Manual for Antimicrobial Stewardship Fourth Edition

Dental Section

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Ministry of Health, Labour and Welfare

Table of Contents

Glossary

[Types of Major Oral Antibiotics in the Dental Field in Japan]

Classification		Nonproprietary Name (Common Name)	Main Brand Names	Abbreviation
β-Lactams	Penicillin	Amoxicillin	Sawacillin Amoxicillin	AMPC
		Clavulanic acid/ Amoxicillin	Augmentin	CVA/AMPC
	First generation Cephalosporins	Cefalexin	Keflex Cefalexin	CEX
	Second generation Cephalosporins	Cefaclor	Kefral Cefaclor	CCL
		Cefuroxime	Oracef	CXM-AX
	Third generation Cephalosporins	Cefcapene	FLOMOX Cefcapene	CFPN-PI
		Cefditoren	MEIACT MS Cefditoren	CDTR-PI
		Cefdinir	Cefzon Cefdinir	CFDN
		Cefteram	TOMIRON	CFTM-PI
		Cefpodoxime	BANAN Cefpodoxime	CPDX-PR
	Penems	Faropenem	Farom	FRPM
Macrolides		Clarithromycin	Klaricid Clarith Clarithromycin	CAM
		Roxithromycin	Rulid Roxithromycin	RXM
		Azithromycin	ZITHROMAC Azithromycin	AZM
Tetracyclines		Minocycline	MINOMYCIN (Transitional measures ended March 31, 2025) Minocycline	MINO
Quinolones (Fluoroquinolones)		Levofloxacin	CRAVIT Levofloxacin	LVFX
		Sitafloxacin	GRACEVIT Sitafloxacin	STFX
Lincosamides		Clindamycin	Dalacin	CLDM

Note: For transitional pharmaceutical products, information regarding transitional measures should be added if within the transitional period or if less than one year has passed since the end of the transitional period.

1. Introduction

(1) Background and Purpose of Development

Antimicrobial agents (in actual clinical practice, the term "antibiotics" is used as a general term for drugs that act against bacteria) refer to drugs with activity against microorganisms and are used for the treatment and prevention of infectious diseases. In recent years, the inappropriate use of antimicrobial agents has led to an increase in drug-resistant bacteria and associated infections, which has become a major global public health problem. Furthermore, while the development of new antimicrobial agents has declined since the 1980s, new drug-resistant bacteria have been increasing primarily in hospitals.[1] Therefore, if antimicrobial agents are not used appropriately, effective antimicrobial agents for treating infectious diseases will become even increasingly limited in the future, potentially resulting in a rise in deaths related to antimicrobial resistance. If no measures are implemented to address inappropriate antimicrobial use, drug-resistant bacteria are estimated to directly cause or contribute to 10 million deaths globally per year by 2050. As of 2021, the estimated number of deaths directly attributable to drug-resistant bacteria was 1.14 million per year with drug-resistant bacteria associated with 4.71 million deaths annually[3-5]

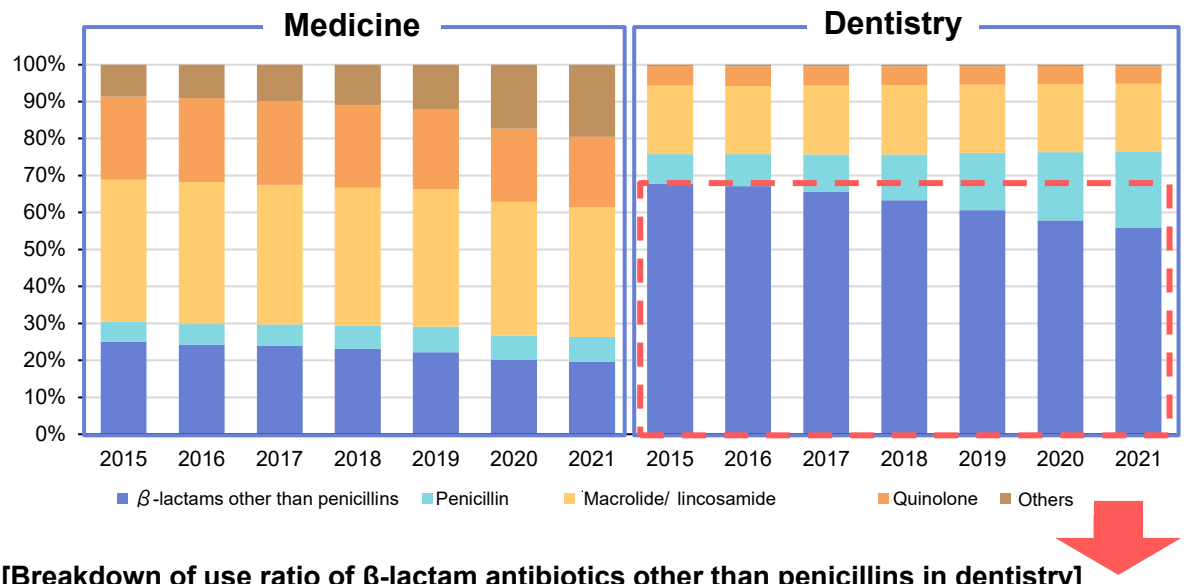
At the World Health Organization (WHO) General Assembly in May 2015, the Global Action Plan on Antimicrobial Resistance (AMR) was adopted, calling on Member States to develop national action plans. Shortly thereafter, at the G7 Summit, participating countries confirmed their commitment to strengthening the One Health Approach, an integrated approach to human and animal health and to advancing the research and development of new drugs. In Japan, the Coordination Council on Antimicrobial Resistance was established in December 2015, and in April of the following year, the National Action Plan on Antimicrobial Resistance (AMR) (2016–2020) was announced, outlining six priority areas and objectives, including the appropriate use of antimicrobial agents. Following the COVID-19 pandemic, a new National Action Plan on AMR (2023-2027)[1] was formulated in April 2023. Furthermore, the following performance indicators were established: reduce daily antibiotic use per 1,000 population by 15% from 2020 levels by 2027 and reduce oral third-generation cephalosporins by 40%, oral fluoroquinolones by 30%, and oral macrolides by 25% compared to 2020. To achieve these performance indicators, the Ministry of Health, Labour and Welfare has issued the Manual for Antimicrobial Stewardship” currently available in its third edition.[6]

While oral antibiotic use in dentistry accounts for approximately 10% of that in medicine, 81.2% of dental antibiotic prescriptions are for the prevention of surgical site infections (SSI) and postoperative complications following tooth extraction.[7] Additionally, compared with medical practice, the proportion of β-lactam antibiotics

other than penicillins is higher in dentistry. Although this proportion has gradually decreased from 68% in 2015, it still accounts for 56% as of 2021. Among these, third-generation cephalosporins, one of the reduction targets in the current action plan, account for more than 80% of all β-lactam antibiotics, excluding penicillins (Figure 1).[8] Contributing factors include unnecessary prescriptions, inappropriate administration, suboptimal antibiotic selection, and insufficient education regarding antibiotic use. Internationally, a meta-analysis has shown that interventions such as education for dentists and the use of digital tools related to appropriate antibiotic use reduced inappropriate antibiotic use by 70%.[9] In Japan, pharmacist interventions have also resulted in changes in dentists' antibiotic prescribing behavior with an increase in penicillins accompanied by a decrease in third-generation cephalosporins and other broad-spectrum antibiotics.[10]

Therefore, it is necessary to promote AMR measures in dentistry through education and awareness-raising initiatives to reduce unnecessary or inappropriate antibiotic use in dental healthcare facilities and to ensure appropriate antibiotic use.

As part of AMR measures in dentistry, a dental edition has been newly developed in the fourth edition of the Manual for Antimicrobial Stewardship based on domestic and international guidelines and relevant scientific literature. It should be noted that this manual was formulated to promote AMR measures and does not stipulate matters related to medical treatment under medical insurance legislation.



[Breakdown of use ratio of β-lactam antibiotics other than penicillins in dentistry]

β-lactams other than penicillins	2015	2016	2017	2018	2019	2020	2021
First-generation cephalosporins	2%	2%	2%	2%	2%	2%	2%
Second-generation cephalosporins	17%	16%	15%	15%	15%	15%	15%
Third-generation cephalosporins	**79%**	**80%**	**81%**	**81%**	**81%**	**81%**	**81%**
Others	2%	2%	2%	2%	2%	2%	2%

Figure1. Proportion of use of oral antibiotics by class in medicine and dentistry

(Adapted from Reference 8)

(2) Target Audience of the Manual

The primary target audience of the fourth edition of the Manual for Antimicrobial Stewardship is shown in Table 1. Regarding the dental edition, the content constitutes essential knowledge for dentists who prescribe antibiotics, and it is also recommended that dental hygienists be familiar with the content.

Table 1. Target Audience of This Manual

Healthcare Professionals	Medicine - Outpatient Edition			Medicine - Inpatient Section	Antimicrobial Stewardship for Infections caused by Drug-Resistant Bacteria Section	Dental Section
	Introduction and General Principles	Adults and School-Age Children in General Outpatient Settings Section	Infants and Toddlers in General Outpatient Settings Section			
Hospital physicians engaged in infectious disease care and infection control (AST, ICT)	●	●	●	●	●	○
Hospital physicians other than the above	●	●	●	●	○	
Clinic physicians	●	●	●			
Nurses engaged in infectious disease care and infection control (AST, ICT)	●	●	●	●	●	○
Hospital nurses other than the above	●	○	○	●		
Clinic nurses	●	●	●			
Pharmacists engaged in infectious disease care and infection control (AST, ICT)	●	●	●	●	●	○
Hospital pharmacists other than the above	●	○	○	●		○
Community pharmacists	●	●	●			●
Clinical laboratory technicians engaged in infectious disease care, infection control (AST, ICT), and microbiological testing	●	○	○	●	●	
Clinical laboratory technicians other than the above	●					
Hospital dentists	●			○	○	●
Clinic dentists	●					●
Dental hygienists working in hospitals or clinics						○

●: Essential knowledge, ○: Recommended knowledge

(3) Target Patient Population

The target patient population is broadly divided into the following two groups:

a) Patients requiring antibiotics for the prevention of SSI following mandibular impacted wisdom tooth extraction or dental implant placement and for the prevention of infective endocarditis (IE) associated with dental treatment
b) Patients requiring antibiotics for the treatment of odontogenic infections

Additionally, patients with renal impairment in whom dose adjustment and dosing intervals are often problematic during antibiotic administration, and patients with suspected penicillin allergy are also included in the target patient population.

It should be noted that this manual assumes adult patients as the target population. For pediatric patients, individual approaches, such as referencing standard textbooks or consulting specialists, are recommended.

(4) Others

Regarding the dental edition, when the condition is not included in the approved indications of the electronic package insert (hereinafter referred to as "electronic PI"), when the dose described in the manual exceeds the upper limit of the recommended dose in the electronic PI, or when it is mentioned in the Cases of Review Information provided by the Health Insurance Claims Review & Reimbursement Services, a "¶" symbol is inserted at the end of the dosage and administration section (refer to the electronic PI for contraindications and drug interactions).

(i) Indications

Although the electronic PI for clavulanic acid/amoxicillin does not include odontogenic infections as an approved indication, the Review Information Case Examples states: "In principle, when potassium clavulanate/amoxicillin hydrate [oral preparation] is prescribed for periodontitis, pericoronitis, or jaw inflammation, such use shall be accepted for review purposes."

The electronic PI for clindamycin includes only cellulitis around the jawbone and jaw inflammation as approved indications for odontogenic infections. However, the Cases of Review Information states: "In principle, when clindamycin hydrochloride [oral preparation] is prescribed for patients with penicillin allergy or similar conditions for periodontitis, pericoronitis, or secondary infection of extraction wounds, such use shall be accepted for review purposes."

Although the electronic PI for clarithromycin pediatric formulations does not include odontogenic infections as an approved indication, the Review Information Case Examples states: "In principle, when clarithromycin (pediatric) [oral preparation] is

prescribed for periodontitis or jaw inflammation, such use shall be accepted for review purposes."

The electronic PI for azithromycin tablets includes periodontitis, pericoronitis, and jaw inflammation as approved indications, and the Cases of Review Information states: "In principle, when azithromycin hydrate [oral preparation] is prescribed or used for current approved indications in pediatric patients, such use shall be accepted for review purposes."

(ii) Dose and Administration

Table 2 shows the dose and administration information from the electronic PI for antibiotics whose doses described in this manual exceed the upper limit of the recommended dose in the electronic PI.

Table 2. Dose and Administration Described in Electronic PI

Nonproprietary Name (Common Name)	Electronic PI
Amoxicillin	Adults: Usually 250 mg orally 3 to 4 times daily Dose may be adjusted according to age and symptoms
Clindamycin	Adults: Usually 150 mg (potency) orally every 6 hours For severe infections: 300 mg every 8 hours orally
Cefalexin (Tablets/Capsules)	Adults and children weighing 20 kg or more: Usually 250 mg orally every 6 hours For severe cases or when the susceptibility of the isolated organism is relatively low: 500 mg orally every 6 hours Dose may be adjusted according to age, body weight, and symptoms
Cefalexin (Sustained-Release Granules)	Adults and children weighing 20 kg or more: Usually 1 g (potency) daily divided into two doses administered orally For severe cases or when the susceptibility of the isolated organism is relatively low: 2 g (potency) daily divided into two doses administered orally Dose may be adjusted according to age and body weight
Clarithromycin	Adults: Usually 400 mg daily divided into two doses administered orally Dose may be adjusted according to age and symptoms

2. General Principles

(1) Inappropriate Use of Antimicrobial Agents

Inappropriate use of antimicrobial agents (hereinafter referred to as antibiotics) can be categorized into "unnecessary use" and "improper use." (Figure 2) "Unnecessary use" refers to situations where antibiotics are administered for conditions that do not require antibiotic administration. "Improper use" refers to situations where antibiotics Therefore, antibiotic use for conditions other than these should be kept to a minimum. should be administered for specific conditions or when postoperative infection prophylaxis is necessary, but the selection, dose, duration, or timing of antibiotic administration deviates from standard treatment or prophylactic regimens.[11]

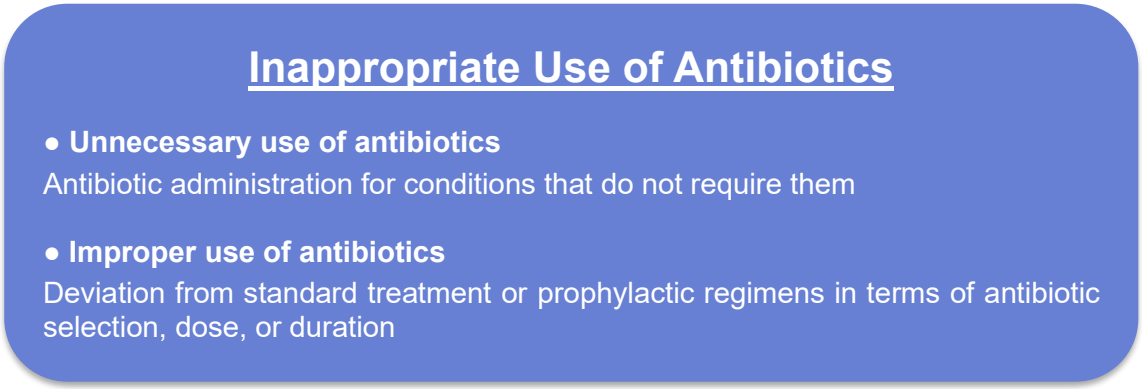


Figure 2. Conceptual Framework for Inappropriate Use

As a general principle, antibiotic treatment is indicated for conditions in which infection has been diagnosed or is strongly suspected, and antibiotic administration is established as standard treatment.

However, in dentistry, antibiotics are more frequently used for the prevention of surgical site infections following procedures such as tooth extraction rather than for the treatment of odontogenic infections. In such cases, it is important to adhere to sasaadministration criteria consistent with guidelines and similar resources.[7]

(2) What is the AWaRe Classification?

As part of AMR measures, the WHO has published the Essential Medicines List (EML), a prioritized list of medicines based on public health needs. Within this framework, antibiotics are categorized into three groups of Access, Watch, and Reserve in the AWaRe classification, taking into account both clinical importance and the risk of antimicrobial resistance development (Table 3).[12]

Table 3. AWaRe Classification*

Access	This category includes many antibiotics used as first- or second-line treatment options for common infections. Even if resistance to these agents develops, other therapeutic options remain available; therefore, the disadvantage associated with resistance is relatively small.
Watch	These antibiotics should be used only for limited diseases or indications, such as infections caused by drug-resistant bacteria that are difficult to treat with Access antibiotics. While these antibiotics have important clinical applications, their inappropriate use may lead to the rapid emergence and spread of clinically significant drug-resistant bacteria.
Reserve	These antibiotics should be used only as a last resort when all other treatment options are ineffective, such as infections caused by multidrug-resistant bacteria. The use of these antibiotics must be strictly controlled and monitored.

*Green: Access antibiotics; Yellow: Watch antibiotics; Red: Reserve antibiotics
Classification as of April 1, 2025
(Adapted from references 12 and 13)

In Japan, while the use of antibiotics classified as Access (hereinafter referred to as “Access antibiotics”) has been increasing and the use of antibiotics classified as Watch (hereinafter referred to as “Watch antibiotics”) has been declining, Access antibiotics was accounted for 23.2% of total antibiotics use in 2023, while Watch antibiotics accounted for 75.7%.[13] indicating a substantial gap from the WHO target of 60% or higher for Access antibiotics use.[12]

Table 4 categorizes representative oral antibiotics used for dental diseases in Japan by class according to the 2025 AWaRe classification. Third-generation cephalosporins and macrolides, which are most frequently used in dentistry, are classified as Watch antibiotics. Furthermore, penicillin-based antibiotics, such as amoxicillin, which are currently the first-line oral antibiotics prescribed in dentistry, are classified as Access antibiotics. Moving forward, dentistry faces a strong imperative to advance AMR measures by reducing the inappropriate use of Watch antibiotics, increasing the proportion of Access antibiotics use, and decreasing overall antibiotics consumption.

Table 4 AWaRe Classification of Representative Oral Antibiotics Used for Dental Diseases in Japan

Classification	Access	Watch	Reserve
Penicillin	Amoxicillin Clavulanic acid/ Amoxicillin	—	—
Cephalosporins	**First generation** Cefalexin	**Second generation** Cefaclor Cefuroxime **Third generation** Cefcapene Cefditoren Cefdinir Cefteram Cefpodoxime	—
Macrolides	—	Azithromycin Clarithromycin Roxithromycin	—
Fluoroquinolones	—	Sitafloxacin Levofloxacin	—
Others	Clindamycin (Lincosamides)	Minocycline (Tetracyclines)	Faropenem (Penems)

(3) Current Status of Antibiotics Prescriptions in Dentistry

(i) Overall Status of Antibiotics Prescriptions in Dentistry

Antibiotic prescriptions in dentistry consist of almost entirely of oral antibiotics, which account for approximately 99% of all prescriptions. Oral antibiotics used in dental outpatient settings are prescribed primarily for (1) prevention of SSI following procedures, such as mandibular impacted wisdom tooth extraction and dental implant placement , and (2) treatment of odontogenic infections, such as apical periodontitis and pericoronitis, and less frequently for (3) prevention of IE associated with surgical procedures and treatments. A study analyzing data from National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) from 2015 to 2017 reported that cephalosporins were the most frequently prescribed oral antibiotics in dentistry, accounting for more than 60% of all oral antibiotic prescriptions.[14] In contrast, in other countries, such as Germany, amoxicillin is predominantly used in dentistry.[15-17] At the time of formulation of the 2015 Action Plan in Japan, however, a major concern was that most dentists relied on broad-spectrum antibiotics, including third-generation cephalosporins and macrolides.[14,18] Consequently, guidelines for appropriate antimicrobial use, such as the "Practical Guidelines for Appropriate Use of Prophylactic Antibiotics for Postoperative Infection Prevention,"[19] were developed, and penicillin-based antibiotics, which are classified as Access antibiotics and are associated with a lower risk of antimicrobial resistance, are now recommended in dentistry as well.

In addition to guideline recommendations, through educational lectures by academic societies and related organizations and awareness campaigns regarding AMR measures via commercial journals and other channels, the proportion of penicillin-based antibiotics use nationwide has gradually increased from the formulation of the Action Plan through 2021 (Figure 1). However, while the proportion of β-lactam antibiotics other than penicillins has been gradually decreasing, their usage rate remains higher in dentistry than medical practice, with the majority consisting of third-generation cephalosporins (Figure 1).[20]

(ii) Current Status of Antibiotics Prescription in Dental Clinics

In Japan, approximately 90% of dentists working in healthcare facilities are employed at dental clinics.[21] Consequently, oral antibiotics prescriptions at dental clinics have a substantial impact on the types and volumes of antibiotics used in dentistry. A cross-sectional study examining antibiotics prescribing trends among dentists using the NDB from 2015 to 2020 revealed that the prescription rate of third-generation cephalosporins at dental clinics decreased only modestly from 60.5% to 53.1%, indicating that more than half of prescriptions still consist of Watch antibiotics.[22] These reports suggest that Watch antibiotics, such as third-generation cephalosporins continue to be frequently used in Japanese dental clinics. Contributing factors may

include habitual prescribing practices based on education during clinical training and dental residency programs, as well as prescribing patterns of supervising dentists, even when the importance of AMR measures is recognized. Nevertheless, following the formulation of the Action Plan, educational lectures on AMR measures by relevant academic societies and awareness campaigns through guideline dissemination have gradually led dentists to increasingly select penicillin-based antibiotics, particularly amoxicillin, as their first-line agents.[18,22-26]

3. Specific Topics

(1) Antibiotic prophylaxis

(i) General Principles

The purpose of antibiotic prophylaxis is to reduce the incidence of SSI.[19,27,29] The goal is not to sterilize tissues but rather to serve as an adjunct to reduce bacterial loads from intraoperative contamination to levels that can be controlled by host defense mechanisms.[27] Therefore, from the perspectives of AMR measures and appropriate antibiotics use, antibiotic prophylaxis should be implemented only when its effectiveness is anticipated.

In surgical infection prophylaxis in general, it is essential that adequate bactericidal concentrations in blood and tissue be achieved at the time surgery begins. For this reason, administration of a single dose one hour before surgery is considered the standard approach.[30,31] Furthermore, when additional postoperative administration is indicated based on factors such as the degree of surgical invasion or the patient's host defense capacity, administration within 24 hours after surgery is the general principle,[19] with a maximum duration of 48 hours postoperatively.[32] However, many reports indicate that postoperative administration is unnecessary when appropriate blood concentrations of antibiotics are maintained for several hours after completion of surgery.[19,33 ,34]

(ii) Antibiotic Prophylaxis for Tooth Extraction

Antibiotic prophylaxis for tooth extraction is not recommended for patients without a risk of IE or systemic risk factors such as immunocompromised status, nor for simple extractions in healthy individuals without local infection or bone removal.[19,35,36]

SSI following tooth extraction is frequently observed after mandibular impacted wisdom tooth extraction,[37-39] and when SSI occurs following such procedures, it can lead to serious infectious complications, such as cellulitis. Numerous clinical studies have been conducted regarding the necessity of antibiotic administration for SSI prevention prior to mandibular impacted wisdom tooth extraction, and the effectiveness of antibiotic prophylaxis has been established.[35,36,40-42,44] Reports indicate that in healthy individuals undergoing mandibular impacted wisdom tooth extractions performed by oral surgeons antibiotic prophylaxis reduces SSI risk by approximately 66% compared with placebo.[36] Additionally, reports have shown that a single dose of amoxicillin or clavulanic acid/amoxicillin administered one hour before mandibular impacted wisdom tooth extraction reduces SSI risk.[42]

Current Japanese guidelines[19] recommend a single dose of amoxicillin 250 mg to 1 g or clavulanic acid/amoxicillin 375 mg to 1.5 g (250 mg to 1 g as amoxicillin) one hour

before mandibular impacted wisdom tooth extraction. However, the clinical trials cited in the meta-analyses[35,36] that form the basis for this recommendation were conducted overseas before the WHO AMR Global Action Plan was issued, and the preoperative single doses of amoxicillin ranged from 500 mg to 3 g. Some reports indicate that while a single dose of clavulanic acid/amoxicillin significantly reduces SSI risk, no significant reduction was observed with amoxicillin alone.[40]

In recent Japanese clinical studies, there was no significant difference in SSI incidence between a group receiving a single 250 mg dose of amoxicillin one hour before extraction and a group receiving 250 mg both preoperatively and postoperatively. However, it has been noted that a single 250 mg dose does not achieve sufficient blood concentrations, suggesting that 500 mg dose is more appropriate.[41] When administering oral antibiotics as a single preoperative dose for SSI prevention, it is important to use a dose that achieves sufficient blood concentrations according to the case difficulty and degree of surgical invasion.[42] Furthermore, another Japanese study group reported that the SSI incidence rate was significantly higher in the group receiving a single 250 mg dose of amoxicillin one hour before mandibular impacted wisdom tooth extraction compared to the group receiving additional postoperative administration of 750 mg/day of amoxicillin.[43]

Therefore, for antibiotic administration to prevent SSI in mandibular impacted wisdom tooth extraction, the first line is a single dose of 250 mg or 500 mg of amoxicillin one hour before extraction. When surgical invasion is substantial, such as cases involving bone removal, or when significant contamination is observed during surgery, additional administration of 250 mg per dose, 3 times daily (750 mg per day) up to 48 hours postoperatively is recommended to maintain sufficient blood concentrations of time-dependent amoxicillin.[19,44]

However, recent UK guidelines do not recommend antibiotic prophylaxis for SSI prevention.[45]

For patients with penicillin allergy requiring SSI prevention, refer to the "In case of penicillin allergy" section in Table 5.

(iii) Antibiotic Prophylaxis for Dental Implant Placement

Regarding antibiotic prophylaxis for dental implant placement, numerous systematic reviews and meta-analyses have examined early dental implant failure, with most demonstrating the significance of antibiotic prophylaxis in preventing early dental implant loss.[46-52] However, the 2015 European Association for Osseointegration (EAO) consensus conference concluded that antibiotic prophylaxis does not affect early dental implant loss in uncomplicated dental implant placements.[53] Additionally, recent meta-analyses have reported that antibiotic prophylaxis does not influence early dental

implant failure.[54,55] Thus, the benefit of antibiotic prophylaxis for the purpose of preventing early dental implant loss has not been clearly established.

Japanese guidelines[19] recommend a single preoperative dose of amoxicillin (250 mg to 1 g) one hour before dental implant placement. However, this recommendation is based on evidence for preventing early implant failure rather than SSI prevention. Meta-analyses indicate that antibiotic prophylaxis before dental implant placement in healthy individuals does not significantly affect SSI prevention.[47-49,55]

Therefore, antibiotic prophylaxis for SSI prevention is not recommended for dental implant placement in healthy individuals when clean operative procedures are ensured.[45] However, in cases involving bone augmentation or bone grafting, a single preoperative dose of antibiotics for SSI prevention is strongly recommended.[45]

Table 5. Recommended Oral Antibiotics and Administration Methods for SSI Prevention in Adults¶

<table>
<tr><th rowspan="2">Procedure</th><th colspan="2">Administration Method</th></tr>
<tr><th>Japan</th><th>International (Reference)</th></tr>
<tr><td>Simple tooth extraction
(No systemic or local risk factors)

Dental implant placement
(No systemic or local risk factors)</td><td colspan="2">Antibiotic prophylaxis is not recommended[19,35,36,44,45,56]</td></tr>
<tr><td rowspan="4">Mandibular impacted wisdom tooth extraction</td><td colspan="2">Amoxicillin</td></tr>
<tr><td>Single dose of 250 mg or 500 mg,
1 hour before surgery[19,39,41,44]

Consider additional administration of 250 mg per dose, 3 times daily up to 48 hours postoperatively only in cases with substantial surgical invasion</td><td>Single dose of 500 mg to 3 g,
1 hour before surgery[40,42]

*However, UK guidelines do not recommend antibiotic prophylaxis.[45]</td></tr>
<tr><td colspan="2">Clavulanic acid/Amoxicillin</td></tr>
<tr><td>Single dose of 125/250 mg (clavulanic acid/amoxicillin),
1 hour before surgery[19,40,42,56]

Consider additional administration of 125/250 mg per dose (clavulanic acid/amoxicillin)
3 times daily up to 48 hours postoperatively only in cases with substantial surgical invasion</td><td>Single dose of 125/500 mg to 125 mg/2 g*1
(clavulanic acid/amoxicillin),
1 hour before surgery[35,40,42]

*However, UK guidelines do not recommend antibiotic prophylaxis.[45]</td></tr>
<tr><td rowspan="2">In case of penicillin allergy*2</td><td colspan="2">Clindamycin</td></tr>
<tr><td>Single dose of 300–450 mg,
1 hour before surgery[19,56]

Consider additional administration of 300 mg per dose, 3 times daily up to 48 hours postoperatively only in cases with substantial surgical invasion</td><td>Single dose of 300–450 mg,
1 hour before surgery[35,36]</td></tr>
</table>

*1 The corresponding formulation (combination drug) is not available in Japan.

*2 Details on penicillin allergy are described in a separate section.

¶ The indications and dose/administration described in electronic PIs are provided in Chapter [1][(4) Others].

(iv) Antibiotic Administration for Infective Endocarditis Prevention

① What is Infective Endocarditis (IE)?

IE is a serious systemic septic disease characterized by the formation of vegetations containing bacterial colonies on heart valves, endocardium, or large vessel endothelium, presenting with diverse clinical manifestations including bacteremia, vascular embolism, and cardiac dysfunction.[57] It is frequently observed in patients with underlying cardiac conditions and without accurate diagnosis and appropriate treatment, it can lead to multiple complications of heart failure, embolism, and renal impairment, often resulting in death. The estimated global incidence of IE in 2019 was 13.8 per 100,000 population, with approximately 66,000 deaths worldwide attributed to IE.[58]

The development of IE is strongly associated with nonbacterial thrombotic endocarditis (NBTE), which occurs because of abnormal blood flow associated with valvular disease or congenital heart disease, as well as the effects of foreign materials following prosthetic valve replacement surgery.

Transient bacteremia frequently occurs during dental procedures, and the risk of IE is further influenced by the type and severity of underlying conditions. When transient bacteremia occurs following invasive dental procedures, oral streptococci and other bacteria are believed to attach to sites of NBTE, proliferate, and form vegetations. It has been reported that 12% of patients who developed IE had undergone dental procedures involving perforation of the gingiva, periapical region, or oral mucosa (excluding anesthetic injections into non-infected tissue) within three months prior to onset.[59] Accordingly, antibiotic prophylaxis can suppress transient bacteremia during tooth extraction and is expected to inhibit bacterial adhesion and proliferation on heart valves 6-9 hours after extraction.[59-62] The oral bacteria most commonly isolated from IE include *Streptococcus sanguinis* and *Streptococcus mutans*.[57,58]

② Clinical Conditions Requiring Antibiotic Prophylaxis

Table 6 presents the primary patient categories requiring antibiotic administration for IE prevention in dental procedures. Antibiotic prophylaxis is strongly recommended prior to dental procedures that may induce bacteremia, such as tooth extraction, for patients at particularly high risk of developing severe IE, including patients with prosthetic heart valves, patients with a history of IE, patients with complex cyanotic congenital heart disease, and patients with systemic-to-pulmonary shunts.[57,58] For such conditions as atrial septal defect, ventricular septal defect, acquired valvular disease, obstructive hypertrophic cardiomyopathy, and mitral valve prolapse with valvular regurgitation, consultation with a cardiologist should be considered to determine the need for antibiotic prophylaxis.[57]

Table 6. Primary Patient Categories Requiring Antibiotic Administration for IE Prevention in Dental Procedures[57,58]

- Patients with prosthetic heart valves, including bioprosthetic and homograft valves
- Patients with a history of IE
- Patients with complex cyanotic congenital heart disease*
  *Single ventricle, complete transposition of great arteries, tetralogy of Fallot
- Patients with systemic-to-pulmonary shunts

③ Dental Procedures Requiring Antibiotic Prophylaxis

Table 7 presents the dental procedures for which antibiotic administration is recommended for the prevention of IE.[58] To prevent the development of IE, it is necessary to reduce the incidence of bacteremia during dental treatment and to suppress the proliferation of bacteria adhering to thrombi on damaged endocardium. Therefore, antibiotic prophylaxis is recommended for invasive dental procedures associated with bleeding that are likely to induce bacteremia.[57,58]

Table 7. Primary Dental Procedures for Which Antibiotic Administration is Recommended for IE Prevention[58,62-65]

- Tooth extraction
- Surgical procedures (invasive procedures, such as dental implant placement and periodontal surgery)
- Dental procedures involving manipulation of the gingival or periapical region (scaling, infected root canal treatment, etc.)

④ Recommended Antibiotics and Administration Methods for IE Prevention

Table 8 presents the antibiotics and administration methods recommended for IE prevention before dental procedures. For high-risk IE patients as shown in Table 6, domestic and European guidelines recommend administration of a single dose of 2 g amoxicillin one hour before the procedure.[56,57,58]

Table 8. Recommended Oral Antibiotics for IE Prevention Prior to Dental Procedures (Adults) ¶[56,57,58]

Patient Category	Nonproprietary Name (Common Name)	Dose	Administration Method
No penicillin antibiotic allergy	Amoxicillin	2 g*1	Single dose 1 hour before procedure
Penicillin antibiotic allergy present	Clindamycin	600 mg	
	Cephalexin*2	2 g	
	Clarithromycin	400 mg	
	Azithromycin	500 mg	

*1 Or 30 mg/kg body weight

*2 Cephalosporins are not recommended for patients with a history of severe adverse reactions to penicillins such as anaphylaxis.

¶ The indications and dose/administration described in electronic PIs are provided in Chapter [1][(4) Others].

(2) Therapeutic Antibiotic Administration

(i) Principles of Antibiotic Use in Odontogenic Infection Treatment

a) Since the treatment of odontogenic infections is fundamentally based on local procedures such as infected root canal treatment, abscess incision, or tooth extraction, oral antibiotics are not indicated for periapical periodontitis without systemic symptoms where local operative management is available, or for post-extraction dry socket.[45,66-68]

b) Clinical response should be evaluated within 3 to 7 days from the initiation of antimicrobial therapy.[36,45,56,66,67] If no improvement is observed during this period, if the condition worsens, or if adverse events occur, additional surgical anti-inflammatory procedures should be performed, or the antibiotic regimen should be changed or discontinued.[66]

c) As a general rule, antibiotic therapy should be discontinued 24 hours after resolution of inflammatory symptoms..[66]

(ii) Causative Microorganisms of Odontogenic Infections

The pathogenic microorganisms of odontogenic infections are primarily polymicrobial involving oral streptococci and anaerobic bacteria indigenous to the oral cavity. From closed abscesses, two to three bacterial species are typically detected per specimen. The main bacteria detected include oral streptococci (*Streptococcus anginosus* group, etc.), *Prevotella* species, anaerobic gram-positive cocci (*Parvimonas* species, *Peptostreptococcus* species, etc.), *Fusobacterium* species, and *Porphyromonas* species. Notably, many *Prevotella* species produce β-lactamase.[36]

(iii) Recommended Antibiotics for Odontogenic Infection Treatment

In both domestic and international guidelines, amoxicillin, which has activity against oral streptococci, is recommended for periodontitis, pericoronitis, and related conditions.[36,45,56] Post-extraction infections also require antibiotic treatment comparable to that for periodontitis and pericoronitis. However, oral antibiotics are not indicated for dry socket;[45] instead, local operative management and protection of the extraction wound using appropriate dressing materials should be performed.[46]

For early stages of jaw inflammation where inflammation becomes severe and obligate anaerobic bacteria are increasingly involved, as well as for chronic osteomyelitis of the jaw and medication-related osteonecrosis of the jaw, clavulanic acid/amoxicillin is recommended because of its high antibacterial activity against β-lactamase-producing anaerobic bacteria.[36,56]

Additionally, severe jaw inflammation accompanied by trismus and dysphagia, as well as cellulitis around the jawbone, should be managed with intravenous antibiotics at specialized medical facilities.

Third-generation cephalosporins are not recommended for odontogenic infections because they are broad-spectrum antibiotics that target Gram-negative bacteria, which are rarely implicated in odontogenic infections, leading to the spread of antimicrobial resistance; and they have low oral bioavailability[Note 11] (see Table 9).[69-71] Furthermore, negative aspects have been reported, such as the emergence of drug-resistant bacteria due to the use of broad-spectrum antibiotics and increased risk of complications, including antibiotic-associated diarrhea caused by *Clostridioides difficile* and other organisms.[72,73]

Table 9. Bioavailability of Major Oral Antibiotics Used in Japanese Dental Practice

Classification	Access	Watch
Penicillin	Amoxicillin (74～92%) Clavulanic acid/Amoxicillin (37～83%)	—
First- and second-generation Cephalosporins	Cefalexin (90%)	Cefaclor (93%)
Third generation Cephalosporins	—	Cefditoren (14～16%) Cefdinir (20～25%) Cefpodoxime (46～50%)
Macrolides	—	Azithromycin (37%) Clarithromycin (50～55%)
Lincosamides	Clindamycin (90%)	—

For patients with penicillin allergy, domestic guidelines recommend clindamycin or clarithromycin for adults.[8] In the United States, for patients with a history of severe penicillin allergy, such as anaphylactic shock, clindamycin or azithromycin are similarly recommended.[56] From the perspective of AMR measures, it is essential to select antibiotics with careful consideration of the risk of inducing drug-resistant bacteria.

Based on these considerations, Table 10 presents the recommended oral antibiotics and administration methods for the treatment of odontogenic infections.

[Note 11] Bioavailability refers to biological availability; an indicator showing what proportion and rate of an administered drug reaches the systemic circulation and becomes available at the site of action.

Table 10. Recommended Oral Antibiotics for Treatment of Odontogenic Infections¶[36,66]

<table>
<tr><th rowspan="2">Odontogenic infection</th><th colspan="2">Administration Method</th></tr>
<tr><th>Japan</th><th>International (Reference)</th></tr>
<tr><td rowspan="5">Periodontitis
Pericoronitis
Jaw inflammation</td><td colspan="2">Oral antibiotics are unnecessary for apical periodontitis and similar conditions where local operative management is available and systemic symptoms are absent.</td></tr>
<tr><td colspan="2">Amoxicillin</td></tr>
<tr><td>250 mg or 500 mg per dose,
3 to 4 times daily[56]</td><td>When systemic symptoms such as fever are present:
500 mg per dose, 3 times daily[45,66]</td></tr>
<tr><td colspan="2">Clavulanic acid/Amoxicillin</td></tr>
<tr><td>125/250 mg
(clavulanic acid/amoxicillin) per dose, 3 to 4 times daily[56]</td><td>When amoxicillin is ineffective:
125/500 mg*1
(clavulanic acid/amoxicillin) per dose, 3 times daily[66]</td></tr>
<tr><td rowspan="4">Jaw inflammation (Chronic osteomyelitis of the jaw, medication-related osteonecrosis of the jaw)</td><td colspan="2">Amoxicillin</td></tr>
<tr><td>500 mg per dose, 3 to 4 times daily[56]</td><td>500 mg per dose, 3 times daily[45]</td></tr>
<tr><td colspan="2">Amoxicillin + Clavulanic acid/Amoxicillin</td></tr>
<tr><td>125/500 mg
(clavulanic acid/amoxicillin) per dose, 3 times daily
[Prescription Example]
Augmentin 250RS
(Clavulanic acid/Amoxicillin)
1 tablet + Amoxicillin 250 mg 1 tablet</td><td>—</td></tr>
</table>

*1 The corresponding formulation (combination product) is not available in Japan.

¶ The indications and dose/administration described in electronic PIs are provided in Chapter [1][(4) Others].

(3) Others

(i) Management of Patients with Renal Impairment

When antibiotics are administered for therapeutic purposes to patients with renal impairment, dose and dosing interval adjustments are required for many agents. Additionally, some antibiotics (such as sulfamethoxazole-trimethoprim combinations and aminoglycosides) are not recommended for administration to patients with renal impairment.[69-71]

In facilities with an Antimicrobial Stewardship Team (AST), dose tables stratified by antibiotic agent and renal function are often available; in such facilities, clinicians are advised to refer to these resources for both oral and intravenous antibiotics.

Conversely, when antibiotics are administered for prophylactic purposes, a single dose is typically given as standard practice, and dose adjustment is generally unnecessary. For β-lactam antibiotics, ensuring an adequate dose per administration to achieve elevated blood concentrations during procedures is important from a pharmacokinetic and pharmacodynamic perspective and is associated with SSI prevention.[43]

Table 11 presents dose recommendations stratified by renal function for antibiotics with relatively common use in the dental field.

Table 11. Dose and Frequency of Therapeutic Oral Antibiotics by Renal Function¶[69-71]

Nonproprietary Name (Common Name)	Therapeutic dose in normal renal function	Renal failure patients (including those on dialysis)
Amoxicillin	250 mg per dose, 3 to 4 times daily or 500 mg per dose, 3 to 4 times daily	250–500 mg per administration Patients with 10 < Ccr*1 < 50: twice daily Patients with Ccr<10 or on hemodialysis: once daily *2
Clavulanic acid/ Amoxicillin	125/250 mg (clavulanic acid/amoxicillin) per dose, 3 to 4 times daily (When used in combination with amoxicillin: amoxicillin 250 mg per dose, 3 times daily) [Prescription Example] Augmentin 250RS (Clavulanic acid/Amoxicillin) 1 tablet + Amoxicillin 250 mg 1 tablet	Dose: 125/250 mg (clavulanic acid/amoxicillin) Patients with 10 < Ccr < 50: twice daily (When used in combination with amoxicillin: amoxicillin twice daily) Patients with Ccr<10 or on hemodialysis: once daily *2 (When used in combination with amoxicillin: amoxicillin once daily)
Cefalexin (Tablets/Capsules)	250–500 mg per dose, 4 times daily	250–500 mg per administration Patients with 10 < Ccr < 30: 2 to 3 times daily Patients with Ccr < 10 or on hemodialysis: 250–500 mg per dose, 1 to 2 times daily*2
Cefalexin (Sustained-Release Granules)	1,000 mg per dose, twice daily	Patients with Ccr < 10 or on hemodialysis: 500 mg per dose, once daily*2
Clindamycin	300–600 mg per dose, 3 times daily	No dose or interval adjustment required
Azithromycin	500 mg per dose, once daily	No dose or interval adjustment required
Clarithromycin	200–400 mg per dose, twice daily	Patients with Ccr < 10 or on hemodialysis: 200-400 mg per dose, once daily*2

*1 Ccr: Creatinine clearance (mL/min)

*2 For hemodialysis patients, administer after dialysis

¶ The indications and dose/administration described in electronic PIs are provided in Chapter [1][(4) Others].

(ii) Antibiotic Allergy

Drug allergies are adverse reactions mediated by immunological mechanisms; however, adverse events associated with antibiotics include both allergic reactions and non-immunological side effects.[74] The importance of distinguishing between these has been increasingly emphasized in recent years as part of AMR measures and antibiotic stewardship programs.[75] When reported allergies lead to avoidance of a particular agent, negative consequences have been described, including treatment failure due to inability to use first-line option, emergence of drug-resistant pathogens due to the

use of broad-spectrum antibiotics, and the increased risk of *Clostridioides difficile* infection.[72,73]

Antibiotics are among the medications most frequently reported by patients as causing allergies[76] with β-lactams particularly commonly implicated.[77] In the United States, patients reporting penicillin allergy represent 1% to 10% of the general population; of these, approximately 10% test positive on skin testing, and the incidence of anaphylaxis is reported to be 0.01% to 0.05%. In fact, patients themselves often perceive non-allergic symptoms as allergies, but healthcare providers often record such misconceptions in the medical record without verification.[69,78] It is important to accurately assess whether the symptoms reported by the patient represent a true drug allergy. However, when an allergy to any antibiotic is reported and cannot be properly evaluated, use of the antibiotic should be avoided.

Severe allergic reactions generally refer to anaphylactic manifestations including cutaneous reactions or respiratory distress. Accordingly, if a patient reports having experienced diarrhea without rash or respiratory distress after taking amoxicillin in the past and has no treatment history for that symptom as an allergy, it is likely to be a non-allergic adverse reaction. Table 12 summarizes the main non-allergic adverse reactions of antibiotics commonly used in dentistry. However, domestic data on evaluation systems for antibiotic allergies remain limited, and the further development of evidence and operational frameworks is required.

Table 12. Main Non-Allergic Adverse Reactions of Oral Antibiotics Commonly Used in Dentistry[69-71]

Nonproprietary Name (Common Name)	Common adverse reactions	Occasional adverse reactions	Rare adverse reactions
Amoxicillin		Diarrhea	Leukopenia, thrombocytopenia, hepatic disorder
Clavulanic acid/ Amoxicillin	Nausea, vomiting, diarrhea		Leukopenia, thrombocytopenia, hepatic disorder
Cefalexin		Diarrhea	Leukopenia, thrombocytopenia, hepatic disorder
Clindamycin	Diarrhea, nausea, vomiting		Hepatic disorder
Azithromycin	Nausea, abdominal pain, diarrhea		Hepatic disorder
Clarithromycin	Nausea, vomiting, diarrhea	Metallic taste, hepatic disorder	Headache

(iii) Prescribing Antibiotics Based on Supply Considerations

In recent years, antibiotics supply shortages have arisen due to disruptions in the manufacturing processes of generic drugs. As a result, clinicians are forced to use alternative agents when the recommended antibiotics are unavailable.[79] Consequently, the use of alternative agents has been associated with adverse outcomes, including increased rates of SSI and treatment failures.[80]

In Japan, cefazolin shortages due to insufficient raw materials in 2019 are well known, and numerous additional supply disruptions have occurred since then.[81] During those shortages, increases in SSI rates in the orthopedic surgery field were reported.[82] Similar challenges have persisted, with at least 600 product-specific shortage cases reported between 2021 and 2023.

It is crucial to identify appropriate alternative antibiotics when the prescribed agent is unavailable. Table 13 presents oral antibiotics facing supply concerns, along with their alternative agents.

Table 13. Oral Antibiotics with Supply Concerns Used as First-Choice in Dentistry and Their Alternative Agents

Oral antibiotics with supply concerns	Alternative antibiotics
●Amoxicillin ●Clavulanic acid/Amoxicillin	Cephalexin, Clindamycin (Access antibiotics)
	Azithromycin, Clarithromycin (Watch antibiotics)

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Background of the Creation of the Manual for Antimicrobial Stewardship, 4th Edition

This manual represents a revision of the Manual for Antimicrobial Stewardship, First Edition published on June 1, 2017, the Manual for Antimicrobial Stewardship, Second Edition published on December 5, 2019 with newly added sections on infants and young children, and the Manual for Antimicrobial Stewardship, Third Edition published on September 28, 2023 with newly added sections on hospitalized patients. This Fourth Edition includes newly added dental section. The manual was discussed at the 6th Meeting of the Working Group on Antimicrobial Stewardship (AMS) (chaired by Norio Ohmagari) held on November 19, 2024. Following this, the manual underwent review at the 7th meeting (May 26, 2025, held on a rotating basis), 8th meeting (June 24, 2025), and 9th meeting (September 19, 2025, held on a rotating basis). Subsequently, it was deliberated at the 12th Subcommittee on Antimicrobial Resistance (AMR) (chaired by Norio Ohmagari, October 8, 2025) and the 99th Health Sciences Council Infectious Disease Committee (chaired by Takaji Wakita, October 22, 2025), before being published on January 16, 2026.

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