]. In practice, the most commonly used clinical instrument is the Centor criteria [5, 6]. It was first suggested for use in adults in 1981 to score symptoms and signs, and a modified Centor criteria (McIsaac criteria) with the addition of age criteria was proposed in 1998 (Fig. 1) [20]. The modified Centor criteria (McIsaac criteria) is the clinical prediction model to classify the likelihood of *S. pyogenes* infection (Table 2) [21]. Although it varies in relation to the prevalence of *S. pyogenes* infection, a Centor score of 3 or higher showed a positivity predictive value of 40-60% and a negativity predictive value of 80% on the diagnosis of *S. pyogenes* infection using a throat swab culture, with 75% sensitivity and specificity [6, 21-23]. The 2008 National Institute of Health and Care Excellence (NICE) guideline recommends antibiotic prescription for three or more Centor criteria [24]. Prior studies have reported that antibiotic therapy that depends on the presence of three or four Centor criteria was conducive to improving symptoms and preventing complications as well as to reducing inappropriate use of antibiotics [22, 23, 25]. The present guideline recommend that clinicians use the modified Centor criteria.

According to the 2012 guideline published by the Infectious Diseases Society of America (IDSA), it is difficult to differentiate between *S. pyogenes*-induced pharyngotonsillitis and viral pharyngotonsillitis merely based on clinical manifestations. The guideline recommends a rapid antigen diagnostic test (RADT) or bacterial culture for cases suggestive of *S. pyogenes*-induced pharyngotonsillitis, except for cases in which a viral disease is highly suspected [11]. Pharyngotonsillitis caused by *S. pyogenes* is diagnosed when *S. pyogenes* is identified using an RADT or culture test with a throat swab [11]. A throat swab follows the steps in the Figure 2 [26].

The RADT is a convenient test that can be performed and provides results at the point of care. Its sensitivity and specificity vary depending on the patient and test method, ranging from 65–91% and 62–97%, respectively, compared with a culture test [27-31]. A throat swab culture can be performed if the RADT is negative, but performing both tests is generally not recommended in adults [11]. If the RADT is positive, the patient can be diagnosed with pharyngotonsillitis caused by *S. pyogenes* without a bacterial culture [11]. Data on the RADT in Korea generally involve children and most studies have reported that the test is useful [32-35]. It is necessary that its use be more activated for proper use of antibiotics [12].

Antistreptolysin O (ASO) titer may be useful in the diagnosis

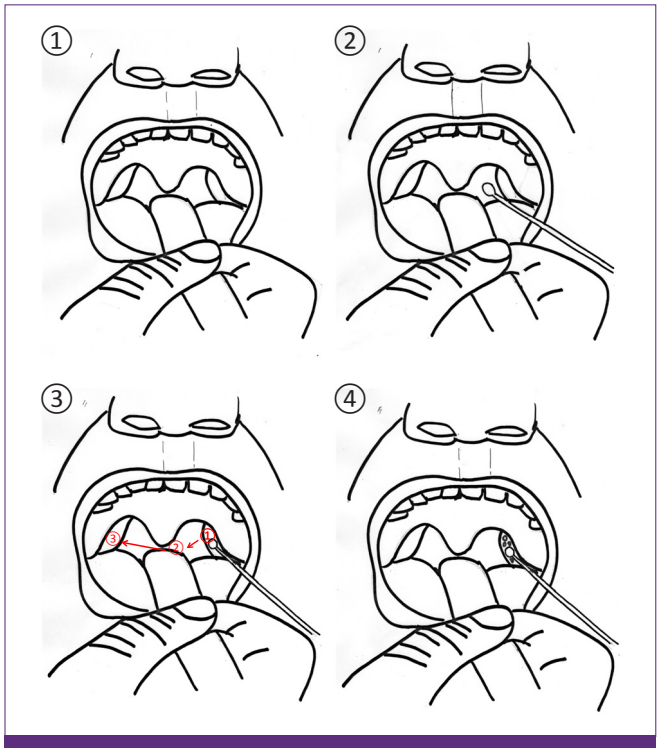

Figure 2. How to take a throat swab. ① Press the tongue with a tongue depressor to reveal both palatine tonsils and uvula. ② Without touching the uvula, place a sterile swab deep inside the throat, past the uvula. ③ Gently stroke one palatine tonsil, posterior nasopharynx, and the other palatine tonsil, in the order specified. ④ Collect samples of lesions such as exudate in the area of sample collection. Be careful not to touch other areas in the mouth, such as the tongue and inner cheek, or to contaminate the swab with saliva. Immediately place the swab in a sterile tube and send it to the laboratory [26].

of non-suppurative complications, such as acute rheumatic fever and acute glomerulonephritis [36]. However, as the titer does not reach peak levels until 3–8 weeks of onset and continues to rise for several months, the ASO is not useful for the diagnosis of acute pharyngotonsillitis [37, 38]. In general, patients with acute pharyngotonsillitis have elevated C-reactive protein, total white blood cell count, and neutrophilic granulocyte count. The ASO test has low sensitivity (66–90%) and specificity (45–75%) for diagnosing acute bacterial pharyngotonsillitis in adults [39]. Procalcitonin and erythrocyte sedimentation rate are also not very useful for differentiating acute bacterial pharyngotonsillitis [40]. One report suggested that using both C-reactive protein level (35 mg/L, or 3.5 mg/dL) and the clinical score may be helpful for diagnosing acute bacterial pharyngotonsillitis [41]; however, blood tests are not generally recommended for patients with suspected acute pharyngotonsillitis.

The 2008 NICE guideline suggests antibiotic prescription for *S. pyogenes* infection depending on the patient's state when the patient has three or more Centor criteria [24, 42]. On the other hand, IDSA recommends that clinicians prescribe antibiotics only after accurate bacteriological diagnosis [11]. The present guideline recommends that antibiotics be prescribed for acute pharyngotonsillitis patients with complications, patients with a modified Centor score (McIsaac score) of more than 3, and patients with a positive RADT. If an RADT cannot be performed, antimicrobial therapy may be considered depending on the modified Centor score (McIsaac score) (Fig. 1).

A recent large-scale cohort study reported that delayed antibiotic therapy led to reductions of suppurative complications similar to those produced by immediate antibiotics therapy [14].

2) Which antibiotics should be used for initial empiric antimicrobial therapy in patients with acute bacterial pharyngotonsillitis?

1. Ten-day amoxicillin therapy may be used; however, amoxicillin may not be used when infectious mononucleosis is suspected. (Quality of evidence: High, Strength of recommendation: Strong)
2. Five-day cefdinir or azithromycin therapy may be used in cases with poor patient compliance or in cases where 10-day antimicrobial therapy may be difficult for the patient. (Quality of evidence: Moderate, Strength of recommendation: Strong)
3. A single intramuscular (IM) injection of benzathine penicillin G (adults: 1,200,000 units IM) may be used. (Quality of evidence: High, Strength of recommendation: Strong) However, this is not recommended as first-line treatment in Korea.
4. For patients who are allergic to penicillin: for type 4 hypersensitivity (*e.g.*, rash), 10-day first-generation cephalosporin (cephalexin, cefadroxil) therapy, 10-day clindamycin, 10-day clarithromycin therapy, 5-day azithromycin therapy, or 5-day cefdinir/cefpodoxime therapy may be used. (Quality of evidence: Moderate, Strength of recommendation: Strong)
5. All beta-lactam antibiotics (*e.g.*, cephalosporin) should not be used for type 1 sensitivity (*e.g.*, anaphylaxis). (Quality of evidence: Moderate, Strength of recommendation: Strong)

Acute bacterial pharyngotonsillitis may also be caused by diverse types of bacteria other than *S. pyogenes*. Therefore, the appropriate antibiotics should be chosen in consideration of the type of pathogen to be treated, antibiotic susceptibility, spectrum of antibiotics, side effects, patient's underlying diseases, drug interactions, and cost. US and European clinical

Table 3. Recommended antibiotic dose and duration for acute pharyngotonsillitis caused by *Streptococcus pyogenes*

Antibiotics			Route	Dose	Duration
Patients with no penicillin hypersensitivity	Preferred	Amoxicillin	Oral	50 mg/kg, once a day (maximum 1,000 mg) 25 mg/kg, twice a day	10 days
	Alternative	Amoxicillin/clavulanate	Oral	500/125 mg, 3 times a day	10 days
		Ampicillin/sulbactam	Oral	500/250 mg, 3 times a day	10 days
		Benzathine penicillin G	IM	1,200,000 units	Once
Type 4 penicillin hypersensitivity (*e.g.*, rash)	Preferred: first-generation cephalosporins	Cephalexin	Oral	500 mg, twice a day	10 days
		Cefadroxil	Oral	1000 mg, once a day	10 days
	Alternative	Cefpodoxime	Oral	100 mg, twice a day	5 days
		Cefdinir	Oral	300 mg, twice a day	5 days
Type 1 penicillin hypersensitivity (*e.g.*, anaphylaxis)		Clindamycin	Oral	300 mg, 3 times a day	10 days
		Azithromycin	Oral	500 mg, once a day	5 days
		Clarithromycin	Oral	250 mg, twice a day	10 days

care guidelines for pharyngotonsillitis recommend penicillin V as the first-line antibiotic therapy [11, 42]. To date, penicillin resistance has not been found in clinical isolates of *S. pyogenes* from acute pharyngotonsillitis specimens in Korea and globally [43-51]. Beta-lactam resistance in *S. pyogenes* has rarely been reported, unlike increased antimicrobial resistance among other bacteria [43-51]. Penicillin is the most useful antibiotics available for first-line therapy for bacterial pharyngotonsillitis as it is a cost-effective, narrow-spectrum antibiotics whose efficacy has been proven through long-accumulated data [43-47].

However, oral penicillin V is not produced or distributed in Korea; amoxicillin can be used as a first-line antibiotics instead (Table 3) [11]. A multicenter study conducted in France reported that 6-day amoxicillin therapy and 10-day penicillin V therapy did not differ significantly in therapeutic efficacy and safety among patients with acute pharyngotonsillitis [52, 53]. A prospective observational study conducted in the US also reported that amoxicillin is superior to penicillin in microbial responses and clinical efficacy [54]. Amoxicillin is particularly beneficial over penicillin in that despite its wider microbiologic spectrum, it has higher oral bioavailability even when taken together with food, and once-daily administration helps to improve patient compliance [55-59]. However, amoxicillin must not be used in cases involving infectious mononucleosis caused by EBV because it induces drug rash in 70–100% of cases [11, 42]. Second-line antibiotics may be considered in such cases.

Since the 1950s, benzathine penicillin G injections, along with penicillin V, have been used as first-line therapy for acute bacterial pharyngotonsillitis. The American Heart Association and IDSA also recommend IM injection of benzathine penicillin G in addition to penicillin V [11, 12]. Compared with injectable antibiotics, oral antibiotics are associated with fewer complications, less severe hypersensitivity reactions, and no pain at the injection site; however, drug compliance may be a problem [12, 60]. Therefore, IM benzathine penicillin G may be used for patients deemed to have difficulty complying with a 10-day oral antibiotic regimen [12, 60, 61]. Studies have found no significant differences in the clinical efficacy of 10-day amoxicillin oral antibiotic therapy and single IM injection of benzathine penicillin G [61, 62].

For patients with type 4 penicillin hypersensitivity (*e.g.*, rash), 10-day first-generation cephalosporin (cephalexin, cefadroxil) therapy, 10-day clindamycin or clarithromycin therapy, 5-day azithromycin therapy, or 5-day cefdinir or cefpodoxime therapy may be used (Table 3) [11]. All types of beta-lactam antibiotics (*e.g.*, cephalosporin) should not be used for patients with type 1 hypersensitivity (*e.g.*, anaphylaxis) (Table 3). Some studies have found that 5-day broad-spectrum cephalosporin therapy had slightly better efficacy than 10-day penicillin V treatment. However, 5-day therapies using cefdinir or cefpodoxime are not generally considered for use as first-line therapy owing to their relatively higher costs and wider antibiotic spectrum (Table 3) [11, 24, 42].

3) When should second-line therapy be prescribed for acute bacterial pharyngotonsillitis?

1. When first-line therapy fails for acute pharyngotonsillitis caused by *S. pyogenes*, ampicillin/sulbactam, amoxicillin/clavulanate, narrow-spectrum cephalosporins or clindamycin may be considered as second-line therapy. (Quality of evidence: Moderate, Strength of recommendation: Weak)
2. Second-line therapy may be considered when *S. pyogenes* continues to be identified from culture or for recurrent infections. (Quality of evidence: Moderate, Strength of recommendation: Weak)
3. A change of antibiotics may be considered when the patient develops acute suppurative complications, such as otitis media and peritonsillar abscess, and non-suppurative complications, such as rheumatic fever and acute glomerulonephritis. (Quality of evidence: Moderate, Strength of recommendation: Strong)

In general, first-line therapy for bacterial pharyngotonsillitis (penicillin V or amoxicillin) includes antibiotics against *S. pyogenes* [63], with treatment responses within 48–72 hours of administration and improvement of clinical symptoms within 4–5 days [8, 64]. If there are no treatment responses within 48–72 hours of administration, first-line treatment should be deemed a failure and the following should be reviewed [64, 65]. First, check drug compliance. Second, although penicillin-resistance is very rare in *S. pyogenes*, ampicillin/sulbactam, amoxicillin/clavulanate, narrow-spectrum cephalosporin, and clindamycin may be considered as second-line antibiotics, after reviewing the patient's recent history of antibiotic therapy (Table 3) [64]. Ten-day cephalexin therapy and 10-day amoxicillin (once daily) therapy have not led to significantly different treatment outcomes [66], and data on the therapeutic outcomes of ampicillin/sulbactam and amoxicillin/clavulanate are very limited [12, 67, 68]. Penicillin are popular as first-line antibiotic therapy owing to their proven clinical efficacy, safety, and low cost. However, the growing popularity of macrolides (such as erythromycin) and clindamycin, in response to concerns about hypersensitivity to penicillin have led to increased resistance to these antimicrobials among *S. pyogenes* strains. Macrolides resistance among *S. pyogenes* strains isolated from patients with acute pharyngitis living in Jinju, Korea reached 51% in 2002 [48]. Erythromycin resistance in Seoul and Masan was 28.5% and 20.5%, respectively, in 1998–2003 [49, 50]. During 2009–2011, resistance to erythromycin, azithromycin, and clindamycin increased to 42.9%, 42.9%, and 30.6%, respectively [51]. Therefore, macrolides and clindamycin are not recommended as first-line antibiotics, and treatment failure should be assessed if they are used.

Third, in addition to *S. pyogenes,* acute pharyngotonsillitis may be caused by a variety of other pathogens, including EBV, adenovirus, mycoplasma, *Fusobacterium* spp., *Corynebacterium diphtheriae, Acanobacterium haemolyticum,* and *N. gonorrhoeae* [69]. Rash that develops after amoxicillin administration may suggest EBV infection [42]. *Fusobacterium* infection should be treated with ampicillin/sulbactam or ampicillin/metronidazole. Penicillin-resistant *Fusobacterium* spp. have been reported in rare cases [70]. Penicillin and erythromycin are the recommended antibiotic therapy for *C. diphtheriae* infection. For acute tonsillitis caused by *N. gonorrhoeae,* follow-up bacterial culture is recommended after treatment completion owing to the difficulty in complete removal of the microorganisms, and the infection is treated with ceftriaxone (single dose, 250 mg IM) [71].

Second-line antimicrobial therapy may be considered if *S. pyogenes* is repeatedly detected in cultures or the infection recurs. Additional details are delineated below the key question 4.

Suppurative complications of acute pharyngotonsillitis include peritonsillar abscess, parapharyngeal abscess, lymphnoditis, sinusitis, otitis media, mastoiditis, necrotizing fasciitis, and toxic shock syndrome [5, 38, 39]. Deep abscesses in the head and neck can be treated with a combination of second- or third-generation cephalosporin (*e.g.*, ceftriaxone, cefuroxime) and clindamycin or ampicillin/sulbactam. Needle aspiration or incision and drainage should be actively considered for treatment and pathogen identification purposes. In rare cases, *Fusobacterium* spp. may also induce Lemierre syndrome caused by septic thrombophlebitis of the internal jugular vein [29]. Non-suppurative complications of *S. pyogenes* infection include rheumatic fever and acute glomerulonephritis [11].

4) What is the recommended antibiotic therapy in patients with frequent recurrent episodes of apparent bacterial pharyngotonsillitis?

1. Prophylactic antibiotic therapy is not recommended for recurrent bacterial pharyngotonsillitis. (Quality of evidence: High, Strength of recommendation: Weak)
2. Recurrent acute bacterial pharyngotonsillitis may be treated more than once with first-line antibiotics, and narrow-spectrum cephalosporin (cephradine, cefadroxil), clindamycin, amoxicillin/clavulanate, or penicillin and rifampin combination therapy may be considered as second-line therapy. (Quality of evidence: High, Strength of recommendation: Weak)

Acute bacterial pharyngotonsillitis may recur despite antibiotic therapy owing to inappropriate use of antibiotics, insufficient antibiotic dosage or treatment duration, low patient compliance, re-infection, and though rare, penicillin resistance [72, 73]. Further, it may be considered for cases in which *S. pyogenes* colonization continues after acute upper respiratory infection due to viral pathogen.

Bacterial culture should be performed after completion of antibiotic therapy for *S. pyogenes* infection if symptoms persist, recurrence is suspected, or the patient has a history of rheumatic fever or acute glomerulonephritis. Culture should generally be performed within 2–7 days of treatment completion. Because treatment failure and chronic carriers must be distinguished [65], antibiotics should not be administered again if the symptoms have improved, even if a bacterial strain is isolated in the follow-up test. However, patients with a history or family history of rheumatic fever are subject to retreatment even if they are asymptomatic. If symptoms persist, first-line antibiotics may be used more than once, and benzathine penicillin G may be considered for patients with low compliance; however, established data is lacking. After treatment failure with penicillin, second-line therapy may involve narrow-spectrum cephalosporins (cephradine, cefadroxil), clindamycin, amoxicillin/clavulanate, or a combination of penicillin and rifampin [12, 65]. Broad-spectrum cephalosporins (*e.g.*, cefprozil, cefuroxime axetil, cefdinir, cefditoren, cefpodoxime, cefaclor) are not generally recommended owing to their high costs and wide microbiologic spectrum [60, 74]. One study reported that 10-day cefaclor therapy had similar clinical effects as those of a 10-day amoxicillin/clavulanate for acute bacterial pharyngotonsillitis, and the incidence of some digestive tract side effects was lower in the former treatment group [75]. Moreover, 5-day cefaclor therapy and 10-day amoxicillin therapy had similar treatment effects [76]. On the other hand, the treatment responses of 10-day cefaclor therapy were superior to those of 10-day erythromycin treatment, which has been reported to be attributable to macrolides-resistant *S. pyogenes* strains [77]. In addition, the treatment responses of 5-day cefditoren pivoxil therapy and 10-day amoxicillin therapy were not significantly different [78].

Previous RCTs have investigated whether antibiotic therapy for patients with acute pharyngotonsillitis reduces the incidence of future episodes of pharyngotonsillitis and whether prophylactic antibiotic therapy reduces recurrent episodes of pharyngotonsillitis [73, 79, 80]. In one study, prophylactic use of benzathine penicillin G in children led to a lower incidence of *S. pyogenes*-induced pharyngitis during a 4-month period after administration compared with the incidence during a 4-month period before administration; however, the study is flawed in that it did not administer a placebo to the control group [79]. Prolonged azithromycin therapy as an alternative to tonsillectomy was ineffective in treating frequent recurrent tonsillitis [73]. In another study, prophylactic use of cefpodoxime proxetil in children reduced the incidence of acute pharyngotonsillitis by 10% after 12 months compared with the group that did not receive prophylactic treatment; however, the study was limited to children, and it only showed the risk of antimicrobial resistance and short-term treatment progress, necessitating a more long-term study [80]. In summary, one of three previous studies have suggested that prophylactic antibiotic therapy is ineffective, and the remaining two studies have showed that it has small but statistically significant effects. However, it is difficult to generalize these findings due to their methodological limitations. These studies also reported that the use of cephalosporin for treatment and prevention purposes lowered the incidence of sore throat but that macrolide, such as azithromycin, did not produce similar effects [79, 80].

5) When is referral to a specialist indicated in a patient with presumed acute bacterial pharyngotonsillitis, for suppurative complications of pharyngotonsillitis?

1. Acute complications of pharyngotonsillitis should be considered when the patient shows severe and persistent symptoms, has difficulty swallowing, and has “hot potato voice” along with other clinical symptoms implying airway obstruction. In such cases, the patient should be referred to a specialist to determine whether surgical treatment is indicated. (Quality of evidence: Very low, Strength of recommendation: Strong)

Peritonsillar abscess is the most common deep neck infection. Other deep neck infections include parapharyngeal abscess and retropharyngeal abscess, and infection of the para-

Table 4. Clinical findings of bacterial pharyngotonsillitis that suggest poor prognosis

Excessive drooling
Trismus
Unilateral facial edema
Dysphagia
Dyspnea
Continuous unilateral tonsillar enlargement
Neck stiffness
Blood in pharynx or ears

Table 5. Comparison of major guidelines for acute pharyngotonsillitis caused by *Streptococcus pyogenes*

Category	Present guideline	Antibiotics guideline for children with acute upper respiratory infection- Korea (2016)	IDSA (2012)	American college of physicians (2001)	American academy of pediatrics (2003)	NICE (2008)
Initial diagnosis of acute pharyn-go-tonsillitis	Modified Centor score or clinical manifestations of *S. pyogenes* infection	Modified Centor score or clinical manifestations of *S. pyogenes* infection	Clinical manifestations and epidemiology suggestive of *S. pyogenes* infection (example: sudden sore throat, fever, tonsillar exudate/nasal drainage, hoarseness, cough, and oral ulcer suggestive of acute viral pharyngitis)		Modified Centor score	Modified Centor score
Recom-mendation for diagnostic testing	Three or more modified Centor criteria	Findings suggestive of *S. pyogenes* or three or more modified Centor criteria	All patients with suspected *S. pyogenes* infection		Three or more modified Centor criteria	Not recom-mended
Additional culture if negative on rapid antigen test	Adults: No	Children: Yes	Children: Yes Adults: No	Children: Yes Adults: Yes in some communities	Children: Yes Adults: No	Not recom-mended
Indication for antibiotics	1. Three or more modified Centor criteria 2. Complication (*e.g.*, otitis media, peritonsillar abscess, acute glomerulo-nephritis, rheumatic fever)	Positive for *S. pyogenes* on rapid antigen test or culture	Positive for *S. pyogenes* on rapid antigen test or culture		1. Empirical antibiotics: four or more modified Centor criteria 2. Antibiotics therapy: positive for *S. pyogenes* on rapid antigen test or culture	Three or more modified Centor criteria
Anti-biotics	Oral amoxicillin	Oral amoxicillin	Oral penicillin V, IM benzathine penicillin G. For children, oral amoxicillin is as effective as penicillin and tastes better.			Not specified
Penicillin allergy	Type 4 (*e.g.*, rash): cephalosporin Type 1 (*e.g.*, anaphylaxis): non-beta-lactams	Not anaphylaxis: first-generation cephalosporin Anaphylaxis: beta-lactams prohibited, only non-beta-lactams	Type 4 hypersensitivity: first-generation cephalosporin (*e.g.*, cephalexin) Type 1 hypersensitivity: clindamycin, clarithromycin, or azithromycin			Not specified

IDSA, Infectious Diseases Society of America; NICE, National Institute of Health and Care Excellence.

pharyngeal space may occur as a complication of pharyngitis [81-84]. Furthermore, these diseases must be differentiated from pharyngotonsillitis from the beginning. Peritonsillar cellulitis or phlegmon is a term used for cases in which the peritonsillar space is infected without the formation of an abscess. Peritonsillar abscess accounts for about 50% of all deep neck infections; it is common among adults and adolescents and possible in children [2, 85]. The most important management strategy for deep neck infection is airway assessment and management [26]. For patients who are restless, have swallowing difficulty, and are drooling, the airway should be closely observed to ensure patency. Further, patients should be assessed to determine whether they need procedures such as intubation and if so, proper procedures should be performed before referring them to a specialist [86]. Serious clinical symptoms and signs are listed in Table 4. Ultrasound or computed tomography (CT) may be required. Ultrasound should be performed by a skilled expert. Although CT is associated with the potential adverse effects of radiation exposure and use of contrasting agents, it can be performed quickly (if the facility is equipped with a CT scan) and it provides objective images. CT is commonly performed for diagnosis and differential diagnosis from other diseases [83, 84]. Magnetic resonance imaging (MRI) may also be used [83]. Abscess in the neck is associated with the teeth in many adults; it is more common as a complication of tonsillitis among children, adolescents, and young adults [26, 81-84].

Immunocompromised individuals may have non-responsive tonsillitis caused by various unusual pathogens, so it is important to refer them to a specialist for a broader approach to identifying the cause and for effective treatment [87, 88].

Table 5 shows a comparison of this guideline with Korean Guidelines for the Antibiotic Use in Children with Acute Upper Respiratory Tract Infection (2016) and other major guidelines for acute pharyngotonsillitis caused by *S. pyogenes*, as suggested by IDSA (2012), the American College of Physicians (2001), American Academy of Pediatrics (2003), and NICE (2008) [11, 89-93].

6) When should empiric antimicrobial therapy be initiated in patients with signs and symptoms suggestive of acute bacterial rhinosinusitis?

1. Antibiotics may be prescribed early after diagnosis of acute bacterial sinusitis. (Quality of evidence: High, Strength of recommendation: Strong)
2. Empirical antimicrobial therapy should be initiated when the patient shows no improvement of symptoms within 7 days of diagnosis of acute bacterial sinusitis or shows exacerbation of symptoms. (Quality of evidence: High, Strength of recommendation: Strong)
3. Antimicrobial therapy should be initiated when the patient shows the following severe symptoms or examination findings: high fever of greater than 39°C, facial pain, or purulent nasal discharge lasting 3-4 days. (Quality of evidence: High, Strength of recommendation: Strong)

Sinusitis is an inflammation of the nasal passage and muco-

Table 6. Definition of acute sinusitis

Term	Definition
Acute sinusitis	Up to 4 weeks of purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, facial pain-pressure-fullness, or both ① Purulent nasal discharge is cloudy or colored, in contrast to the clear secretions that typically accompany viral upper respiratory infection, and may be reported by the patient or observed on physical examination. ② Nasal obstruction may be reported by the patient as nasal obstruction, congestion, blockage, or stuffiness, or may be diagnosed by physical examination. ③ Facial pain-pressure-fullness may involve the anterior face, periorbital region, or manifest with headache that is localized or diffuse.
Viral sinusitis	Acute sinusitis that is caused by, or is presumed to be caused by, viral infection. A clinician should diagnose viral rhinosinusitis when: symptoms or signs of acute sinusitis are present less than 10 days and the symptoms are not worsening
Acute bacterial sinusitis	Acute sinusitis that is caused by, or is presumed to be caused by, bacterial infection. A clinician should diagnose the acute bacterial rhinosinusitis when: ① Symptoms or signs of acute sinusitis fail to improve within 10 days or more beyond the onset of upper respiratory symptoms, or ② Symptoms or signs of acute sinusitis worsen within 10 days after an initial improvement (double worsening)

sa lining the sinuses resulting from infection, allergy, and autoimmunity. Because it is usually accompanied by inflammation of the nasal cavity and paranasal sinuses, sinusitis is also commonly referred to as rhinosinusitis [94]. Sinusitis may be classified according to the main site of infection such as maxillary, frontal, ethmoid, and sphenoid sinusitis; it is also classified according to the stage of infection, such as acute (less than 4 weeks), subacute (4 weeks–3 months), and chronic (more than 3 months) [95]. Moreover, sinusitis can be classified into community-acquired, healthcare-associated, and nosocomial infection depending on the location of pathogen exposure. More detailed definitions of acute sinusitis are given in Table 6 [94-97]. In addition to identifying the infectious causes of sinusitis, differentiating the noninfectious causes is important, such as in vasomotor and atrophic sinusitis as well as the recently increasing allergic sinusitis [98].

Infectious causes of sinusitis encompass a variety of microorganisms, including viruses, bacteria, or fungal organisms. Bacterial causes only account for 2–10%, with viral infections accounting for the remaining 90–98% of cases [99]. About 0.5–2% of acute viral sinusitis cases may progress to acute bacterial sinusitis [100, 101]. Bacterial pathogens that have been identified with needle biopsies of maxillary sinus specimens in patients with acute sinusitis include *S. pneumoniae, H. influenzae,* anaerobic bacteria, streptococcal species, *M. catarrhalis,* and *Staphylococcus aureus*. Other known viral pathogens include rhinovirus, parainfluenza virus, and influenza virus; though rare, fungal pathogens, such as *Aspergillus,* zygomycetes*, Phaeohyphomycis, Pseudallescheria,* and *Hyalohyphomycis* have also been identified [102, 103].

About 85% of acute sinusitis in adults, including acute community-acquired bacterial sinusitis, shows improvement of symptoms within 7–15 days without antibiotic therapy [104]. However, bacterial sinusitis generally requires antibiotic therapy because the sinuses are normally a sterile environment. In addition, certain types of acute bacterial sinusitis may lead to severe complications, such as bacterial encephalomeningitis, brain abscess, and periocular tissue infection. Further, the possibility of chronic sinus disease cannot be completely eliminated [105, 106]. In fact, proper antibiotic therapy for acute community-acquired bacterial sinusitis leads to a more than 90% eradication rate in the sinuses, which is superior to that in the inappropriate antibiotic therapy group [106]. However, inappropriate antibiotic therapy increases antimicrobial resistance and drug side effects, thereby elevating medical costs. This situation calls for efforts to differentiate acute viral and bacterial sinusitis in the clinical setting [106].

Unfortunately, it is very difficult to differentiate acute viral sinusitis from acute bacterial sinusitis in the clinical setting owing to the low agreement among examination, imaging, and laboratory findings that are used for diagnosis in addition to the clinical symptoms of acute sinusitis, such as nasal congestion, nasal drainage, sneezing, and nose itching [105, 107]. Nevertheless, clinicians must try to differentiate viral and bacterial sinusitis based on the symptoms and signs as well as the typical manifestations and chronological changes of symptoms [108].

Although needle aspiration cultures of sinus specimens may be performed to diagnose acute bacterial sinusitis, clinicians generally make clinical diagnoses because this method is an invasive technique that cannot be performed in the clinical setting. Clinical diagnosis of acute bacterial sinusitis generally requires progress observation for 7 days, and radiologic testing may aid in clinical diagnosis if symptoms (such as purulent nasal drainage, unilateral maxillary toothache, facial pain, and unilateral tenderness of the maxillary sinus) improve initially but worsen over time [4, 108]. According to the IDSA guideline, the clinical symptoms and signs of acute bacterial sinusitis persist for more than 10 days without any improvement, and severe symptoms and signs such as high fever of 39°C or more that lasts 3–4 days, purulent nasal drainage, and facial tenderness, develop after onset. According to guideline recommendations, when double sickening, such as new fever, headache, and increased nasal drainage, begins after acute viral upper respiratory infection symptoms had begun to improve 5–6 days after symptom onset, acute bacterial sinusitis should be suspected and antibiotic therapy initiated [108]. In addition, foul smelling discharge is suggestive of anaerobic bacterial infection, and clinicians should assess the possibility of tooth infections and begin antibiotic therapy.

Previous RCTs have shown that antibiotic therapy groups (7–10 days) had a higher rate of improvement (91%) than placebo groups (86%). And the duration of pain or morbidity were not correlated with initial treatment for acute bacterial sinusitis [94, 96]. Therefore, antibiotics may be prescribed during primary care for patients with acute bacterial sinusitis without complications; however, clinicians may also delay initial antibiotic therapy and opt for a watchful waiting approach depending on the case at hand. However, early antibiotic therapy should only be delayed in cases where the clinician is confident that the patient will attend follow-up appointments [94]. Empirical antibiotic therapy should be initiated in cases where the patient shows no improvement of symptoms or when symptoms worsen within 7 days of proper non-antibiot-

ic, symptomatic treatment after the diagnosis of acute bacterial sinusitis [109, 110]. Further, empirical antibiotic therapy should also be initiated in cases involving symptoms or findings suggestive of severe acute bacterial sinusitis, such as fever of 39°C or higher, facial pain lasting more than 3–4 days, and purulent nasal drainage (Fig. 3) [108, 111-114].

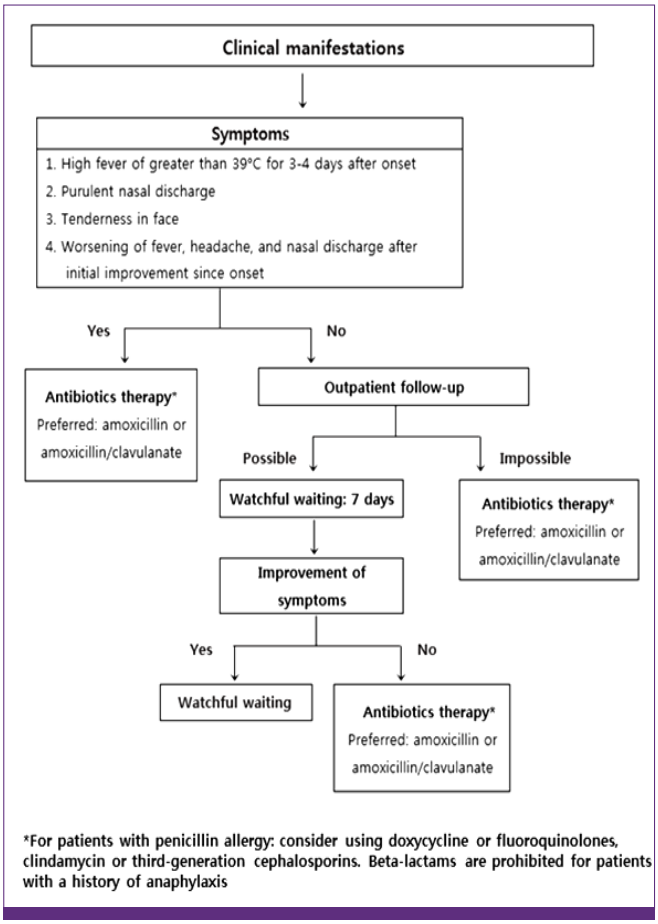

Figure 3. Flowchart for early use of empirical antibiotic therapy in patients with acute bacterial sinusitis.

7) Which antibiotics should be used for initial empiric therapy of acute bacterial rhinosinusitis?

1. Amoxicillin or amoxicillin/clavulanate are recommended for initial empirical therapy for acute bacterial sinusitis in adults. (Quality of evidence: High, Strength of recommendation: Strong)
2. High doses of amoxicillin or amoxicillin/clavulanate should be considered for patients in areas with high prevalence of penicillin-resistant *S. pneumoniae,* patients with severe symptoms, older patients, patients with recent hospital admission, patients with a history of antimicrobial therapy within the past month, and immunocompromised patients. (Quality of evidence: Moderate, Strength of recommendation: Strong)
3. Patients allergic to penicillin: for patients with type 4 hypersensitivity (*e.g.*, rash), doxycycline or fluoroquinolones or third-generation cephalosporins or clindamycin may be considered. For type 1 hypersensitivity (*e.g.*, anaphylaxis), all beta-lactam antibiotics (*e.g.*, cephalosporins) should not be used. Non-beta-lactam antibiotics should be used. (Quality of evidence: High, Strength of recommendation: Strong)
4. Empirical antibiotic therapy should be maintained for a short period (within 5–10 days or 4–7 days of symptom/sign improvement) unless the patient has severe acute sinusitis. (Quality of evidence: High, Strength of recommendation: Strong)

To choose the appropriate antibiotics for acute bacterial sinusitis, the main causative pathogen and its antibiotic susceptibility must be considered. Although there are no Korean epidemiological data on the causative pathogens of acute bacterial sinusitis, data from other countries show that *S. pneumoniae, H. influenzae, M. catarrhalis,* and *S. aureus* are the most common, and *S. pneumoniae* and *H. influenzae* account for about 75% of all isolated strains [102, 103]. However, epidemiological changes are anticipated in Korea in response to the progressive rise in the pneumococcal vaccination rate [115]. Among clinical isolates taken from patients who visited

Table 7. Oral antibiotics that may be used for acute bacterial sinusitis

Antibiotics		Dose for adults
Preferred	Amoxicillin	500–875 mg, twice a day
	Amoxicillin/clavulanate	500 mg, three times a day or 875 mg twice a day
Alternative	Cefpodoxime proxetil	200 mg, twice a day
	Cefdinir	300 mg, twice a day or 600 mg once a day
	Cefuroxime	250–500 mg, twice a day
	Levofloxacin	500 mg, once a day
	Moxifloxacin	400 mg, once a day

primary care clinics for sinusitis between 1999 and 2000 in the United States, the sensitivity of *S. pneumoniae* to penicillin, azithromycin, and levofloxacin was 65%, 64.7%, and 99.8%, respectively, whereas the sensitivity of *H. influenzae* to azithromycin and levofloxacin was 99.4% and 100% [103].

There are two RCTs and one systematic literature review pertaining to the possible first-line empirical antibiotics for acute sinusitis. According to these reports, there are no differences in the clinical treatment outcomes for several antibiotics, including amoxicillin, cefuroxime axetil, amoxicillin/clavulanate, levofloxacin, moxifloxacin, and clarithromycin, in patients radiologically or bacteriologically diagnosed with acute sinusitis [116-118]. In particular, considering the safety, efficacy, price, and narrow-spectrum of the amoxicillin or amoxicillin/clavulanate [108, 111, 119], amoxicillin or amoxicillin/clavulanate (amoxicillin 500 mg/clavulanate 125 mg three times a day or amoxicillin 875 mg/clavulanate 125 mg twice a day) should be preferentially considered as first-line empirical antibiotics for acute sinusitis (Table 7) [108, 111]. Further, amoxicillin/clavulanate may be preferred over amoxicillin in cases suspected to involve antimirobial-resistant bacteria, such as beta-lactamase-producing *H. influenzae* [120], for patients showing moderate to severe infection, for older patients, and for patients with chronic diseases or immune-related diseases [121]. Although adults are at lower risk of acute bacterial sinusitis caused by *M. catarrhalis* than are children, *M. catarrhalis* is resistant to amoxicillin but susceptible to amoxicillin/clavulanate.

A high dose of amoxicillin (90 mg/kg/day) or amoxicillin/clavulanate (amoxicillin 2 g or 90 mg/kg/day, twice a day) should be considered in the following cases: 1) patients live in areas with high prevalence of penicillin-resistant *S. pneumoniae* (endemic rate >10%), 2) patients display severe symptoms, such as high fever of 39°C or greater or possibility of suppurative complications, 3) patients older than 65 years, 4) patients with a recent history of hospitalization, 5) patients with a history of antibiotic therapy within the past month, and 6) patients with compromised immunity [94, 108, 122-125].

For patients with type 4 penicillin allergy (*e.g.*, rash), doxycycline or fluoroquinolones, third-generation cephalosporins, or clindamycin may be considered. For patients with type 1 allergy (*e.g.*, anaphylaxis), all beta-lactams (*e.g.*, cephalosporins) are prohibited [94]. Only non-beta-lactams should be used (*e.g.*, doxycycline, clindamycin, fluoroquinolone) [94]. According to a meta-analysis, the treatment success rate with use of fluoroquinolones in patients without penicillin allergy (87%) was not significantly different from that with use of beta-lactams (86%), but the former is associated with a higher incidence of adverse effects [126]. Foreign data reveal that the main pathogens of acute sinusitis, namely *S. pneumoniae* and *H. influenzae,* are highly resistant to macrolides and trimethoprim/sulfamethoxazole [102, 103, 121, 127].

In general, the recommended duration of first-line empirical antibiotics for adults with acute bacterial sinusitis without complications is 5–10 days or 4–7 days after improvement of symptoms/signs [94, 108, 128]. According to a review of 12 RCTs that investigated the duration of antibiotic therapy for patients radiologically diagnosed with acute sinusitis, there were no significant differences in the treatment success rate between the short-duration antibiotic therapy group (3–7 days) and long-duration antibiotic therapy group (6–10 days) [122]. The antibiotics group showed about 10–12% greater incidence of adverse drug response than the non-antibiotics group. Moreover, the long-duration antibiotic therapy group (more than 10 days) had higher incidences of adverse drug responses than other groups [116, 123]. As stated in the treatment guideline for children, additional antibiotics may be administered for 4–7 days even after the symptoms have improved after antibiotic therapy in patients with delayed drug response [129]. Thus, first-line empirical antibiotics are recommended to be used in short durations, within 5–10 days or 4–7 days after improvement of symptoms/signs, with the exception of cases of severe acute sinusitis involving high fever (>39°C) or potential suppurative complications [94, 108, 128].

8) When should second-line therapy be prescribed in patients with acute bacterial rhinosinusitis?

1. Second-line therapy should be considered when patients' symptoms worsen within 72 hours of initial empirical therapy or when patients show no improvement even after 3–5 days of treatment. (Quality of evidence: Moderate, Strength of recommendation: Strong)
2. Reassess the patient based on imaging, microbial cultures, and antibiotic susceptibility tests. (Quality of evidence: Very low, Strength of recommendation: Strong)
3. If microbial culture and sensitivity tests for the causative pathogens are difficult, use antibiotics that treat multidrug-resistant *S. pneumoniae* and *H. influenzae*, *M. catarrhalis*, which produce beta-lactamase (*e.g.*, high-dose amoxicillin/clavulanate, fluoroquinolones, doxycycline, clindamycin, and third-generation cephalosporins combination therapy). (Quality of evidence: Moderate, Strength of recommendation: Strong)
4. Drugs such as ampicillin/sulbactam, ceftriaxone, cefotaxime, levofloxacin, and moxifloxacin may be used for severe conditions that require hospitalization. (Quality of evidence: Moderate, Strength of recommendation: Strong)

5. Second-line antibiotics to treat acute bacterial rhinosinusitis should be chosen in consideration of the following: prevalence of the causative pathogen of acute bacterial rhinosinusitis in Korea, prevalence of antimicrobial-resistant bacteria in Korea, antibacterial effects against three pathogens of acute bacterial rhinosinusitis (*i.e.*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*), properties of individual antibiotics (*e.g.*, dose, duration of effects, side effects). (Quality of evidence: Very low, Strength of recommendation: Strong)

If symptoms worsen within 72 hours of beginning the initial treatment or the symptoms do not show improvement even after 3–5 days of beginning treatment, the patient should be reassessed in terms of 1) the accuracy of diagnosis, 2) non-infectious cause, 3) antimicrobial-resistant bacteria, and 4) presence of structural problems. Imaging techniques, such as paranasal sinus plain radiography and CT/MRI, as well as microbial cultures and antimicrobial resistance testing can be performed in the reassessment. It is best to perform cultures with fine needle aspiration of the sinus, but cultures can be performed using samples taken from the middle nasal meatus via nasal endoscopy [94, 108]. Cultures using nasopharyngeal swabs are not recommended [94, 108].

If the patient is indeed diagnosed with acute bacterial rhinosinusitis after reassessment, initiate antibiotic therapy for patients who initially had been placed on watchful waiting, and change antibiotics for patients who had been on antibiotic therapy [94, 108]. Although it is best to choose antibiotics according to the results of bacterial cultures and susceptibility tests, in cases where empirical antibiotics are warranted, use 1) high-dose amoxicillin/clavulanate, 2) doxycycline, or 3) clindamycin/third-generation cephalosporins, which can treat multidrug-resistant *S. pneumoniae* or beta-lactamase-producing *H. influenzae* and *M. catarrhalis* [108, 116].

The following must be considered if a second-line regimen must be chosen due to failure of the initial empirical antibiotic therapy. However, if low-dose amoxicillin/clavulanate was chosen as the initial treatment, high-dose amoxicillin/clavulanate therapy may be used [108, 116]. Cefaclor and cefprozil, a second-generation cephalosporin, are not recommended because the most common pathogens of acute bacterial rhinosinusitis, namely, *S. pneumoniae, H. influenzae,* and *M. catarrhalis* have low susceptibility to these antibiotics [108, 130-133]. Oral cefditoren and cefcapene and cefpodoxime have been reported to be efficacious for treating acute bacterial rhinosinusitis caused by penicillin-resistant *S. pneumoniae* and that by *H. influenzae* and *M. catarrhalis*, respectively [116, 132-135]. Oral cefuroxime and cefdinir are known to be effective for acute bacterial rhinosinusitis caused by moderately penicillin-resistant *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* but its therapeutic efficacy in Korea is uncertain owing to the high proportion of penicillin-resistant *S. pneumoniae* in the country [136, 137]. To widen the microbiologic spectrum to cover anaerobes, additional use of metronidazole or clindamycin is recommended with cephalosporin [108].

The fluoroquinolones such as levofloxacin, and moxifloxacin may be effective, but the possibility of resistance to these antibiotics among *Myocobacterium tuberculosis* and *S. pneumoniae* should be noted. It should further be noted that the FDA recommended in 2016 that fluoroquinolones be used for sinusitis, bronchitis, and urinary tract infection without complications only when there are no other treatment alternatives [1, 6, 138].

Canadian and British studies have reported that the susceptibility rates of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* to doxycycline exceeds 90% [139-141]. Doxycycline may be used as the second-line antibiotic therapy for adults with acute bacterial rhinosinusitis as an alternative to fluoroquinolones when the patient has difficulty receiving or has not responded to the initial empirical antibiotic therapy [108]. This choice is supported by the pharmacokinetic superiority of doxycycline and the finding that doxycycline and levofloxacin have no differences in clinical outcomes but that doxycycline is associated with lower medical costs in patients admitted to community hospitals with pneumonia [142, 143].

Some have raised concerns about the uncertain therapeutic efficacy of the macrolides such as erythromycin, roxythromycin, azithromycin, and clarithromycin in Korea due to the high proportion (80-90%) of macrolides-resistant *S. pneumoniae* in the country. Although telithromycin, a ketolide, is known to have antibacterial activity against macrolide-resistant *S. pneumoniae,* it is not yet a viable option in Korea [108, 136, 137, 144].

For severe cases of acute sinusitis that require hospitalization, the following antibiotics may be used: ampicillin/sulbactam (1.5–3 g, injection every 6 hours), ceftriaxone (1–2 g, injection 1–2 times), cefotaxime (1–2 g, injection every 6–8 hours), levofloxacin (500–750 mg, oral/injection), and moxifloxacin (400 mg, oral). IV ceftriaxone and cefotaxime have been found to act on all strains of *S. pneumoniae,* including penicillin-resistant *S. pneumoniae* [124]. Furthermore, if the prevalent *S. pneumoniae* 19A strains continue to exhibit about 30% rates of clindamycin minimum inhibitory concentrations (MICs) >0.5 mg/L, levofloxacin or moxifloxacin may be recommended as empirical therapy for patients with severe conditions that require hospitalization, rather than clindamycin

plus ceftriaxone [127].

Additional tests and surgical treatment may be considered when symptoms worsen without improvement within 48–72 hours after proper antibiotic therapy or when ocular or central nervous system complications are suspected [145]. Treatment duration is generally 4–7 additional days after the improvement of clinical symptoms, and total treatment duration generally ranges 10–14 days.

Regarding the treatment of acute bacterial rhinosinusitis, the Health Insurance Review and Assessment Service (HIRA) suggests in their General Principles of Antibiotics Use (Announcement No. 2013-127): 1) Choosing antibiotics is based on drug susceptibility tests rather than by indication, so antibiotics should be phased in within the permitted range, with reference to the patient's history. 2) In cases of severe infection where oral administration alone cannot produce an adequate treatment outcome, parenteral injections may be additionally used.

9) What is the recommended management strategy in patients who clinically worsen within 72 hours or fail to improve after 3–5 days of initial empirical antimicrobial therapy with first- or second-line regimens?

1. For patients who show no improvement despite appropriate first- or second-line antimicrobial therapy or patients with recurrent acute sinusitis, additional diagnosis should be performed in consideration of allergic rhinitis, immune abnormalities, and tooth infections. (Quality of evidence: Very low, Strength of recommendation: Strong)
2. When a related comorbidity is diagnosed, provide treatment according to the guideline for each morbidity. Consider environmental therapy, immune therapy, and drug therapy for patients with hypersensitivity. (Quality of evidence: Very low, Strength of recommendation: Strong)
3. Surgical treatment may be considered when recurrent acute sinusitis is nonresponsive to appropriate drug therapy. (Quality of evidence: Moderate, Strength of recommendation: Strong)

In cases where the patient fails to show improvement despite appropriate first- and second-line antibiotic therapy, including antibiotic therapy, and cases defined as recurrent acute sinusitis (more than four episodes of sinusitis per year with symptom-free intervals) [146], differential diagnosis in consideration of allergic rhinitis, immune abnormalities, and tooth infections, is recommended. Surgical treatment may be considered for continual episodes of acute sinusitis [147].

According to a systematic literature review, allergy tests may be run for recurrent acute sinusitis or chronic sinusitis [148]. Allergic patients characteristically have obstructions of the natural ostium caused by the edema of the nasal cavity and sinus mucosa. Particularly, the ethmoid sinus with several natural ostia is susceptible to allergic sinusitis or nasal polyp. If a patient is indeed positive for allergy, environmental therapy, immune therapy, or drug therapy may be considered depending on the patient. However, there is limited evidence supporting that environmental therapy and immune therapy are effective in improving the clinical outcome of recurrent acute sinusitis or chronic sinusitis [149, 150].

Asthma is closely related to recurrent acute sinusitis or chronic sinusitis and is the cause of frequent recurrent episodes of sinusitis [151]. For patients diagnosed with immunodeficiency, such as antibody deficiency, prophylactic antibiotic therapy, pneumococcal vaccination, or regular IV IgG may be considered [151]. In addition, sinusitis may be induced by dental caries or extraction of maxillary molars and premolars, trauma, malnutrition, prolonged steroid therapy, general weakness as a result of diabetes, and tumor in the nasal cavity or sinus; therefore, the corresponding examinations should be performed when such conditions are suspected.

10) When is referral to a specialist indicated in a patient with presumed acute bacterial sinusitis?

1. Cases in which the patient fails to show improvement or has recurrent inflammation despite appropriate treatment require additional tests, such as nasal endoscopy and radiological imaging, and referral to a corresponding specialist. (Quality of evidence: Very low, Strength of recommendation: Weak)
2. Patients with suspected orbital or intracranial complications of acute rhinosinusitis should be immediately referred to a specialist. (Quality of evidence: Very low, Strength of recommendation: Strong)

A lack of improvement or worsening of symptoms even after 3–5 days of antibiotic therapy for acute rhinosinusitis is considered a treatment failure. The exact cause should be identified when the patient is nonresponsive even to the second-line antibiotic regimen as well as in cases of recurrent rhinosinusitis, defined as more than four episodes of acute rhinosinusitis per year with symptom-free intervals [108].

Potential causes include chronic rhinosinusitis, allergic rhinitis, abnormal anatomical structure within the nasal cavity, reduced immunity, fungal infection, granuloma, and tumor. For accurate differentiation of the cause and administration of

Table 8. Comparison of major guidelines pertaining to the diagnosis of acute sinusitis and antibiotic therapy thereof

Category	Present guideline	IDSA (2012)	American Academy of Otolaryngology-Head and Neck Surgery (2015)	Korean Guideline for Antibiotics Usage in Children with Acute Upper Respiratory Infections (2016)	American Academy of Pediatrics (2013)
Diagnosis of acute bacterial sinusitis	One or more of the following symptoms/signs: 1. Severe condition: high fever of 39°C or more, purulent nasal drainage, facial pain (≥3 days) 2. Persistent symptoms: nasal discharge, daytime cough (≥10 days) 3. Double sickening: new episode of fever, headache, cough, or nasal drainage while the above symptoms were showing improvement				
Imaging test	X-ray is not recommended for differentiating the cause of sinusitis; sinus CT or MRI is recommended when ocular or central nervous system complications are suspected				
Indications of antibiotic therapy	Antibiotics may be prescribed initially when acute bacterial sinusitis is diagnosed	Antibiotics may be prescribed when bacterial sinusitis is clinically diagnosed	Watchful waiting without antibiotic therapy, or antibiotics may be prescribed initially for acute bacterial sinusitis without complications	Antibiotics prescribed in severe conditions or when symptoms worsen When symptoms are persistent, choose between immediate prescribing of antibiotics or 3 days of watchful waiting	
First-line antibiotics	Standard or high dose of amoxicillin or amoxicillin/ clavulanate	Standard or high dose of amoxicillin/ clavulanate	Standard or high dose of amoxicillin or amoxicillin/ clavulanate	Standard or high dose of amoxicillin/ clavulanate	Standard or high dose of amoxicillin or amoxicillin/ clavulanate
Penicillin allergy	Type 4 (*e.g.*, rash): consider doxycycline or cephalosporins, clindamycin Type 1 (*e.g.*, anaphylaxis): Non-beta-lactam antibiotics	Third-generation cephalosporins (with the exception of patients with type 1 penicillin hypersensitivity)		Third-generation cephalosporins	
Duration of antibiotic therapy	5–10 days or 4–7 days after improvement of symptoms/signs (first-line empirical antibiotics)	5–7 days for adults without complications (10–14 days for children)	5–10 days	Total 10–28 days, or 7 days after improvement of symptoms/signs	
Reassessment	If symptoms do not improve or worsen or new symptoms/signs develop within 72 hours of initiating treatment, reassess the initial treatment regimen				

IDSA, Infectious Diseases Society of America; CT, computer tomography; MRI, magnetic resonance imaging.

appropriate treatment, the patient must be referred to a specialist who can perform nasal endoscopy and, when necessary, imaging tests such as CT and MRI [152].

Paranasal sinuses are in close proximity to the orbits laterally and to the base of the skull superiorly. Therefore, an infection in the sinuses may spread to the orbits and cranium, causing fatal diseases such as cellulitis, cerebromeningitis, and abscess [153]. A lack of proper antibiotic therapy and surgical drainage may lead to blindness, brain injury, and in severe cases, to death [154, 155].

Severe ocular pain, periocular edema, oculomotor disability, exophthalmos, purulent conjunctivitis, and reduced visual acuity in patients with acute rhinosinusitis are suggestive of ocular complications whereas high fever, severe headache, meningeal irritation sign, and insanity are suggestive of intracranial complications. Patients with such conditions must be referred to a specialist immediately [128].

Table 8 shows a comparison of the recommendations pertaining to acute sinusitis of the present guideline, IDSA (2012), American Academy of Otolaryngology-Head and Neck Surgery (2015), American Academy of Pediatrics (2013), and Korean Guideline for Antibiotics Usage in Children with Acute

Upper Respiratory Infections (2016) [89, 94, 108, 156].

Limitations of this clinical guideline and future additions

Despite the high prevalence of acute URI, relevant research with good evidence-based findings is critically lacking. Furthermore, most clinical trials that were used as the basis of reference for this guideline was conducted abroad, with little research data involving Korean patients, thus requiring clinicians to adequately take note of this limitation when utilizing this guideline in the clinical setting. Studies involving Korean subjects are essential to accumulate relevant data, to make appropriate revisions to Korean guidelines.

First, the causative pathogen of acute URI in Korean adults must be identified. Seasonal variations of viruses and bacteria and their proportions should be investigated to minimize inappropriate use of antibiotics. Second, more data are needed to support appropriate selections of empirical antibiotics based on various patterns of antibiotic susceptibility among bacterial strains isolated from patients with acute bacterial URI. Third, studies must analyze the effectiveness of rapid antigen tests using pharyngeal swabs and bacterial cultures for Korean adults as well as assessing the usefulness of cultures using sinus-related specimens. In addition, studies should also assess the impact of relevant tests, ASO, C-reactive protein, and procalcitonin tests on the treatment outcome, to lay the foundation for developing a clinically applicable diagnostic flowchart. Fourth, studies should assess the therapeutic efficacy of amoxicillin and amoxicillin/clavulanate, which are recommended by guidelines in other countries as first-line antibiotics, in Korean patients and also compare their doses and treatment durations. Finally, medical professionals' adherence to this guideline should be assessed, to estimate its utilization and analyze factors that hamper adherence so as to make necessary revisions to the guideline in the future. Furthermore, comparing actual antibiotic prescribing patterns and recommendations using HIRA insurance claims data may also provide useful data to help lower inappropriate use of antibiotics for acute upper respiratory infection.

Plans for revision

This guideline will be regularly revised to keep abreast of the latest key research findings in Korea and abroad.

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Conflicts of Interest

No conflicts of interest.

ORCID

Young Kyung Yoon *https://orcid.org/0000-0001-8435-935X*
Shin Woo Kim *https://orcid.org/0000-0002-3755-8249*

Supplementary material

Guideline Korean version.

Supplementary material can be found with this article online http://www.icjournal.org/src/sm/ic-49-326-s001.pdf.

Supplementary data including one table can be found with this article online http://www.icjournal.org/src/smsm/ic-49-326-s002.pdf.

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