JCS 2017 Guideline on Prevention and Treatment of Infective Endocarditis

Satoshi Nakatani; Takahiro Ohara; Kyomi Ashihara; Chisato Izumi; Shiro Iwanaga; Kiyoyuki Eishi; Yutaka Okita; Masao Daimon; Toshimi Kimura; Kazunori Toyoda; Hiroyuki Nakase; Kazuhiro Nakano; Masahiro Higashi; Kotoro Mitsutake; Tomoaki Murakami; Satoshi Yasukochi; Shuhei Okazaki; Haruo Sakamoto; Hiroshi Tanaka; Ichiro Nakagawa; Ryota Nomura; Katsuhito Fujii; Takashi Miura; Toshio Morizane; on behalf of the Japanese Circulation Society Joint Working Group

Table of Contents

I. Introduction ......................................................... 2
   1. Preface to Revision ............................................. 2
   2. About Recommendations .................................... 3
II. General Remarks .................................................. 4
   1. What Is IE? .................................................... 4
   2. Team Medicine ............................................... 4
   3. Timing of Referral to Specialized Hospital ............... 4
III. Diagnosis ........................................................... 4
   1. Diagnostic Criteria for IE .................................. 4
   2. Symptoms and Physical Findings (omitted from the English version) .................................. 4
   3. Microbiological Examination ................................ 4
   3.1 Blood Culture .............................................. 4
   3.2 Other Test Methods ....................................... 6
   4. Echocardiography ............................................. 7
      a. Positive Criteria ......................................... 7
      b. Significance of Vegetation ............................... 7
      c. Accuracy of Diagnosis ................................ 7
   d. Indication of TTE and TEE ................................ 7
   e. Timing of Follow-up Echocardiography ................ 7
   f. Echocardiography at the End of Treatment .......... 8
   5. Other Imaging Diagnosis .................................... 8
      a. CT ................................................................ 8
      b. MRI .......................................................... 8
      c. Gallium Scintigraphy/CT .................................. 8
      d. ¹⁸F-FDG PET/CT ............................................ 8
      e. Labeled Leukocyte Scintigraphy ........................ 9
   6. Risk Evaluation at Admission (omitted from the English version) .................................. 9
IV. Medical Treatment .................................................... 9
   1. Antimicrobial Treatment: Policy and General Principles ................................................. 9
      a. General Principles and PK/PD .......................... 9
      b. Duration of Treatment .................................... 9
      c. Relationship Between the Recommended Dose of Antibiotics and the Doses Approved in Japan ............................................. 9
   d. New Antimicrobials (Daptomycin and Linezolid) ....................................................... 9
   e. Treatment of Infection Foci as Portal of Entry and Remote Site Infection ....................... 10
II. Empirical Treatment .................................................. 10
   a. Recent Trends in Causative Microorganisms .......... 10
   b. Native Valve IE ................................................ 11
   c. Prosthetic Valve/Intracardiac Device IE .................. 11
   d. Culture-Negative IE .......................................... 11
   3. Targeted Therapy ............................................... 11
      3.1 Streptococci .............................................. 11
      3.2 Enterococci ............................................... 11
      3.3 Staphylococci (Including HACEK) .................... 12
      3.4 Gram-Negative Bacteria (Including HACEK) ....... 14
      3.5 Fungi ....................................................... 15
   4. Efficacy Evaluation and Duration of Antibiotic Treatment ............................................. 15
V. Evaluation and Management of Complications ................................................................. 16
   1. Heart Failure (omitted from the English version) ....................................................... 16
   2. Uncontrolled Infection and Perivalvular Infection (omitted from the English version) ......... 16
   3. Embolism ......................................................... 16
      3.1 Evaluating the Risk of Embolism (omitted from the English version) .................... 16
      3.2 Neurological Complications ......................... 16
      [CQ 1] Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE? .......................... 17
      3.3 Other Embolism (omitted from the English version) ............................................ 18
   4. Renal Dysfunction (omitted from the English version) .............................................. 18
   5. Disseminated Intravascular Coagulation (omitted from the English version) .................. 18

(Table of Contents continued the next page.)
VI. Surgical Treatment ........................................... 18
1. Evaluation of Surgical Risk and Preoperative Assessment ........................................... 18
   a. Evaluation of Surgical Risk ........................................... 18
   b. Preoperative Assessment: Evaluation of Cerebral Vessels, Coronary Arteries, and Other Organs ........................................... 19
2. Indications of Surgical Treatment and Timing of Operation ........................................... 19
   a. General Remarks on Indications of Surgical Treatment ........................................... 19
   b. Congestive Heart Failure ........................................... 20
   c. Uncontrolled Infection ........................................... 20
   d. Infectious Embolism ........................................... 20
   [CQ 2] Should early surgery be conducted if a large vegetation is present? .......................... 20
   [CQ 3] Should surgery of IE be conducted at an early timing when neurological complications have occurred? ........................................... 21
   e. Prosthetic Valve Endocarditis ........................................... 22
3. Surgical Treatment and Postoperative Management ........................................... 22
   a. Mitral Valve IE ........................................... 22
   b. Aortic Valve IE ........................................... 23
   c. Postoperative management ........................................... 23
   [CQ 4] Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for patients with high-risk heart diseases? ........................................... 27
   [CQ 5] Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for pediatric/congenital heart diseases? ........................................... 32
   3.6 IE on Cardiac Devices ........................................... 32
   a. Definition ........................................... 32
   b. Pathophysiology ........................................... 33
   c. Diagnosis ........................................... 33
   d. Treatment Strategy ........................................... 33
   e. Timing of Re-Implantation of Device ........................................... 34
3.7 Right-Sided IE (omitted from the English version) ........................................... 34
   3.8 IE in Pregnancy ........................................... 34
   3.10 Non-Bacterial Thrombotic Endocarditis (omitted from the English version) ........................................... 34
   6. IE in Elderly Patients ........................................... 34
   References ........................................... 35
   Appendix 1 ........................................... 42
   Appendix 2 ........................................... 43

I. Introduction

1. Preface to Revision

In March 2018, the revised version of the guidelines regarding infective endocarditis (IE) was published in Japanese from the Japanese Society of Cardiology (the Guidelines for Prevention and Treatment of Infective Endocarditis (JCS2017)). On the revision of the guidelines we reorganized the Guideline Writing Group. In addition to the Japanese Circulation Society, the Japanese Association for Thoracic Surgery, the Japanese Society of Pediatric Cardiology and Cardiac Surgery, and the Japanese College of Cardiology as previous members, new members, namely, the Japanese Society of Echocardiography, the Japanese Society for Cardiovascular Surgery, the Japanese Society for Adult Congenital Heart Disease, the Japan Stroke Society, the Japanese Association for Infectious Diseases, the Japanese Society of Chemotherapy, dentists specializing in IE, a visiting chief researcher of EBM Medical Information Division (Minds) of the Japan Council for Quality Health Care, joined the team. Furthermore, Japan Medical Library Association also joined to cooperate with the aim of developing clinical questions (CQs) of good quality and the responses to them.

Major points of updating from the previous revision are shown below.

1) Description of advancement of imaging techniques and bacteriological examination in the diagnosis of IE was added.
2) Indication of early surgery for IE, and the timing of surgery after the occurrence of neurological complications were discussed on the basis of accumulated evidence.
3) Many issues discussed about prevention of IE were reconsidered, and the opinions at the present time point were displayed.
4) New chapters were created to discuss device infection, right-sided IE. IE during pregnancy, non-bacterial
thrombotic endocarditis (NBTE), and IE in elderly people.

This English version is a translated, abbreviated form of the Japanese version; the sections are selected based on importance, novelty, and difference from the existing guidelines. Thus, some parts were omitted from the English version. We hope the guidelines will help not only cardiologists but also physicians in other fields and dentists lead to achievement of prevention of IE and treatment of good quality. Please remember that these guidelines intend to provide just one policy for helping diagnosis and decision of treatment strategy, and are not designed to deny the discretion of physicians.

### 2. About Recommendations

For the present guidelines, systematic review was conducted

<table>
<thead>
<tr>
<th>Class of Recommendation</th>
<th>Strength of recommendation</th>
<th>Strength of body of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful</td>
<td>C (weak)</td>
</tr>
<tr>
<td>Class II</td>
<td>There is no consistent evidence and/or general agreement that a given procedure or treatment is effective and/or useful</td>
<td>C (weak)</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence and opinion is in favor of usefulness and/or effectiveness</td>
<td>C (weak)</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness or effectiveness is not fully established by evidence or opinion</td>
<td>C (weak)</td>
</tr>
<tr>
<td>Class III</td>
<td>There is evidence and/or general agreement that the procedure or treatment is not effective and/or useful or may even be harmful</td>
<td>C (weak)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Demonstration with multiple randomized, controlled studies or meta-analyses</th>
<th>Established with a single randomized intervention clinical study or non-randomized, non-intervention studies</th>
<th>Consensus opinion of experts and/or small-scale clinical studies (including retrospective studies and registration)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>Level B</td>
<td>Level C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Questions Examined in Present Guidelines and Recommendations</th>
<th>Evaluation by systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CO1</strong></td>
<td>Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE? (In “Chapter V. 3. 2. Neurological Complications”, [Related section] “Chapter V. 3. 2. b. Methods of Diagnosis of Neurological Complications”, Table 14)</td>
</tr>
<tr>
<td>It is proposed to obtain brain MRI (including DWI, FLAIR images, T2*WI, and MRA) at an early timing in the patients without neurological symptoms who have or are suspected to have IE</td>
<td>2 (weak) C (weak)</td>
</tr>
<tr>
<td><strong>CO2</strong></td>
<td>Should early surgery be conducted if a large vegetation is present? (In “Chapter VI. 2. Indications of Surgical Treatment and Timing of Operation”, [Related section] “Chapter VI. 2. a. General Remarks on Indications of Surgical Treatment”, Table 16)</td>
</tr>
<tr>
<td>Surgery at the earliest timing possible is recommended for the patients with IE in the native valve (aortic valve or mitral valve) who have a vegetation of 10 mm or larger accompanying severe valve dysfunction</td>
<td>1 (strong) B (moderate)</td>
</tr>
<tr>
<td><strong>CO3</strong></td>
<td>Should surgery of IE be conducted at an early timing when neurological complications have occurred? (In “Chapter VI. 2. Indications of Surgical Treatment and Timing of Operation”, [Related section] “Chapter VI. 2. a. General Remarks on Indications of Surgical Treatment”, Table 16)</td>
</tr>
<tr>
<td>(1) Surgery of IE is recommended not to be postponed if it is indicated, even when concurrent cerebral infarction is present* *Except for the cases with concurrent coma, hemiation, or cerebral hemorrhage, as well as major central lesions</td>
<td>1 (strong) B (moderate)</td>
</tr>
<tr>
<td>(2) If new intracranial hemorrhage* is observed, it is proposed to wait 4 weeks to conduct open heart surgery if the hemodynamic condition is stable *Except for cerebral microbleeds</td>
<td>2 (weak) C (weak)</td>
</tr>
<tr>
<td>(1) Antibiotic prophylaxis is recommended before dental procedures inducing bacteremia, such as tooth extraction, in adult highest-risk patients</td>
<td>1 (strong) B (moderate)</td>
</tr>
<tr>
<td>(2) Antibiotic prophylaxis is proposed before dental procedures inducing bacteremia, such as tooth extraction, in adult moderate-risk patients</td>
<td>2 (weak) C (weak)</td>
</tr>
<tr>
<td><strong>CO5</strong></td>
<td>Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for pediatric/congenital heart diseases? (In “Chapter IX 1. 5 Prevention”, [Related section] “Chapter IX. 1. 2 Risks According to Underlying Heart Disease”, Table 22)</td>
</tr>
<tr>
<td>(1) Antibiotic prophylaxis is recommended before dental procedures inducing bacteremia, such as tooth extraction, in highest-risk patients with pediatric/adult congenital heart disease</td>
<td>1 (strong) C (weak)</td>
</tr>
<tr>
<td>(2) Antibiotic prophylaxis is proposed before dental procedures inducing bacteremia, such as tooth extraction, in moderate-risk patients with pediatric/adult congenital heart disease</td>
<td>2 (weak) C (weak)</td>
</tr>
</tbody>
</table>

IE, infective endocarditis; MRI, magnetic resonance imaging; DWI, diffusion weighted image; FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography; T2*WI, T2*-weighted image.
focusing on five CQs (Table 3). For each CQ, systematically collected articles were evaluated with respect to the ability to support recommendations, and the strength of recommendation was determined according to the rule of unanimity. To discriminate the recommendations based on systematic review and other recommendations, the former was presented using the method of Minds 2014 (strong recommendation, weak recommendation, and strength of body of evidence from A to D) to evaluate the body of evidence, and the latter was presented using the conventional method (Class I to III, level of evidence A to C).

The strength of recommendation and the strength of body of evidence for 5 CQs are expressed as follows.3

- Strength of Recommendation
  - “1”: Strongly recommended.
  - “2”: Weakly recommended (proposed).

- Strength of Body of Evidence
  - A (strong): Strongly confident of the estimate of effect
  - B (moderate): Moderately confident of the estimate of effect
  - C (weak): Limited confidence of the estimate of effect
  - D (very weak): Very little confident of the estimate of effect

Class of recommendation and level of evidence for other parts are expressed in Table 1 and Table 2.

### II. General Remarks

#### 1. What Is IE?

IE is a systemic septic disease accompanying generation of vegetation containing bacterial aggregation on the valve, endocardium, and intima of large vessels, and showing various clinical symptoms such as bacteremia, vascular embolization, and cardiac disorders. Abnormal blood flow associated with valvular disease, congenital heart disease, or prosthetic valve replacement causes non-bacterial thrombotic endocarditis (NBTE) which is considered important precursors for IE. When transient bacteremia occurs in a patient with NBTE after dental or other procedures, bacteria adhere to the site of NBTE and grow to generate vegetation.

While IE often occurs in the patients with some underlying heart diseases, it may occur in the patients without a history of heart diseases. The predisposing event is unclear in many cases. It is important to keep the possibility of IE in mind when examining the patients with fever or embolism of unknown origin.

The diagnosis of IE is made on the basis of clinical symptoms associated with sepsis, identification of causative microorganisms in blood, and confirmation of destruction of the intracardiac structure associated with infection, including vegetation. Therefore, the major criteria in Duke criteria for diagnosis of IE are comprised of blood culture and echocardiography.7,8 However, revision of the diagnostic criteria may become necessary in the future because identification of causative microorganisms by gene analysis, usefulness of computed tomography (CT) in evaluation of the intracardiac structure, and usefulness of positron emission tomography (PET), which visualizes inflammation itself, have come to be known.

#### 2. Team Medicine

A team covering a wide range of areas (IE team) is required in the clinical management of IE presenting in various clinical aspects and necessitating advanced expertise.4,5 It is not easy to constantly involve a group of specialists in actual clinical settings. However, at least close discussion with the specialists from the relevant areas should be continued.

#### 3. Timing of Referral to Specialized Hospital

Not all IE patients visit a specialized hospital with an IE team. Therefore, when an institution finds it difficult to control a patient at their institution, they should consult another institution providing team medicine, or should refer the patient to such an institution for the purpose of transfer.

### III. Diagnosis

#### 1. Diagnostic Criteria for IE

Duke criteria (modified) are helpful for the diagnosis of IE (Table 4).7,8 While the diagnostic sensitivity of Duke criteria is approximately 80%, the sensitivity in the early stage of disease is even lower. In particular, it becomes particularly low in cases with abscess formation, cases after prosthetic valve replacement, and cases after pacemaker implantation.9,10 Recently, the usefulness of CT and 18F-fluorodeoxyglucose (18F-FDG) PET/CT in depicting annular abscess in cases of IE following prosthetic valve replacement has been reported. Since 18F-FDG PET/CT is useful in searching systemic inflammation, it has been reported to be useful in detecting the remote lesion causing IE. Table 5 and Figure 1 show the criteria of diagnosis according to the guidelines of the European Society of Cardiology (ESC).

#### 2. Symptoms and Physical Findings

This section is omitted from the English version.

#### 3. Microbiological Examination

##### 3.1 Blood Culture

Blood culture is very important in the diagnosis of IE in
the same way as sputum culture for pneumonia. IE may be suspected on the basis of positive results in blood cultures, and IE is observed in approximately 5 to 30% of the patients with bacteremia caused by *Staphylococcus aureus*.

Isolation of the causative microorganisms on blood culture will enable bacterial identification and sensitivity testing. The positive rate on blood culture becomes 90% or higher if blood specimens are collected before antibiotic treatments, but the positive rate on blood culture may decrease dramatically for some bacterial species if antibiotics have already been administered. At least three sets of specimens should be submitted for blood culture. Submission of specimens for multiple times increases the volume of blood to be subjected to culture, and may increase detection sensitivity. The interval for collection of blood specimens has not been established, although there have been some recommendations such as collection of every 30 minutes, the interval of 1 hour between the first and last collection, or 6 hours or more. No difference in detection rate has been observed for arterial blood and venous blood, and it is unnecessary to collect blood specimens in the presence of high fever. Blood collection via catheters should be avoided in order to avoid contamination during blood collection. Even before the causative microorganisms determined, antibiotic treatment should be started in the emergency cases showing sepsis, and at least two sets of blood specimens should be collected within 1 hour. Conversely, antibiotic treatment may be transiently...
suspended in cases with a subacute course. The appropriate duration of suspension is believed to be 2 or 3 days. However, antibiotics should not be discontinued in the patients with an unstable cardiorespiratory condition due to heart failure, patients with progressive infection foci (such as annular abscess), and patients who have embolism or are at high risk of embolism. Suspension of antibiotics must be avoided also in the IE patients with prosthetic valve.

For the patients with positive blood cultures, blood cultures should be repeated within several days after the start of treatment (approximately 3 days, or 48 to 72 hours after the start of treatment) to check the effect of the treatment. Although it is unnecessary to discontinue antibiotic treatment before collection of specimens, it is reasonable to collect specimens immediately before administration of antibiotics when the blood concentration of antibiotics is low. Blood culture should be repeated until negative results are obtained. Once the result has turned negative, additional blood culture is unnecessary unless changes in symptoms are observed.

3.2 Other Test Methods

a. Serologic Diagnosis and Polymerase Chain Reaction (PCR)

Microorganisms which are difficult to culture by usual blood culture, such as Bartonella and Coxiella burnetii, may cause IE. Concerning Bartonella, Bartonella quintana, which is known for trench fever, and Bartonella henselae, which is known as causative microorganism for cat scratch disease, may cause IE. Although the number is small, there have been case reports. However, the percentage of

<table>
<thead>
<tr>
<th>Table 5. New Imaging Diagnostic Criteria (ESC Guidelines 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging positive for IE</td>
</tr>
<tr>
<td>a. Echocardiogram positive for IE:</td>
</tr>
<tr>
<td>• Vegetation;</td>
</tr>
<tr>
<td>• Abscess, pseudoaneurysm, intracardiac;</td>
</tr>
<tr>
<td>• Valvular perforation or aneurysm;</td>
</tr>
<tr>
<td>• New partial dehiscence of prosthetic valve</td>
</tr>
</tbody>
</table>
| b. Abnormal activity around the site of prosthetic valve implan-
  tation detected by 18F-FDG PET/CT (only if the prosthesis was
  implanted for >3 months) or radionuclide labelled leukocytes
  SPECT/CT                                                   |
| c. Definite paravalvular lesions by cardiac CT                |

ESC guidelines incorporates these new imaging diagnostic criteria as major criteria in addition to modified Duke criteria (Table 4).

Figure 1. Criteria for diagnosis of infective endocarditis incorporating new imaging diagnostic criteria (modified from Habib et al. 2015). IE, infective endocarditis; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.
**Bartonella** in the cases of IE is less than 1%, and routine antibody tests are unnecessary.

The positive rate on blood culture is also low in the cases of IE caused by fungi. Especially as to filamentous fungus such as Aspergillus, the positive rate is less than 10%. Although blood β-glucan and blood aspergillus antigen are useful, they are used for auxiliary diagnosis (even if the β-glucan level is high, differentiation of *Candida* and other fungi including Aspergillus is difficult, and cautions are required for non-specific reactions).

**b. PCR for Extracted (Surgical) Specimens**

The valve tissues obtained at the time of surgery can be subjected to culture and histological examination. While PCR and sequencing using 16S RNA amplification can be outsourced in Japan, they are not covered by insurance, and they are not conducted as routine tests in laboratories. The cases in which PCR is considered useful are the following: the cases with negative blood cultures, the cases in which blood culture is positive only once, and rare microorganism or normal bacterial flora on the skin are suspected to be causative microorganisms.\(^9\) However, contamination at the time of extraction of specimens may cause false positive results. Therefore, the clinical course and the results of blood cultures should also be taken into consideration when making judgement.\(^9\) Detection by PCR becomes difficult after formalin fixation of specimens.

### 4. Echocardiography

Echocardiography plays the most important role in the diagnosis, treatment, follow-up and estimation of prognosis of IE. When IE is suspected, it should be performed in all cases, including the cases with negative blood cultures.\(^21,22\)

**a. Positive Criteria**

The major items related to echocardiographic findings on Duke criteria for diagnosis (Table 4) include (1) vegetation, (2) abscess or pseudoaneurysm, (3) new partial dehiscence of prosthetic valve, and (4) emergence of new valvular regurgitation (exacerbation of existing murmur alone is insufficient).

**b. Significance of Vegetation**

Vegetation is defined as periodically vibrating mass echo adhering to the endocardium mainly around the valve, or intracardiac device. When findings suggestive of vegetation are observed, the size, shape, adhesion site, and mobility should be monitored.

Examination of the changes in the size and mobility of vegetation after treatment is useful for evaluation of the effects of antibiotics. However, observation of the vegetation echo after treatment does not always mean recurrence.

**c. Accuracy of Diagnosis**

The sensitivity of transthoracic echocardiography (TTE) in detecting vegetation is approximately 70% for native valves, and approximately 50% for prosthetic valves. The sensitivity of transesophageal echocardiography (TEE) in detecting vegetation is 90% or more for both native valves and prosthetic valves. Both TTE and TEE show high specificity of approximately 90% in detecting vegetation. On the other hand, the sensitivity in detecting perivalvular abscess was low at 30 to 50% for TTE, and it varied from 50% to 90% among reports in TEE. Both TTE and TEE showed high specificity of 90% or more in detecting peri-valvular abscess. The detection rate of positive findings for IE was low in cases with poor images, cases showing small vegetation (<3 mm), prosthetic valve, and valvular changes (including prolapse, thickening, and calcification), and cases with placement of devices such as pacemakers.

**d. Indication of TTE and TEE (Table 6)**

While TTE is inferior to TEE in terms of sensitivity and specificity, it is noninvasive and can be performed repeatedly. Moreover, it is superior to TEE in evaluation of cardiac functions and hemodynamics using Doppler method. Therefore, it should be performed as soon as possible in all cases of suspected IE.\(^21,22\)

TEE should be performed when TTE cannot be used for diagnosis because of poor images, when IE is clinically suspected in spite of the negative result on TTE,\(^21,23,25\) and when IE is suspected in the cases with prosthetic valve or the cases with insertion of other devices.\(^21,24,26\)

It is recommended to conduct TEE even in the cases with positive results on TTE for the purpose of evaluating the presence or absence of intracardiac complications.\(^27\) Since TEE may fail to detect abnormalities in the early stage, the test should be performed again 3 to 7 days later if IE is clinically suspected.

Since IE is highly likely in the cases of staphylococcal bacteremia, TTE or TEE should proactively be performed in these cases.\(^11,28\)

**e. Timing of Follow-up Echocardiography**

Follow-up echocardiography should be conducted after 3
has been used for the diagnosis of IE and its complications. See “Chapter III. 1. Diagnostic Criteria for IE” for the procedure of diagnosis of IE.

a. CT
Reduction of the scan time and improvement of temporal resolution can be achieved by increasing the number of detectors in multidetector-row CT (MDCT) and shortening the gantry rotation time, and it has become easier to obtain favorable images in the field of cardiology.

On contrast-enhanced CT, vegetation is visualized as a low-density nodule adhering to the valve or blood vessel. When the height is low, it is visualized as the thickening of the valve. Diagnosis is difficult when the movement of vegetation is fast or vegetation is small.\(^{29,30}\)

TEE is better for the diagnosis of vegetation, and addition of CT information does not improve the diagnostic ability. However, addition of CT improves the ability to diagnose perivalvular abnormality.\(^{31}\) The features of CT in diagnosis of IE include the following:\(^{29,33}\)

1) It is capable of visualizing vegetation, and the size shows good correlation with TEE, but diagnosis of small vegetation is difficult.

2) It shows good ability to detect perivalvular abnormalities such as abscess. If IE is suspected after prosthetic valve replacement, additional information can be expected.

3) If vegetation with a risk of embolism is observed in the aortic valve or the aortic wall, it can be used for preoperative examination of the coronary artery.

4) It can be used for the search of embolism in the whole body.

b. MRI
Magnetic resonance imaging (MRI) shows good ability in diagnosis of cerebrovascular diseases. It is recommended to conduct MRI, if possible, even in the patients without neurological symptoms (See “[CQ 1] Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE?”). It is also useful for diagnosis of osteomyelitis in the spine, etc. However, since it is inferior to CT in terms of spatial resolution and the scan time is longer, the situation in which it is used for the diagnosis of vegetation and perivalvular abscess is limited.\(^{29}\)

c. Gallium Scintigraphy/CT
Sensitivity of gallium scintigraphy for unidentified fever has been suggested to be 30% or lower. Gallium scintigraphy may be useful when definite diagnosis cannot be made by other methods. However, diagnostic accuracy for IE has not been established.\(^{34,35}\)

d. \(^{18}\)F-FDG PET/CT
Although insurance coverage of \(^{18}\)F-FDG PET and \(^{18}\)F-FDG PET/CT for heart diseases has been approved for viability assessment of the myocardium in patients with heart failure caused by ischemic heart disease, and diagnosis of inflammation sites in cardiac sarcoidosis, the use for IE and unidentified fever is not covered by Japanese medical insurance. However, improvement of diagnostic ability after addition of \(^{18}\)F-FDG PET/CT has been reported in patients with unidentified fever and patients with implantation of a prosthetic valve or devices.\(^{36,37}\)

5. Other Imaging Diagnosis (Table 7)
Imaging diagnostic technology other than echocardiography
to 7 days when IE is clinically suspected even if the results on TTE and TEE are negative, or for the purpose of evaluating the effects of antibiotics or onset of intracardiac complications in the cases with the established diagnosis of IE. If staphylococci are the causative microorganism, follow-up should be conducted after an even shorter interval. Follow-up echocardiography should also be conducted if any changes have occurred in clinical findings.

f. Echocardiography at the End of Treatment
Echocardiography should always be conducted at the end of treatment to obtain follow-up basic data after completion of treatment. The shape of valves, condition of residual vegetation, and extent of regurgitation should be evaluated.

<table>
<thead>
<tr>
<th>Table 7. Recommendations of Imaging Diagnosis Other Than Echocardiography and Level of Evidence in Diagnosis of IE and Its Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class of</strong></td>
</tr>
<tr>
<td><strong>recommendation</strong></td>
</tr>
<tr>
<td>It should be considered to conduct CT to detect vegetation or perivalvular abnormality, to diagnose coronary arterial disease, and to search systemic embolism in the patients who have or who are suspected to have IE in the native valve or IE in the prosthetic valve (it is preferred to use contrast, if possible)</td>
</tr>
<tr>
<td>It is recommended to conduct MRI to diagnose cerebrovascular diseases in the patients who have or who are suspected to have IE in the native valve or IE in the prosthetic valve</td>
</tr>
<tr>
<td>It may be considered to conduct MRI to diagnose systemic complications such as vegetation, perivalvular abscess, and osteomyelitis in the patients who have or who are suspected to have IE in the native valve or IE in the prosthetic valve</td>
</tr>
<tr>
<td>It may be considered to conduct gallium scintigraphy in the patients who are suspected to have IE if definite diagnosis cannot be made by other methods</td>
</tr>
<tr>
<td>In the patients who are suspected to have IE, especially the patients with implantation of a prosthetic valve or any devices, (^{18})F-FDG PET/CT should be considered if definite diagnosis cannot be made by other methods (IE is not covered by insurance in Japan)</td>
</tr>
<tr>
<td>In the patients who are suspected to have IE, labeled leukocyte scintigraphy should be considered at a facility with the capability to conduct it, if definite diagnosis cannot be made by other methods</td>
</tr>
</tbody>
</table>

\(^{*}\) If neurological symptoms are absent, class of recommendation is IIa. See “Chapter V. 3. 2. b. Methods of Diagnosis of Neurological Complications” and “[CQ 1] Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE?”.

IE, infective endocarditis; \(^{18}\)F-FDG, \(^{18}\)F-fluorodeoxyglucose.
e. Labeled Leukocyte Scintigraphy
It is not used very frequently in Japan because the labeling procedure is complicated. Concerning diagnostic ability of labeled leukocyte scintigraphy for IE, sensitivity of 90% and specificity of 100% have been reported.38

6. Risk Evaluation at Admission
This section is omitted from the English version.

IV. Medical Treatment

1. Antimicrobial Treatment: Policy and General Principles
In the treatment of IE, the choice and treatment period of the antibiotics recommended in the existing guidelines and present guidelines are mainly based on the type of causative microorganisms, antibiotic susceptibility results, and the type of the valve (native valve or prosthetic valve). Isolation and identification of causative microorganisms is very important. Moreover, the factors related to the treatment results are the duration before diagnosis, immune status of hosts, causative microorganisms, severity of valvular regurgitation, progression of lesions (such as anular abscess), concurrent embolism, and organ dysfunction such as heart failure and renal failure, as well as surgical treatment and its timing. Multidisciplinary treatment provided through cooperation of not only cardiologists but also specialists from multiple fields (IE team) is required.

As to antimicrobial treatment, the roles of infectious disease specialists and pharmacists are important. In addition to the choice of antibiotics for bacteria with decreased susceptibility or multidrug-resistance and fungi, they should take pharmacokinetics (PK) and pharmacodynamics (PD) into consideration. They also play important roles in modifying and changing antibiotics against adverse reactions.

a. General Principles and PK/PD
When designing administration of antimicrobials, it is important to consider PK/PD parameters in order to avoid the emergence of resistant strain and to ensure efficacy. Administration design based on therapeutic drug monitoring (TDM) should be employed for vancomycin, teicoplanin, and aminoglycosides15,39 (Table 8). It is necessary to administer over 1 hour for vancomycin and at least 30 minutes for teicoplanin (particular attention should be paid for the initial loading dose) in order to avoid red man syndrome (condition in which erythema and itching appear in the face and neck).

b. Duration of Treatment
Duration of treatment should be the period recommended in the present guidelines. The necessary treatment period starts on the first day when negative blood cultures are obtained.

c. Relationship Between the Recommended Dose of Antibiotics and the Doses Approved in Japan
In IE treatment, antibiotics are often used at higher doses. Since aminoglycosides are used aiming at synergetic effect, they are used at stipulated doses.

d. New Antimicrobials (Daptomycin and Linezolid)
Daptomycin and linezolid are anti-methicillin-resistant Staphylococcus aureus (MRSA) drugs. Non-inferiority of daptomycin to vancomycin in the treatment of IE has been

<table>
<thead>
<tr>
<th>Table 8. Relationship Between Recommended Method of Use of Drugs for Therapeutic Drug Monitoring and Method of Use Approved in Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gentamicin</strong></td>
</tr>
<tr>
<td><strong>Dosage regimen (when renal functions are normal)</strong></td>
</tr>
<tr>
<td><strong>Timing of blood sampling (when renal functions are normal)</strong></td>
</tr>
<tr>
<td><strong>Timing of blood sampling</strong></td>
</tr>
<tr>
<td><strong>Target blood concentration</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Dosage regimen in package insert</strong></td>
</tr>
</tbody>
</table>

*The recommended target level is not set for once daily administration. TDM, therapeutic drug monitoring.
Table 9. Factors Associated With IE and Frequent Isolates

<table>
<thead>
<tr>
<th>Associated area and item</th>
<th>Frequent isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric</td>
<td>Staphylococcus aureus, VGS, CNS, enterococci, and Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Native valve</td>
<td>VGS, Staphylococcus aureus, CNS, enterococci, and other streptococci</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>CNS, Staphylococcus aureus, VGS, enterococci, and Streptococcus gallolytics (bovis)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>VGS, Staphylococcus aureus, CNS, Streptococcus gallolytics (bovis), and enterococci</td>
</tr>
<tr>
<td>Healthcare-associated</td>
<td>Staphylococcus aureus, enterococci, VGS, CNS, and Streptococcus gallolytics (bovis)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Staphylococcus aureus, CNS, enterococci, VGS, and Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Drug injection</td>
<td>Staphylococcus aureus, VGS, CNS, enterococci, and Candida albicans</td>
</tr>
</tbody>
</table>

Table 10. Recommendations of Empirc Treatment or Blood Culture* Negative IE

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dose</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulbactam/ampicillin</td>
<td>3g, 3–4 times daily</td>
<td>IIb</td>
<td>C</td>
<td>When MRSA is unlikely When following a subacute clinical course</td>
</tr>
<tr>
<td>+Ceftriaxone</td>
<td>2g, once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>8–10 mg/kg per dose, once daily</td>
<td>IIb</td>
<td>C</td>
<td>In the case of penicillin allergy</td>
</tr>
<tr>
<td>+Ceftriaxone</td>
<td>+2g, once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>8–10 mg/kg/day, once daily</td>
<td>IIb</td>
<td>C</td>
<td>MRSA is considered</td>
</tr>
<tr>
<td>+Sulbactam/ampicillin, or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panipenem/betamipron</td>
<td>3g, 3–4 times daily</td>
<td>IIb</td>
<td>C</td>
<td>In the case of penicillin allergy Enterococcus is also considered Precautions are required in the patients with decreased renal functions and elderly patients</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1g, twice daily, or 15 mg/kg, twice daily</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>+Gentamicin</td>
<td>2 to 3 mg/kg, once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>8–10 mg/kg, once daily</td>
<td>IIb</td>
<td>C</td>
<td>Ceftriaxone can be replaced with sulbactam/ampicillin</td>
</tr>
<tr>
<td>+Ceftriaxone</td>
<td>2g, once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>8–10 mg/kg, once daily</td>
<td>IIb</td>
<td>C</td>
<td>MRSA is considered</td>
</tr>
<tr>
<td>+Panipenem/betamipron</td>
<td>0.5g, 3–4 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1g, twice daily, or 15 mg/kg, twice daily</td>
<td>IIb</td>
<td>C</td>
<td>Gentamicin can be administered at 1 mg/kg, 2 to 3 times daily Precautions are required in the patients with decreased renal functions and elderly patients</td>
</tr>
<tr>
<td>+Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Targeted therapy should be conducted after the causative microorganisms has been identified. IE, infective endocarditis.
of all cases of IE. Enterococci account for approximately 10%, and are common in elderly people (mean age of approximately 70 years).43,44

b. Native Valve IE (Table 9 and Table 10)
For community-acquired IE, VGS, staphylococci and enterococci should be covered. A choice of anti-MRSA drugs should be considered in cases of healthcare-associated onset or the cases with a history of MRSA colonization. When the date of onset is relatively clear, the clinical course is acute and the patient's condition is rather severe, staphylococci and β-hemolytic streptococci are likely to be the causes, while VGS and enterococci can still be the causes.

c. Prosthetic Valve/Intracardiac Device IE (Table 9 and Table 10)
Staphylococci are causative microorganisms in 40% or more of the cases of prosthetic valve IE.45 Early-onset IE within 2 months after valve surgery is attributable to staphylococci in a majority of cases. Coagulase negative staphylococci (CNS) are more predominant than *Staphylococcus aureus*. CNS in many of such cases are methicillin-resistant.46,47 The causative microorganisms in the cases of onset more than 1 year after the operation are similar to those for IE in the native valve. Major causative microorganisms of IE associated with intracardiac devices are bacterial flora of the skin, and are staphylococci in 80% or more.48 The choice of empiric antibiotics is similar to that for methicillin-resistant staphylococci.49

d. Culture-Negative IE
The following three reasons are plausible explanations for negative blood cultures. (1) The causative microorganisms are *Coxiella, Bartonella*, and other bacteria which are difficult to culture, (2) nutritionally variant streptococci, HACEK (*Haemophilus aphrophilus, Haemophilus paratrophus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*), fungi and so on are likely to be the cause, and (3) antibiotics have been administered before blood culture.14,52 In Japan, (3) is believed to be the main reason.20

3. Targeted Therapy

### 3.1 Streptococci

a. Penicillin-Susceptible Streptococci (Table 11 and Table 12)
Among streptococci, VGS as an oral streptococcus is detected frequently, and is a main causative microorganism for the community-acquired IE in the native valve and IE in the prosthetic valve more than 1 year after an operation. For penicillin G, isolates with minimum inhibitory concentration (MIC) ≤0.12 μg/mL is considered susceptible. Most of VGS, *Streptococcus gallelicus* (*Streptococcus bovis*), and other streptococci show good susceptibility to penicillin G. Since penicillin G shows a short half-life in blood (30 minutes, when renal functions are normal), it is administered every 4 hours53 or is administered continuously. Ampicillin can also be a choice of antibiotics. If the patient does not have immediate-type allergy to penicillin, cefazolin or ceftriaxone can be alternative of choice. If the patient cannot tolerate β-lactams including penicillin, vancomycin or teicoplanin should be selected. Some experts recommend addition of gentamicin for 2 weeks in the treatment regimen for prosthetic valve IE.45

b. Penicillin Non-Susceptible Streptococci (Table 11 and Table 12)
In evaluation of susceptibility to penicillin, VGS is regarded to be non-sensitive (moderate resistance or resistance) when MIC of penicillin G is ≥0.25 μg/mL and MIC of ampicillin is ≥0.5 μg/mL. Consultation with infectious disease specialists is recommended about the combined use of gentamicin and so on. For non-susceptible strains, penicillin G or ampicillin should be administered in combination with gentamicin for 2 to 4 weeks (4 to 6 weeks for prosthetic valve).54 In the cases susceptible to ceftriaxone, gentamicin-including regimen is reasonable. In the cases non-susceptible to ceftriaxone, carbapenems can be selected.55,56 If the patients are intolerant to β-lactams, combination of vancomycin or teicoplanin with gentamicin can be administered. Daptomycin has not been studied sufficiently. If administration of aminoglycosides is difficult in patients with renal dysfunction, monotherapy with vancomycin or teicoplanin with TDM, or combination of ampicillin and ceftriaxone can be considered.

c. Other Streptococci
*Streptococcus pyogenes* and *Streptococcus agalactiae* are highly pathogenic, and follow a relatively acute clinical course similar to that of staphylococci. Clinical symptoms are severe, and the mortality rate is also high (20% or higher).57 Since susceptibility to penicillin is almost constantly good, penicillin G, ampicillin, or ceftriaxone is selected choice, while some experts recommend combination with gentamicin (Table 11).4

### 3.2 Enterococci (Table 11 and Table 12)
For enterococci, species identification and susceptibility tests should be performed. *Enterococcus faecalis* accounts for 90% or more of enterococci causing IE, and shows favorable susceptibility to penicillin. However, enterococci are resistant to many drugs including β-lactams, and long-term treatment is necessary. Since combination with gentamicin, which is used as the standard treatment, accompanies a problem of renal dysfunction, long-term administration of gentamicin is difficult, particularly in elderly patients.

In the treatment of enterococcal IE, ampicillin or vancomycin should be administered in combination with gentamicin (cases with MIC ≤500 μg/mL). For vancomycin, TDM should be conducted. The trough level should be 15 μg/mL according to that for MRSA (Table 8). The daily dose of gentamicin should be administered once daily or divided into 2 to 3 doses. The treatment results do not show differences even when gentamicin is administered once daily, and renal toxicity is less.58,59

Concerning the duration of gentamicin administration, some reports suggest that the treatment results do not differ even when the duration is 2 weeks.59,60 However, 2 weeks treatment should be avoided when IE is in the prosthetic valve, the vegetation size is large, and the patient is immunocompromised. The combination of ampicillin and ceftriaxone is also selected when renal dysfunction (creatinine clearance <50 mL/min) is present or when the strain shows high resistance to gentamicin (MIC >500 μg/mL).61,63 Ampicillin and ceftriaxone combination should not be used for *Enterococcus faecium*. 
Some researchers suggest that daptomycin does not exhibit sufficient efficacy as a monotherapy. At present, its use is limited to the cases with vancomycin resistant enterococci (VRE) or salvage use in the same way as linezolid. For VRE, monotherapy with linezolid, or combination of daptomycin with ampicillin or gentamicin should be used.

### 3.3 Staphylococci

Staphylococci account for one-third of the cases of IE. The clinical course is acute, occasionally shows sudden changes, and is likely to become severe. Valve destruction and perivalvular progression are rapid, and remote lesions are frequent. Therefore, treatment with appropriate anti-
biotics and decision of operation without delay are required.

**a. Staphylococcus Aureus (Table 11 and Table 12)**

*Staphylococcus aureus* is associated with in-hospital mortality in IE. The mortality rate from IE caused by *S. aureus* is 20% or more, and that in cases of IE in the prosthetic valve is even higher (47.5%). MRSA accounts for 7.5% of all cases in which the pathogen is identified, and associated with age (elderly patients), and prosthesis-associated or healthcare-associated infection. The

### Table 12. Recommendations of Targeted Therapy for Prosthetic Valve IE

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dosage</th>
<th>Period (weeks)</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) Streptococci (VGS, Streptococcus gallolytics, and other streptococci)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>24 million unit/day* in 6 doses, or continuously</td>
<td>6</td>
<td>IIa</td>
<td>B</td>
<td>Monotherapy is permitted for the cases susceptible to penicillin G (MIC ≤0.12 μg/mL) Gentamicin can be administered at the dose of 1 mg/kg, 2–3 times daily</td>
</tr>
<tr>
<td>± Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td>2–6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8–12 g/day in 4–6 doses, or continuously</td>
<td>6</td>
<td>IIa</td>
<td>B</td>
<td>Gentamicin can be administered at the dose of 1 mg/kg, 2–3 times daily</td>
</tr>
<tr>
<td>± Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td>2–6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin + Ceftriaxone</td>
<td>2 g, twice daily</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g, twice daily, or 15 mg/kg, twice daily</td>
<td>6</td>
<td>IIa</td>
<td>C</td>
<td>Patients allergic to β-lactams</td>
</tr>
<tr>
<td><strong>2) Enterococci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8–12 g/day in 4–6 doses, or continuously</td>
<td>6</td>
<td>I</td>
<td>B</td>
<td>Not allowed for the strains highly resistant to gentamicin Gentamicin can be administered at the dose of 1 mg/kg, 2–3 times daily</td>
</tr>
<tr>
<td>+ Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin + Ceftriaxone</td>
<td>2 g, twice daily</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g, twice daily, or 15 mg/kg, twice daily</td>
<td>6</td>
<td>IIb</td>
<td>C</td>
<td>Should not be used for <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td><strong>3) Methicillin-sensitive staphylococci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2 g, three times daily</td>
<td>6–8</td>
<td>I</td>
<td>C</td>
<td>Cefazolin can be replaced with sulbactam/ampicillin Gentamicin can be administered at the dose of 1 mg/kg, 2–3 times daily</td>
</tr>
<tr>
<td>+ Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td>2**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± Rifampicin</td>
<td>450–600 mg/day in 1–2 doses</td>
<td>6–8</td>
<td></td>
<td></td>
<td>See the text for the effects of rifampicin</td>
</tr>
<tr>
<td>Daptomycin + β-lactams, etc.</td>
<td>8–10 mg/kg, once daily</td>
<td>6–8</td>
<td>IIa</td>
<td>C</td>
<td>See the text for doses and combination therapy</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g, twice daily, or 15 mg/kg, twice daily</td>
<td>6–8</td>
<td>IIa</td>
<td>C</td>
<td>Patients allergic to β-lactams Gentamicin can be administered at the dose of 1 mg/kg, 2–3 times daily</td>
</tr>
<tr>
<td>+ Gentamicin</td>
<td>2–3 mg/kg, once daily</td>
<td>2**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>± Rifampicin</td>
<td>450–600 mg/day in 1–2 doses</td>
<td>6–8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4) Methicillin-resistant staphylococci</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin + β-lactams, etc.</td>
<td>8–10 mg/kg, once daily</td>
<td>6–8</td>
<td>I</td>
<td>C</td>
<td>See the text for doses and combination therapy</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g, twice daily, or 15 mg/kg, twice daily</td>
<td>6–8</td>
<td>I</td>
<td>C</td>
<td>Adjusted to 15 to 20 μg/mL by TDM aiming at the initial concentration of 10 to 15 μg/mL Teicoplanin can be used (TDM is necessary) See the text for aminoglycosides (including arbekacin) Gentamicin can be administered at the dose of 1 mg/kg per dose, 2 to 3 times daily</td>
</tr>
<tr>
<td>± Rifampicin</td>
<td>450–600 mg/day in 1–2 doses</td>
<td>6–8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Doses should be adjusted according to the body weight and renal functions. 12 million unit to 30 million unit/day at maximum. **Some opinion recommends concomitant administration of gentamicin for more than 2 weeks. IE, infective endocarditis; VGS, viridans group streptococci.*
mortality rate in the cases caused by MRSA has been reported to exceed 60%.68,69
Cefazolin is the drug of first choice for methicillin-sensitive *S. aureus* (MSSA) in Japan. Daptomycin,70 vancomycin, or teicoplanin should be used in cases intolerant of β-lactams because of allergy, etc. Addition of gentamicin is not recommended for staphylococcal native valve IE because of the nephrotoxicity risk.71 The recommended duration of treatment is 4 to 6 weeks after negative conversion of blood culture. In cases accompanied by brain abscess or meningitis, other drugs rather than cefazolin should be selected, because delivery of cefazolin to the central nervous system is poor. Panipenem/betamipron, meropenem, or vancomycin should be considered as in the treatment of meningitis.72 Some experts recommend treatment with 3 drugs including gentamicin and rifampicin for IE in the prosthetic valve4,15,73 but the level of evidence is not sufficiently high.

For MRSA, daptomycin or vancomycin should be selected as the drug of first choice. While the indication of daptomycin in Japanese health insurance is limited to right-sided IE, it is also used for left-sided IE.74 The duration of administration should be 4 to 6 weeks after negative conversion of blood culture. The duration should be 6 weeks or longer, approximately 8 weeks, for prosthetic valve IE. When daptomycin is selected, administration should be started at 8 to 10 mg/kg per dose, once daily. Better efficacy has been observed at higher doses (8 to 10 mg/kg) than once daily administration of 6 mg/kg per dose,75 and some experts recommend a dose of ≥10 mg/kg.76 The usefulness of administration of daptomycin in combination with β-lactams, aminoglycosides, rifampicin, fosfomycin, or sulfamethoxazole/trimethoprim has been suggested in some experimental and clinical studies.77-80 Combination therapy should be considered under consultation with infectious disease specialists. In particular, combination therapy is recommended for prosthetic valve IE. The choices of additional antibiotics are the following: β-lactams such as panipenem/betamipron 2.0 to 3.0 g/day and sulbactam/ampicillin 9 g (or ampicillin 6 g/day), gentamicin at 2 to 3 mg/kg/day, rifampicin at 450 to 600 mg/day, fosfomycin at 6.0 g/day, and sulfamethoxazole/trimethoprim such as trimethoprim at 5 to 8 mg/kg/day. As adverse reactions to daptomycin, attention should be paid to elevation of the blood creatine kinase (CK) level, eosinophilia, and eosinophilic pneumonia.

When vancomycin is selected, designing before administration and TDM should be conducted. The target blood trough level should be approximately 15 to 20 μg/mL (Table 8).

The MIC of vancomycin ≤2 μg/mL means susceptible. However, if the MIC of vancomycin to the isolated MRSA is >1 μg/mL, the efficacy may be compromised even though target trough level is obtained. Therefore, efficacy evaluation should be conducted carefully for IE patients on the basis of confirmation of negative conversion of blood culture and the clinical course.

Combination of vancomycin and gentamicin is not recommended for native valve IE, because of the risk of renal toxicity. Three-drug combination therapy with vancomycin, gentamicin and rifampicin (6 weeks) is recommended as the standard therapy for staphylococcal prosthetic valve IE.4,15,73 However, the addition of rifampicin is not based on sufficient evidence. Moreover, since rifampicin requires precautions for hepatic toxicity and drug interactions, and rifampicin resistance is easy to occur within a short period, consultation with pharmacists and infectious disease specialists is recommended.

Teicoplanin and linezolid are the drugs of second choice.81,82 Teicoplanin is characterized by a quite long half-life in blood of approximately 50 hours, and loading dose is necessary for the blood concentration to reach a steady state at an early timing.83 The target trough level should be 20 μg/mL or higher (not exceeding 30 μg/mL). Linezolid is not a drug approved for IE in Japan, and administration for a duration longer than 2 weeks is related to thrombocytopenia.84 However, efficacy in the treatment of IE has been observed in the case series with prosthetic valve, and strains with low susceptibility to vancomycin, cases intolerant of vancomycin, and cases of unsuccessful treatment.85,86 Because linezolid shows favorable organ distribution, the cases accompanied by meningitis or brain abscess, and the cases accompanied by pneumonia are believed to be good indications. Infectious disease specialists should be consulted for combination therapy with other anti-MRSA drugs.

Concerning treatment with antibiotics other than anti-MRSA, combination therapy with imipenem/cilastatin and fosfomycin, which has been found to be useful in a multi-center study,87 and combination of sulfamethoxazole/trimethoprim and clindamycin have been considered in some cases, although they were intended for salvage therapy.88

b. *Coagulase-Negative Staphylococci (CNS)* (Table 11 and Table 12)

CNS accounts for approximately 10% of all cases of IE,42 and is frequently detected as a causative microorganism in the prosthetic valve IE at a relatively early timing after valve replacement surgery. Although it is often regarded as less virulent than *S. aureus*, the in-hospital mortality rate of IE caused by CNS is almost the same as that caused by *S. aureus*. In particular, the mortality rate in methicillin-resistant cases is high (40%).48,49 The percentage of the cases that required surgical treatment was even higher than in the cases caused by *S. aureus*. Antibiotic treatment of IE caused by CNS should be conducted in the same way as that for *S. aureus*. The combination therapy including rifampicin for IE in the prosthetic valve is based on a study of IE caused by CNS.

### 3.4 Gram-Negative Bacteria (Including HACEK)

HACEK is a group of gram-negative bacilli (*Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) accounting for about 1% of IE.42 Although isolation from blood cultures is rare, their association with IE is strongly suspected. The mean age of the patients with IE caused by HACEK is approximately 10 years younger than that of all IE patients. Most cases are of community-acquired infection, and the prognosis is relatively good.

HACEK organisms show good susceptibility to the third-generation and fourth-generation cephalosporins (Table 13). Most strains are susceptible to ampicillin,87 but some are β-lactamase producing. Therefore, the susceptibility of isolated strains should be confirmed.88 In cases intolerant with β-lactams, quinolones such as ciprofloxacin and levofloxacin also become choices89 (Table 13).

IE caused by gram-negative bacteria other than HACEK
is rare, accounting for only several percents. Among them, *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae* account for a majority, while *Pseudomonas aeruginosa* is common next to *Escherichia coli*. Antibiotics should be selected from the third- and fourth-generation cephalosporins, carbapenems, and quinolones according to the susceptibilities of isolates, and should be administered for up to approximately 6 weeks. Recommended treatment is combination of β-lactams and amikacin or gentamicin as the treatment of refractory gram-negative bacterial infection, but there has been no established treatment method, including the duration of aminoglycosides administration. Treatment is often difficult with antibiotics alone, and early surgery should be considered. However, the mortality rate exceeds 20% in spite of surgical treatment.

### 3.5 Fungi

The incidence of fungal IE is rare but refractory, and the mortality rate is extremely high (30 to 50%). Fungal IE is common in patients with prosthetic valve. Most cases of fungal IE are caused by *Candida*, and the cases caused by filamentous fungi such as *Aspergillus* are rare.

In the cases of fungal IE, it is difficult to control infection with medical treatment only, and some researchers recommend surgery within 1 week (native valve IE) or within several days (prosthetic valve IE). However, surgical treatment does not necessarily improve the survival rate, and the cases of IE in the prosthetic valve that could be controlled with antifungal drugs have been reported.

As the drug of first choice for antifungal treatment, amphotericin-B lipid preparation, candins (micafungin and caspofungin), or voriconazole should be selected. However, combined administration of 2 drugs can be considered from the beginning of treatment for example, amphotericin-B+candid. Infectious disease specialists should be consulted.

After surgery, treatment with antifungal drugs should be added for 6 to 8 weeks. The cases in which infection could be controlled with medical treatment alone should be treated for several months or more than 1 year (or lifelong) with oral azoles.

### 4. Efficacy Evaluation and Duration of Antibiotic Treatment

Efficacy should be evaluated at approximately 72 hours (48 to 72 hours) after the start of treatment with antibiotics under careful monitoring. Overall judgement should be made basically on the basis of vital signs, as well as subjective symptoms such as pyrexia, dyspnea, malaise, and anorexia, physical findings (changes in cardiac murmur, edema in limbs, and symptoms of embolus), test data, and imaging findings (echocardiography, chest radiography, head and body CT/MRI, etc.). Negative conversion on blood culture is mandatory in the cases with positive blood cultures before initiation of treatment. In cases caused by *S. aureus* and cases in an unstable condition such as heart failure, immediate judgement for surgery is necessary. Cooperation with several specialists and judgement for early surgery are required at any time after the start of treatment (See “Chapter II. 2. Team Medicine”).

One of the clinical parameters for efficacy evaluation is body temperature. Among the patients who have received appropriate treatment with antibiotics, 70 to 75% of the patients get afebrile within 1 week, but it tends to take time when mucocutaneous findings (such as petechia and Janeway lesion) are present, the size of vegetation is large, embolism is present in large vessels, and diagnosis has taken many days. The number of days required for becoming afebrile is 2 to 4 days on average for VGS and enterococci, and approximately 7 to 10 days for *S. aureus*.

Pyrexia persists in spite of antibiotic treatment due to several reasons: progression of infection into the annular region, intracardiac abscess, formation of pulmonary embolism and other remote lesions, heart failure, and drug-induced fever. Uncontrolled infection is an important indication for early surgery, and may necessitate repeating blood culture and evaluation on echocardiography. If fever recurs, drug-induced fever is the most common cause (common around week 3 or week 4, and observed in approximately 30% of patients). Infection focus inside and outside of the heart still can be a cause for recurrent fever. In addition, complications such as catheter-related bloodstream infection, urinary tract infection, and pneumonia should be considered. As laboratory test findings, the white blood cell count, C-reactive protein (CRP), and other inflammation markers can ancillary be referred to for prediction of prognosis or estimation of complications.

The duration of antibiotic treatment recommended in the present guidelines is not always based on sufficient comparative studies. While careful monitoring of the course is necessary even after completion of the scheduled treatment, routine blood culture is unnecessary if there are no findings suggestive of recurrence.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dosage</th>
<th>Period (weeks)</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>2g, once daily</td>
<td>4</td>
<td>Ila</td>
<td>B</td>
<td>Administration for 6 weeks for IE in the prosthetic valve (class of recommendation Iib and level of evidence C)</td>
</tr>
<tr>
<td>Sulbactam/ampicillin*</td>
<td>3g, 3–4 times daily</td>
<td>4</td>
<td>Ilb</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin, or</td>
<td>300mg, twice daily</td>
<td>4</td>
<td>Ilb</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500mg, once daily</td>
<td>4</td>
<td>Ila</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

*Amoxicillin can be administered in sensitive cases. IE, infective endocarditis.
## V. Evaluation and Management of Complications

### 1. Heart Failure

*This section is omitted from the English version.*

### 2. Uncontrolled Infection and Perivalvular Infection

*This section is omitted from the English version.*

### 3. Embolism

#### 3.1 Evaluating the Risk of Embolism

*This section is omitted from the English version.*

#### 3.2 Neurological Complications

**a. Frequency and Types of Neurological Complications**

Symptomatic neurological complications are observed in 10 to 35% of IE patients. When asymptomatic cases are included, 65 to 80% of the patients show one or more neurological complications. For patients who are suspected to have IE, examination with brain MRI or contrast-enhanced CT is recommended even when obvious focal neurological symptoms are absent (see Table 14 and “[CQ 1] Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE?”).

The most common types of neurological complications are cerebral infarction and transient ischemic attack. Cerebral hemorrhage, subarachnoid hemorrhage, mycotic aneurysm, brain abscess, encephalomeningitis, toxic/medical encephalopathy, and epilepsy are also seen.

Cerebral infarction, including asymptomatic cases, is observed in approximately 50% of IE patients and cerebral hemorrhage and subarachnoid hemorrhage are observed in 5 to 10% of the patients. In studies using brain MRI-T2*-weighted images (T2*WI), cerebral microbleeds have been observed in a large percentage of cases (approximately 60%), in addition to the above findings. The percentage of the cases accompanied by mycotic aneurysm has been reported to be approximately 4 to 9%. When cerebral hemorrhage or subarachnoid hemorrhage is observed, the percentage of the cases accompanied by mycotic aneurysm increases to 22%. Mycotic aneurysm is often observed distal to the middle cerebral artery, and approximately 25% of the cases have multiple aneurysms. When cerebral hemorrhage or subarachnoid hemorrhage is observed in a patient who is suspected to have IE, it is strongly recommended to search mycotic aneurysm by cerebrovascular imaging (cerebral angiography, computed tomography angiography [CTA], or magnetic resonance angiography [MRA]) (Table 14).

#### 3.2.1 Neurological Complications of Infective Endocarditis

<table>
<thead>
<tr>
<th>Neurological Complication</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>When cerebral hemorrhage or subarachnoid hemorrhage is observed in a patient who is suspected to have IE, mycotic aneurysm should be searched by cerebrovascular imaging (cerebral angiography, CTA, or MRA)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>For the patients who are suspected to have IE, precise examination of neurological complications using brain MRI should be considered, even when obvious focal neurological symptoms are not observed (see “CQ 1 Is brain MRI useful for the patients without neurological symptoms who have or are suspected to have IE?”)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>When MRI cannot be obtained in the patients who are suspected to have IE or when the systemic condition of the patients is unstable, head plain CT may be considered, and three-dimensional CT angiography and head contrast-enhanced CT may be added, if necessary</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>As imaging methods of MRI, DWI, FLAIR images, T2*WI or SWI, and MRA may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

IE, infective endocarditis; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DWI, diffusion weighted image; FLAIR, fluid attenuated inversion recovery; SWI, susceptibility-weighted imaging; T2*WI, T2*-weighted image.

### 4. Evaluation and Management of Complications of Infective Endocarditis

#### Table 14. Recommendations for Diagnosis of Neurological Complications of Infective Endocarditis and Level of Evidence

<table>
<thead>
<tr>
<th>Neurological Complication</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>When cerebral hemorrhage or subarachnoid hemorrhage is observed in a patient who is suspected to have IE, mycotic aneurysm should be searched by cerebrovascular imaging (cerebral angiography, CTA, or MRA)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>For the patients who are suspected to have IE, precise examination of neurological complications using brain MRI should be considered, even when obvious focal neurological symptoms are not observed (see “CQ 1 Is brain MRI useful for the patients without neurological symptoms who have or are suspected to have IE?”)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>When MRI cannot be obtained in the patients who are suspected to have IE or when the systemic condition of the patients is unstable, head plain CT may be considered, and three-dimensional CT angiography and head contrast-enhanced CT may be added, if necessary</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>As imaging methods of MRI, DWI, FLAIR images, T2*WI or SWI, and MRA may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

The percentage of the cases accompanied by mycotic aneurysm has been reported to be approximately 4 to 9%. When cerebral hemorrhage or subarachnoid hemorrhage is observed, the percentage of the cases accompanied by mycotic aneurysm increases to 22%. Mycotic aneurysm is often observed distal to the middle cerebral artery, and approximately 25% of the cases have multiple aneurysms. When cerebral hemorrhage or subarachnoid hemorrhage is observed in a patient who is suspected to have IE, it is strongly recommended to search mycotic aneurysm by cerebrovascular imaging (cerebral angiography, computed tomography angiography [CTA], or magnetic resonance angiography [MRA]) (Table 14).

#### b. Methods of Diagnosis of Neurological Complications (Table 14)

Brain MRI is most useful for the diagnosis of neurological complications accompanying IE. When MRI cannot be obtained, head plain CT should be obtained, and three-dimensional CT angiography and head contrast-enhanced CT should be added, if necessary (class of recommendation IIb, level of evidence C).

As imaging methods of MRI, diffusion weighted image (DWI), fluid attenuated inversion recovery (FLAIR) image, T2*WI or susceptibility-weighted image (SWI), and MRA are recommended (class of recommendation IIb, level of evidence C).

Since mycotic aneurysm often develops on the peripheral side of the middle cerebral artery, a larger field of view should be selected to include the entire middle cerebral artery (M3 or distal) when MRA is obtained. In the cases with cerebral hemorrhage or subarachnoid hemorrhage, cerebral angiography or three-dimensional CT angiography should be considered. In patients with IE, cerebral microbleeds are observed frequently on T2*WI and SWI, and association with mycotic aneurysm is suspected. Brain abscess shows marked high signals on DWI of MRI, and is depicted as a low-density area on CT. Characteristic capsular ring-enhancing effect is observed on contrast MRI and contrast-enhanced CT.

When headache, disturbance of consciousness, or meningeval irritation symptoms are present and meningitis or subarachnoid hemorrhage is suspected, cerebrospinal fluid examination by lumbar puncture should be conducted.
CQ 1 Is brain MRI useful for patients without neurological symptoms who have or are suspected to have IE?

Answer: It is proposed to obtain brain MRI (including DWI, FLAIR images, T2*WI, and MRA) at an early timing in the patients without neurological symptoms who have or are suspected to have IE.

Strength of recommendation 2: Weakly recommended (proposed)
Strength of body of evidence C (weak)

[Related section] “Chapter V. 2. b. Methods of Diagnosis of Neurological Complications”, Table 14

Commentary:
As described in detail in the previous section, various neurological complications are seen in patients with IE (See “Chapter V. 2. a. Frequency and Types of Neurological Complications”). Several studies have shown that, even in the IE patients without obvious neurological symptoms, screening tests using MRI show neurological complications in 40 to 80% of them. As compared with CT, MRI is able to detect small infarctions at a higher rate when DWI and FLAIR images are used. Moreover, when T2*WI or SWI is used, cerebral microbleeds can be detected. Cerebral microbleeds have been used as an indicator for diseases of cerebral small vessels such as hypertensive cerebral small vessel disease and amyloid angiopathy, but cerebral microbleeds are also observed at a high rate in IE patients, and its association with cerebral hemorrhage after open heart surgery is suspected. Cerebral microbleeds are used as an indicator in the diagnosis of diseases of cerebral small vessels such as cerebral microbleeds. In addition to the above considerations, the prevalence of brain MRI in the patients without neurological symptoms who have or are suspected to have IE. While MRI is more expensive than CT, latent costs for CT associated with adverse effects by radiation exposure or contrast medium need to be taken into consideration.

In addition to the above considerations, the prevalence of brain MRI in the patients without neurological symptoms who have or are suspected to have IE were also taken into consideration to generate the recommendation for this CQ. Thus, it is proposed to obtain brain MRI (including DWI, FLAIR images, T2*WI, and MRA) at the earliest timing in patients without neurological symptoms who have or are suspected to have IE.

c. Treatment of Neurological Complications (Figure 2 and Table 15)

The types of neurological complications include cerebral infarction, transient ischemic attack, cerebral hemorrhage, mycotic aneurysm, meningitis, brain abscess, and epileptic seizure. The most important treatment to prevent the onset and recurrence of neurological complications is believed to start appropriate antibiotic treatment at an early timing. Open heart surgery for the patients who have cerebral infarction or intracranial hemorrhage as comorbidity is separated (See “[CQ 3] Should surgery of IE be conducted at an early timing when neurological complications have occurred?”).

i. Antithrombotic Therapy for Neurological Complications
When intracranial hemorrhage (except for cerebral microbleeds) has occurred as comorbidity, antiplatelet therapy and anticoagulant therapy should be discontinued immediately (Table 15). On the other hand, consensus has not been established at present regarding whether or not anticoagulant therapy should be continued for the patients who have been receiving anticoagulant therapy when ischemic cerebrovascular disease occurs. Therefore, the decision whether anticoagulant therapy is continued or not should carefully be made considering risks of both the options.

On the other hand, it is not recommended to newly start antiplatelet therapy in IE patients because a possibility to increase the risk of hemorrhagic complications has been suggested (Table 15). Although evidence regarding anticoagulant therapy is limited, it is not recommended to newly start anticoagulant therapy because it is also likely to increase the risk of hemorrhagic complications (Table 15).

ii. Acute Reperfusion Therapy for Neurological Complications
Intravenous thrombolytic therapy for acute cerebral infarction accompanying IE is not recommended because the incidence of intracranial hemorrhage after treatment is very high (approximately 20%) (Table 15). For acute major artery occlusion by vegetation, endovascular thrombectomy is suggested to be safe and effective even in patients receiving anticoagulant therapy.
iii. Treatment for Intracerebral Hemorrhage and Hemorrhagic Infarction
When symptomatic intracerebral hemorrhage or hemorrhagic infarction exhibiting mass effect is observed, discontinuation or suspension of anticoagulant therapy should be considered. In some cases, craniotomy for removal of hematoma or decompressive craniectomy should be considered.\textsuperscript{130}

iv. Coil Embolization/Surgical Treatment for Mycotic Aneurysm (Figure 2 and Table 15)
Although evidence based on a randomized controlled trial is not available regarding treatment methods, Figure 2 summarizes treatment algorithm for mycotic aneurysm. While endovascular treatment has been conducted more often, surgical treatment may be preferred when intracerebral hemorrhage is present or revascularization is necessary.\textsuperscript{131,132} In selection of treatment methods, judgement should be made on the basis of thorough examination of the systemic condition for each patient.

Table 15. Recommendations for Treatment of Neurological Complications of Infective Endocarditis and Level of Evidence

<table>
<thead>
<tr>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet therapy and anticoagulant therapy should be discontinued immediately if IE is accompanied by intracranial hemorrhage (except for cerebral microbleeds)</td>
<td>I B</td>
</tr>
<tr>
<td>Surgical or endovascular treatment should be considered for ruptured mycotic aneurysm (see Figure 2)</td>
<td>I C</td>
</tr>
<tr>
<td>It is not recommended to newly start antiplatelet therapy aiming at prevention of embolism in IE patients</td>
<td>III B</td>
</tr>
<tr>
<td>Intravenous thrombolytic therapy is not recommended for acute cerebral infarction accompanying IE</td>
<td>III B</td>
</tr>
<tr>
<td>It is not recommended to newly start anticoagulant therapy aiming at prevention of embolism in IE patients</td>
<td>III C</td>
</tr>
</tbody>
</table>

IE, infective endocarditis.

3.3 Other Embolism
This section is omitted from the English version.

4. Renal Dysfunction
This section is omitted from the English version.

5. Disseminated Intravascular Coagulation
This section is omitted from the English version.

VI. Surgical Treatment

1. Evaluation of Surgical Risk and Preoperative Assessment

a. Evaluation of Surgical Risk
Surgical risk can be evaluated using JapanSCORE,\textsuperscript{133,134} STS score,\textsuperscript{135} and EuroSCORE.\textsuperscript{136} Operative mortality is high in patients requiring emergency surgery, cardiogenic/septic shock, infection by fungi or multidrug-resistant bacterium such as MRSA, prosthetic valve endocarditis, paravalvular abscess, neurological complications, renal failure, diabetes mellitus, and so forth.
Table 16. Recommendations of Early Surgery for IE and Level of Evidence

<table>
<thead>
<tr>
<th>Situation</th>
<th>Indication/recommendation*1</th>
<th>Timing</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Refractory pulmonary edema and cardiogenic shock due to acute severe valve dysfunction or fistula formation</td>
<td>Emergency</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Heart failure due to severe valve dysfunction or rapidly worsening paravalvular leakage</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Uncontrolled infection</td>
<td>Annular abscess, pseudoaneurysm formation, fistula formation, increasing size of vegetation, and atrioventricular conduction disturbance</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Persistent infection exists despite no presence of other infection foci. Persistent infection includes (1) positive blood culture obtained at 2 to 3 days after appropriate antibiotic treatment or (2) sustained fever for 3 to 5 days or more after appropriate antibiotic treatment</td>
<td>Urgent</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Infection by fungi or highly multijug-resistant bacteria</td>
<td>Urgent/elective</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Prosthetic valve endocarditis due to resistant staphylococci or non-HACEK Gram-negative bacteria</td>
<td>Urgent/elective</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Recurrent prosthetic valve endocarditis</td>
<td>Urgent/elective</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Prevention of embolism</td>
<td>One or more embolisms after the initiation of appropriate antibiotic treatment and non-disappearing (size &gt;10mm) or growing vegetation</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Native valve endocarditis with mobile vegetation exceeding 10mm in size and severe valve dysfunction</td>
<td>Urgent</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Isolated huge vegetation exceeding 30mm in size</td>
<td>Urgent</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Mobile vegetation exceeding 10mm in size</td>
<td>Urgent</td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td>Timing of surgery in patients with neurological complications*5</td>
<td>Surgery should not be postponed in patients with non-hemorrhagic cerebral infarction when surgical treatment is appropriate Note: Except for cases with coma, brain herniation, or huge major central lesions</td>
<td>–</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Surgery should be postponed at least 4 weeks when new intracranial hemorrhage is detected Note: Except for cases involving cerebral microbleeds</td>
<td>–</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>

*1: Unless otherwise specified, the statements apply to both native valve endocarditis and prosthetic valve endocarditis.
*2: Infectious condition should be comprehensively evaluated on the basis of negative conversion of blood culture in addition to the degree of lowering of body temperature or inflammatory markers such as the white blood cell count and CRP value.
*3: Early surgery is recommended, especially when the risk of surgery is low (See “CQ 2 Should early surgery be conducted if a large vegetation is present?”).
*4: Especially in cases with prosthetic valve endocarditis, anterior leaflet of mitral valve involvement, or the presence of other relative surgical indications.
*5: See “CQ 3 Should surgery of IE be conducted at an early timing when neurological complications have occurred?”
IE, infective endocarditis.

b. Preoperative Assessment: Evaluation of Cerebral Vessels, Coronary Arteries, and Other Organs

Preoperative assessment of intracranial lesions is essential because IE accompanies neurological complications at high rates. The diagnosis of neurological complications is described in detail in “Chapter V. Evaluation and Management of Complications”. Patients with suspected myocardial ischemia require cardiac CT or coronary angiography. Optimal modality should be selected based on patient’s clinical condition. Cardiac CT can simultaneously evaluate coronary arteries and aortic root infection. Coronary angiography precisely evaluates stenosis with calcification or with tachycardia, but it carries the risk of catheter manipulation-related embolism, especially in patients with aortic valve IE. Assessment of embolism and abscess in the spleen or kidneys is possible to be performed with minimal contrast medium by additional late-phase systemic CT following cardiac CT.

2. Indications of Surgical Treatment and Timing of Operation

a. General Remarks on Indications of Surgical Treatment

In the treatment of IE, surgical treatment should be always kept in mind as an option. Early surgical treatment should be considered when there are possibilities of progressing heart failure, destruction of intracardiac structure, refractory infection, and embolism. The team should discuss the treatment strategy for each patient because the appropriate timing of surgery and postoperative results are varied according to the type of causative microorganisms, comorbidities and so on. Early surgery can be classified as emergency surgery (within 24 hours), urgent surgery (within several days), and elective surgery (1 to 2 weeks after antibiotic treatment). Table 16 shows the indications of early surgery. In the cases not meeting the indications of early surgery, the indication and timing of surgery should be determined as usual valvular heart diseases. However, since the severity of valvular disease/bacteremia and possibility of embolism change from time to time in the
cases of IE, careful monitoring is required to avoid missing the optimal timing of surgery.

See “[CQ 3] Should surgery of IE be conducted at an early timing when neurological complications have occurred?” as well as Figure 3 and Table 16 for the timing of surgery in the cases in which neurological complications occur in the patients for whom early surgery is indicated.

b. Congestive Heart Failure (Table 16)

Congestive heart failure is triggered by regurgitation mainly caused by valvular destruction, but it can also be caused by intracardiac shunt, and valvular obstruction caused by vegetation. Heart failure of NYHA III to IV can become an indication of emergency surgery.146–149 Heart failure of NYHA II accompanied by severe valvular regurgitation also becomes an indication of early surgery if echocardiography suggests elevation of the left ventricular end-diastolic pressure and pulmonary hypertension.148–152

Even the cases accompanying severe valvular regurgitation can be treated with conservative treatment with antibiotics and management of heart failure, if there are no apparent signs of heart failure and there are no other reasons for surgical indication, such as large vegetation. In such cases, surgical indication should be determined as usual valvular heart diseases.

c. Uncontrolled Infection (Table 16)

Uncontrolled infection is an indication for urgent surgery. Uncontrolled infection is defined as continuing positive blood culture and/or sustained infection findings such as fever, elevated white blood cell count, and high CRP level despite appropriate antibiotic treatment for a certain period (approximately 3 to 5 days).16,99 Mortality is reported to be doubled if blood culture obtained at 48 to 72 hours after the initiation of antibiotics remains positive,16 and surgery should be performed without delay.

Patients with positive conversion of blood culture after confirming the absence of other infection foci are diagnosed as recurrent infection, and early surgery should be considered. Fungi, gram-negative bacteria,153 or MRSA, which is less likely to respond to antibiotic treatment, often follows a clinical course of uncontrolled infection. Annular abscess, pseudoaneurysm formation, increasing size of vegetation, or heart block (complete atrioventricular block and left bundle branch block) are all characteristic of uncontrolled infection.27,156,152,154,155 The incidence of paravalvular abscess is higher in prosthetic valve endocarditis than in native valve endocarditis (55 to 78% vs. 10 to 32%).156,161 In native valve endocarditis, aortic valve endocarditis is associated with a high rate of paravalvular abscess. In prosthetic valve endocarditis, the incidence of paravalvular abscess is high in endocarditis at the mitral position as well.

d. Infectious Embolism (Table 16)

Embolism, especially cerebral embolism, dramatically exacerbates the patients’ activities of daily living, even if it does not directly endanger life. Generally, the use of appropriate antibiotics will decrease the risk of embolism.101 However, it has been reported that the risk of embolism does not decrease even after antibiotic treatment in the cases of giant vegetation larger than 30 mm.102 If embolic events repeat even after the start of appropriate antibiotic treatment, the risk of subsequent embolic events should be high, and early surgery is reasonably indicated.4 Vegetation adhering to anterior mitral leaflet also accompanies a high risk of embolism.73

CQ 2 Should early surgery be conducted if a large vegetation is present?

Answer:

Surgery at the earliest timing possible is recommended for the patients with IE in the native valve (aortic valve or mitral valve) who have a vegetation of 10 mm or larger accompanying severe valve dysfunction.

Strength of recommendation 1: Strongly recommended

Strength of body of evidence B (moderate)

[Related section] “Chapter VI. 2. a. General Remarks on...”
Indications of Surgical Treatment. Table 16

Commentary:
In the observational studies, early surgery of IE has been associated with better prognosis.\(^{162-164}\) The usefulness of early surgery has been reported in Asian countries and Japan.\(^{165-166}\) The indication of early surgery for IE cases accompanying heart failure, embolism which occurs repeatedly in spite of sufficient antibiotic treatment, uncontrollable local infection (abscess, pseudoaneurysm, and fistula), and drug-resistant causative microorganisms such as fungi has been generally established (see “Chapter VI. 2. a. General Remarks on Indications of Surgical Treatment”). On the other hand, implementation of early surgery in all cases of IE accompanies concerns about the risk of surgery-associated death and the risk of recurrence. Therefore, identification of the subgroup to be treated by early surgery has been needed.\(^{166}\)

In addition to mortality due to heart failure and other complications, IE may cause serious disabilities due to cerebral infarction caused by embolism of vegetation. A large vegetation of 10 mm or larger in size has been reported to be a risk factor of recurrent embolism.\(^{167-169}\) The risk of embolism after the onset of IE is high in the early stage after onset, and appropriate antibiotic treatment is known to reduce the risks. However, it has been suggested that the risk of embolism does not decrease in cases with huge vegetation, as well as the cases in which vegetation grows in size during antibiotic treatment.\(^{191}\) Therefore, surgical indication has been discussed for prevention of embolism in cases with a large vegetation. In observational studies, the usefulness of early surgery for a large vegetation has been reported in Western countries and Japan,\(^{148-156}\) while some reports have concerned the incidences of early death, recurrence of IE, and valve dysfunction was high in early surgery.\(^{169,170}\)

In 2012, the only randomized study at present regarding surgical indication of IE was reported.\(^{271}\) Inclusion criteria were as follows: patients aged 18 years or older who have left-sided native valve IE accompanying a vegetation larger than 10 mm, who also have severe valve dysfunction (valvular regurgitation in most cases), and for whom emergency surgery is not indicated (moderate-to-severe heart failure, atrioventricular conduction block, abscess, destructive penetrating lesions, and IE caused by fungi). Patients aged 80 years or older, who had severe complications such as large cerebral infarction accompanying the risk of hemorrhagic changes and cancer were excluded. Patients with prosthetic valve IE and right-sided IE were also excluded. The patients were divided into the group to be surgically treated within 48 hours after randomization (37 patients) and the group receiving conventional treatment (39 patients). In both groups, appropriate antibiotics were administered. In the conventional treatment group, 30 patients (77%) were surgically treated (27 patients during the index hospitalization and 3 patients in the late phase), and 8 patients received semi-emergency surgery (6 to 10 days after randomization). Therefore, this study could be regarded to test the usefulness of urgent surgery for the patients with a large vegetation accompanying valve dysfunction.

Significant differences were observed in primary composite endpoints (in-hospital death, embolic events within 6 weeks after randomization) between the early surgery group and the conventional treatment group (hazard ratio 0.10 [95% confidence interval, 0.01–0.82, P=0.03]). While no difference was seen in the total number of deaths within 6 months (3% versus 5%, hazard ratio 0.51 [95% confidence interval 0.05–5.66, P=0.59]), differences were seen in the presence or absence of embolism observed within 6 weeks (0% versus 21%, P=0.005). In both groups, no patients were re-hospitalized because of embolic events and heart failure during the follow-up period. Moreover, there were few cases of recurrence of IE within 6 months: no significant differences were observed between the groups.

In the above report, randomization was conducted, but concealment of randomization was not performed. Blinding was not conducted, but systemic differences in other treatments are deemed to be unlikely. Embolic events were confirmed on images at the time of periodic visits to the hospital, and detection bias is thought to be small. Image inspection was conducted only when symptoms were present, and asymptomatic embolism was not evaluated. The necessary number of patients was calculated, and intention to treat analysis was conducted.

The frequencies of causative microorganisms were typical, with VGS accounting for 30% of the cases, other streptococci 30%, and Staphylococcus aureus 10%. The cases of cerebral infarction represented 30%. On the other hand, the patients were young (between 40 and 49 years), were relatively low risk, and were treated at the hospitals coping with a large number of surgical cases. A report suggested that the cases satisfying the conditions of this study was only 11.3% of the actual cases of left-sided native valve IE undergoing validity of the results.\(^{172}\) This cohort was followed up for 7 years. Although no difference was seen in total mortality, composite endpoints (total death, embolism, and recurrence of IE) were significantly better in the early surgery group (8.1%) than the conventional treatment group (30.8%).\(^{173}\)

On the basis of these results, the present guidelines recommend urgent surgery for the patients with IE in the native valve (aortic valve or mitral valve) who have a vegetation of 10 mm or larger accompanying severe valve dysfunction. However, the risk of surgery should be evaluated carefully. Moreover, prosthetic valve IE should not be included in the targets of this indication.

CQ3 Should surgery of IE be conducted at an early timing when neurological complications have occurred?

Answer:
(1) Surgery of IE is recommended not to be postponed if it is indicated, even when concurrent cerebral infarction is present.*
*Except for the cases with concurrent coma, herniation, or cerebral hemorrhage, as well as major central lesions.

Strength of recommendation 1: Strongly recommended. Strength of body of evidence B (moderate)

(2) If new intracranial hemorrhage* is observed, it is proposed to wait 4 weeks to conduct open heart surgery if the hemodynamic condition is stable.
*Except for cerebral microbleeds.

Strength of recommendation 2: Weakly recommended (proposed).
Advancing into the study period, the mortality rates in the cases in which surgery was conducted after onset as compared with the cases in which surgery was conducted within 7 days after onset showed significant exacerbation when early surgery was performed in the registration study. Nevertheless, in-hospital mortality and one-year mortality have not been significantly different when early surgery was performed by the patients who underwent surgery in the early stage after onset of neurological complications. Therefore, it has been recommended to wait 4 weeks before surgery for IE accompanied by neurological complications. However, patients who show exacerbation of the condition while waiting for surgery are often observed. Furthermore, these early studies were retrospective observational studies, without risk stratification, and did not examine the impacts of the presence or absence of symptoms, the size of infarction lesion, and the size of vegetation.

In recent years, findings about early surgery in cases with neurological complications have been accumulated, and it has been revealed that the prognosis is not as bad as initially anticipated even if early surgery is conducted in cases accompanied by cerebral infarction. When risks were stratified in a prospective multi-center registration study, neither in-hospital mortality nor one-year mortality showed significant exacerbation when early surgery was conducted within 7 days after onset as compared with the cases in which surgery was conducted after that period. Surgical mortality is high in the cases of cerebral infarction in the middle cerebral arterial region and cerebral infarction accompanied by cerebral hemorrhage, meningitis, and brain abscess; however, early cardiac surgery in the cases of cerebral infarction of 15 to 20 mm has been reported when the hemorrhagic focus is 20 to 30 mm smaller in some reports, but others reported early surgery within 7 days after onset was associated with exacerbation of neurological complications, as such enlargement of hemorrhagic focus. Many reports recommend to wait approximately 4 weeks if cerebral hemorrhage accompanies, but preceding clipping or craniotomy may enable cardiac surgery to be performed earlier in cases of mycotic aneurysms (see “Chapter V. 3. 2. c. Treatment of Neurological Complications”). The risks and conditions of cardiac lesions and cerebral lesions in individual cases should be examined carefully before surgery is performed. Figure 3 shows the treatment algorithm for the cases with neurological complications.

**Prosthetic Valve Endocarditis (Table 16)**

Prosthetic valve endocarditis should be treated with the potential for surgery. Indication for surgery is considered on the basis of three conditions, i.e., heart failure, uncontrolled infection, and risk of embolism, similar to native valve endocarditis. Heart failure due to rapidly worsening paravalvular regurgitation or prosthetic valve dysfunction is an indication for urgent surgery. Emergent or urgent surgery is required in patients with cardiogenic shock, fistula formation, or fluctuation of a prosthetic heart valve. Surgery for such patients improves their prognosis.

### 3. Surgical Treatment and Postoperative Management

The objective of surgery for IE is complete elimination of infection foci and tissue reconstruction. The infection recurrence rate after prosthetic valve replacement is comparable for mechanical valves and bioprosthetic valves. When annular abscess is formed, small cavities can be closed after dissection of infected tissues, but large cavities necessitate drainage into the pericardium or blood flow.

#### a. Mitral Valve IE

In cases of mitral valve IE, resection and reconstruction of infection foci can be achieved by mitral valve replacement if infection is confined to the valve or a part of subvalvular tissues. However, when durability of prosthetic mitral valves and complications are taken into consideration, mitral valvuloplasty is preferred in many cases. Patch repair with autologous pericardium or heterogeneous pericardium can be used for the lesion of valve perforation, and repair as comorbidity, these results seem to support the feasibility of early surgery in the cases of non-severe cerebral infarction.
with artificial chordae tendineae can be performed for ruptured chordae tendineae. In the cases of more extensive valve destruction, it is important to judge feasibility of valve repair with residual tissues after dissection of infected tissues. On the other hand, valve replacement and reconstruction of the periannular region are necessary in severe cases in which infection reaches the periannular region to form abscess or the normal anatomic structure has been disrupted. The missing part should be reconstructed with autologous or heterogeneous pericardium after complete resection and dissection of infected tissues.

b. Aortic Valve IE
Replacement is effective when infection is confined to the valve.\textsuperscript{191,192} When annular abscess is formed, patch formation after dissection can be conducted if the abscess cavity is small, but drainage into the pericardium should be performed if the abscess cavity is large. In such cases, replacement of the root becomes necessary. When extensive abscess accompanies, simultaneous replacement of the mitral valve can become an option. When the root replacement is performed, no significant differences are observed in the results in the cases using allografts, and the cases using prosthetic valves (bioprosthetic valve and mechanical valve) with Dacron grafts.\textsuperscript{193} Favorable results of Ross surgery have been reported by facilities with good experience.\textsuperscript{194,195}

c. Postoperative Management
The differences from postoperative management for usual valvular heart disease are that exacerbation or new perioperative neurological complications can be observed, that the incidence of perivalvular regurgitation is high, and that infection as a cause of these complications may persist. The use of a bioprosthetic valve or valvuloplasty not needing anticoagulant therapy should be considered in the patients who have or who may have neurological complications.

### VII. Follow-up After Discharge

This section is omitted from the English version.

### VIII. Prevention

#### 1. General Remarks on Prevention of IE

The incidence of IE in general population is reported to be 3 to 7/100,000 person-year.\textsuperscript{73} It has become common to classify the patients with high risk of IE as the highest-risk group who is very likely to lead to serious outcome, including death, once developed IE, and as the moderate-risk group for others.\textsuperscript{196-198}

Western guidelines are less willing to recommend antibiotic prophylaxis before dental procedures because bacteria can be induced by daily activities including tooth brushing, and the incidence of IE after dental procedures is extremely low. In particular, the guidelines released by the National Institute for Health and Care Excellence (NICE) in 2008 stated that antibiotic prophylaxis is unnecessary in all kinds of invasive dental procedures (however, the expression was modified in 2016 to that “it is not always unnecessary”).\textsuperscript{199} The present guidelines recommend antibiotic prophylaxis for the high-risk patients with IE (both highest-risk and moderate-risk) (see Table 17 and “[CQ 4] Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for the patients with high-risk heart diseases?”). The appropriateness of these recommendations should be

| Table 17. Risks of Infective Endocarditis in Adults According to Underlying Heart Disease, Recommendations of Antibiotic Prophylaxis During Dental and Oral Surgical Procedures, and Level of Evidence |
|---|---|---|
| Risk of IE | Class of recommendation | Level of evidence |
| **1. Highest risk: high incidence, morbidity and mortality of infective endocarditis** | | |
| • Patients after prosthetic valve replacement (bioprosthetic/mechanical valve), or patients with annular ring | I | B |
| • Patients with a previous episode of IE | | |
| • Patients with complex, cyanotic congenital heart disease (single ventricle, complete transposition of great arteries, tetralogy of Fallot) | | |
| • Patients underwent shunting between systemic and pulmonary circulation | | |
| **2. Moderate risk: lower morbidity and mortality despite high incidence of infective endocarditis** | | |
| • Most of congenital heart diseases*1 | IIa | C |
| • Acquired valvular heart diseases*2 | | |
| • Hypertrophic cardiomyopathy with obstruction | | |
| • Mitral valve prolapse with regurgitation | | |
| • Patients with intracardiac devices (pacemaker, implantable cardioverter defibrillator) | I Ib | C |
| • Patients with a long-term central venous catheter | | |

See “[CQ 4] Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for the patients with high-risk heart diseases?” for details about evaluation of evidence.

*1: Except for simple atrial septal defect (ostium secundum type).
*2: The risk of IE is low in mitral valve stenosis without regurgitation.
continuously verified in epidemiological studies.

Since the level of risk may differ among the diseases classified as moderate-risk of IE, the IE risk of each disease is described for each section in “Chapter VIII. 2. What Types of Patients With Heart Disease Are Likely to Develop IE?” Antibiotic prophylaxis was examined mainly in relation to dental procedures. Other risks in treatment are also stated in “Chapter VIII. 3. Procedures, Treatment, and Background for Risks of IE and Prevention”. Concerning the route of entrance of causative microorganisms for IE, invasion via skin is known to be common.\(^\text{200}\) It is important to pay attention to the diseases causing decreases in the skin barrier functions, and to keep the skin clean during procedures. The conditions and the methods of prophylaxis are described in each section of “Chapter VIII. 3. Procedures, Treatment, and Background for Risks of IE and Prevention”.

2. What Types of Patients With Heart Disease Are Likely to Develop IE?

a. Patients With Prosthetic Valve or Previous IE
This section is omitted from the English version.

b. Adult Congenital Heart Disease
This section is omitted from the English version.

c. Aortic Valvular Disease
This section is omitted from the English version.

d. Mitral Valvular Disease / Mitral Valve Prolapse
This section is omitted from the English version.

e. Right-Sided Valvular Disease
This section is omitted from the English version.

f. Hypertrophic Cardiomyopathy
This section is omitted from the English version.

g. After Device Implantation
Infection associated with implantable cardiac devices tends to increase in recent years as treatment with devices, such as pacemaker, increases (see “Chapter IX. 2. IE on Cardiac Devices”). According to a cross-sectional study, the incidence of IE in patients with device implantation is estimated to be 40 events/100,000 person-year, which is higher than the incidence in the general population. In the present guidelines, patients after device implantation are classified as being at moderate risk of IE. However, antibiotic prophylaxis before dental procedures, and gastrointestinal and urogenital treatment in the patients with device implantation is not recommended in the guidelines of American Dental Society, American Heart Association (AHA), American College of Cardiology (ACC), and European Society of Cardiology (ESC).\(^\text{201, 203}\)

h. Others
This section is omitted from the English version.

3. Procedures, Treatment, and Background for Risks of IE and Prevention

3.1 Introduction
The procedures for which antibiotic prophylaxis is recom-

<table>
<thead>
<tr>
<th>Antibiotic prophylaxis</th>
<th>Situation</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis is strongly recommended</td>
<td>Dental and oral surgery: All invasive dental procedures causing bleeding and bacteremia (oral surgery such as tooth extraction, periodontal surgery, dental implant surgery, dental scaling, infected root canal treatment etc.)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Otolaryngologic field: Tonsillectomy and adenoidotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular field: Implantation of pacemaker and implantable cardioverter defibrillator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis is preferable</td>
<td>Invasive procedures for local infection foci: Abscess drainage and endoscopic examination and treatment for infection foci (including biliary obstruction)</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular field: Implantation of prosthetic valve and other cardiovascular prostheses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transurethral prostatectomy: Especially patients with prostate valve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis can be performed. However, antibiotic prophylaxis is recommended for the patients with a history of IE</td>
<td>Gastrointestinal field: Sclerotherapy for esophageal varices, dilatation of esophageal stenosis, mucosal biopsy or polypectomy by colonoscopy and proctoscopy, and biliary tract surgery</td>
<td>IIIB</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Urogenital/reproductive field: Urethral dilatation, vaginal delivery/vaginal hysterectomy, intrauterine curettage, therapeutic abortion/induced abortion, and insertion and removal of intrauterine devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular field: Cardiac catheterization/percutaneous intravascular catheter intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin incision associated with surgery (especially in the patients with atopic dermatitis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis is not recommended</td>
<td>Dental and oral surgery: Local anesthesia from uninfected site, orthodontic procedures, dental pulpectomy</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Respiratory field: Bronchoscopy/laryngoscopy, endotracheal intubation (transnasal/oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Otolaryngologic field: Tube insertion for tympanic perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal field: Transesophageal echocardiography, gastrointestinal endoscopy (including biopsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urogenital field: Urethral catheterization and transurethral endoscopy (cystourethroscopy and pyelourethroscopy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular field: Central venous catheterization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IE, infective endocarditis.
mended include invasive dental procedures including scaling, tonsillectomy/adenoidectomy, and implantation of pacemaker and implantable cardioverter defibrillator (ICD). Antibiotics should also be administered before invasive treatment of local infection. Antibiotic prophylaxis is also recommended before surgical implantation of prosthetic valve and other cardiovascular prostheses, and transurethral resection of the prostate (TUR-P) in the patients with prosthetic valve. However, it is not recommended for bronchoscopy/laryngoscopy, endotracheal intubation, TEE, gastrointestinal endoscopy, urethral catheterization, transurethral endoscopy, and central venous catheterization. Antibiotic prophylaxis is recommended only in the cases with a history of IE for sclerotherapy for esophageal varices, dilatation of esophageal stenosis, colonoscopic test/treatment, biliary tract surgery, urethral dilatation, vaginal delivery and therapeutic abortion, cardiac catheterization, and skin incision. These are summarized in Table 18.

### 3.2 Dental Diseases

#### a. Anatomy, Pathophysiology, and Situation in Japan

The two major dental diseases are dental caries and periodontal diseases, and are believed to be caused by respective causative oral bacterial species (Figures 4, 5). Caries is known to be induced mainly by a type of Gram-positive facultative bacteria, *Streptococcus mutans*, and periodontal diseases are known to be induced by mixed infection with several Gram-negative obligatory anaerobes.

**Figure 4** schematically shows progression of caries (healthy, and C1 to C4). When dental plaque containing *Streptococcus mutans* adheres to the surface of the crown, caries begins to develop. When enamel and dentin decay along with progression of caries, tissues called pulp cavity, which are composed of dental pulp (nerves) and capillary vessels, are exposed. Under such a condition, oral bacteria can enter blood flow anytime, and dental pulp infection occurs.

**Figure 5** schematically shows progression of periodontal diseases (healthy, gingivitis, and periodontitis). When gingivitis progresses from a healthy state, hemorrhage is induced by stimulation with tooth brush, etc., and oral bacteria become able to enter blood flow. When inflammation progresses even more, ulcers are formed, and oral bacteria become able to enter blood flow easily anytime.
Tooth extraction, oral surgical treatment accompanying bleeding, dental implantation, and removal of dental calculous (scaling) are recognized as the dental procedures causing bacteremia. On the other hand, chewing and tooth brushing in daily life may cause bleeding, and bacteremia may be induced. When a state susceptible to bacteremia is generated, an environment for the IE-causing microorganisms present in the oral cavity to enter blood flow is established. Most of the causative microorganisms originating from the oral cavity are considered to be oral streptococci. As major bacteria, mitis group streptococci, such as *Streptococcus sanguinis*, are known. However, it is extremely rare that major causative microorganisms for periodontal disease are isolated from blood of the patients with IE.

According to a questionnaire survey of general dental practitioners conducted in Japan, only a half of the respondents answered that they used antibiotics for the purpose of preventing IE. Only a half of them mentioned guidelines as the help to be referred to in deciding antibiotic prophylaxis. It is necessary to extensively distribute the guidelines among dentists in the future.

### Table 19. Incidence of Bacteremia Caused by Oral Procedures

<table>
<thead>
<tr>
<th>Oral procedure</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth extraction</td>
<td>18–100</td>
</tr>
<tr>
<td>Wisdom tooth extraction</td>
<td>55</td>
</tr>
<tr>
<td>Dental scaling</td>
<td>8–79</td>
</tr>
<tr>
<td>Periodontal surgery</td>
<td>36–88</td>
</tr>
<tr>
<td>Infectious root canal treatment</td>
<td>42</td>
</tr>
<tr>
<td>Rubber dam insertion</td>
<td>29</td>
</tr>
<tr>
<td>Tooth brushing</td>
<td>23</td>
</tr>
<tr>
<td>Chewing</td>
<td>38</td>
</tr>
</tbody>
</table>


### Table 20. Recommended Prophylactic Antibiotics Before Dental Procedures (Adults)

<table>
<thead>
<tr>
<th>Route</th>
<th>Allergic to <em>β</em>-lactam antibiotics</th>
<th>Antibiotics</th>
<th>Dose</th>
<th>Frequency of administration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Absent</td>
<td>Amoxicillin</td>
<td>2 g*1,*2</td>
<td>Single</td>
<td>1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Clindamycin</td>
<td>600 mg</td>
<td>Single</td>
<td>1 hour before treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin</td>
<td>500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin</td>
<td>400 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to take oral medication</td>
<td>Absent</td>
<td>Ampicillin</td>
<td>1–2 g</td>
<td>Single</td>
<td>Intravenous injection or intramuscular injection within 30 minutes after the start of surgery, or intravenous drip infusion over 30 minutes or more from the start of surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefazolin</td>
<td>1 g</td>
<td></td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drip infusion over 30 minutes or more from the start of surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftriaxone</td>
<td>1 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Clindamycin</td>
<td>600 mg</td>
<td>Single</td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drip infusion over 30 minutes or more from the start of surgery</td>
</tr>
</tbody>
</table>

*1: Or 30 mg/kg body weight.
*2: If the dose of amoxicillin is decreased from 2 g for some reasons, additional administration of 500 mg of amoxicillin should be considered 5 to 6 hours after first dose.
are recommended in the cases of allergic to β-lactams, and ampicillin, cefazolin, ceftriaxone, and clindamycin are recommended if oral medication is unable to take (Table 20). If the dose of amoxicillin is reduced from 2 g for some reasons, additional administration of amoxicillin should be considered 5 to 6 hours after the first administration for a pharmacological reason to suppress growth of the bacteria adhered to the valve.

CQ 4 Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for the patients with high-risk heart diseases?

Answer:
(1) Antibiotic prophylaxis is recommended before dental procedures inducing bacteremia, such as tooth extraction, in adult highest-risk patients.*1

Strength of recommendation 1: Strongly recommended
Strength of body of evidence (moderate)

(2) Antibiotic prophylaxis is proposed before dental procedures inducing bacteremia, such as tooth extraction, in adult moderate-risk patients.*2

Strength of recommendation 2: Weakly recommended (proposed).
Strength of body of evidence C (weak)

*1Highest-risk group (patients susceptible to infection whose condition becomes severe easily) includes 1) the cases after prosthetic valve surgery, 2) history of IE, 3) un repaired cyanosis type congenital heart disease including the cases using palliative anastomosis and artificial blood vessels, 4) within 6 months after the repair of congenital heart disease using artificial materials regardless of surgery or catheterization, 5) cases accompanying residual lesions at the repair site in spite of repair with patch or artificial materials, and 6) aortic coarctation.

*2Moderate-risk group (patients whose condition is not always serious but who are likely to show endocarditis) includes congenital heart diseases other than highest- and low-risk, hypertrophic obstructive cardiomyopathy, and mitral valve prolapse accompanying valvular regurgitation.

[Related section] “Chapter VIII. 1. General Remarks on Prevention of IE”, Table 18

Commentary:
Antibiotic prophylaxis for IE in dental procedures has been recommended in guidelines since 1950s, but there is no definite evidence for efficacy of antibiotic prophylaxis. Cochrane Review in 2013 also concluded that no evidence was observed for efficacy of antibiotic prophylaxis. Concerns about the allergic reaction induced by antibiotic prophylaxis and emergence of resistant bacteria have also been mentioned. Reflecting these concerns, antibiotic prophylaxis in dental procedures has been reconsidered in the United States and Europe. As described in a different section, there are heart diseases with higher risk of IE than usual population. Among the patients with high risks of IE, it has been accepted to differentiate the patients who are likely to have a serious outcome, including death, after the onset of IE (highest-risk group) from other patients (moderate-risk group). The guidelines issued in France in 2007 and in the United States in 2007 and in Europe in 2009 did not recommend antibiotic prophylaxis for the moderate-risk group but continuously recommended it for the highest-risk group. On the other hand, the recommendations by NICE in the United Kingdom in 2008 advised that antibiotic prophylaxis is not recommended for all patients including the highest-risk group. Under such circumstances, the previous guidelines in Japan continued to recommend antibiotic prophylaxis. In the present revision, a new recommendation has been generated on the basis of review of documents issued after revision of various guidelines in the 2000s.

The articles searched by systematic review and used for the present guidelines can be divided into three groups. The first is case control studies conducted before revision of the guidelines, which examined the presence or absence of antibiotic prophylaxis in the patients with and without IE. The second group is reports on the changes in the incidence of IE in foreign countries before and after revision of the guidelines. The third one is others, which includes a survey on the awareness of medical doctors and dentists about the guidelines, details about the cases in which IE occurred in spite of antibiotic prophylaxis, incidences of adverse reactions including allergy to antibiotics, and estimated data on IE which is believed to have been prevented by antibiotic prophylaxis and their economic analyses.

Three articles are listed as case control studies. Some reports found association between the onset of IE and antibiotic prophylaxis, while other reports did not find any association. There are some limitations because of the method of subject registration or retrospective study design, and it is difficult to draw conclusions regarding antibiotic prophylaxis from these studies.

Articles of the second group, i.e., articles on the changes in the incidence of IE before and after changes of various guidelines, can be further divided into two subgroups. One is the studies conducted before and after discontinuation of antibiotic prophylaxis in all patients with heart diseases in the United Kingdom, and the other is the studies conducted in the United States and Europe other than the United Kingdom, in which antibiotic prophylaxis was continued in the highest-risk group and was discontinued in the moderate-risk group. In the former type, the changes of the number of prescriptions of antibiotics before and after the guidelines were recorded because of the insurance system in which the advice from NICE is linked with payment of medical expenses. For the latter, no clear data are available regarding to which extent the changes in the guidelines were complied with.

After the changes of the guidelines, the number of cases of antibiotic prophylaxis decreased dramatically in the United Kingdom. While no change was observed in the incidence of IE at first, a slight, but statistically significant increase in the incidence of IE was observed as of 5 years after the changes of the guidelines. Because of the nature of observational studies, it is impossible to demonstrate the causal relationship between the decrease of antibiotic prophylaxis and the increase in the incidence of IE. Moreover, it needs to be kept in mind that spontaneous increases of IE over time regardless of the changes of the guidelines have been reported. However, temporal agreement was observed between the changes of the guidelines and the increase in the incidence of IE. Moreover, increases in the number of IE were observed not only in the highest-risk group but also in the groups with moderate or lower
risk. The results from the United States and Europe other than the United Kingdom showed no consistent tendency in the increase or decrease in the incidence of IE before and after changes of the guidelines.\textsuperscript{56,229,232,238,240} For all of these results, the data regarding whether or not the amount of antibiotics prescribed decreased after revision of the guidelines are missing. Articles on the increase of IE before and after revision of the guidelines include reports on the increase of IE induced by oral streptococci, and a causal relationship with the presence or absence of antibiotic prophylaxis in dental procedures is suggested.\textsuperscript{231} On the other hand, another article suggests that IE induced by streptococci has not increased or has rather decreased, and thus consensus has not been achieved.\textsuperscript{238,244} The difference from the report from the United Kingdom may support the policy to continue antibiotic prophylaxis limited to the highest-risk group. However, it is also possible that the changes of the guidelines did not sufficiently modify the behaviors of physicians and dentists in the fields.\textsuperscript{245} In the United Kingdom, the awareness of the guidelines was high but the compliance rate was not as high as the awareness, and many physicians were thought to have continued antibiotic prophylaxis in spite of the new guidelines.\textsuperscript{239} This may be a reason why the increase of IE after the release of the guidelines remained small.

Antibiotic prophylaxis may not be able to prevent IE in some cases.\textsuperscript{240} Moreover, an estimation shows that antibiotic prophylaxis can prevent IE in only a very small number of cases.\textsuperscript{242} However, since IE causes a serious outcome once it has occurred, the effect on the patients’ life and economic impact are great even if the number of cases of successful prevention is very small.\textsuperscript{243} On the other hand, adverse events caused by antibiotic prophylaxis for IE have been extremely rare.\textsuperscript{241}

On the basis of the above considerations, the present guidelines recommend antibiotic prophylaxis for the highest-risk group. Moreover, considering the results showing that IE increased also in the patients at moderate or lower risk after discontinuation of antibiotic prophylaxis in the United Kingdom, and that IE induced by streptococci, which is resident bacterial flora in the oral cavity, increased in the United States and Europe other than the United Kingdom, the present guidelines also suggest antibiotic prophylaxis for the moderate-risk group. The number of patients with heart diseases classified into the moderate-risk group is huge, and cost-effectiveness of conducting antibiotic prophylaxis in all patients has not been established. However, once IE occurs, it may lead to hospitalization, surgery, cerebral infarction or death, and the impact on individual patients is tremendous. Although the possibility of leading to a serious outcome after the onset of IE is not very large in the moderate-risk group, it is advisable to prescribe antibiotic prophylaxis for each patient on the basis of thorough discussion with the patient. Adequate measures for preventing IE other than antibiotic prophylaxis, including maintenance of oral hygiene, and education for early detection are also important. We hope that this recommendation further improves the awareness of patients and health professionals about IE and its prevention.

\section{3.3 Skin Disease}
This section is omitted from the English version.

\section{3.4 Steroid Usage}
This section is omitted from the English version.

\section{3.5 Pneumonia and Other Remote Site Infection}
This section is omitted from the English version.

\section{3.6 Chronic Central Venous Catheter}
This section is omitted from the English version.

\section{3.7 Catheterization and Intracardiac Device Implantation}
This section is omitted from the English version.

\section{3.8 Prevention Before Respiratory, Esophageal, Gastrointestinal, Genitourinary Procedures}
This section is omitted from the English version.

\section{3.9 Cardiac Surgery}
This section is omitted from the English version.

\section{3.10 Education on IE in High-Risk Patients and Education on Measures for Coping With Pyrexia}
Moderate-risk or highest-risk patients should be instructed to voluntarily report to medical personnel that they have a risk of IE. Attending physicians need to notify to the patients the name of the underlying heart disease, presence or absence of intracardiac prostheses or pacemaker, and necessity of antibiotic prophylaxis. It is recommended to distribute a document like the one shown in Table \ref{table:example-document} to patients.

Moderate-risk or highest-risk patients should be instructed to consult a medical institution if pyrexia persists for 4 days or longer. The usefulness of oral antibiotics in the Table \ref{table:example-document}. Example of Document to be Distributed to High-Risk Patients for IE

\begin{table}[h]
\begin{center}
\begin{tabular}{|l|}
\hline
You have a heart disease which is prone to infective endocarditis (a condition in which bacteria growth on the valves and inner membranes inside the heart, and induce high fever, heart failure, brain stroke, and so on) \\
Therefore, \\
1. Appropriate prevention is necessary when you have your tooth extracted or pyorrhea incision. Be sure to notify it to your dentist and ask for appropriate prophylactic treatment \\
2. If you leave pyorrhea or dental caries reaching the tooth root untreated, you easily get infective endocarditis. You should consult dentists for regular check-up of your oral condition \\
3. Keep your mouth clean by regular tooth brushing and care of the gums, and receive appropriate guidance from dentists \\
4. Some procedures and surgery may cause infective endocarditis. Before the procedure or surgery, please inform your physician that you are prone to infective endocarditis \\
5. Do not take oral antibiotic drugs carelessly when you have high fever, when you cannot identify the cause of the fever, or when the fever cannot be resolved immediately. Consult with your cardiologist in such cases \\
\hline
\end{tabular}
\end{center}
\caption{Example of Document to be Distributed to High-Risk Patients for IE}
\label{table:example-document}
\end{table}

IE, infective endocarditis.
case of pyrexia is unclear, and it may lower the detection rate on blood culture. Daily oral and skin hygiene control is important for prevention of infection. It is also necessary to encourage them to visit dentists so that they can receive information regarding appropriate oral hygiene control. Since IE in the patients with atopic dermatitis becomes severe, consultation with dermatologists should also be considered.

IX. Management of Specific Situations

1. Congenital Heart Disease and Pediatric IE

1.1 General Remarks on Congenital Heart Disease and Pediatric IE

While the incidence of IE in general pediatric population is 0.34 to 0.64 per 100,000 person-year, which is lower than that in adults. However, the incidence becomes higher, 41 per 100,000 person-year, in the population with congenital heart disease. The percentage of the patients with congenital heart disease in the entire pediatric patients with IE is 30 to 80%.

The risks of IE in pediatric patients are (1) presence of congenital heart disease, (2) abnormal hemodynamics sustained after the surgical repair of congenital heart disease, and the presence of prostheses used in surgery, such as prosthetic valve and patch, (3) catheter placement in surgery, (4) decreased immune defense mechanism, and (5) susceptibility to infection with *Staphylococcus aureus*. The reasons for high risks of IE in patients with congenital heart disease are that they are susceptible to intimal damage caused by disturbed blood flow and jet lesion, and that bacteria are likely to adhere to the surface of prostheses used in surgical operation. Among disease groups, the higher incidence of IE is found in cases with heterotaxy syndrome especially in asplenia (right isomelism) which is prone to *Streptococcus pneumoniae* infection.

The most common causative microorganisms in pediatric cases is *Staphylococcus aureus*, followed by VGS and CNS in this order. Beyond that *Staphylococcus aureus* infection is common, the condition tends to become severe in pediatric age. Infection of placed catheter and nosocomial infection may also be caused by gram-negative bacteria and fungi.

1.2 Risks According to Underlying Heart Disease

In the AHA Guidelines, the group in which complications are likely to occur and the mortality rate is high is defined as the highest risk, and antibiotic prophylaxis is recommended only for this group. On the other hand, “Management and Prevention of Infective Endocarditis in Congenital Heart Disease and Pediatric Cardiac Disease” issued by the Japanese Society of Pediatric Cardiology and Cardiac Surgery classified the risks for each underlying heart disease into three groups, highest-risk, moderate-risk, and low-risk. Highest-risk is a group in which the condition is likely to occur and is likely to become severe, moderate-risk is a group in which the condition is likely to occur but the risk of becoming severe is low, and low-risk is a group in which the risk is almost the same as in the cases without the disease. Thus, antibiotic prophylaxis is recommended in the highest-risk and moderate-risk groups. This is because many of the patients with IE occurred after dental procedures were in the moderate-risk group according to

### Table 22. Risks of Infective Endocarditis in Pediatric/Congenital Heart Disease According to Underlying Heart Disease, Recommendations of Antibiotic Prophylaxis During Dental and Oral Surgical Procedures, and Level of Evidence

<table>
<thead>
<tr>
<th>Risk of infective endocarditis</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Highest risk: high incidence, morbidity and mortality of infective endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• After prosthetic valve surgery</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• History of IE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unrepaired cyanosis type congenital heart disease including palliative anastomosis and use of artificial blood vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Within 6 months after the repair of congenital heart disease using artificial materials regardless of surgery or catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cases accompanying residual lesions at the repair site in spite of repair with patch or artificial materials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aortic coarctation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate risk: lower morbidity and mortality despite high incidence of infective endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Congenital heart diseases except for those in the highest-risk group and the low-risk group (including bicuspid aortic valve)</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy with obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mitral valve prolapse with regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Low risk: No particular risk of infection, and almost the same risk of infection as ordinary people</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Isolated atrial septal defect of ostium secundum type</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>• Repaired ventricular septal defect or patent ductus arteriosus 6 months after surgery and without residual shunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• After coronary artery bypass surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mitral valve prolapse without valvar regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Physiological, functional or innocent cardiac murmur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• History of Kawasaki disease without valve dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See “CQ 5 Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for pediatric/congenital heart diseases?” for details about evaluation of evidence. IE, infective endocarditis.
the national survey in Japan.

In this revision, the risk classification of the Japanese Society of Pediatric Cardiology and Cardiac Surgery was followed, and antibiotic prophylaxis in dental procedures was strongly recommended for the highest-risk group, and weakly recommended for the moderate-risk group (Table 22) (Also see “[CQ 5] Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for pediatric/congenital heart diseases?”). Bicuspid aortic valve theoretically has a risk of IE if mild eccentric regurgitation is present even if stenosis is absent.

In the national survey of the Japanese Society of Pediatric Cardiology and Cardiac Surgery, 170 pediatric patients with IE included 23 patients who did not show underlying heart disease (14%). Therefore, IE should be considered in differential diagnosis in the cases of pyrexia of unknown causes even if underlying heart disease is absent.

### 1.3 Diagnosis

**a. General Remarks on Diagnosis of Congenital Heart Disease and Pediatric IE**

The modified Duke criteria for diagnosis (Table 4) is widely used in clinical settings because the sensitivity of diagnosis exceeds 70% even in pediatric cases although the early diagnostic accuracy is low. In imaging for diagnosis, not only TEE but also MRI, CT, and PET should be considered as useful modalities for pediatric cases. It is also a key to improve the accuracy and the detection rate of blood culture in pediatric cases, by setting the proper timing, method, frequency, number of specimens of blood sampling as well as the storing method during sample collection.

### Table 23. Recommendations of Antibiotics in Pediatric Infective Endocarditis and Level of Evidence

<table>
<thead>
<tr>
<th>Causative microorganisms</th>
<th>Antibiotics</th>
<th>In the case of allergy to penicillin</th>
<th>Administration period (weeks)</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ampicillin + Gentamicin</td>
<td>Vancomycin</td>
<td>Ampicillin: 4 Vancomycin: 4–6</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (meticillin-resistant)</td>
<td>Vancomycin (or Teicoplanin) + Gentamicin</td>
<td>Vancomycin</td>
<td>Vancomycin: 6–8 Gentamicin: 2 Teicoplanin: 6–8</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Daptomycin: 6–8</td>
<td></td>
<td></td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td>Gram-negative bacteria, <em>Enterobacteriaceae</em></td>
<td>Broad-spectrum cephems (cefepime, cefotaxime, cefazidime, ceftriaxone) +gentamicin</td>
<td>Broad-spectrum cephems: ≥6</td>
<td></td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td><em>Haemophilus</em> (HACEK)</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone: 4–6</td>
<td></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Ampicillin+gentamicin</td>
<td></td>
<td></td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Blood culture negative (postoperative cases)</td>
<td>Vancomycin ± gentamicin</td>
<td>Vancomycin: 6–8 Gentamicin: 2</td>
<td></td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td>Blood culture negative (non-postoperative cases)</td>
<td>Cefazolin+gentamicin ± penicillin G</td>
<td>Cefazolin: 6–8 Gentamicin: 2 Penicillin G: 6–8</td>
<td></td>
<td>Ilb</td>
<td>C</td>
</tr>
<tr>
<td>Fungi</td>
<td>Lipid amphotericin B</td>
<td>Lipid amphotericin B: 8</td>
<td></td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

**Daily dose for children with normal renal functions**

- **Ampicillin:** 50 mg/kg per dose, 4 to 6 times daily
- **Gentamicin**: 1 to 2.5 mg/kg per dose, 3 times daily
- **Sulbactam/ampicillin:** 50 mg/kg per dose, 4 to 6 times daily
- **Cefazolin:** 25 mg/kg per dose, 4 times daily
- **Cefepime:** 50 mg/kg per dose, 3 times daily
- **Cefotaxime:** 50 mg/kg per dose, 4 times daily
- **Cefazidime:** 50 mg/kg per dose, 3 times daily
- **Ceftriaxone:** 50 mg/kg per dose, twice daily
- **Daptomycin:** 6 mg/kg per dose, once daily (in the case of MRSA, 6 to 10/kg per dose, once daily)
- **Teicoplanin**: 10 mg/kg is administered three times at 12-hour intervals, followed by intravenous drip infusion of 10 mg/kg, once daily, over 30 minutes or more. Neonates are treated with intravenous drip infusion at the dose of 16 mg/kg only at the first dose, followed by drip infusion at the dose of 8 mg/kg/over 30 minutes or more.
- **Vancomycin**: 15 to 20 mg/kg per dose, 4 times daily (younger than 13 years), intravenous drip infusion over 1 hour
- **Penicillin G:** 50,000 unit/kg per dose, 4 to 6 times daily
- **Rifampicin:** 8 to 10 mg/kg per dose, twice daily
- **Lipid amphotericin B:** 2.5 to 5 mg/kg per dose, once daily

*Blood concentrations should be determined periodically for gentamicin and vancomycin (TDM: Therapeutic drug monitoring), and the doses and administration should be planned.

**Since the half-life of teicoplanin is long (approximately 50 hours), TDM should aim at the peak of approximately 40 \( \mu \)g/mL (25 mg/kg) and the trough of approximately 10 \( \mu \)g/mL (10 mg/kg), if possible.

IE, infective endocarditis.
transportation until conduct of the culture test.

b. Symptoms
This section is omitted from the English version.

c. Blood Culture
This section is omitted from the English version.

d. Echocardiography
This section is omitted from the English version.

e. Other Imaging Diagnosis
This section is omitted from the English version.

f. Evaluation of Complications (Heart Failure, Perivalvular Abscess, Embolism and Intracranial Complications)
This section is omitted from the English version.

## 1.4 Treatment

### a. Medical Treatment

The recommendations for adults should be basically followed in the choice of antibiotics in pediatric cases. Recommendations of antibiotic treatment in pediatric cases are shown in Table 23.

For IE caused by streptococci, the guidelines of the Japanese Society of Pediatric Cardiology and Cardiac Surgery recommends concomitant administration of penicillin G and aminoglycoside if the strain is non-sensitive to penicillin G (benzylpenicillin). The statement of AHA recommends administration of penicillin G alone or ceftriaxone alone to avoid adverse reactions to aminoglycosides in the cases sensitive to penicillin.

Although IE caused by enterococci is not common in pediatric patients, concomitant administration of penicillin and gentamicin is recommended in the case of strains sensitive to penicillin. Involvement of specialists of infection is desired in cases of resistant strains.

As antibiotic treatment for staphylococci, the AHA Statement recommends penicillin G for the strains sensitive to penicillin G, penicillinase-resistant penicillin (oxacillin and cloxacillin) for resistant strains, vancomycin for methicillin-resistant strains, and daptomycin for vancomycin-resistant strains. The guidelines of the Japanese Society of Pediatric Cardiology and Cardiac Surgery recommends cefazolin for methicillin-sensitive strains, and vancomycin for methicillin-resistant strains. Among the cases of MRSA infection, concomitant administration of anti-MRSA drug and other antibiotics such as rifampicin should be considered for IE in the prosthetic valve and the cases refractory to early treatment.

For antibiotic treatment in the cases negative on blood culture, the recommendations of the Japanese Society of Pediatric Cardiology and Cardiac Surgery should be followed. The AHA Statement recommends concomitant administration of sulbactam/ampicillin and gentamicin instead of cefazolin for non-postoperative cases of IE negative on blood culture.

### b. Surgical Treatment
This section is omitted from the English version.

## 1.5 Prevention

### a. Treatment Necessitating Prophylactic Measures and Current Status

The dental procedures necessitating prophylactic measures in the field of pediatrics are basically the same as the dental procedures for adults, although there are some unique points. Generally, the dental procedure which is most likely to induce bacteremia is tooth extraction. However, extraction of a primary tooth, which accompanies absorption of the root of the tooth, is not so invasive as extraction of a permanent tooth. Moreover, although bleeding may be observed when a primary tooth falls off, bacteremia is not considered in usual cases.

### b. Oral administration is possible

<table>
<thead>
<tr>
<th>Route</th>
<th>Allergy to β-lactam antibiotics</th>
<th>Antibiotics</th>
<th>Dose</th>
<th>Frequency of administration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Amoxicillin</td>
<td>50mg/kg (2g at maximum)</td>
<td>Single</td>
<td>1 hour before treatment</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Clindamycin</td>
<td>20mg/kg (600mg at maximum)</td>
<td>Single</td>
<td>1 hour before treatment</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Azithromycin</td>
<td>15mg/kg (500mg at maximum)</td>
<td>Single</td>
<td>1 hour before treatment</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Clarithromycin</td>
<td>15mg/kg (400mg at maximum)</td>
<td>Single</td>
<td>1 hour before treatment</td>
<td></td>
</tr>
</tbody>
</table>
| Oral administration is impossible

<table>
<thead>
<tr>
<th>Route</th>
<th>Allergy to β-lactam antibiotics</th>
<th>Antibiotics</th>
<th>Dose</th>
<th>Frequency of administration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Ampicillin</td>
<td>50mg/kg (2g at maximum)</td>
<td>Single</td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drug infusion over 30 minutes or more from the start of surgery</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Cefazolin</td>
<td>50mg/kg (1g at maximum)</td>
<td>Single</td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drug infusion over 30 minutes or more from the start of surgery</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Ceftriaxone</td>
<td>50mg/kg (1g at maximum)</td>
<td>Single</td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drug infusion over 30 minutes or more from the start of surgery</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Clindamycin</td>
<td>20mg/kg (600mg at maximum)</td>
<td>Single</td>
<td>Intravenous injection within 30 minutes after the start of surgery, or intravenous drug infusion over 30 minutes or more from the start of surgery</td>
<td></td>
</tr>
</tbody>
</table>
In March 2017, a questionnaire survey was conducted among all members with cooperation of the Japanese Society of Pediatric Dentistry. The results suggested that the dental procedure which may become a risk of IE is recognized on the basis of the degree of bacteremia, which is assumed to be induced by each treatment.

b. Recommended Prophylactic Measures and Recurrent Status

Table 24 shows the type and dose of antibiotics used in antibiotic prophylaxis for pediatric patients.*2,*26 The guidelines state that amoxicillin should be selected for the cases in which oral administration is possible, and that the drug should be orally taken at the dose of 50 mg per kg body weight (2 g at maximum) 1 hour before the procedure. How the antibiotics are used is discussed in detail in the section for adults.

The prevalence of neonatal heart diseases in Japan is reported to be approximately 1 out of 100 patients,*26 and general dental practitioners have many chances to encounter pediatric patients with a risk of IE. Further educational activities about the guidelines are important in order to enable all pediatric patients with a risk of IE to receive dental procedures with appropriate prevention of IE.

**CQ 5  Is antibiotic prophylaxis necessary for prevention of IE in dental procedures for pediatric/congenital heart diseases?**

**Answer:**
(1) Antibiotic prophylaxis is recommended before dental procedures inducing bacteremia, such as tooth extraction, in highest-risk patients with pediatric/adult congenital heart disease.*1

Strength of recommendation 1: Strongly recommended

Strength of body of evidence C (weak)

(2) Antibiotic prophylaxis is proposed before dental procedures inducing bacteremia, such as tooth extraction, in moderate-risk patients with pediatric/adult congenital heart disease.*2

Strength of recommendation 2: Weakly recommended (proposed)

Strength of body of evidence C (weak)

The highest-risk group (patients susceptible to infection whose condition becomes severe easily) includes the patients who have received bioprosthetic valve, prosthetic valve replacement including bioprosthetic valve and allo- geneic valve, patients with a history of IE, complex, cyanotic congenital heart disease, and patients created shunts between systemic and pulmonary circulation.

Moderate-risk group (patients whose condition is not always serious but who are likely to show endocarditis) includes most congenital heart diseases, acquired valvular diseases, hypertrophic obstructive cardiomyopathy, and mitral valve prolapse accompanying valvular regurgitation.

[Related section] “Chapter IX. 1. 2 Risks According to Underlying Heart Disease”, Table 22

Commentary:

There have been no randomized studies to conclude this question. Moreover, it is difficult to expect that a meaningful randomized study is conducted in the future because the incidence of the condition is low. After revision of the AHA Guidelines in 2007, antibiotic prophylaxis for IE was completely discontinued or was changed to the policy to administer the drugs only to highest-risk patients. Recently, the late-phase outcomes in adults after revision of the AHA Guidelines in 2007 have been reported. As described in the section for adults, the number of cases of IE increased in the United Kingdom after revision of the guidelines.*28 On the other hand, the risk of serious adverse reactions caused by a single dose of antibiotic prophylaxis is extremely low.*24 Considering these results, the present guidelines recommend antibiotic prophylaxis in dental procedures for adult highest-risk patients, and weakly recommends it to moderate-risk patients.

Concerning the changes of the incidence of IE after modification of the guidelines, the present systematic review found only two reports each from the United States and Canada regarding the study focused on pediatric/congenital heart disease.*23,*24 Moreover, the results did not demonstrate increases of IE after modification of the guidelines. However, these are not considered to demonstrate the uselessness of antibiotic prophylaxis for pediatric/congenital heart disease. According to a study using the database of the Canadian Institute for Health Information, inpatients with IE of the age younger than 18 years accounts for only 2.4% of all inpatients with IE, and there have been no reports of statistical analysis focused on the changes in the number of inpatients with IE aged younger than 18 years.*22 A study from the pediatric database in the United States incorporated only the data until the third year after modification of the guidelines, and it is considered to be too early to draw any conclusions.*23 Even after the modification of the AHA Guidelines, changes in the behaviors for antibiotic prophylaxis in actual clinical settings were not marked.*24

Because congenital heart disease is common among pediatric patients with IE and is likely to become serious, prophylaxis is believed to be more important than in adults.*25 Moreover, considering the reports that antibiotic prophylaxis in pediatric patients reduces bacteremia in tooth extraction,*26,*27 it has been decided to continue recommendation of antibiotic prophylaxis for the pediatric patients except for those in the low-risk group. It is strongly recommended for the highest-risk group, and weakly recommended for the moderate-risk group.

2. IE on Cardiac Devices

Along with the development of various cardiac implantable electronic devices (CIEDs) and the increasing number of patients with CIED, infection of CIED continues to increase every year.*27,*28 Since CIED infection can often become serious and fatal,*24 early diagnosis and appropriate decision of the treatment strategy are important.

a. Definition

Device-related infection can be classified into local device infection and cardiac device-related IE (CDRIE).*4 Local device infection is the infection localized to the pocket of the cardiac device, and local clinical findings of inflammation are present at the device implantation site.*25 On the other hand, CDRIE is a condition in which infection reaches the leads or endocardium including the cardiac valve leaflets.
b. Pathophysiology

The main route of CIED infection is the pocket infection during the process of implantation surgery, or percutaneous infection via the part where the device or the electrodes are exposed to skin surface. When inflammation reaches the cardiac chamber from the pocket infection via the intravascular portion of the electrode, IE occurs. The pocket infection or infection in the intravascular portion of the electrode can also occur in a secondary manner as a result of the bacteremia from the distant infected foci. Vegetation induced by IE can occur at any sites in the superior vena cava, tricuspid valve, right atrial wall, and right ventricular wall from the insertion vein. Septic pulmonary embolism is a frequent complication in association with the formation of vegetation.\textsuperscript{276}\textsuperscript{–}\textsuperscript{278} but it is often asymptomatic.\textsuperscript{279} The most common causative microorganisms is staphylococci in CDRIE.\textsuperscript{279}\textsuperscript{–}\textsuperscript{280} Polymicrobial infection is also sometimes identified as causative microorganisms.\textsuperscript{280}\textsuperscript{–}\textsuperscript{282}

c. Diagnosis

The most important thing is to suspect CIED infection first and perform necessary examinations when unexplained fever is observed in the patients with CIED. On the other hand, fever is often blunted in CDRIE, particularly in elderly patients. Thus, attention should also be paid to laboratory tests including the white blood cell count and increases of CRP. It should be noted that CDRIE may develop with respiratory symptoms or chest pain induced by septic pulmonary embolism.

Similarly to other cases of IE, diagnosis of CDRIE is based mainly on blood culture and echocardiography. Echocardiography is useful for evaluation of vegetation adhered to the electrodes and in the cardiac chambers. While TEE is considered to be superior to TTE in diagnosing CDRIE,\textsuperscript{280}\textsuperscript{–}\textsuperscript{285} better images may be obtained by TTE in some cases. Therefore, it is recommended to combine TTE and TEE for evaluation of vegetation. On the other hand, in some cases, vegetation may not be detected because of artifacts even if these two methods are used, or vegetation may not be evaluated adequately because it is located along the lead course.\textsuperscript{286}\textsuperscript{–}\textsuperscript{288} Intracardiac echocardiography is effective in such cases. If vegetation cannot be ruled out for the diagnosis in CDRIE suspected cases,\textsuperscript{289}\textsuperscript{–}\textsuperscript{291} Positive culture of intravascular electrode may support the diagnosis of CDRIE; however, the possibility of a pseudo-positive culture result cannot be ruled out, due to contamination from the skin or the wound site during the removal procedure of the lead. Using aforementioned imaging modalities enables evaluation of the location of inflammation in the lead, cardiac chamber or septic pulmonary embolism.\textsuperscript{37}\textsuperscript{–}\textsuperscript{290}\textsuperscript{–}\textsuperscript{291}

d. Treatment Strategy

The essential treatment strategy in CDRIE is continuous antibiotic therapy and complete removal of CIED including the leads. Antibiotic therapy should be started after blood culture and before removal of the device, and should be continued for at least 2 weeks, or for 4 to 6 weeks, if necessary, after removal of the device.\textsuperscript{4}

Table 25 shows the indication of CIED removal. Complete removal of CIED including the leads is recommended for all patients diagnosed as CDRIE (class of recommendation I). Medical treatment alone in CDRIE without removal of CIED is associated with high risk of recurrent IE and poor prognosis.\textsuperscript{292}\textsuperscript{–}\textsuperscript{294} On the other hand, removal of CIED by open heart surgery involves a high risk of perioperative mortality.\textsuperscript{291} Thus, percutaneous lead extraction with limited risks is recommended in the removal of infected CIED\textsuperscript{295}\textsuperscript{–}\textsuperscript{297} (Table 26). In cases more than 1 year after device implantation, percutaneous lead extraction by simple manual traction may be difficult because of strong adhesion of the lead to veins or myocardium or adhesion of multiple leads. In such cases, percutaneous extraction using excimer laser may be effective.\textsuperscript{298}\textsuperscript{–}\textsuperscript{300} Since percutaneous

<table>
<thead>
<tr>
<th>Table 25. Recommendations for Device Removal in CIEDs Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class of recommendation</strong></td>
</tr>
<tr>
<td>Complete removal of the device is recommended in patients diagnosed as definite CDRIE</td>
</tr>
<tr>
<td>Complete removal of the device is recommended in patients diagnosed as device local infection</td>
</tr>
<tr>
<td>Complete removal of the device should be considered in patients in whom CIEDs infection is strongly suspected and without other apparent sources of infection</td>
</tr>
<tr>
<td>Complete removal of the device may be considered in patients in whom IE infection of native valve or prosthetic valve was diagnosed but CIEDs infection is not definitive</td>
</tr>
</tbody>
</table>

CIEDs, cardiac implantable electronic devices; CDRIE, cardiac device-associated IE.

<table>
<thead>
<tr>
<th>Table 26. Recommendations for Method of Device Removal for CIEDs Infection and Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class of recommendation</strong></td>
</tr>
<tr>
<td>Percutaneous extraction of the device including the lead is recommended in patients diagnosed as CDRIE (including the cases with vegetation of 10 mm or larger)</td>
</tr>
<tr>
<td>Percutaneous extraction of the device including the lead is recommended in patients diagnosed as device local infection</td>
</tr>
<tr>
<td>Percutaneous extraction of the device should be performed at experienced centers where sufficient surgical back-up is available</td>
</tr>
<tr>
<td>Surgical removal of the device should be considered in patients diagnosed as CDRIE if percutaneous extraction of the device is expected to be difficult or impossible</td>
</tr>
<tr>
<td>Surgical removal of the device should be considered in patients diagnosed as CDRIE if concomitant surgical repair is required for destruction of valves or cardiac chambers</td>
</tr>
<tr>
<td>Surgical removal of the device may be considered in patients diagnosed as CDRIE with large vegetation of 20 mm or larger one</td>
</tr>
</tbody>
</table>

CIEDs, cardiac implantable electronic devices; CDRIE, cardiac device-associated IE.
Table 27. Recommendations for Re-Placement of CIEDs After Device Removal and Level of Evidence

<table>
<thead>
<tr>
<th>Clinical indication of the device implantation should be carefully re-evaluated after removal of the device</th>
<th>Class of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>If re-implantation of the device is considered to be necessary, antibiotic therapy should be continued and device implantation should be conducted after confirming that blood culture is negative and findings of inflammation have subsided</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>In patients requiring re-implantation of the pacemaker, the temporal pacing on the contralateral side may be considered until re-implantation</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Routine temporal pacing is not recommended after removal of the infected device</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

CIEDs, cardiac implantable electronic devices.

extraction of CIED may induce complications such as postoperative cardiac tamponade, it should be performed at experienced centers where sufficient surgical back-up is available in the cases of emergency. Surgical removal of CIED should be considered if percutaneous extraction is expected to be difficult or impossible. It also should be considered if concomitant surgical repair is required for destruction of valves or cardiac chambers. Since the patients having large vegetation are at a high risk of pulmonary embolism at percutaneous extraction, surgical resection of vegetation may be considered at the same time with surgical removal of CIED. On the other hand, septic pulmonary embolism is clinically asymptomatic in many cases, and clinical evidence is limited regarding the specific size of vegetation requiring surgery. Therefore, the present guidelines recommend surgical removal as Class IIb in the cases with a vegetation of 20 mm or larger and recommended percutaneous extraction as Class I in the cases with a vegetation of smaller than 20 mm according to the guidelines of ESC. However, surgical risk greatly depends on the individual condition of patients. It is essential to determine the method of device removal considering the procedural risks in each case.

e. Timing of Re-implantation of Device
Past history of CIED infection is associated with a high risk of recurrent device infection after re-implantation of the device. Therefore, clinical indication of CIED re-implantation should be carefully evaluated after removal of the device. Re-implantation should be performed at a timing when adequate infection control is obtained by antibiotic therapy. The device should be re-implanted on the contralateral side of the site of device infection. Surgical device implantation using the epicardial lead may be useful for preventing recurrence of infection. Leadless pacemaker is one of the options in the cases in which the risk of recurrence of pocket infection is high and VVI mode is indicated. Temporal pacing can become a risk factor for subsequent infection of re-implanted device and should be avoided if possible.

3. Right-Sided IE

This section is omitted from the English version.

4. IE in Pregnancy

While IE associated with pregnancy is extremely rare, the mortality rate of pregnant women and fetuses is very high. The risk factors for IE in pregnancy are maternal congenital heart disease and rheumatic heart disease. In Western countries, intravenous drug user is listed as a risk factor. Guidelines in Japan and abroad recommend antibiotic prophylaxis before delivery for pregnant women at high risk for IE. See “Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heat Disease” of The Japanese Circulation Society for specific prophylactic methods.

5. Non-Bacterial Thrombotic Endocarditis

This section is omitted from the English version.

6. IE in Elderly Patients

IE in elderly patients tends to increase. It is slightly more dominant in men, and infection with Staphylococcus aureus and healthcare-associated IE are common. The risk factors for IE in elderly patients tend to increase. The intestinal tract infections are likely to become the portal of entry of causative microorganisms. Since symptoms are atypical, the thresholds for blood culture and echocardiography could be set low. Vegetation is often small, and concurrent embolism is less frequent. The lesion is often difficult to visualize on echocardiography because of calcification of the valve. Since it has been reported that vegetation is small in IE in elderly patients and abscess is likely to occur concomitantly, TEE may be more useful than TTE. Contrast CT is often difficult because of poor renal functions, and abdominal ultrasonography and brain MRI may be needed instead.

The incidence of adverse reactions to antibiotics is high because of renal dysfunction. Renal dysfunction and cognitive impairment may occur concomitantly, and surgery is not conducted in many cases in spite of surgical indication. The in-hospital prognosis is comparable in elderly patients and non-elderly patients, but the prognosis after discharge from the hospital is worse in elderly patients because complications are more common.

Acknowledgments

We would like to thank the members of the Independent Assessment Committee, Directors of Cardiovascular Surgery, Kawasaki Medical School, and Kazuo Tanemoto (Department of Cardiovascular Surgery, Kawasaki Medical School).
References


and microbiological diagnosis of 19 infective endocarditis cases in which causative microbes were identified by PCR-based DNA sequencing from the excised heart valves. J Infect Chemother 2012; 18: 318–323. PMID: 22045162


Mehta S, Singh C, Plata KB, et al. β-Lactams increase the


Infect Dis 1994; 157 prophylaxis for endocarditis: What is the optimal dose?

JAMA 599 279: 1998; infective endocarditis after surgery for congenital heart defect.

Heart Association recommendations for antibiotic prophylaxis.

and impact on dental practitioners and patients of American

children and adult congenital heart disease (the second report).

Nakazawa M, Niwa K, Yoshinaga M, et al. The national survey

Can J Cardiol 894 28: 2012; of infective endocarditis.

Nakazawa M, Seguchi M, Takao A. The occurrence of newb

endocarditis prophylaxis recommendations on the practices of

American Heart Association Antibiotic Prophylaxis Guidelines.


Di Filippo S, Delahaye F, Semiond B, et al. Current patterns of

incidence and predictors.

J Pediatr 807 280. PMID: 25064162


Roberts GJ, Holzel HS, Sury MR, et al. Dental bacteremia in


Clinic Infective Endocarditis Investigators. The changing

epidemiology of infective endocarditis in the twenty-first century.


Yuan SM. Right-sided infective endocarditis: Recent epidemiolo-


2442708

Sridhar AR, Lavu M, Ylaragadva V, et al. Cardiac implantable

electronic device-related infection and extraction trends in the U.S.

Pacing Clin Electrophysiol 2017; 40: 286–293. PMID:

2808462

Sohail MR, Uslan DZ, Khan AH, et al. Management and

outcome of permanent pacemaker and implantable cardiover-


PMID: 17481444

Meier-Ewert HK, Gray ME, John RM. Endocardial pacemaker

or defibrillator lead-related infected vegetations: A single-center

experience and consequences of transvenous extraction. Am

Heart J 2003; 146: 339–344. PMID: 12891205

Klug D, Lacroix D, Savoye C, et al. Systemic infection related
to endocarditis on pacemaker leads: Clinical presentation and


pulmonary embolism in adults: A systematic review. Respir Med

2014; 108: 1–8. PMID: 24183289

Villamil Cajoto I, Rodriguez Framil M, Van den Eynde Collado
A., et al. Permanent transvenous pacemaker infections: An


17826260

Bongiorni MG, Tascini C, Tagliafierri E, et al. Microbiology of

cardiac implantable electronic device infections. Europace 2012;

14: 1334–1339. PMID: 22390207

del Rio A, Anguera I, Miró JM, et al. Hospital Clinic Infective


Satoshi Toyoda, Department of Cardiology, Tokyo Women’s Medical University

Members:

- Kyomi Ashihara, Department of Cardiology, Tokyo Women’s Medical University
- Masao Daimon, Department of Clinical Laboratory/Cardiology, the University of Tokyo
- Kiyoyuki Eishi, Division of Cardiovascular Surgery, Nagasaki University Graduate School of Biomedical Sciences
- Masahiro Higashi, Department of Radiology, National Hospital Organization, Osaka National Hospital
- Shiro Iwanaga, Department of Cardiology, Saitama Medical University International Medical Center
- Chisato Izumi, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center
- Toshimi Kimura, Department of Pharmacy, Tokyo Women’s Medical University Hospital
- Kotaro Mitsutake, Department of Infectious Diseases and Infection Control, Saitama Medical University International Medical Center
- Tomoaki Murakami, Department of Cardiology, Chiba Children’s Hospital
- Kazuhiko Nakano, Division of Oral Infection and Disease Control, Osaka University Graduate School of Dentistry
- Hiroyuki Nakase, Department of Neurosurgery, Nara Medical University
- Takahiro Ohara, Division of Community Medicine, Tohoku Medical and Pharmaceutical University
- Yutaka Okita, Cardio-Aortic Center, Takatsuki General Hospital
- Kazunori Toyoda, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center
- Satoshi Yasukochi, Heart Center, Nagano Children’s Hospital

Collaborators:

- Katsushito Fujii, Department of Cardiovascular Medicine, the University of Tokyo
- Takashi Miura, Division of Cardiovascular Surgery, Nagasaki University Graduate School of Biomedical Sciences
- Toshiro Morizane, Japan Council for Quality Health Care
- Ichiro Nakagawa, Department of Neurosurgery, Nara Medical University
- Ryota Nomura, Division of Oral Infection and Disease Control, Osaka University Graduate School of Dentistry
- Shuhei Okazaki, Department of Neurology, National Cerebral and Cardiovascular Center
- Haruo Sakamoto, Department of Oral and Maxillofacial Surgery, Tokai University Hachioji Hospital
- Hiroshi Tanaka, Department of Surgery, Division of Cardiovascular Surgery, Kobe University
Independent Assessment Committee:
• Makoto Akaishi, Department of Cardiology, Tokai University Tokyo Hospital
• Takashi Akasaka, Department of Cardiovascular Medicine, Wakayama Medical University
• Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University
• Junjiro Kobayashi, Department of Cardiac Surgery, National Cerebral and Cardiovascular Center
• Yutaka Otsuji, Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine
• Kazuo Tanemoto, Department of Cardiovascular Surgery, Kawasaki Medical School
(The affiliations of the members are as of January, 2019)

Appendix 2 Disclosure of Potential Conflicts of Interest (COI):
JCS 2017 Guideline on Prevention and Treatment of Infective Endocarditis in Japan

<table>
<thead>
<tr>
<th>Author</th>
<th>Employment or leading position (Private company)</th>
<th>Shareholder</th>
<th>Royalty of patent right</th>
<th>Remuneration</th>
<th>Payment for a manuscript</th>
<th>Provision of research fund</th>
<th>Scholarship donation / Endowed Chair</th>
<th>Other rewards</th>
<th>Declaration regarding spouse, relative in the first degree, or other persons sharing income/property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Team leader: Satoshi Nakatanji</td>
<td>Edwards Lifesciences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team member: Yutaka Okita</td>
<td>JMS Edwards Lifesciences TERUMO CORPORATION Medtronic Japan Japan Lifeline</td>
<td></td>
<td></td>
<td></td>
<td>St. Jude Medical</td>
<td></td>
<td>Century Medical, Inc. CSL Behring Senko Medical Instrument</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team member: Toshimi Kimura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meiji Seika Pharma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team member: Kazunori Toyoda</td>
<td>Daichi Sankyo Bayer Yakuhin Bristol-Myers Squibb Boehringer Ingelheim Takeda Pharmaceutical Company</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team member: Kotaro Mitsutake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Team member: Satoshi Yasukochi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Actelion Pharmaceuticals Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooperator: Katsuhito Fuji</td>
<td>Daichi Sankyo Medtronic Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notation of corporation is omitted. Nothing special to be mentioned for team members and cooperators other than those mentioned above.
Team member: Kyomi Ashihara, Absent
Team member: Chisato Izumi, Absent
Team member: Shiro Iwanaga, Absent
Team member: Kiyoyuki Eishi, Absent
Team member: Takahiro Ohara, Absent
Team member: Masao Daimon, Absent
Team member: Hiroyuki Nakase, Absent
Team member: Kazuhiko Nakano, Absent
Team member: Masahiro Higashi, Absent
Team member: Tomoaki Murakami, Absent
Cooperator: Shuhei Okazaki, Absent
Cooperator: Haruo Sakamoto, Absent
Cooperator: Hiroshi Tanaka, Absent
Cooperator: Ichiro Nakagawa, Absent
Cooperator: Ryota Nomura, Absent
Cooperator: Takashi Miura, Absent
Cooperator: Toshio Morizane, Absent