Guideline

The 2016 JAID/JSC guidelines for clinical management of infectious disease—Odontogenic infections

The Japanese Association for Infectious Disease/Japanese Society of Chemotherapy*, The JAID/JSC Committee for Developing Treatment Guide and Guidelines for Clinical Management of Infectious Disease, Odontogenic Infection Working Group

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1. Preface

In 2011, the Japanese Association for Infectious Disease and Japanese Society of Chemotherapy published the JAID/JSC Guide to Clinical Management of Infectious Disease 2011. As there was no section for odontogenic infections in the document, this section was added in the revision (2014 JAID/JSC Guide to Clinical Management of Infectious Disease).

The present healthcare environment is faced with the emergence of various antibiotic resistant microorganisms which has necessitated policy changes and the field of odontogenic infection is no exception. In light of the spread of antibiotic resistant microorganisms, the inclusion of odontogenic infection in JAID/JSC Guide 2014 was necessary. Specifically, the Guide urged reconsideration of the use of the most widely used third-generation cephems in dental outpatient clinics. Prevotella, which is the leading cause of odontogenic infections, produce β-lactamase which degrade penicillins and third-generation cephems, but this enzyme activity is inhibited by β-lactamase inhibitors. As the use of penicillin combined with β-lactamase inhibitors, as the first line antibiotic, for the treatment of odontogenic infections due to oral streptococci and anaerobic bacteria is consistent with antibiotic stewardship, a section on odontogenic infections was added in JAID/JSC Guide 2014. In the present Guide to Clinical Management of Infectious Disease, the document was re-formatted by adding explanations between sentence lines to facilitate better understanding.

We hope that the guidelines are widely adopted and used in the treatment of odontogenic infections as well as for education in Japan, and contribute to the health of people by improving the quality of dental practice and preventing the increase in antibiotic resistant microorganisms.

In closing, we extend our deep gratitude to the members of the committee and secretariat, who devoted tremendous time and effort to the preparation of the guidelines.

Supplementary notes:

1. The recommendation grades or strength of recommendation, and quality or evidence level of the literature were determined according to the Outline for the Preparation of the Guidelines to Clinical Management of Infectious Disease established by the Japanese Association for Infectious Disease/Japanese Society of Chemotherapy

Recommendation grades
A: Strongly recommended
B: General recommendation
C: A clinical decision to be made by the attending physician based on a comprehensive consideration of factors

Evidence level
I: Randomized comparative study
II: Non-randomized comparative study
III: Case report
IV: Specialist's opinion

2. Definition of first- and second-line drugs

The first- and second-line drugs were defined according to the General Outline for Preparing the Guidelines to Clinical Management of Infectious Diseases by the Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy.

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First-line drugs: Recommended antimicrobial agents for initial treatment
Second-line drugs: Alternative drugs when first-line drugs cannot be used due to allergy, organ disorder, or local factors

3. Cautions

In this section, recommendations concerning the selection, route of administration, and, in particularly, the dosage, is based on the principle of achieving sufficient dosage. Therefore, dosage should be adjusted appropriately taking into consideration each healthcare institution’s formulary as well as antibioticgram, severity of illness, underlying disease, age and presence or absence of organ disorders.

4. When treatment is not covered by the criteria established by national healthcare insurance (indications for usage, dosage, and bacterial agents in Japan).

5. A list of antimicrobial drug abbreviations is presented on the last page.

2. Odontogenic infections

[Points to consider in antibacterial chemotherapy]

1. Since antibiotic tissue penetration into oral tissues such as the infected jaw bone and abscess cavity is low resulting in low antibiotic concentration at the site, it is important to perform local procedures such as treatment of infected root canal, abscess incision and drainage in parallel. Furthermore, anti-inflammatory procedures such as incision and drainage is extremely useful in reducing the bacterial load at the infected site and resolving the anaerobic environment in the infected site caused by anaerobic bacteria.

2. The selection of antibiotics with strong antibacterial activities against oral streptococci and anaerobic bacteria, which are the primary causes of odontogenic infections. The frequency of involvement of obligate anaerobes increases with the severity of the inflammation. For severe odontogenic infections, antimicrobials with strong antibacterial activities against anaerobic bacteria that produce β-lactamase should be selected.

[Clinical classification of odontogenic infections]

Odontogenic infections are classified into groups 1 to 4 [1].

Group 1 [periodontitis]: Infectious sequelae of pulptitis including apical periodontitis and marginal periodontitis which can lead to other diseases such as gingival abscess, alveolar abscess, and palatal abscess.

Group 2 [pericoronitis]: This condition is primarily associated with an impacted wisdom tooth. Reddening, swelling, and pus discharge are observed around the crown of the impacted wisdom tooth. Abscess formation is rare. Pericoronitis may develop into jaw inflammation and phlegmon. If the inflammation extends to the space around the jaw bone, difficulty opening mouth and pain on swallowing are observed.

Group 3 [jaw inflammation]: A condition including osteitis and osteomyelitis that can develop from periodontis (Group 1) and peri-coronitis (Group 2). This condition is more severe than Group 1 or 2 necessitating subperiosteal drainage and the use of antibiotics administered by injection are often required. Osteomyelitis may be acute, chronic, or sclerotic and occurs frequently in the mandible.

Group 4 [phlegmon of the jaw bone area]: A spreading inflammatory process developing from Groups 1–3. It includes space infections such as infections of the sublingual, submandibular, submental, pterygomandibular, lateral pharyngeal, and pharyngeal spaces. Drainage of these cavities is important. Antibiotics administered by injection are used in many patients.

[Major causative bacteria of odontogenic infections and frequency of detection]

During the period 2005–2009, of the 3112 isolates of major causative bacteria recovered from oral closed abscesses, 73% were Streptococcus, 48% were Prevotella, and 47% were Peptostreptococcus. P. intermedia was the most frequently isolated Prevotella sp. and Parvimonas micra (P. micros) was the most frequently isolated Peptostreptococcus (includes those genera listed within the Peptostreptococcus genus under previous taxonomy and currently re-classified as Peptostreptococcus, Parvimonas, Finegoldia, Peptoniphilus, etc.). The isolation frequency of Fusobacterium and Porphyromonas were about 9 and 6%, respectively [2]. Within the Streptococcus genus, S. constellatus and S. intermedius were most frequently isolated, followed by S. mitis and S. oralis.

No marked difference was observed in the isolation frequency of major causative bacteria for odontogenic infections Groups 1–4, but anaerobic bacteria tended to be more frequently isolated in phlegmon (Group 4), which was severe in many patients. Excluding periconoritis and odontogenic maxillary sinusitis within odontogenic infection Group 2, species within the Streptococcus anginosus group (S. anginosus, S. intermedius, and S. constellatus) were detected more frequently than other streptococcal species [2].

[Antimicrobial susceptibility profile of the major causative bacteria associated with odontogenic infections (Table 1 and 2)]

Among Gram negative rods, antimicrobial susceptibility testing of isolates recovered from closed oral abscesses during 2008–2009 showed high MIC values against Prevotella to ABPC (ampicillin), CFDN (cefdinir), and CTRX (ceftaxone) with a MIC90 of 16 μg/mL or above due to the high frequency of β-lactamase-producing strains. The MIC90 of STFX (stefoxacin) and clindamycin was high at 16 μg/mL or above, but the MIC50 of clindamycin was 0.015 μg/mL. The MIC90 of MNZ (metronidazole), which is the first-line antibiotic for anaerobic bacterial infection in Western countries and added to indications and usage for anaerobic bacterial infection in Japan, was 4 μg/mL. As there are few β-lactamase-producing Porphyromonas sp, few strains resistant to penicillins and cephems were found as evidenced by a MIC90 of 0.12 μg/mL. The AZM MIC90 against Fusobacterium was high because of the presence of strains intrinsically resistant to macrolides, but the MIC90 for other antibiotics were low [3].

For the Gram-positive cocci, the MIC90 of β-lactam antibiotics against Peptostreptococcus and Streptococcus anginosus group was generally low. AZM and CLDM showed a two-peak distribution of MIC values with a low MIC50 and a high MIC90 against viridans group Streptococcus [3].

During the clinical trials for STFX (stefoxacin), the MIC90 was 0.1 μg/mL or lower with antibacterial activity 8–256 times stronger than those of existing fluoroquinolone antibiotics [4]. For the Prevotella genus, which is the most frequently isolated anaerobic bacteria, many of the isolates produced β-lactamase. In general, β-lactamase is classified into Molecular Classes A–D, which are the penicillinases, carabapenemases, cephalosporinases, and oxacillinases, respectively. The genus Prevotella, which produces β-lactamase belonging to subclass A2e, shows...
ampicillin (ABPC), sulbactam/ampicillin (ABPC/SBT), cefdinir (CFDN), ceftriaxone (CTRX), clindamycin (CLDM), azithromycin (AZM), metronidazole (MNZ).

resistance to penicillin and cephems including the third generation cephalosporins, but enzyme activity is inhibited by β-lactamase inhibitors such as sulbactam and tazobactam. Of the 681 Prevotella tested, 240 (35%) were β-lactamase-producing strains; the resistant rate according to CLSI criteria was 37% for ABPC, 13% for CTRX, and 10% for CLDM [5].

[Recommended antimicrobial therapy]

As a general rule, the effectiveness of antibiotics in treating odontogenic infections should be assessed within 3 days. If the condition worsens, the addition of a surgical anti-inflammatory procedure and a change to another antibiotic should be considered. According to the American Academy of Periodontology, the duration of antibiotic treatment using a particular antimicrobial agent for odontogenic infections should be about 8 days [6].

1. First-line oral drugs

(1) Group 1 or 2 (mild to moderate symptoms)

In patients with abscesses, anti-inflammatory treatment such as an incision should be administered,

- AMPC (amoxicillin) 250 mg given 3–4 times/day (10–15 mg/kg, 3 times/day in children) [A IV [11]]

If there is penicillin allergy.

2. Second-line oral drugs

When no response to penicillin or cephem antibiotics are observed in the advanced stages of inflammation, the presence of β-lactamase-producing organisms should be considered dictating the need for administration of the following antibiotics:

- STFX (sitafloxacin) 100 mg given 2 times/day (children: 15 mg/kg given 3 times/day) [C IV]

If there is clindamycin allergy,

- CLDM: 150 mg given every 6 h [B I [78]]
- AZM 500 mg given once a day for 3 days (not indicated for children in dentistry) [B I [9,10]]
- AZM 2 g given once a day (not indicated for children in dentistry) [C IV]
- CAM (clarithromycin) 200 mg, given 2 times/day (for children: 7.5 mg/kg given 2 times/day) [B II [11]]

* According to information from the Social Insurance Medical Fee Payment Claims and Reimbursement Services in Japan, CAM is approved in children, if upon review, it has been prescribed for "periodontitis, osteitis".

(2) Group 3 or 4 (severe infections)

In severe odontogenic infections such as phlegmon of the jaw bone area and cervical abscesses, there is a need to take into consideration β-lactamase-producing anaerobic bacteria.

In patients for whom the prognosis is exacerbation of jaw bone inflammation,

- SBTPC (sultamicillin) + 375 mg given 2–3 times/day (not indicated for dentistry in children) [C IV]

* According to information from the Social Insurance Medical Fee Payment Claims and Reimbursement Services, the use of SBTPC is approved, if upon review, it has been prescribed for osteitis, and phlegmon of the jaw bone area and other secondary infections following surgery.

- CVA/AMPC (clavulanic acid/amoxicillin) + 250 mg given 4 times/day (not indicated for children in dentistry) [C IV]
- AMPC once 500 mg given 3 times/day (children: 15 mg/kg given 3 times/day) [C IV]

If there is clindamycin allergy,

- CLDM: 150 mg given every 6 h [C I [12]]
- CCI (cefaclor) 250 mg given 3 times/day (children: 15 mg/kg, 3 times/day) [B]

Caution should be exercised as about 15% of children with penicillin allergy also have allergy to cepham antibiotics.

- STFX (sitafloxacin) 100 mg given 2 times/day (not indicated for children in dentistry) [C III [4]]

2. Antibiotics administered by the injection route

Medical treatment while hospitalized is recommended for those patients with severe osteitis accompanied by difficulties in opening the mouth and swallowing (Group 3) or phlegmon (Group 4) showing severe symptoms of acute inflammation. Many patients will require pus drainage by incision. In particular, for phlegmon, incision of the cavity or place of phlegmonous process is necessary.

Table 1
Antimicrobial activities against clinical isolates of Prevotella species and Porphyromonas species (MIC,μg/mL).

<table>
<thead>
<tr>
<th>Organism (strains)</th>
<th>Drug</th>
<th>MIC range</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella (252)</td>
<td>ABPC</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.12</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>ABPC/SBT</td>
<td>≤ 0.015—&gt; 8</td>
<td>0.12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CFDN</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.12</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>CTRX</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.25</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>CLDM</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 16</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>AZM</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.5</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>MNZ</td>
<td>≤ 0.015—&gt; 16</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Porphyromonas (41)</td>
<td>ABPC</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>ABPC/SBT</td>
<td>≤ 0.015—&gt; 2</td>
<td>≤ 0.015—&gt; 12</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>CFDN</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 0.03</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>CTRX</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 12</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>CLDM</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 16</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>AZM</td>
<td>≤ 0.25—&gt; 16</td>
<td>2</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>MNZ</td>
<td>≤ 0.015—&gt; 1</td>
<td>0.06</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 2
Antimicrobial activities against clinical isolates of Peptostreptococcus species and Viridans Streptococcus (MIC,μg/mL).

<table>
<thead>
<tr>
<th>Organism (strains)</th>
<th>Drug</th>
<th>MIC range</th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptostreptococcus (258)</td>
<td>ABPC</td>
<td>≤ 0.015—&gt; 16</td>
<td>&lt; 0.015—&gt; 16</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>ABPC/SBT</td>
<td>≤ 0.015—&gt; 8</td>
<td>&lt; 0.015—&gt; 12</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>CFDN</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.03</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>CTRX</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.06</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>CLDM</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.06</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>AZM</td>
<td>≤ 0.015—&gt; 16</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>MNZ</td>
<td>≤ 0.015—&gt; 16</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Viridans Streptococcus (194)</td>
<td>ABPC</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CFDN</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CTRX</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.12</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CLDM</td>
<td>≤ 0.015—&gt; 16</td>
<td>≤ 0.015—&gt; 16</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>AZM</td>
<td>≤ 0.015—&gt; 16</td>
<td>0.03</td>
<td>&gt; 16</td>
</tr>
<tr>
<td></td>
<td>MNZ</td>
<td>&gt; 16—&gt; 16</td>
<td>&gt; 16</td>
<td>&gt; 16</td>
</tr>
</tbody>
</table>

ampicillin (ABPC), sulbactam/ampicillin (ABPC/SBT), cefdinir (CFDN), ceftriaxone (CTRX), clindamycin (CLDM), azithromycin (AZM), metronidazole (MNZ).
It is necessary to perform needle aspiration, collect samples, and perform a Gram stain to determine the likely causative agent followed by bacterial identification and drug susceptibility testing. Patients with severe phlegmon of the oral floor or deep neck abscess must be diagnosed by imaging using CT [A IV].

(1) Moderate infections

- SBT/ABPC (sulbactam/ampicillin)* administered by IV injection or drip infusion at 3 g divided into 2–4 doses (children: 75 mg/kg given 3 times/day by IV injection or drip infusion) [C]

4. Prevention of infective endocarditis

According to the guidelines of the 2008 American Heart Association (AHA) [15] and 2009 European guidelines [16], prophylactic administration of antibiotics during dental treatments should be limited to those patients following an artificial valve replacement, those with a history of infective endocarditis (IE), and those with congenital heart disease (unrepaired cyanotic congenital heart disease, within 6 months after surgery). In 2008, the English National Institute for Health and Clinical Excellence (NICE) declared prophylactic administration of antibiotics and gargling with chlorhexidine before dental treatment to be unnecessary for the prevention of IE [17]. After NICE recommendation decided to cease antibiotics prophylaxis for prevention of IE, Dayer et al. pointed that incidence of IE in UK has increased because of decreased AMPC prescription by dentists [18]. With some serious discussions, NICE declared that antibiotic prophylaxis against IE is not recommended routinely for people undergoing dental procedures in 2016 [19].

The Japanese Guidelines for the Prevention and Treatment of IE recommends prophylactic administration of antibiotics in patients at high risk of developing IE including those with congenital diseases and valve disease [20,21]. These Guidelines recommend prophylactic oral administration of the following antibiotics 1 h before treatment.

First-line drugs

- AMPC 2 g 1 h before treatment (can be reduced to 30 mg/kg depending on the body weight) [AIV1 [5,16,20,21]]
- CLDM 600 mg (2 g in the European guidelines) [BIV [20,21]]
- AZM 500 mg [BIV [20,21]]
- CAM500 mg [BIV [20,21]]
- CEX (cephalexin) or CDX (cefoxaxil) 2 g [BIV [20,21]]

For prophylaxis in children, see the following (Table 3) [20,21].

Self-reporting of conflicts of interest

The author, Naoki Tsumura, has received lecture fees from MSD KK.

References


Table 3

Prophylactic use of antibiotics in dentistry and oral surgery procedures and treatment in children [19].

<table>
<thead>
<tr>
<th>Patients</th>
<th>Antibiotics</th>
<th>Administration method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be administered orally</td>
<td>AMPC</td>
<td>Orally administered at 50 mg/kg 1 hour before treatment</td>
</tr>
<tr>
<td>Not orally administrable</td>
<td>ABPC</td>
<td>Administered by IV injection or drip infusion at 50 mg/kg within 30 minutes before treatment</td>
</tr>
<tr>
<td>Patients with penicillin allergy</td>
<td>CLDM</td>
<td>Orally administered at 20 mg/kg 1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td>CEX</td>
<td>Orally administered at 50 mg/kg 1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td>AZM</td>
<td>Orally administered at 15 mg/kg 1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td>CAM</td>
<td>Orally administered at 15 mg/kg 1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td>CLDM</td>
<td>Administered by IV injection at 20 mg/kg within 30 minutes before treatment</td>
</tr>
<tr>
<td></td>
<td>CEZ</td>
<td>Administered by IV injection or drip infusion at 50 mg/kg within 30 minutes before treatment</td>
</tr>
</tbody>
</table>


