PSEHB/PED Notification No. 1023-3
October 23, 2017

To: Director of each prefectural department of health

Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW
(Official seal omitted)

Guideline for Clinical Evaluation of Antibacterial Drugs

A guideline for clinical studies of antibacterial drugs aimed to conduct for marketing approval has been provided through the PMSB/ELD Notification of "Guideline for Clinical Evaluation of Antibacterial Drugs" (Notification No. 743 by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW, dated August 25, 1998, hereinafter referred to as "Former GL Notification").

More than 15 years have passed since "Guideline for Clinical Evaluation of Antibacterial Drugs" was prepared. During this period, the number of new drug application and review process based on the result of simultaneous global drug development strategies has increased. In addition, the necessity of the convergence of the data requirement for antibacterial drug approval among regulatory authorities of Japan, Europe, and the US became to be recognized. Based on this situation, Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, prepared a new "Guideline for Clinical Evaluation of Antibacterial Drugs" as provided in the attachment.

This guideline provides basic concepts based on the knowledge of current scientific findings. Therefore, applicants may not necessarily follow the methods described in the guideline strictly as long as their alternative methods are properly rationalized by the advancement of academic knowledge. The same applies to the program endorsed by rational reasons, such as the clinical studies of which have already been initiated.

Hereby, on the premise of understanding descriptions above, please consider to inform sponsors under your jurisdiction of this notification.

Accordingly, the former GL Notification is repealed from today.

Attachment

Guidelines for Clinical Evaluation of Antibacterial Drugs

Table of Contents

Attachment: Applicable microorganism

[General statement]

1. Background and Positioning of This Guideline

Unlike other ordinary drugs that act directly on human cell, chief pharmacological action expected of antibacterial drugs is antibacterial activity against pathogenic bacteria. Consequently, the effects to host often means adverse effects. Because of these characteristics, antibacterial drugs need microbiological evaluation of causative bacteria as well as clinical evaluations including efficacy and safety evaluation based on the signs and symptoms of infectious diseases patients under the study drug administration.

Since 1998, clinical development of antibacterial drugs have been implemented based on the PMSB/ELD Notification of "Regarding Guidelines for Clinical Evaluation of Antibacterial Drugs" (Notification No.743 dated August 25, 1998). During this period, the trend of antibacterial drug development in Japan has been shifted from "broad-spectrum antibacterial drugs" to "antibacterial drugs targeting specific strain or infection", the trend of which does not necessarily suite the previous guideline. In addition, development of the new antibacterial drugs against globally emerging or re-emerging infectious diseases and infectious diseases caused by antibiotic-resistant bacteria has been desired in recent years. Based on this situation, the guideline is now revised with the cooperation of the Japanese Society of Chemotherapy, Update Committee for Guidelines for Clinical Evaluation of Antibacterial Drugs (Chairperson: Shigeru Kohno, Professor, Nagasaki University), in order to address current difficulties in clinical development of antibacterial drugs.

This guideline indicates comprehensive principles of clinical evaluation in the development of antibacterial drugs. Therefore, sponsors may not necessarily follow the guideline strictly as long as their programs are based on rationalized reasons, and flexible approach will be necessary.

This guideline covers ordinal pathogenic bacterium and does not include mycobacteria, fungi, or viruses. Specific discussion of applicable microorganism species and Evaluationology in each disease area are described in Appendix 1–15.

It should be also noted that, in principle, the implemental methods of nonclinical and clinical studies of pharmaceutical development process should follow the related laws and regulations including "Ministerial Ordinance on Good Clinical Practice for Drugs" (Ordinance of Ministry of Health and Welfare, No. 28 dated March 27, 1997. GCP: Good Clinical Practice), and guidelines provided by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

2. Nonclinical Evaluations

This guideline covers studies that demonstrate the efficacy of antibacterial activities and does not cover other secondary pharmacology studies, safety pharmacology studies, or toxicity studies. However, in case that the antibacterial activity of test drug is related to secondary pharmacology studies, safety pharmacology studies, or toxicity studies, guidance of those would be found in the following items.

2.1. Pharmacological Studies

2.1.1. Significance of Bacteriological Studies

The aims of bacteriological studies are to investigate the property of the test drugs as well as to explore those characteristics in antibacterial activity by *in vitro* studies and *in vivo* studies using infected animal model, in advance of administrating them to human. These studies are positioned as important nonclinical investigations that provide findings necessary to examine clinical efficacy.

The methodology of bacteriological studies vary depending on the property of test drug. However, investigations of the following items are recommended in general:

1) Measurement of drug susceptivity of various pathogenic bacterium.
2) Investigation of the mode of action and drug resistance mechanisms.
3) Investigation of the treatment and prophylactic effect on infectious diseases using infected animal models.
4) Others (Analysis of, post-antibiotic effect [PAE], intracellular transferability, pharmacodynamic [PD] interactions depending on the property of test drug)

Identifying the property of test drugs based on the results of bacteriological studies provide important information to consider those target indications and applicable microorganism as well as to prepare the clinical trial protocols. Regarding *in vivo* studies using infected animal models, those are positioned as studies to estimate clinical efficacy, and provide useful information for estimating clinical dose and dosing schedules. In addition, evaluating microbiological efficacies of test drugs based on the combination of bacteriological studies and pharmacokinetic (PK) assessments are useful for investigating those efficacies in rare infectious diseases and diseases with difficulty in conducting clinical evaluation.

2.1.2. *In vitro* Antibacterial Activity

Drug susceptibility of various pathogenic bacterium for test drug should be analyzed to confirm the *in vitro* antibacterial activity. The methodology for investigating minimum inhibitory concentration (MIC) of the test drug on the target species (standard species and fresh clinical isolates) are recommended to use the standard method of Clinical and Laboratory Standards Institute (CLSI) or the standard method of Japanese Society of Chemotherapy. Among various expected applicable microorganism, commonly isolated representative species should be investigated for the relationship between drug exposure time and viable cell counts (killing curve). Minimum Bactericidal Concentration (MBC) and Mutant Prevention Concentration (MPC) should also be investigated with necessity. In addition, analyzing the alteration of drug susceptibility depending on the culture conditions may be useful in estimating the effect of *in vivo* condition in infected host on antibacterial activity.

In the case setting the target values of PK/PD analysis for clinical trials, susceptibility distribution of target

species should be referred while considering the profile of test drug and characteristics of target diseases. In addition, setting of the break point will be useful as susceptibility /resistance cut off value with considering the susceptibility distribution and pharmacokinetic parameters. Likewise, break point of CLSI and European Committee on Antibacterial Susceptibility Testing (EUCAST) will become a reference in the case those values has been determined.

Regarding the data of test drug susceptibility, the latest antibiotic susceptibility data of clinical isolates are generally required, and applicable microorganism should be estimated by considering these antibiotic susceptibility data.

2.1.3. Mode of Action / Resistance Mechanism

2.1.3.1. Mode of Action

For drugs with novel chemical structure, clarification of the mode of action is important, since those investigation will provide useful information for the characterization of test drug in the course of clinical development.

As for the test drugs with known chemical structure, drug action on the known target proteins as well as binding affinity with them should be investigated, since those mode of action can be estimated by structure-activity relationships. In particular, for test drugs expected to have efficacy on bacterial strains resistant to pre-existing antibiotics, investigating the difference of mode of actions from those pre-existing drugs is important. Additionally, revealment of the property of pharmacological action of test drugs will be useful by analyzing the morphological changes of bacterium exposed to drugs.

2.1.3.2. Information on Acquisition of Resistance

For investigating the resistance mechanisms for the test drug, analyzing the incidence of resistant bacteria *in vitro*, as well as comparing mechanisms of resistance in test drugs with known resistance mechanisms are useful to predict the potential to develop and spread resistance to the test drug. In the case that study drug may have MPC for certain bacterial strains, analysis of Mutant Selection Window (MSW) will be useful in relation with pharmacokinetic evaluation. When comparing the mechanisms of drug resistance with known mechanisms, analysis of the presence of cross-resistance between antibacterial drugs of same or different classes are useful, along with the investigations including examination of the possibility of enzymatic inactivation, analysis of the presence of the drug efflux mechanisms and performing microbiological analysis aimed to explore resistance transfer. In addition, information necessary to prevent the development of resistance to test drugs should be acquired based on the results of above analyses.

2.1.4. *In vivo* Studies

For infected animal model studies, investigation of the efficacy, safety, and PK/PD using available disease models such as sepsis models, respiratory infection models are useful. In advance of the investigational study using infected animal models, PK study of test drug in same animal species is necessary. Together with the information of secondary pharmacological effects other than antibacterial activity and safety information obtained from nonclinical studies, investigating PK of test drug in animals will provide useful information in estimating the clinical efficacy and safety as well as PK in human. Based on the results of these studies, the target bacterial species and disease for clinical evaluation should be considered.

Additionally, investigating the synergism with host immunity and the transferability to inflammatory cells as well as examinating the association of these results with the findings obtained from infected animal model

studies may provide useful information to support the efficacy of test drugs in clinical trials.

2.1.5. Others

Useful information may also be obtained from following studies according to the property of study drug.

2.1.5.1. Postantibiotic Effect, Post-sub-MIC Effect

According to the drug characteristics, postantibiotic effect (PAE) and post-sub-MIC effect should be examined. For study drugs that have PAE *in vitro*, it is desirable to investigate those *in vivo* efficacy and PAE in infected animal models, such as thigh infection models, and estimate those influence on clinical efficacy by combining the result of PK/PD analysis.

2.1.5.2. Intracellular Transferability

Regarding study drugs targeting intracellular parasites, information on intracellular transferability or intracytoplasmic concentration is useful.

2.1.5.3. Combination Effect

Regarding study drugs (or other antibacterial drugs) that may affect the efficacy of other antibacterial drugs (or study drug) based on those mode of action, analyses of the PD interactions (synergistic effect, additive effect, inhibitory effect) are useful as study drugs may be administrated in combination with other antibacterial drugs in the clinical practice.

3. Clinical Evaluation

This section describes the points to consider when conducting clinical trials in Japan (including international collaborative clinical trials participated from Japan). Note that even in such development strategy, available information may be obtained from the results of foreign clinical trials.

When utilizing the results of foreign clinical trials, methodology for those usage should be discussed after considering the timing of the foreign clinical trials, intrinsic and extrinsic ethnic factors (See "Ethnic Factors in the Acceptability of Foreign Clinical Data" (Notification No.672 of the Evaluation and Licensing Division [ELD], the Pharmaceutical and Medical Safety Bureau [PMSB] dated August 11, 1998) and "Basic principles on Global Clinical Trials" (Notification No.0928010 of the ELD, the Pharmaceutical and Food Safety Bureau [PFSB] dated September 28, 2007)).

In the development program of antibacterial drugs which utilize results of foreign clinical trials, the information of pathogenic bacterium isolated from target disease and bacterial susceptibility of those in both inside and outside Japan should also be considered. Additionally, international, collaborative studies that cover the areas with high incidence of specific pathogenic bacteria, resistant strains, or diseases may enable to evaluate the drug efficacy on rare pathogenic bacteria and diseases in Japan.

3.1. Clinical Trials

Clinical evaluation of the efficacy and safety of test drug should be based on the results of clinical trials shown below. Additionally, accumulating data necessary for conducting PK/PD analysis should be considered. The clinical trial protocol proceeding to the next stage should be prepared carefully all after the detailed examination of safety information obtained from nonclinical studies and efficacy and safety results obtained from previous clinical trials. The sample size in each trial is recommended to be set by considering the trial feasibility and consulting with the Pharmaceuticals and Medical Devices Agency.

3.1.1. Phase I Studies

A phase I study is a clinical trial aimed to investigate the clinical safety margin and PK. In a single dose study, evaluation of the blood concentration of test drug and observation of the occurrence of adverse events and abnormality of laboratory examination should be done as well as investigating the relationship between adverse events and dose of test drug. The dosage should be estimated based on the nonclinical assessments of animal PK studies and drug sensitivity of assumed targeted bacterial species along with PK/PD in human, and tolerability of test drug should be confirmed in the dose exceeding the estimated maximum clinical dose.

A repeated dose study is conducted to examine the blood concentration of test drug under administrating expected recommended clinical dose and maximum clinical dose, as well as to observe the occurrence of adverse events and laboratory abnormalities. Additionally, in the case that the test drugs potentially have extensive influence on the intestinal flora, those effect on the intestinal flora should also be investigated. Ideally, the treatment duration of repeated dose study should be determined as the duration enable to estimate steady-state blood concentration of the test drug. Nevertheless, in determining treatment duration, characteristics of the test drug, property of target disease and usage of drug in clinical practice should be also be considered.

3.1.2. Phase II Studies

A phase II study is a clinical trial aimed to estimate the clinical dose of the test drug for patients with infectious diseases. Dosage and administration of the test drug should be considered based on the result of PK/PD analysis in nonclinical studies, PK data and incidence of adverse events in the phase I studies. If the results of clinical trials that have already been conducted outside Japan are available, a clinical trial aimed to determine dosage and administration for Japanese patients may be omitted based on the premise that similarity of PK data obtained from the clinical pharmacology study (phase I study) between Japanese and non-Japanese subjects has been confirmed, and that the drug susceptibility of target bacterial species is estimated to be similar between inside and outside Japan. However, in such a case, PK in Japanese patients should be investigated in the phase III study to confirm the appropriateness of selected dosage and administration.

3.1.3. Phase III Studies

A phase III study is a clinical trial aimed to investigate efficacy and safety of the study drug in the patients with infectious disease.

3.1.3.1 Clinical Development plan aimed for One Disease Area of Indication

In principle, a randomized, double-blind, parallel group, comparative study should be conducted to demonstrate non-inferiority or superiority to an appropriate control for representative disease with the largest patient population of specific disease area which is planned to obtain approval for indication. However, this does not necessarily apply to disease area with difficulty in conducting randomized, double-blind, parallel group, comparative study base on the reasons that the patient population is extremely limited even in the representative disease, and so on. Additionally, an open-label, uncontrolled study may suffice for the related disease of same disease area if substantial data are expected to be acquired from the study of representing disease, and those data can be applied to corresponding related disease based on scientific evidence. In such a case, study protocol and plocedure should be planed to minimize the bias in the evaluation of efficacy and safety. In addition, sample size in the comparative study should be determined to demonstrate non-inferiority or superiority to an appropriate control, and to be sufficient for evaluating the safety of test drug.

3.1.3.2 Clinical Development plan aimed for the approval of More Than One Disease Area of Indication, or wide range of Applicable Microorganism

In the case that the clinical development programs planned to obtain approval for two or more indications (e.g., respiratory infections and genitourinary tract infections) or the programs planned to obtain approval for the wide range of applicable microorganism, points to be noted are as same as the clinical development plan aimed for one desease area of indication.

3.1.3.3 Others

To develop switch therapy from IV therapy to oral administration, conduction of clinical trials aimed to evaluate those efficacy and safety should be considered.

3.2. Studies in Special Populations

Special study populations include pregnant women, nursing women, low birth weight infants, newborns, infants, small children, children, elderly, and patients with hepatic or renal disorders.

For clinical studies in elderly, see notifications and related documents including "Studies in Support of Special Populations: Geriatrics" (Notification No. 104 of the New Drug Division, the Pharmaceutical Affairs Bureau [PAB] dated December 2, 1993), and "Questions & Answers (Q&A): "Studies in Support of Special Populations: Geriatrics" (Office Communication of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated September 17, 2010).

As for clinical studies in pediatric patients, see "Clinical Investigation of Medicinal Products in the Pediatric Population" (Notification No.1334 of the ELD, PMSB dated December 15, 2000) and "Questions & Answers (Q&A): "Clinical Investigation of Medicinal Products in the Pediatric Population" (Office Communication of ELD, PFSB, MHLW dated June 22, 2001).

3.2.1. Pregnant Women

Generally, pregnant women should be excluded from clinical trials of the test drugs except for the drugs principally aimed to use during pregnancy. If a subject becomes pregnant, or pregnancy is suspected during the administration of the test drug, the drug should be discontinued immediately. In such a case, outcome of the pregnancy, fetus and neonate must be followed up. Similarly, in the case that pregnant women participate in a clinical trial of an test drug to be used during pregnancy, the outcome of the pregnancy, fetus and neonate must be followed up.

3.2.2. Nursing Women

Excretion of test drug or its metabolite into breast milk should be investigated where necessary. If nursing women participate in a study, nursing should be suspended temporarily in consideration of the influence of test drug on breast-fed babies.

3.2.3. Patients with Hepatic or Renal Disorders

For test drugs mainly excreted by the kidney, the influence of the severity of renal impairment and dialysis on PK should be clarified.

Similarly, for test drugs metabolized mainly in liver, conduction of PK study in patients with hepatic disorder should be considered, in particular of the test drugs metabolized by oxidation in the liver and the drugs whose metabolite has pharmacological activity.

3.3. Method of Clinical Trials

3.3.1. Inclusion Criteria

To clarify subject population for the clinical trial, the inclusion criteria such as target disease, the severity of infectious disease, age, sex, pregnancy status, and patient status (inpatient/outpatient) should be clearly indicated in the study protocol.

3.3.2. Exclusion Criteria

Exclusion criteria and relevant procedures should be clearly indicated in the study protocol by anticipating various situations. The following items can be used for reference to prepare the exclusion criteria, while the criteria should be established according to the characteristics of the test drug to be developed.

- Patients with a history of serious adverse reactions possibly associated with antibacterial drugs which belongs to the same class as the study drug (including control drug in case of comparative studies)
- Patients receiving a drug known to have negative influence on efficacy and safety profile of the test drugs, such as a drug which have excessive influence on the PK of the test drug (including control drug in case of comparative studies), or a drug of which coadministration of test drugs is known to amplify the toxicity of the drug.
- Patients with infectious disease apparently caused by the bacterial species insusceptible to the test drug (including control drug in case of comparative studies) and the efficacy of those study drugs can hardly be expected
- Patients who are difficult to complete clinical trial safely or to be evaluated clinical efficacy appropriately, including patients expected to have poor prognosis, patients with serious or progressive underlying disease, and patients with complicated disease
- Patients whose symptoms are resolving due to other antibacterial drugs or patients whose outcomes cannot be assessed. (excluding the study protocol for switch therapy, switching to oral administration after IV therapy of test drug.)

3.3.3. Clinical Evaluation

The study protocol should clearly indicate the schedule for evaluating efficacy, safety, and PK. Examination items on each Timing of Evaluation should also be clarified. The examination items and Timing of Evaluation should be specified while considering the characteristics of the test drug and the pathophysiology of target infectious disease. For efficacy evaluation, it is recommended to employ multiple evaluation items including clinical efficacy immediately after the drug administration, clinical efficacy based on the clinical symptoms and the laboratory examination in a certain period after the end of administration (Test of cure), microbiological efficacy at the end of administration or at the time of test of cure. In case these data are utilized for evaluating efficacy of the test drug, they should ideally be specified as evaluation items in the study protocol beforehand.

4. Utilization of Foreign Clinical Data

In the case utilizing foreign clinical data, see "Handling of Data on Clinical Trials on Drugs Performed in Foreign Countries" (Notification No.739 of the PMSB dated August 11, 1998), "Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data" (Notification No.672 of the ELD, PMSB dated August 11, 1998), "Q&A: 'Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data'" (Office Communication of ELD, PFSB, MHLW dated February 25, 2004), and "Q&A: 'Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data' (Part 2)" (Office Communication, ELD, PFSB, MHLW dated October 5, 2006).

As acquisition of all information related to the safety and efficacy of test drug during development before marketing is difficult, information should be continuously gathered even after the approval, on the condition that the information acquired before approval are summarized. Such information include data of alteration of the susceptibility of the applicable microorganism.

For post-marketing pharmacovigilance activities, see "Risk Management (RMP) Guidance" (Notification No.0411-(1) of the Safety Division of PFSB and No. 0411-(2) of the Evaluation and Licensing Division of PFSB both dated April 11, 2012).

5. Safety Evaluation

For safety evaluation, see "Safety Assessment Standards for Antimicrobial Drugs" provided by the Public interest incorporated association Japanese Society of Chemotherapy.

6. Reference

Guidelines for clinical trials

http://www.pmda.go.jp/int-activities/int-harmony/ich/0070.html

http://www.ich.org/products/guidelines.html

Major ICH guidelines (International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)

E4: Dose-Response Information to Support Drug Registration (Notification No. 494 of the Evaluation and Licensing Division [ELD], the Pharmaceutical Affairs Bureau [PAB] dated July25, 1994)

E5(R1): Handling of Data on Clinical Trials on Drugs Performed in Foreign Countries (Notification No.739 of the Pharmaceutical and Medical Safety Bureau [PMSB] dated August 11, 1998), Ethnic Factors in the Acceptability of Foreign Clinical Data (Notification No.672 of the ELD, PMSB dated August 11, 1998)

Q&A: 'Ethnic Factors in the Acceptability of Foreign Clinical Data' (Office Communication of the ELD, Pharmaceutical and Food Safety Bureau [PFSB], Ministry of Health, Labour and Welfare [MHLW] dated February 25, 2004)

Q&A: 'Ethnic Factors in the Acceptability of Foreign Clinical Data' (Part 2) (Office Communication of the ELD, PFSB, MHLW dated October 5, 2006)

E6(R1): Ministerial ordinance on Good Clinical Practice for Drugs (Ordinance of the Ministry of Health and Welfare No. 28 dated March 27, 1997), Enforcement of Ministerial ordinance on Good Clinical Practice for Drugs (Notification No.430 of the PAB dated March 27, 1997)

E7: Studies in Support of Special Populations: Geriatrics (Notification No. 104 of the New Drugs Division, PAB dated December 2, 1993)

E8: General Considerations for Clinical Trials (Notification No.380 of the ELD, PMSB dated April 21, 1998)

E9: Statistical Principles for Clinical Trials (Notification No.1047 of the ELD, PMSB dated November 30, 1998)

E10: Regarding 'Choice of Control Group in Clinical Trials' (Notification No.136 of the ELD, PMSB dated February 27, 2001)

E11: Clinical Investigation of Medicinal Products in the Pediatric Population (Notification No.1334 of the ELD, PMSB dated December 15, 2000)

Questions and answers (Q&A): Clinical Investigation of Medicinal Products in the Pediatric Population (Office Communication of the ELD, PFSB, MHLW dated June 22, 2001)

M3 (R2): Regarding 'Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals' (Notification No. 0219-4 of the ELD, PFSB dated February 19, 2010)

S7A: Safety Pharmacology Studies for Human Pharmaceuticals (Notification No.902 of the ELD, PMSB dated June 21, 2001)

S7B: The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval

Prolongation) by Human Pharmaceuticals (Notification No. 1023-4 of the ELD, PFSB dated October 23, 2009)

Others

Clinical Pharmacokinetic Studies on Drugs (Notification No.796 of the ELD, PMSB dated June 1, 2001)

Methods of Investigating Drug Interactions (Notification No.813 of the ELD, PMSB dated June 4, 2001)

Points to be considered by the Review Staff Involved in the Evaluation Process of New Drug (FINAL) (April 17, 2008<https://www.pmda.go.jp/files/000153830.pdf>)

Basic Principles on Global Clinical Trials (Notification No.0928010 of the ELD, PFSB dated September 28, 2007<https://www.pmda.go.jp/files/000157900.pdf>)

Clinical Trials That Use Pharmacogenomics (Notification No.0930007 of the ELD, PFSB dated September 30, 2008)

Guideline for PK/PD of Antibacterial Drugs' (Notification No. 1225-10 of the Pharmaceutical Safety and Environmental Health Bureau dated December 25, 2015)

Risk Management Guidance (Notification No. 0411-(1) of the Safety Division of PFSB and No.0411-(2) of the ELD of PFSB both dated April 11, 2012)

Japanese Society of Chemotherapy: Safety Assessment Standards for Antibacterial Drugs (Japanese Journal of Chemotherapy 2010; 58. 484-93)

Guidance for the Clinical Evaluation of Sepsis/Infective Endocarditis

1. Object

"Sepsis" in this guideline is defined as a pathological condition in which systemic inflammation occurs with bacteremia.

1.1. Major Target Species

Major causative bacteria of sepsis include *Staphylococcus* sp., *Enterococcus* sp., *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., and *Pseudomonas aeruginosa,* etc.

Major causative bacteria of infective endocarditis include *Streptococcus* sp. and *Staphylococcus* sp., but the target species should be determined according to characteristics of the antibacterial drug.

1.2. Target Diseases

Sepsis and infective endocarditis potentially caused by the above bacteria

2. Inclusion Criteria/Exclusion Criteria

2.1. Inclusion (diagnosis) Criteria

2.1.1. Sepsis

Target patients are those with bacteremia has been proven by culture or gram-staining of a blood specimen collected through a non-catheter route at least once, and the pathological condition is not complicated by endocarditis.

If indigenous dermal bacteria (coagulase-negative *Staphylococcus*, *Bacillus* sp., *Corynebacterium* sp., etc.) are detected, bacteremia should be proven by different specimens at least twice.

2.1.2. Infective Endocarditis

Target patients are those who meet any of the following criteria.[1)]

1) Target patients are those with infective endocarditis in whom a vegetation is found by echocardiography (for patients who have undergone prosthetic valve replacement, transesophageal echocardiography is desirable), and bacteremia has been proven by culture or gram-staining of a blood specimen collected through a non-catheter route at least once.
2) Target patients are those with infective endocarditis in whom a cardiac disease is underlying with symptomatic bacterial arterial embolism, subungual or mucosal bleeding points, immunoreaction (Osler's node, etc.), or focal findings, and bacteremia has been proven by culture or gram-staining of a blood specimen collected through a non-catheter route at least once.

2.2. Exclusion Criteria

1) Patients who are not suitable for clinical evaluation of the antibacterial drug due to an extremely serious underlying disease and infection, or who are not expected to survive the study period (septic shock, etc.).
2) Patients with infectious mononucleosis.

3) Patients with cystic fibrosis.

3. Dosing Methods and Treatment Duration

Doses, dosing interval, and treatment duration should be determined according to characteristics of the antibacterial drug to be developed. In principle, clinical response of the test drugs should be able to be assessed after administrating them for at least the first 3 consecutive days.

4. Timing of Evaluation and Observations

4.1. Timing of Evaluation

Evaluation should be made not only at the end of treatment but also 4 weeks after the end of treatment (Test of Cure). Usually, cure assessment is performed at the later timepoint. The following observation of signs and symptoms and laboratory test should be performed on each observation day.

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

4.1.2. During Treatment

Evaluation should be made 3, 7, and 14 days after the first dose (Days 3, 7, and 14) and then at an interval of 1 week, if the treatment duration extends beyond 21 days.

4.1.3. End of Treatment (0 to 3 days after the end of treatment)

The efficacy and safety at the end of treatment should be evaluated. When treatment is discontinued or terminated in response to cure or resolution within the specified number of days, observations applicable at this timing should be assessed.

4.1.4. Test of Cure (4 weeks after the end of treatment)

At this timing, whether the target disease is cured or not should be assessed. In foreign countries, this timing is deemed as the primary evaluation timepoint and thus critical for comparison with foreign data.

4.2. Observations

4.2.1. Symptoms and Findings

Clinical symptoms and findings, vital signs, hematology tests, blood biochemistry tests, urinalysis, blood culture, etc. should be followed for any change with time. In addition, endotoxin, etc. may be followed where necessary. In patients with infective endocarditis, vegetation should be followed by echocardiography.

Clinical symptoms and findings should be observed every day until the end of treatment wherever possible. Body temperature should be measured twice daily wherever possible.

4.2.2. Collection of Specimens for Microbiology Test

Blood specimens for microbiology test should be collected before treatment and at the end of treatment (and during the treatment period where necessary).

5. Evaluation

5.1. Clinical Efficacy

5.1.1. Sepsis

1) The clinical efficacy at the end of treatment should be assessed based on changes in clinical symptoms and findings (body temperature, pulse, respiratory rate, white blood cell count, differential white blood cell count, CRP, etc.).
2) In Test of Cure, the result is assessed as “Cure,” “Failure,” or “Indeterminate.” The clinical efficacy is the most important efficacy endpoint followed by the microbiological efficacy.

5.1.2. Infective Endocarditis

1) The clinical efficacy at the end of treatment should be assessed based on changes in clinical symptoms and findings (body temperature, pulse, respiratory rate, white blood cell count, differential white blood cell count, CRP, and vegetation by echocardiography, etc.).
2) In Test of Cure, the result is assessed as “Success,” “Failure,” or “Indeterminate.” The clinical efficacy is the most important efficacy endpoint followed by the microbiological efficacy.

5.2. Microbiological Efficacy

The microbiological efficacy should be assessed at the End of Treatment and Test of Cure in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

In patients with mixed infection, the microbiological efficacy on individual microorganisms should be separately evaluated.[2)] For evaluation of relapse or reinfection, specimens for culture after starting treatment should be collected when the antibacterial drug is not present at high concentrations in blood, tissue, or body fluid.

6. References

1) Beam Jr TR, Gilbert DN, Kunin CM: General guidelines for the clinical evaluation of anti-infective drug products. Clin Infect Dis 1992; 15(Suppl 1): S5-S32
2) Li JS, Sexton DJ, Mick N, et al.: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30: 633-638

Guidance for the Clinical Evaluation of Skin and Soft Tissue Infection

1. Introduction

While skin and soft tissue infections are generally treated by various medical specialities including surgery and dermatology, clinical trials for those in the past were conducted by two medical speciality groups in Japan. Generally, trials of orally administrated antibiotics indicated for the treatment of skin infectious diseases are conducted by dermatologist, and trials of injectable antibacterial drugs for secondary infections associated with injury, burn, and surgical wounds are conducted by the medical speciality group including surgery and emergency medicine. Consequently, clinical response of the study drugs have been assessed based on the evaluation criteria developed individually by both groups, and drug approval application have been done by consolidating these results. Therefore, revision of the guidance this time was done under assumption of preparing clinical trial (controlled trial) protocol for treating skin and soft tissue infections in Japan

2. Object

2.1. Major Target Species

Major causative bacterium of skin infections mainly involving dermis and/or subcutaneous tissue include *Staphylococcus* sp., *Streptococcus* sp., etc. Major causative bacterium of secondary infection associated with injury, burn, and surgical wound include *Staphylococcus* sp., *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., *Pseudomonas aeruginosa*, *Peptostreptococcus* sp., *Bacteroides* sp., etc.

2.2. Target Diseases

- Skin infections mainly involving dermis and/or subcutaneous tissue
- Secondary infections associated with injury, burn, surgical wound, etc.

3. Inclusion Criteria/Exclusion Criteria

3.1. Inclusion (Diagnostic) Criteria

3.1.1. Skin infections mainly involving dermis and/or subcutaneous tissue

1) Patients with apparent infectious signs including redness, swelling, spontaneous pain/tenderness of skin.[1)]
2) Patients who have at least one of the following systemic inflammatory findings, a. Elevated body temperature (Over 37.0°C at axillary temperature), b. Abnormal white blood cell count (Above or below normal range), and c. CRP (Above normal range).

3.1.2. Secondary infection associated with injury, burn, surgical wound, etc.

Patients who have at least 2 of the following 6 local findings in the lesion,[2)] a. Redness, b. Spontaneous pain/tenderness, c. Bogginess, d. Warmth, e. Swelling/induration, f. Pustular discharge/exudate, as well as at least 1 of the following systemic inflammatory findings, a. Elevated body temperature (Over 37.0°C at axillary temperature), b. Abnormal white blood cell count (Above or below normal range), and c. CRP

(Above normal range).

3.2. Exclusion Criteria

1) Patients accompanied with osteomyelitis or infectious arthritis.[3)]
2) Patients with infections due to unremovable implanted foreign bodies.[3)]
3) Patients with multiple infectious ulcers. [4)]
4) Patients who are unsuitable for clinical evaluation of the antibacterial drugs due to the extremely serious underlying diseases or infectious diseases.

4. Dosing Methods and Treatment Duration

Doses, dosing interval, and treatment duration should be determined according to the characteristics of test drugs to be developed. In principle, clinical response of the test drugs should be able to be assessed after administrating them for the initial 3 consecutive days at the minimum.

5. Timing of Evaluation and Observations

Observation of the following clinical findings, symptoms and laboratory findings should be performed on each evaluation date.

5.1. Timing of Evaluation

5.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

5.1.2. Three Days after the First Dose (Day 3)

The observation on 3 days after the first dose (Day 3) is critical to make a decision on continuing treatment with the test drug or not. In the case that signs and symptoms are not resolving, clinical investigators are required to make an appropriate decision including termination of the clinical trial and switching to other antibacterial drugs, in due consideration of patient's pathophysiological condition.

5.1.3. Seven Days after the First Dose (Day 7)

When the treatment duration is extended to 8 days or longer, clinical course of patients under treatment should be observed on Day 7.

5.1.4. End of Treatment (day of the end of treatment to 2 days after that)

The efficacy and safety of study drugs should be evaluated at the end of treatment. In addition, when treatment is discontinued or terminated within the specified period because of cure or resolution, the observations applicable at this timing should be assessed.

5.1.5. Test of Cure (7 to 14 days after the end of treatment)

At this point, whether the target disease is cured or not should be evaluated.

5.2. Observations

5.2.1. Signs and Symptoms

Signs and symptoms of study subjects should be observed on the evaluation date specified in "5.1 Timing of Evaluation".

5.2.2. Collection of Specimens for Microbiological Test

Desirably, collection of specimens (exudate or pustule from the infection site) should be done in advance of the administration of study drugs, and conduct appropriate aerobic and anaerobic cultures as well as perform susceptibility tests. In the cases of skin disease, specimens collected from infectious sites can be easily contaminated with non-targeted bacterium. Therefore, specimens may be collected by appropriate methods other than using swab testing (such as needle aspiration) where necessary. In addition, gram staining may be performed where necessary.

6. Evaluation

6.1. Clinical Efficacy

6.1.1. Clinical Efficacy at the End of Treatment (End of Treatment)

The clinical efficacy should be evaluated based on the changing of respective signs and symptoms from the baseline to the end or discontinuation of the administration.

6.1.2. Efficacy Evaluation at the time of Test of Cure

The efficacy should be assessed at the period of Test of Cure based on the following criteria.

	Definition
Cure:	Signs and symptoms attribute to the target disease have resolved or improved, and no longer require treatment with antibacterial drugs for the target disease.
Failure:	- The condition that the signs and symptoms persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease. - The patient died from the target disease.
Indeterminate:	- Information of signs and symptoms are missing, for reasons such as the non-attendance of subject at the date evaluating Test of Cure. - Cases where other antibacterial drugs have been administrated (systemically) for a disease other than the target disease before the end of treatment, even though the signs and symptoms attribute to the target disease had resolved or improved.

6.2. Microbiological Efficacy

The microbiological efficacy should be assessed based on the changing of pathogenic bacterial load between baseline and the end of treatment by following Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

7. References

1) Committee for Antibacterial Susceptibility Test and Clinical Evaluation, Japanese Society of Chemotherapy: Clinical effect criteria in clinical studies of antibacterial drugs for skin diseases. Japanese Journal of Chemotherapy 49(12); 992-994, 2001
2) Beam Jr TR, Gilbert DN, Kunin CM: General guidelines for the clinical evaluation of anti-infective drug products. Clin Infect Dis 1992; 15 (Suppl 1):S5-S32
3) Weigelt J, Itani K, Stevens D, et al.: Linezolid versus Vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005; 49:2260-2266.
4) Arbeit RD, Maki D, Tally FP, et al.: The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004; 38: 1673-1681

Guidance for the Clinical Evaluation of Orthopedic Infections

1. Object

1.1. Major Target Bacterial Species

Staphylococcus aureus (including methicillin-resistant *Staphylococcus aureus* or MRSA), *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Streptococcus pneumoniae,* etc.

1.2. Target Diseases

Suppurative osteomyelitis and suppurative arthritis potentially caused by the above bacterium.

(Note: Consideration should be separately given to purulent tendosynovitis and purulent myositis other than the above 2 diseases.)

2. Inclusion Criteria/Exclusion Criteria

2.1. Inclusion Criteria

Suppurative osteomyelitis and suppurative arthritis

Patients in whom pathogenic bacteria are detected in bone tissue or synovial fluid, or local findings (pain, redness and swelling), blood examination data, or image (conventional radiography, magnetic resonance imaging, bone scintigraphy) findings suggestive of bacterial infection are observed.

For the others, patients should be included in accordance with the integrated rules under the *General* section

(Note: Consideration should be separately given to purulent tendosynovitis and purulent myositis other than the above 2 diseases.)

2.2. Exclusion Criteria

Patients with refractory infections should be excluded, because they are considered to be unsuitable for evaluation of the antibacterial drug.

(Patients who are not expected to respond to the antibacterial drug, with infections such as subsequent to internal fracture fixation or replacement arthroplasty)

3. Dosing Methods and Treatment duration

In principle, clinical evaluation should be made after administration for at least the first 3 consecutive days.

The treatment duration should be 14 days or shorter in principle, but may be extended until the therapeutic goal is achieved.

The extended duration should be up to 4 to 6 weeks, and the treatment should be terminated when the therapeutic goal is achieved.

4. Timing of Evaluation and Observations

The following observation of signs and symptoms and laboratory test should be performed on each observation day.

Osteomyelitis: Body temperature, pus discharge, redness, swelling, pain, and warmth

Arthritis: Body temperature, pus discharge, redness, swelling, pain, warmth, and limited range of motion

Body temperature: Measured value (descriptions such as normal temperature may be used for patients in whom body temperature is not measured because the body temperature is reduced to < 37°C)

- Scoring of inflammatory findings

  Pus discharge, redness, swelling, pain, warmth, and limited range of motion

  3 points: Remarkable

  2 points: Moderate

  1 point: Mild

  0 points: None

- Scoring of laboratory test results

  Erythrocyte sedimentation rate, CRP, white blood cell count, and radiographic findings

  3 points: Highly abnormal laboratory value

  2 points: Moderately abnormal laboratory value

  1 point: Mildly abnormal laboratory value

  0 points: Normal laboratory value

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be adequately observed to confirm that suitable subjects are included.

4.1.2. Three Days after the First Dose (Days 3-4)

Observation during the treatment is critical in deciding whether to continue the treatment with the antibacterial drug or not. If signs and symptoms are not resolving, the clinical investigators are required to make an appropriate decision, for instance, to discontinue the clinical study and switch to the other antibacterial drug, in due consideration of the subject's health.

4.1.3. End of Treatment

The efficacy and safety at the end of treatment should be evaluated. When treatment is discontinued or terminated within the specified period because of cure or resolution, the observations applicable at this timing should be assessed.

4.1.4. Test of Cure (1-2 weeks after the end of treatment)

At this point, whether the target disease is cured or not should be evaluated.

4.2. Observations

4.2.1. Sings and Symptoms

Subjective symptoms and objective findings, radiographic findings, and laboratory examination (blood, erythrocyte sedimentation rate, CRP, liver function, kidney function, serum electrolyte, urinalysis findings)

4.2.2. Collection of Specimens for Microbiological Test

Before treatment, during treatment, and at the end of treatment (at the time of discontinuation)

5. Evaluation

5.1. Clinical Efficacy

5.1.1. Clinical Efficacy at End of Treatment

The clinical efficacy is rated as "Success (including Excellent)," "Failure," or "Indeterminate" based on a change in scores for the inflammatory findings and laboratory test values from the baseline to the end of treatment (time of discontinuation) as provided in the Definition below.

	Definition
Success	Score at the baseline (score for inflammatory findings + score for laboratory test results) – score at the end of treatment (score for inflammatory findings + score for laboratory test results) = 3-4
Failure	Score at the baseline (score for inflammatory findings + score for laboratory test results) – score at the end of treatment (score for inflammatory findings + score for laboratory test results) = ≤ 2
Indeterminate	Patients in whom evaluation at the end of treatment are impossible due to dropout or exclusion are rated as "Indeterminate."

5.1.2. Efficacy Evaluation at the time of Test of Cure

The efficacy should be evaluated at the time of Test of Cure in accordance with the following criteria.

	Definition
Cure	Signs and symptoms attribute to the target disease have resolved or improved, and no longer require treatment with anti-bacterial drugs for the target disease.
Failure	- The condition that the signs and symptoms persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease. - The patient died from the target disease.
Indeterminate	- Information of signs and symptoms are missing, for reasons such as the non-attendance of subject at the date evaluating Test of Cure. -Cases where other antibacterial drugs have been administrated (systemically) for a disease other than the target disease before the end of treatment, even though the signs and symptoms attribute to the target disease had resolved or improved.

5.2. Microbiological Efficacy

The microbiological efficacy should be assessed in accordance with Appendix 15 "Guidance for Microbiological Evaluation" in this guideline.

6. References

1) Yoshiaki Ishii, Kouichi Saotome, Yoshiki Yamano, Takehiko Torisu: Bone and joint tissue levels of doripenem, and clinical evaluation in orthopedics infections Journal of the Japanese Society for Study of Bone and Joint Infections 2005; 19; 56-59

Guidance for the Clinical Evaluation of Respiratory Infections

1. Introduction

Respiratory infections (pneumonia and acute bacterial exacerbation of chronic respiratory disease) are one of the most important infection and thus positioned as the target disease in pivotal comparative studies for clinical evaluation of an antibacterial drug. Pneumonia is the major disease used in efficacy evaluation of an antibacterial agent against respiratory infections. Previously, the target disease was collectively set as "pneumonia," but community acquired pneumonia (CAP) and hospital acquired pneumonia (HAP) differ in terms of etiology and basic pathological condition and thus are evaluated using different endpoints. Therefore, CAP and HAP should be handled separately. Accordingly, it is desirable to design a clinical study in which CAP and HAP are distinguished and thereby evaluate the efficacy on them separately.

1.1. Points to Consider for Phase II Trials

The objective of a phase II trials should be to explore the efficacy, safety, and recommended clinical dose of the antibacterial drug for respiratory infections based on non-clinical data from drug susceptibility tests and pharmacokinetics (PK)/pharmacodynamics (PD) analysis in animal experiments as well as clinical pharmacology studies in healthy adults. It is desirable for the phase II trial to evaluate the efficacy of the antibacterial drug on CAP or acute bacterial exacerbation of a chronic respiratory disease in otherwise healthly non-elderly unless the drug target on particular respiratory infections or specific causative bacteria. Because PK/PD analysis provides important information, blood concentrations of the antibacterial drug should be determined in as many patients as possible, and pharmacokinetic data including the sputum concentrations of the antibacterial drug should be collected even from the limited number of patients.

The objective of the study should be clarified to draft the study plan, because recommended dosage and administration in clinical settings may not have to be investigated in an exploratory clinical study in patients with respiratory infections, if data on the dosage and administration of the drug to be developed are adequately obtained from foreign clinical studies; and the pharmacokinetics in Japanese is known to be similar to that in non-Japanese; or PK/PD parameters correlated to the drug efficacy have been identified for the drug to be developed as with β-lactams and new quinolones.

Because the population in Japan is aging, and the elderly account for the large percentage of the patients with respiratory infection, it is desirable to investigate the efficacy and safety in the elderly at an early stage.

1.2. Points to Consider for Phase III Studies

In a phase III study, the specific respiratory infection considered to be an appropriate target disease of the antibacterial drug is extensively investigated. For the investigation, the trial should be basically conducted in a randomized controlled manner for comparison with the existing antibacterial drug in patients with a representative disease (e.g. CAP) potentially set as the indication, and an uncontrolled trial may be conducted in patients with other respiratory infections. The objective of either study should be to investigate the efficacy and safety of the antibacterial drug as well as to verify the characteristics in clinical usage. Especially, the study for comparison with the existing antibacterial drug is important and pivotal in identifying the clinical positioning of the antibacterial drug and therefore should be conducted in a randomized double-blind trial.

Furthermore, in order to collect data on PK/PD to the maximum, PK should be investigated in such a study wherever possible in addition to sequential measurements of microbiologic response and drug susceptibility of clinical isolates.

1.2.1. Randomized Controlled Trials

In a randomized controlled study, noninferiority or superiority of the antibacterial drug to an appropriate control drug should be verified generally in patients with CAP using the recommended dosage and administration in clinical settings. Unless the target is limited to the specific respiratory diseases such as atypical pneumonia, the target sample size should be set to ensure statistical analysis for the noninferiority or superiority.

This type of a trial may be designed to target both pneumonia and acute bacterial exacerbation of a chronic respiratory disease. However, it should be designed as a comparative study to ensure that subgroup analysis can be performed for each group.

1.2.2. Open-label Uncontrolled Trials

The objective of an open-label uncontrolled trial should be to investigate the efficacy and safety in a wide range of respiratory infections by including patients in severe conditions who are not suitable for a comparative trial and patients with rare diseases those patients those who are hardly enrolled in a comparative trial. In this type of a trial, high doses may be administered to patients in severe conditions or those with a refractory disease.

Because an open-label uncontrolled trial does not set the control drug as an indicator of the drug efficacy, it is desirable to set the expected value based on the previous clinical trial data as a guide of the efficacy against the target respiratory infection.

2. Object

2.1. Major Target Bacteria Species

Major causative bacteria of respiratory infectious diseases include *Streptococcus pneumoniae* (including drug-resistant *Streptococcus pneumoniae* [DRSP]), *Haemophilus influenzae*, *Moraxella* (*Branhamella*) *catarrhalis*, *Staphylococcus aureus* (including methicillin-resistant *Streptococcus aureus* [MRSA]), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (including multi-drug resistant *Pseudomonas aeruginosa* [MDRP]), *Legionella* sp, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Chlamydia psittaci*. The target bacterial species should be determined according to characteristics of the test drug.

2.2. Target Diseases

CAP, HAP, and acute bacterial exacerbation of chronic respiratory disease (respiratory tract infection in patients who have underlying disease such as chronic obstructive pulmonary disease [COPD], chronic bronchitis, bronchiectasis, diffuse panbronchiolitis, pulmonary fibrosis, emphysema, past history of pulmonary tuberculosis, etc.)

2.2.1. To Develop a Broad-Spectrum Antibacterial Drug

Taking isolation frequency of causative bacteria of respiratory infectious disease in clinical settings into consideration, enough major causative bacteria should be collected without being limited to specific ones.

2.2.2. To Develop the Antibacterial Drug Targeting Specific Causative Bacteria

Although the General section in this guideline has a description about development of antibacterial drugs targeting specific causative bacteria such as MRSA, it is desirable to conduct an appropriate comparative study according to the isolation frequency of the target causative bacteria. Although an open-label uncontrolled study may be conducted when infections with the specific bacteria are so rare that comparative trial is unfeasible, it is necessary to take a measure by which the clinical study data can be scientifically evaluated, such as the setting of an appropriate efficacy target index based on the previous clinical study data on the target causative bacteria, as described above.

3. Inclusion Criteria/Exclusion Criteria[1)]

3.1. Community-Acquired Pneumonia

3.1.1. Inclusion Criteria (CAP)

1) Acute onset patients who have no history of hospitalization or long term care facility institutionalization within 2 weeks before the onset.
2) Patients who present acute manifestation of obvious infiltrates in chest X-ray or computed tomography (CT) image obtained within 48 hours from the start of its study. Such patients should be those who "have not received any antibacterial drug" and "do not exhibit any improvement" between the radiography and the first dose of the study drug.
3) According to characteristics of the antibacterial drug and nature of the clinical study to be conducted, patients who have appropriate clinical symptoms and physical findings among those listed below.
   - Cough
   - Purulent sputum or sputum with increased purulence
   - Abnormal findings in auscultation or percussion (moist rale, dullness to percussion, and decreased breath sounds, etc.)
   - Worsening of one or both of dyspnea or tachypnea
   - Fever: ≥ 37°C (axillary temperature)

     Note) Although axillary temperature is generally used as body temperature in clinical setting of Japan, appropriate method of measurement should be determined in each study especially when compatibility with foreign data (e.g. oral or rectal temperature), such as those in a multiregional clinical trial, is required.
   - Increased white blood cell count (> 10,000/mm^3) or stab cells > 15%, or decreased white blood cell count (< 4,500/mm^3)
   - CRP positive
   - Hypoxemia

3.1.2. Exclusion Criteria (CAP)

Patients who meet the following criteria are excluded in addition to general exclusion criteria applied in the other areas of studies.

1) Patients with bronchial obstruction or a past history of obstructive pneumonia. Patients with COPD should not be excluded.
2) Patients with lung cancer or lung metastasis of malignant tumor

3) Patients with cystic fibrosis, acquired immune deficiency syndrome (AIDS), Pneumocystis pneumonia (including suspected case), and active pulmonary tuberculosis (including suspected case)

3.1.3. Pneumonia severity index (PSI) and Pneumonia Outcomes Research Team (PORT) score

PSI and PORT score[1)] are useful indices to investigate pneumonia severity and prognosis risk. As PORT score indicates the prognosis of pneumonia, be careful not confuse this with conventional severity classification.

3.2. Hospital-Acquired Pneumonia (including ventilator-associated pneumonia)

3.2.1. Inclusion Criteria (HAP)

1) Patients who stay at a hospital or rehabilitation facility, etc. for more than 48 hours (including duration after intubation/mechanical ventilation), who have new HAP symptoms, new manifestation of infiltrates or aggravation of infiltrates in chest X-ray or CT image.
2) Patients with fever and abnormal white blood cell count
   - Fever: ≥ 37°C (axillary temperature)

     Note: Although axillary temperature is generally used as body temperature in clinical setting of Japan, appropriate method of measurement should be determined in each study especially when compatibility with foreign data (e.g. oral or rectal temperature), such as those in a multiregional clinical trial, is required.
   - Increased white blood cell count (> 10,000/mm^3) or stab cells > 15%, or decreased white blood cell count (< 4,500/mm^3)

   According to characteristics of the antibacterial drug and nature of the clinical study to be conducted, appropriate clinical symptoms and findings should be determined
   - Cough
   - New manifestation of purulent sputum or secretion from the respiratory tract or worsening of sputum
   - Abnormal findings in auscultation or percussion (moist rale, dullness to percussion, and decreased breath sounds, etc.)
   - Worsening of Any or all of symptoms, dyspnea, tachypnea, and increased respiratory rate (> 30/min)
   - Hypoxemia
   - CRP positive

3.2.2. Exclusion Criteria (HAP)

Patients who meet the following criteria are excluded in addition to general exclusion criteria applied in the other areas of studies.

1) Patients with a past history of obstructive pneumonia. Patients with COPD should not be excluded.
2) Patients with lung cancer or lung metastasis of malignant tumor
3) Patients with cystic fibrosis, acquired immune deficiency syndrome (AIDS), Pneumocystis pneumonia (including suspected case), and active pulmonary tuberculosis (including suspected case)
4) Patients with circulatory failure or in a shock state who need a vasopressor to maintain the blood pressure, but present < 90 mmHg of the systolic blood pressure for at least 2 hours even receiving appropriate bolus infusion.
5) Patients with concomitant infection who need additional systemic treatment or those with suspected

concomitant infection.

6) Patients with neutropenia (such as neutrophil count < 1,000/mm$^{3)}$

3.3. Acute Bacterial Exacerbation of Chronic Respiratory Disease (secondary infection of chronic respiratory disease)

3.3.1. Inclusion Criteria (acute bacterial exacerbation of chronic respiratory disease)

Patients with confirmed chronic respiratory disease in whom acute bronchitis and pneumonia are ruled out based on the medical history or chest X-ray. Patients in whom inflammation around the respiratory tract is confirmed in the CT image are not diagnosed as pneumonia.

Furthermore, patients must meet the following conditions:

1) New manifestation of cough and sputum, or increased sputum or aggravated purulent sputum
2) CRP positive (≥ 0.7 mg/dL, or > institutional upper limit)

In addition, meeting the following conditions is desirable.

3) Qualified specimens (purulent sputum) by which causative bacteria are identified, or likely to be identified, are available.
4) Fever: ≥ 37°C (axillary temperature)
5) Increased peripheral white blood cell count (≥ 8,000/mm^3, or > institutional upper limit)
6) Worsening of dyspnea or general fatigue
7) Hypoxemia (or its worsening)

3.3.2. Exclusion Criteria (acute bacterial aggravation of chronic respiratory disease)

Patients who meet the following criteria are excluded in addition to general exclusion criteria applied in the other areas of studies.

1) Patients with cystic fibrosis, lung cancer, active pulmonary tuberculosis, and nontuberculous mycobacteriosis (including suspected case)
2) Patients who need to receive the other antibacterial drug concomitantly: however; those who have been receiving low-dose macrolide long-term therapy before participation of the study without dose change may be included in the study.
3) Patients who receive immunosuppressive therapy with immunosuppressive drugs. If patients who systemically receive steroids are included (> 10 mg/day as calculated dose of prednisolone), stratification analysis should be performed according to usage of steroids.

4. Dosing Method and Treatment Duration

Treatment duration should not be set uniformally, because antibacterial drugs with the reduced treatment duration reduced by pharmaceutical technology have been developed in recent years. The duration should be set according to characteristics of each antibacterial drug. In general, patients who have received the drug for at least the first 3 consecutive days should be subjected to clinical evaluation.

The treatment duration should be 7 to 14 days in general. Treatment duration and the shortest acceptable period for clinical evaluation should be determined according to characteristics of the antibacterial drug to be developed.

5. Timing of Evaluation and Observations

Conventionally, the primary focus in evaluation of an antibacterial drug was the efficacy and safety at the end of treatment (EOT). In this guideline, the Test of Cure (TOC) 7 to 10 days after the end of treatment is set as the primary endpoint in consideration of the compatibility with foreign clinical study data. When the objective of a comparative study is to confirm superiority, the clinical positioning of the drug would be clear. However, in most studies, the major objective is to demonstrate the noninferiority to existing antibacterial drugs. In such cases, demonstration of the noninferiority is not enough to clarify the clinical characteristics of the antibacterial drug in treatment of respiratory infections, which means that the evaluation in Test of Cure alone cannot support clinical significance of the drug. Therefore, separately from Test of Cure, other evaluation measures by which unmet medical needs and intention of development of the antibacterial drug are clarified should be actively adopted. Such measures include assessment on Day 3 for early clinical effect and assessment from the viewpoint of health economics such as reduction of the treatment period and hospitalization period. The secondary endpoints set in consideration of the above measures will contribute to obtainment of information useful for the differentiation of the antibacterial drug from existing drugs. Especially when the effects on severe infections or infections caused by drug-resistant bacteria are investigated, evaluation on the secondary endpoints often provides important information. In a comparative study, the control drug should be known to be most effective against the target respiratory infection, regardless of the antibacterial class, old or new, although same class drugs were widely used as control drug in antibacterial drug development in the past. If the efficacy has to be compared with that of the existing antibacterial drug, it should be noted that evaluation on the clinical efficacy at the end of treatment, the endpoint used in previous studies, also provides useful information.

In addition, the objective evaluation of an antibacterial drug is the microbiological efficacy. The efficacy of the antibacterial drug should be evaluated from the view point of both microbiologic response and clinical symptoms. The maximum effort should be made to search for causative bacteria, for it is difficult to detect causative bacteria in sputum specimens compare to those from patients with urinary tract infection, which is another major disease used in clinical studies for evaluation of an antibacterial drug. As is well known, collection of desirable quality of sputum specimens and appropriate sputum culture are critical in defining causative bacteria. In addition, when causative bacteria are suspected to be difficult to detect by cultures such as *Mycoplasma*, *Chlamydia*, and *Legionella*, immunological and genetic testing techniques should be considered. If these techniques are applied, however, careful considerations should be given to false positive / negative results and the possibility of detection of unviable bacteria.

5.1. Timing of Evaluation

5.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be adequately observed to confirm that suitable subjects are included.

5.1.2. Three Days after the First Dose (Day 3)

Observation during the treatment is critical in deciding whether to be able to continue or not. The early clinical effect should be assessed based on changes in symptoms and signs, radiological findings, and laboratory data on 3 days after the first dose. If these changes are not favorable, the investigator should make an appropriate decision, to discontinue the study drug and switch to the other antibacterial agents, in due consideration of the patient's safety.

5.1.3. End of Treatment (0 to 3 days after the end of treatment)

The efficacy and safety at the end of treatment should be evaluated. When the treatment is discontinued, or terminated in response to cure or resolution within the planned days, items applicable at this timing should be observed.

5.1.4. Test of Cure (7 to 10 days after the end of treatment)

Usually, cure should be evaluated for pneumonia 7 to 10 days after the end of treatment and for acute bacterial exacerbation of chronic respiratory disease 7 to 21 days after the end of treatment. This timing should be the primary evaluation timepoint.

5.2. Observations

5.2.1. Symptoms and Findings

Observations or examinations should cover clinical symptoms and physical findings as described in "Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections (version 2),"[1] such as signs including vital signs, clinical symptoms, and chest X-ray or CT findings at the baseline. Observation items should be specified in the study protocol.

5.2.2. Collection of Specimens for Microbiology Test

Sputum culture and sputum gram-staining microscopic examination:

The maximum effort should be made to identify causative bacteria and substituted bacteria by isolation of microorganisms and evaluation of the amount of bacteria in sputum. In addition, if the detected bacteria are microorganisms that constitute normal microbial flora but suspected to be pathogenic based on the clinical condition of the patient, each of the microorganisms should be evaluated. It is desirable to evaluate the concerned causative bacteria based on smear and gram-stain findings of sputum.

6. Evaluation

6.1. Evaluation

6.1.1. Clinical Efficacy on 3 Days after the First Administration

The clinical efficacy should be assessed based on changes in clinical symptoms, body temperature, CRP, and chest radiographic findings (only in patients with pneumonia) from the baseline to 3 days after the first administration in accordance with the clinical efficacy criteria in "Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections (version 2)"[1] by Japanese Society of Chemotherapy.

6.1.2. Clinical Efficacy at the End of Treatment (End of treatment)

The clinical efficacy should be assessed based on changes in clinical symptoms and findings, inflammatory findings, and chest radiographic findings (only in patients with pneumonia) from the baseline to the end of treatment (discontinuation) in accordance with the clinical efficacy criteria in "Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections (version 2)"[1] by Japanese Society of Chemotherapy.

6.1.3. Efficacy Evaluation at the Time of Test of Cure (Test of cure)

The clinical efficacy should be assessed based on changes in clinical symptoms and findings, presence or absence of recurrence or relapse, presence or absence of alternative antibacterial treatment at the time of Test of Cure (normally, 7 to 10 days after the end of treatment for pneumonia and 7 to 21 days for acute bacterial

exacerbation of chronic respiratory disease) in accordance with the clinical efficacy criteria in “Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections (version 2)”[1] by Japanese Society of Chemotherapy.

6.2. Microbiological Efficacy

The microbiological efficacy should be assessed based on changes in the amount of causative bacteria from the baseline to the end of treatment and the time of Test of Cure in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

Identification of causative bacteria should be performed generally and integrally, not only based on results from microbiology tests, but also in consideration of the clinical course. Results from quantitative culture and information from gram-staining should also be included in the evaluation. In some sputum specimens from patients without a history of treatment, a certain amount of causative bacteria may be isolated like pure culture, while in many of those from patients who have received antibacterial treatment a sufficient amount of bacteria is rarely obtained. It is, therefore, not appropriate to define causative bacteria based on the bacterial count alone. Accordingly, causative bacteria should be identified comprehensively by collecting useful information even from the previous medication, clinical condition and course of the patient.

7. References

1) Committee for Review of Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections, Japanese Society of Chemotherapy: Clinical Evaluation of New Antibacterial Drugs in Respiratory Infections (version 2) Japanese Journal of Chemotherapy 2012; 60:29-45

2) Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment DRAFT GUIDANCE. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), January 20143) Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment DRAFT GUIDANCE. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), May 2014

Guidance for the Clinical Evaluation of Genital and Urinary Tract infections.

1. Introduction

This section describes points to consider for objective and scientific clinical evaluation of genital and urinary tract infections.

Urinary tract infection is classified as acute or chronic infection based on the clinical course, as uncomplicated or complicated infection based on presence or absence of an underlying disease, and furthermore as cystitis or pyelonephritis based on the site of infection. Usually, diagnosis is made based on status of the clinical course, presence or absence of an underlying disease, and site of infection. Patients with uncomplicated urinary tract infection are those who do not have any underlying disease that affects urodynamics. On the other hand, patients with complicated urinary tract infection are those who have an underlying disease that affects urodynamics in a narrow sense, but in a broad sense, additionally target patients are those who have an underlying disease (diabetes, immunosuppressed condition, etc.) that contributes to induction, progression, and prolongation of urinary tract infection and are males. In the previous evaluation criteria of drug efficacy against urinary tract infections, patients with complicated urinary tract infection were supposed to have an underlying disease in the urinary tract, that is, such patients were identified based on the narrow-sense definition. In this guideline, however, patients with complicated urinary tract infection are identified based on the broad-sense definition,[1)] because even internal comorbidity such as diabetes contributes to induction, progression, and prolongation of urinary tract infection as with an underlying disease in the urinary tract; urinary tract infection is a type of retrograde infection and less likely to develop in males than in females due to anatomy of the urethra, which is 5 to 7 folds longer in males than in females; and actually male patients with urinary tract infection are frequently found to have an underlying disease such as excretory disorder by investigation, although they were initially supposed to have no underlying disease in the urinary tract.

Genital infections are classified into urethritis, prostatitis, epididymitis, or orchitis according to the site of infection. Because urethritis is sexually transmitted in most of the patients, evaluation in patients with urethritis is described in the section for guidance of sexually transmitted infections. Prostatitis is classified according to the pathological condition. The US National Institute of Health (NIH) classifies prostatitis in the following 4 categories: Category I, Acute bacterial prostatitis; Category II, Chronic bacterial prostatitis; Category III, Chronic pelvic pain syndrome/prostatic pain syndrome (A. Inflammatory, B. Non-inflammatory); and Category IV, Asymptomatic prostatitis.[2)] Of these categories, only Category I, that is, acute bacterial prostatitis, is considered applicable to evaluation of antibacterial drugs, because it is clearly associated with bacteria; and antibacterial drugs are used for treatment; and the drug effect can be evaluated relatively in a short term. Although epididymitis is classified in acute and chronic diseases, only acute epididymitis is considered applicable for the same reason as that for prostatitis. Orchitis is not considered as target disease, because it is mostly inflammatory progressed consequence of acute epididymitis or caused by virus infection.

2. Object

2.1. Major Target Species

Staphylococcus sp., *Streptococcus* sp., *Enterococcus* sp., *Enterobacteriaceae*, non-fermenting gram-negative bacilli (except for acute uncomplicated cystitis and acute uncomplicated pyelonephritis), *Chlamydia trachomatis* (acute epididymitis), and *Haemophilus influenzae* (acute epididymitis), etc.

2.2. Target Diseases

Although indications of antibacterial drugs for genital and urinary tract infections and listed in marketing approval may be cystitis, pyelonephritis, prostatitis, and epididymitis, the target diseases in actual clinical studies should be acute uncomplicated cystitis, acute uncomplicated pyelonephritis, complicated urinary tract infections (cystitis, pyelonephritis), acute bacterial prostatitis, and acute epididymitis, as specified in "Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition".[1)]

3. Inclusion Criteria/Exclusion Criteria

3.1. Acute Uncomplicated Cystitis

Target patients are those who are considered to have bacterial infection.

<Inclusion Criteria>

- Sex: Female
- Symptoms: Patients who have any of miction pain, pollakisuria, urinary urgency, and suprapubic pain.
- Pyuria: Patients who meet any of the following criteria before treatment.
    - White blood cell (WBC) count in non-centrifuged urine specimen determined with a specified device ≥ 10 WBCs/μL
    - WBC count in non-centrifuged urine specimen determined with a counting chanber ≥ 10 WBCs/mm^3
    - WBCs in non-centrifuged urine specimen determined with a dipstick (based on esterase activity), Positive (On condition that a false negative result is frequently observed, it is desirable to check the specimen with the negative result by another method.)
    - WBC count under microscopic examination of urinary sediment ≥ 5 WBCs/high power field (HPF)

<Exclusion Criteria>

- Patients with viable cell count in urine before treatment < 10^5 CFU/mL (midstream urine and catheter urine).
- Patients who had symptoms of cystitis within 4 weeks before this onset.

3.2. Acute Uncomplicated Pyelonephritis

Target patients are those who are considered to have bacterial infection, which developed within past 3 days.

<Inclusion Criteria>

- Sex: Female
- Symptoms: Patients who have any of fever ≥ 37.5°C, lumbago, flank pain or costvartebral angle knocking pain
- Pyuria: Patients who meet any of the following criteria before treatment.

- WBC count in non-centrifuged urine specimen determined with a specified device ≥ 10 WBCs/μL
- WBC count in non-centrifuged urine specimen determined with a counting chamber ≥ 10 WBCs/mm^3
- WBCs in non-centrifuged urine specimen determined with a dipstick (based on esterase activity), Positive (On condition that a false negative result is frequently observed, it is desirable to check the specimen with the negative result by another method.)
- WBC count under microscopic examination of urinary sediment ≥ 5 WBCs/HPF

<Exclusion Criteria>

- Patients with viable cell count in urine before treatment < 10^5 CFU/mL (midstream urine and catheter urine).
- Patients who had symptoms of pyelonephritis within 4 weeks before this onset.

3.3. Complicated Urinary Tract Infection (pyelonephritis, cystitis)

Target patients are those with non-catheterized complicated urinary tract infections (pyelonephritis, cystitis) for which antibacterial drugs are expected to result in clinical cure.

<Inclusion Criteria>

- Patients who have fever, miction pain, urinary urgency, pollakisuria, suprapublic pain, lumbago, discomfort on micturition, lower abdominal discomfort, and residual urine caused by urinary tract infection.
- Pyuria: Patients who meet any of the following criteria before treatment.
    - WBC count in non-centrifuged urine specimen determined with a specified device ≥ 10 WBCs/μL
    - WBC count in non-centrifuged urine specimen determined with a counting chamber ≥ 10 WBCs/mm^3
    - WBCs in non-centrifuged urine specimen determined with a dipstick (based on esterase activity), Positive (On condition that a false negative result is frequently observed, it is desirable to check the specimen with the negative result by another method.)
    - WBC count under microscopic examination of urinary sediment ≥ 5 WBCs/HPF

<Exclusion Criteria>

- Patients with viable cell count in urine before treatment < 10^5 CFU/mL (midstream urine and catheter urine).
- Patients who have received a diagnosis of complication of urethritis, prostatitis, or epididymitis.

3.4. Acute Bacterial Prostatitis

Target patients are those who are considered to have bacterial infection, which developed within past 10 days.

<Inclusion Criteria>

- Sex: Males
- Patients who have fever ≥ 37.5°C and miction pain considered to have acute prostatitis based on the clinical condition.
- Pyuria: Patients who meet any of the following criteria before treatment (midstream urine).
    - WBC count in non-centrifuged urine specimen determined with a specified device ≥ 10

WBCs/μL

- WBC count in non-centrifuged urine specimen determined with a counting chamber ≥ 10 WBCs/mm^3
- WBCs in non-centrifuged urine specimen determined with a dipstick (based on esterase activity), Positive (On condition that a false negative result is frequently observed, it is desirable to check the specimen with the negative result by another method.)
- WBC count under microscopic examination of urinary sediment ≥ 5 WBCs/HPF

<Exclusion Criteria>

- Patients with bacterial count in midstream urine before treatment < 10^5 CFU/mL.
- Patients who have just undergone prostate biopsy or catheterization.

3.5. Acute Epididymitis

Target patients are those with acute bacterial (except for that caused by *Chlamydia trachomatis*) or acute chlamydial epididymitis.

<Inclusion Criteria>

- Sex: Males
- Symptoms and findings: Patients with acute swelling and pain in the epididymis

<Exclusion Criteria>

- Bacterial infections: Patients with viable cell count in midstream urine before treatment < 10^5 CFU/mL.
- Chlamydial infections: Patients who present a urine specimen (first-catch urine) before treatment in which no *Chlamydia trachomatis* is detected.

  Chlamydia trachomatis should be detected using nucleic acid amplification techniques (polymerase chain reaction [PCR], transcription mediated amplification [TMA], strand displacement amplification [SDA], TaqManPCR, real-time PCR, etc.).

4. Dosing Methods and Treatment Duration

Although the treatment duration may vary depending on the target disease, it should be within 1 (single dose) to 14 days in principle and specified according to characteristics of the test drug.

Acute uncomplicated cystitis: 1 (single dose) to 7 days

Acute uncomplicated pyelonephritis, complicated urinary tract infection: Up to 14 days

Acute bacterial prostatitis, acute epididymitis: At least 14 days for oral drugs

5. Timing of Evaluation and Observations

The following observation of symptoms and findings and laboratory test should be performed on each observation day.

5.1. Timing of Evaluation

5.1.1. Baseline

During baseline, patients should be screened to confirm that suitable patients are included.

5.1.2. End of Treatment of IV therapy (approximately 4 to 6 days after the first dose of injection)

In a clinical study of IV therapy where switching to the oral drug is permitted, the assessment should be

made at the end of IV therapyas well (approximately 4-6 days after the first dose of IV formulationinjection).

5.1.3. Five to 9 Days after End of Treatment (Test of Cure)

For bacterial infections, assessment of cure should be made 5 to 9 days after the end of treatment.

For infectious diseases including chlamydial epididymitis of which causative bacteria are identified using nucleic acid amplification techniques, assessment should be made 2 to 4 weeks after the end of treatment to avoid amplifying nucleic acids from dead bacteria, which can lead to a false positive result.

5.1.4. Twenty one to 28 Days after the First Dose (assessment for recurrence)

Only for bacterial infections, assessment should be made for recurrence at this timing.

Patients to be assessed at this timing are those in whom “Response” to the primary endpoint was confirmed 5 to 9 days after the end of treatment and at the end of treatment with the injection (approximately 4 to 6 days after the first dose of injection).

5.2. Observations

5.2.1. Symptoms and Findings

Bacteriuria and signs and symptoms should be observed at each Timing of Evaluation specified in 5.1. Pyuria should be examined with a specified flow cytometry system, counting chanmber method, dipstick (based on esterase activity) or urinary sediment under microscope. For details, see “Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition”.[1)]

5.2.2. Collection of Specimens for Microbiology Test

Desirable urine specimens are midstream urine in males and urine collected through a catheter in females. Only for acute epididymitis, first-catch urine should be used as a specimen instead of midstream urine.

6. Evaluation

See “Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition”.[1)]

7. References

1) Yasuda M, Muratani T, Ishikawa K, et al.: Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition. J Infect Chemother 2016; 22(10):651-661

2) Krieger JN, Nyberg LJ, Nickel JC: NIH consensus definition and classification of prostatitis. JAMA 1999; 282 (3): 236-237

Guidance for the Clinical Evaluation of Sexually Transmitted Infections (Urethritis and Cervicitis)

1. Introduction

This section describes clinical evaluation of urethritis and cervicitis separately, because different inclusion criteria and efficacy evaluation criteria are specified for each of them. Furthermore, because evaluation of antibacterial drugs requires follow-up of causative bacteria, patients with nongonococcal sexually transmitted infections discussed in this guidance are limited to those in whom *Chlamydia trachomatis* or *Mycoplasma genitalium* has been isolated or detected.

In addition, patients should be instructed to refrain from sexual activity from the first dose to day of the final evaluation, or to use a condom consistently and correctly from the beginning to the end of sexual act, because sexual activities during the study period critically affect the evaluation.

2. Urethritis

2.1. Object

2.1.1. Target Diseases

- Gonococcal urethritis
- Nongonococcal urethritis (caused by *Chlamydia trachomatis* or *Mycoplasma genitalium*)

2.1.2. Target Bacterial Species

Target should be the following bacteria isolated or detected in urethral secretion or first-catch urine before treatment.

<Gonococcal urethritis>

Neisseria gonorrhoeae

<Nongonococcal urethritis>

Chlamydia trachomatis

Mycoplasma genitalium

2.2. Inclusion Criteria/Exclusion Criteria

2.2.1. Gonococcal urethritis

<Inclusion Criteria>

- Sex: Male
- Symptoms: Patients with symptoms compatible with gonococcal urethritis
- Microbiological test: Culture for *Neisseria gonorrhoeae* should be obtained from urethral secretion if available, or first-catch urine instead.

<Exclusion Criteria>

Patients with a negative culture for *Neisseria gonorrhoeae* performed from urethral secretion or first-catch urine before treatment.

2.2.2. Nongonococcal urethritis

<Inclusion Criteria>

- Sex: Male
- Symptoms: Symptoms compatible with nongonococcal urethritis
- Microbiology test: *Chlamydia trachomatis* should be detected using nucleic acid amplification tests (NAATs) (polymerase chain reaction (PCR), transcription mediated amplification (TMA), strand displacement amplification (SDA), TaqManPCR, real-time PCR, etc.). *Mycoplasma genitalium* should be also detected using NAATs (PCR, real-time PCR, etc.). (Microbiological specimens may be obtained from urethral secretion if available, or first-catch urine instead for culture.).

<Exclusion Criteria>

- Patients with a negative result for both *Chlamydia trachomatis* and *Mycoplasma genitalium* performed from first-catch urine before treatment.
- Patients with a positive result for *Neisseria gonorrhoeae*.

2.3. Dosing Method and Treatment Duration

The treatment duration should be specified as the following range according to the characteristics of the antibacterial drug.

- Gonococcal urethritis: 1 (single dose) to 7 days
- Nongonococcal urethritis: 1 (single dose) to 14 days

2.4. Timing of Evaluation and Observations

2.4.1. Timing of Evaluation

2.4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

2.4.1.2. Five to 9 Days after the End of Treatment (only for gonococcal urethritis)

At this point, whether the target disease is cured or not should be assessed.

2.4.1.3. Two to 4 Weeks after the End of Treatment (only for nongonococcal urethritis)

For nongonococcal urethritis caused by *Chlamydia trachomatis* and *Mycoplasma genitalium*, detected by NAATs, evaluation should be made 2 to 4 weeks after the end of treatment to avoid false positive results caused by amplifying nucleic acids from dead bacteria.

2.4.2. Observations

Clinical symptoms attributable to urethritis, and clinical findings of volume and description of urethral secretion should be evaluated.

2.5. Evaluation (Criteria)

See "Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition".[1)]

2.5.1. Efficacy Evaluation against Gonococcal Urethritis

i) Microbiological efficacy [primary endpoint]

Based on presence of *Neisseria gonorrhoeae*, the patient should be evaluated as either "Eradicated" or "Failure" as follows:

Eradicated	*Neisseria gonorrhoeae* is not detected in culture.
Failure	*Neisseria gonorrhoeae* is detected in culture, or change of the antibacterial drug or additional treatment has been implemented.

ii) Clinical Efficacy

Based on clinical symptoms, patients should be evaluated as either "Cure" or "Failure" as follows: Patients with mixed infection of *Chlamydia* and *Mycoplasma* should be excluded from the evaluation.

Cure	Symptoms attributable to urethritis are not observed
Failure	Symptoms attributable to urethritis are observed, or change of the antibacterial drug or additional treatment has been implemented.

2.5.2. Efficacy Evaluation against nongonococcal urethritis

i) Microbiological efficacy [primary endpoint]

Based on presence of *Chlamydia trachomatis* or *Mycoplasma genitalium* (examined by the same method as the baseline), patients should be evaluated as either "Eradicated" or "Failure" as follows:

Eradicated	*Chlamydia trachomatis* and *Mycoplasma genitalium* are not detected by NAATs.*
Failure	*Chlamydia trachomatis* or *Mycoplasma genitalium* are detected by NAATs, or change of the antibacterial drug or additional treatment has been implemented.

* *Chlamydia trachomatis* should be detected using NAATs (PCR, TMA, SDA, TaqManPCR, real-time PCR, etc.).
Mycoplasma genitalium should be detected using NAATs (PCR, real-time PCR, etc.).

ii) Clinical Efficacy

Based on clinical symptoms, patients should be evaluated as either "Cure" or "Failure" as follows:

Cure	Symptoms attributable to urethritis are not observed
Failure	Symptoms attributable to urethritis are observed, or change of the antibacterial drug or additional treatment has been implemented.

3. Cervicitis

3.1. Object

3.1.1. Target Diseases

Gonococcal cervicitis

Nongonococcal cervicitis (caused by *Chlamydia trachomatis* or *Mycoplasma genitalium*)

3.1.2. Target Bacterial Species

Target should be the following bacteria isolated or detected in cervical secretion or from an endocervical swab specimen before treatment.

<Gonococcal cervicitis>

Neisseria gonorrhoeae

<Nongonococcal cervicitis>

Chlamydia trachomatis

Mycoplasma genitalium

3.2. Inclusion Criteria/Exclusion Criteria

3.2.1. Gonococcal cervicitis

<Inclusion Criteria>

1) Patients who are female aged ≥ 16 years who have symptoms or findings of cervicitis.
2) Patients who have apparent clinical signs of sexually transmitted infections based on inflammatory findings and in whom presence of *Neisseria gonorrhoeae* is confirmed by microbiological tests using cervical secretion or endocervical swab specimens.

<Exclusion Criteria>

1) Patients in whom presence of *Neisseria gonorrhoeae* is not confirmed by culture before treatment.
2) Patients who concurrently have pelvic inflammatory disease such as uterine adnexitis or peritonitis.

3.2.2. Nongonococcal Cervicitis

<Inclusion Criteria>

1) Female patients aged ≥ 16 years who have symptoms or findings of cervicitis.
2) Patients who have clinically confirmed sexually transmitted diseases based on inflammatory findings and in whom presence of *Chlamydia trachomatis* or *Mycoplasma genitalium* is confirmed or suggested using cervical secretion or endocervical swab specimen. *Chlamydia trachomatis* should be detected using NAATs PCR, TMA, SDA, TaqManPCR, real-time PCR, etc. *Mycoplasma genitalium* should be detected using PCR, real-time PCR, etc.

<Exclusion Criteria>

1) Patients in whom neither Chlamydia trachomatis nor Mycoplasma genitalium is detected by microbiological tests at the baseline.
2) Patients in whom presence of *Neisseria gonorrhoeae* is confirmed by culture before treatment.
3) Patients who have pelvic inflammatory disease such as uterine adnexitis or peritonitis concurrently.

3.3. Dosing Method and Treatment Duration

Dosages, dosing interval, and treatment duration should be determined according to the characteristics of the antibacterial drug being developed. In principle, the clinical efficacy can be evaluated for patients who receive the test drug for at least 3 consecutive days, but this shall not apply to cases where short-course regimens such as a single dose are appropriate for the test drug. In addition, the longest recommended treatment duration should be 14 days.

3.4. Timing of Evaluation and Observations

3.4.1. Timing of Evaluation

3.4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

3.4.1.2. End of Treatment (day of the end of treatment to 7 days after that)

The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated within the specified period because of cure or resolution, the observation items applicable at this point should be assessed.

3.4.1.3. Test of Cure (1 to 3 weeks after the end of treatment)

At this point, whether the target disease is cured or not should be evaluated. This must be done because it serves as the primary endpoint.

Evaluation based on genetic testing should be made 1 to 3 weeks after the end of treatment, because such an evaluation immediately after the end of treatment could present a false positive result. Furthermore, the Timing of Evaluation may be specified in each protocol according to the particular characteristics of the bacterial pathogen. In addition, when multiple evaluation sessions are necessary, the required number of sessions may be specified.

3.4.2. Observations

Observation should cover leukorrhea, discomfort, lower abdominal pain, and genital itching as subjective symptoms, and body temperature, abnormal cervicovaginal erosion, redness, edema, and volume and description of cervical secretion as clinical findings.

3.5. Evaluation

3.5.1. Clinical Efficacy Evaluation

Clinical cure is defined as the condition in which infection signs have resolved and no additional antibacterial treatment is required. More specifically, the clinical efficacy should be evaluated in accordance with the following criteria.

	Definition
Success:	Signs and symptoms attributable to cervicitis have resolved or improved, and no longer require treatment with antibacterial drugs for the target disease.
Failure:	Patients who meet any of the following conditions. • Signs or symptoms attributable to cervicitis have deteriorated. • Cases where the antibacterial drug was changed or additional treatment has been implemented for the target disease because the microbiological efficacy was evaluated as "Persists", etc.
Indeterminate:	• Cases where the microbiological efficacy is evaluated as "Indeterminate" and no other antibacterial drugs have been used for cervicitis since the end of treatment with the investigational antibacterial drug. • Cases where other antibacterial drugs have been used (systemically) for a disease other than the target disease before the end of treatment, even though symptoms and signs attributable to cervicitis had resolved or improved.

3.5.2. Microbiological Evaluation

An adequate microbacteriological specimen for the target infection (cervical secretion or endocervical swab specimen, etc.) should be collected before treatment and at the end of treatment. These microbiological specimens should be examined by an applicable method for the target diseases (molecular microbiology methods and culture, etc.) to examine the presence of bacterial pathogens.

The microbiological efficacy should be evaluated after the end of treatment and by the pre-determined final follow-up timepoint in accordance with the following criteria:

[Gonococcal cervicitis]

Changes in *Neisseria gonorrhoeae* should be evaluated as either "Eradicated" or "Persists" as follows:

Eradicated	*Neisseria gonorrhoeae* is not detected in culture.
Persists	*Neisseria gonorrhoeae* is detected in culture, or change of the antibacterial drug or additional treatment has been implemented.

[Nongonococcal cervicitis]

Changes in *Chlamydia trachomatis* or *Mycoplasma genitalium* (examined using the same method as the baseline) should be evaluated as either "Eradicated" or "Persists" as follows:

Eradicated	*Chlamydia trachomatis* or *Mycoplasma genitalium* are not detected by NAATs.*
Persists	*Chlamydia trachomatis* or *Mycoplasma genitalium* are detected by NAATs*, or change of the antibacterial drug or additional treatment has been implemented.

* *Chlamydia trachomatis* should be detected using NAATs (PCR, TMA, SDA, TaqManPCR, real-time PCR, etc.).
Mycoplasma genitalium should be detected using NAATs (PCR, real-time PCR, etc.).

4. References

1) Yasuda M, Muratani T, Ishikawa K, et al.: Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition. J Infect and Chemother 2016; 22(10):651-661

Guidance for the Clinical Evaluation of Intra-Abdominal Infections

1. Object

1.1. Major Bacterial Target Species

Major bacterial pathogens responsible for intra-abdominal infections include *Staphylococcus* sp., *Enterococcus* sp., *Escherichia coli, Klebsiella* sp., *Enterobacter* sp., *Pseudomonas aeruginosa*, *Peptostreptococcus* sp., *Bacteroides* sp., etc. The target bacterial species should be determined according to the characteristics of the investigational antibacterial drug.

1.2. Target Diseases

The following infectious diseases suspected to have been caused by the above bacterial pathogens.

- Peritonitis (peritonitis progressed from pelvic inflammatory diseases may be included)
- Intra-abdominal abscess
- Hepatobiliary infectious diseases (cholecystitis, cholangitis, liver abscess)

2. Inclusion Criteria/Exclusion Criteria

2.1. Inclusion (Diagnosis) Criteria

1) Patients who have apparent clinical signs of intra-abdominal infection based on inflammatory findings, abdominal findings, and image findings, and who meet any of the following i) cases where surgical procedure, percutaneous drainage of the infection site, or biliary drainage, etc. is planned or has been implemented within 24 hours. For pelvic inflammatory disease or cholecystitis, cases where drainage is not implemented according to the clinical decision that no surgery is required may be included (even in such cases, specimens must be collected from aspiration, etc.). ii) Cases with postoperative infection in whom gastrointestinal fluid or purulent discharge isdiscerned from the drain placed during the surgery.
2) Patients who have not responded to the initial treatment or the other antibacterial drugs (in which cases where the patient has been evaluated as “failure” to the other antibacterial drugs administration for 3 days or longer). Patients who are enrolled after the surgery or procedures such as drainage are allowed to have received other antibacterial drugs than the investigational antibacterial drug only once for the surgery or procedure.
3) Patients in whom microbiological specimens can be obtained during the baseline or within 24 hours of the first dose of the investigational antibacterial drug.

2.2. Exclusion Criteria

1) Patients who underwent surgery for perforation of intestine within 12 hours.
2) Patients who underwent surgery for perforated peptic ulcer within 24 hours.
3) Patients with complicated appendicitis (except for gangrenous or perforated appendicitis)
4) Patients with necrotizing pancreatitis
5) Patients with Spontaneous bacterial peritonitis or SBP
6) Patients with open peritoneal drainage[1 to 3)]

7) Patients who have not received appropriate surgical procedures such as drainage, even though abscess formation has been demonstrated by image findings for cases with perforative peritonitis.
8) Patients with symptoms that are already resolving in response to surgical procedures such as drainage.
9) Patients who are unsuitable for clinical evaluation of the antibacterial drugs due to extremely serious underlying diseases or infectious diseases, or those who are not expected to survive the trial period.[4] When acute physiology and chronic health evaluation (APACHE) II score is used for severity evaluation, patients with > 15 score are likely to be excluded.

3. Dosing Method and Treatment Duration

Dosages, dosing interval, and treatment duration should be determined according to characteristics of the investigational antibacterial drugs being developed. In principle, the efficacy can be evaluated for patients who are administrated the testl drug for at least 3 consecutive days. In addition, the longest recommended treatment duration should be 14 days.[5,6] Patients with intra-abdominal infection should continue the antibacterial drug until 24 hours afebrile, leukocytosis is improved, and bowel movements are restored, in general.[7,8]

4. Timing of Evaluation and Observations

4.1. Timing of Evaluation

Evaluation should be made not only at the end of treatment but also at the time of Test of Cure (7 to 14 days after the end of treatment). Usually, Test of Cure is evaluated at the later timepoint. Test of Cure evaluation is recommended to be performed at 4 to 6 weeks after the first dose (evaluation at outpatient clinic is acceptable).[5] If surgery is planned or performed within 24 hours of the time of enrollment, surgical site infection should be an object for the evaluation as well, which should be followed up until 1 month after the surgery and be evaluated. Observation of the following clinical findings, symptoms, and laboratory findings should be performed on each observation day.

4.1.1. Baseline (Day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable patients are included. Abscesses and ascites associated with peritonitis should be collected for culture during the surgery or invasive procedures such as percutaneous drainage. Infection sites should be precisely identified.

4.1.2. Three days after the First Dose (Day 2 to 4)

Vital signs and abdominal findings should be observed every day. Complete blood count, blood chemistry tests, urinalysis, and observation of exudate from the infection site (description and volume) should be performed where necessary. When a case with a closed drain, which has a low contamination risk, is evaluated clinically “failure”, the discharge form the drain should be obtained for culture to evaluate the bacterial pathogen.

4.1.3. End of Treatment (0 to 3 days after the end of treatment)

When treatment is discontinued or terminated within the specified period because of cure or resolution, the observation items applicable at this point should be assessed.

4.1.4. Test of Cure (7 to 14 days after the end of treatment)

At this point, whether the target disease is cured or not should be evaluated. This is the primary evaluation point for foreign clinical trials, and as such using this point is critical to allow comparison with them.

4.2. Observations

4.2.1. Clinical Findings and Symptoms

Vital signs, physical findings (spontaneous pain, tenderness, peritoneal irritation), and complete blood count (hematocrit, red blood cell count, white blood cell count, platelet count), blood chemistry test (total bilirubin, liver/biliary enzymes, serum creatinine, C-Reactive Protein (CRP)), urinalysis, and blood culture should be followed up.

Exudate from the infection site (description and volume) must be observed during the baseline and at the end of treatment or discontinuation (when specimens can be obtained).

To assess the focus of an intra-abdominal infection, imaging tests should be performed on the day of the first dose if possible. If any inflammaion is observed on images duringthe baseline, imaging tests should be performed at the end of treatment or discontinuation and at the time of Test of Cure. The same imaging modality should be used for the evaluation throughout the trial period, even though various imaging modalities such as conventional radiography, ultrasonography, CT, and MRI are available.

If the trials target patients with severe infection, hemodynamics and respiratory function should be evaluated to score the severity.

4.2.2. Collection of Specimens for MicrobiologicalTest

Microbiological specimens (exudate or pustule from the infection site) should be obtained in advance of the administration of the investigational antibacterial drugs to conduct appropriate aerobic and anaerobic cultures as well as perform susceptibility tests for the study drug. In the cases whom specimens are not collected before the treatment, specimens should be collected within 24 hours after the first dose.[6)] Specimens should be collected for culture where necessary after the first dose, however, collection of the post-treatment specimens is difficult in some cases due to removal of a drain during the treatment.

5. Evaluation

5.1. Clinical Efficacy

1) Clinical cure is defined as the condition in which infection signs have resolved, and no longer require treatment with antibacterial drugs.[5)] Clinical failure is defined as follows:
   i) Persistent or recurrent intra-abdominal infection is documented by image findings, specimens from percutaneous drainage, or findings at reoperation.
   ii) Postoperative surgical site infection
   iii) Death from persistent intra-abdominal infection
   iv) Treatment with the other antimicrobial drugs is implemented during the trial period, even if intra-abdominal infection is not documented (When anti-MRSA drugs are concomitantly used to treat MRSA-mixed infection during a trial of a drug without antibacterial activity of MRSA, or when antifungal drugs are concomitantly used to treat fungal infection, the independ expert panel should determine whether to evaluate such a case or not).

2) At the final evaluation, cases should be categorized as cure, failure, or indeterminate.[5)] Clinical efficacy is the most important evaluation followed by microbiological efficacy. If follow-up culture is not available due to absence of purulent drainage, and the clinical course is favorable, the microbiological efficacy should be evaluated as potentially eradicated.[5)]

5.2. Microbiological Efficacy

The microbiological efficacy should be evaluated at the end of treatment with the investigational antibacterial drug and also at a point by the end of the final follow-up timepoint in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

In patients with mixed infection, the microbiological efficacy on individual bacterial species should be separately evaluated.[4)] For evaluation of relapse or reinfection, specimens for culture after starting treatment should be collected when the investigational antibacterial drug is not present at high concentrations in blood, tissues, or body fluid.

6. References

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Guidance for the Clinical Evaluation of Obstetrical and Gynecological Infections

1. Object

1.1. Major Target Species

Bacteria that should be isolated from evaluatable patients for microbiological efficacy and requiring susceptibility test are as follows: The other bacteria to be listed in the applicable microorganism of the investigational antibacterial drug should be determined based on separately reported results from *in vitro* susceptibility tests and PK/PD analysis.

Staphylococcus sp., *Streptococcus* sp., *Enterococcus* sp., *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., *Haemophilus* sp., *Pseudomonas aeruginosa*, anaerobic Gram-positive bacteria (cocci) (*Peptostreptococcus* sp., etc.), anaerobic Gram-negative bacteria (bacilli) (*Bacteroides* sp., *Prevotella* sp., *Porphyromonas* sp., *Fusobacterium* sp., etc.), *Mycoplasma* sp., and *Chlamydia* sp.

2. Inclusion Criteria/Exclusion Criteria

2.1. Inclusion Criteria

2.1.1. Pelvic inflammatory disease, vulvitis

Patients who have clinical infectious signs based on systemic inflammatory findings (fever, high WBC count, elevated CRP), abdominal findings (lower abdominal pain, lower abdominal tenderness), cervical findings (purulent leukorrhea, purulent discharge), or image findings, and in whom bacterial infection is diagnosed by a clincialinvestigator.

2.1.2. Bacterial vaginosis

Any of the following diagnostic criteria should be applied.

(1) Patients who meet at least 3 of the following conditions: [1)]

- Vaginal discharge is thin and homogeneous.
- Clue cells with a granular appearanceare observed on saline wet mount.
- Positive whiff-amine test; a drop of 10% KOH added to a sample of vaginal discharge produces an amine odor.
- Vaginal pH is 4.5 or higher.

(2) Patients who scores at least 7 in total in gram-stained preparations of vaginal discharge (by Nugent's method[2)])

type	*Lactobacillus* type					*Gardnerella* type (including Gram-negative small bacilli such as *Prevotella*)					*Mobiluncus* type				
Score (Bacterial count/ view)	0	<1	1-4	5-30	>30	0	<1	1-4	5-30	>30	0	<1	1-4	5-30	>30
	4	3	2	1	0	0	1	2	3	4	0	1	1	2	2

If the total score is ≥ 4, culture should be performed for microorganisms associated with bacterial vaginosis including obligate anaerobes for definitive diagnosis.

2.2. Exclusion Criteria

Patients with the following backgrounds should be excluded. The other exclusion criteria should be established in each study protocol as appropriate according to the characteristics of the investigational antibacterial drugs being developed. In addition, the severity of each items should also be set in each study protocol.

- Patients who are unsuitable for clinical evaluation of the antibacterial drugs due to the extremely serious underlying disease or infectious diseases, or those who are not expected to survive the trial period. When acute physiology and chronic health evaluation (APACHE) II score is used for severity evaluation, patients with > 15 score are likely to be excluded.

3. Dosing Method and Treatment Duration

Treatment duration should be set according to the characteristics of the investigational antibacterial drugs because antibacterial drugs with short treatment periods have been developing by pharmaceutical technology in recent years. In principle, the clinical efficacy can be evaluated for patients who receive the test drug for at least 3 consecutive days. In addition, the longest recommended treatment duration should be 14 days.

Treatment duration and the shortest acceptable period for clinical evaluation should be determined according to the characteristics of the investigational antibacterial drugs being developed or the class it belongs to.

4. Timing of Evaluation and Observations

The following signs and symptoms and laboratory test should be assessed on each evaluation day.

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

4.1.2. Three days after the First Dose (Day 2 to 4)

Observation during the treatment is critical for deciding whether or not to continue the treatment with the investigational antibacterial drug. If signs and symptoms are not improving, the investigator should make an appropriate decision to discontinue the treatment and switch to the other antibacterial drugs, in due consideration of the subject's health.

4.1.3. End of Treatment (0 to 3 days after the end of treatment)

The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated within the specified period because of cure or resolution, the observation items applicable at this point should be assessed.

4.1.4. Test of Cure (1-2 weeks after the end of treatment)

At this point, whether the target disease is cured or not should be evaluated. This point is in deemed as the primary evaluation timepoint in foreign clinical trials, which is important point for comparison with them.

4.2. Observations

Body temperature, physical findings (spontaneous pain, tenderness, peritoneal irritation), complete blood count (hematocrit, red blood cell count, white blood cell count, platelet count), blood biochemistry test (total

bilirubin, liver enzymes, serum creatinine, CRP), urinalysis, and exudate from the infection site (description and volume) should be followed up at appropriate intervals. Coagulation test may be performed. Imaging tests may be performed as appropriate, even though it is not essential. These examinations must be assessed at the end of treatment and at the time of the final Test of Cure (1 to 2 weeks after the end of treatment).

4.2.1. Collection of Samples for Microbiological Test

Microbiological specimens (uterine content, culdocentesis fluid, pelvic dead space fluid, secretion, and other fluid) should be obtained in advance of the administration of the investigational antibacterial drugs to conduct appropriate aerobic and anaerobic cultures as well as perform susceptibility tests for the study drug. (Anaerobe culture must be conducted because anaerobes are the important bacterial pathogen in female genital infections.) In the cases whom specimens are not collected before the treatment, specimens should be collected within 24 hours after the first dose. If the first blood culture is positive, blood culture should be repeated at an appropriate interval as with drainage culture. Specimens should be collected for culture where necessary after the first dose, however, collection of the post-treatment specimens is difficult in some cases due to removal of a drain during the treatment.

5. Evaluation

5.1. Clinical Efficacy

5.1.1. Pelvic Inflammatory Disease

1) Clinical efficacy should be evaluated not only at the end of treatment but also 1 to 2 weeks after the end of treatment. Usually, Test of Cure is evaluated at the later timepoint. In addition, Test of Cure is recommended to be evaluated at 4 to 6 weeks after the end of treatment (evaluation at outpatient clinic is acceptable). If surgery is planned or performed within 24 hours of the time of enrollment, surgical site infection should be an object for the evaluation as well, which should be followed up until 1 month after the surgery and evaluated.
2) Clinical cure is defined as the condition in which infection signs have resolved, and no longer require additional antibacterial treatment. Because the clinical efficacy is the most important endpoint, it is recommended to evaluate the clinical efficacy based on changes in clinical findings and symptoms (scoring).Clinical failure is defined as follows:
   i) Persistent or recurrent intra-abdominal infection is documented by image findings, samples from percutaneous drainage, or findings at reoperation.
   ii) Postoperative surgical site infection
   iii) Death from persistent infection at the same site
   iv) Treatment with the other antibacterial drugs is implemented during the trial period, even if pelvic infection is not documented (When anti-MRSA drugs are concomitantly used to treat MRSA-mixed infection during a trial of an antibacterial drug without antibacterial activity of MRSA, or when antifungal drugs are concomitantly used to treat fungal infection, the indepent expert panel should determine whether to evaluate such a case or not).

5.1.2. Vulvitis (including Bartholinitis and abscess)

1) Clinical efficacy should be evaluated not only during the treatment (3 days after the first dose) and at the end of treatment but also 1 to 2 weeks after the end of treatment. Test of Cure should be evaluated at the later timepoint. Test of Cure evaluation is recommended to be evaluated 4 to 6 weeks after the end of treatment.
2) Clinical cure is defined as the condition in which infection signs (pain, size of the inflammation site, and pus) have resolved, and no longer require additional antibacterial treatment. Clinical failure is defined as follows:
   i) Signs and symptoms persist or have deteriorated.
   ii) An additional antibacterial therapy has been implemented to treat the target disease.
   iii) Treatment with the other antibacterial drugs is implemented during the trial period, even if infection is not documented (When anti-MRSA drugs are concomitantly used to treat MRSA-mixed infection during a trial of an antibacterial drug without antibacterial activity of MRSA, or when antifungal drugs are concomitantly used to treat fungal infection, the assessment committee should determine whether to evaluate such a case or not).

5.1.3. Bacterial vaginosis

Clinical efficacy for this disease should be evaluated not only based on the clinical symptoms but also according to Amsel's diagnostic criteria for bacterial vaginosis[1)] or the Nugent score[2)].

5.2. Microbiological Efficacy

Microbiological efficacy should be evaluated at the end of treatment with the investigational antibacterial drug and also at a point by the end of the final follow-up timepoint in accordance with Appendix 15 "Guidance for Microbiological Evaluation" in this guideline. In patients with mixed infection, the microbiological efficacy on individual bacterial species should be separately evaluated. For evaluation of relapse or reinfection, specimens for culture after starting treatment should be collected when the investigational antibacterial drug is not present at high concentrations in blood, tissues, or body fluid.

6. References

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Guidance for the Clinical Evaluation of Intestinal Infections

1. Object

1.1. Major Target Species

Bacteria that are isolated from patients evaluable for microbiological outcome and requiring susceptibility test results are as follows:

Shigella

Salmonella

Campylobacter

The other bacteria to be listed in the indication of the antibacterial drug (for instance, pathogenic *Escherichia coli*, *Vibrio*, and *Aeromonas*) may be determined based on results from *in vitro* susceptibility tests and PK/PD consideration in which concentrations of the antibacterial drug in stool ans others are included, because accumulation of the clinical cases is difficult.

1.2. Target Diseases

Intestinal infections. Or carriers of the target species (including post-infection carriers)

2. Inclusion Criteria

1) Patients with suspected intestinal infections caused by the target species.
2) Patients who experienced at least 5 bowel movements on (before) the day of the first dose.
3) Age: ≥ 20 years in general, but eligible age may be determined as appropriate for the antibacterial drug.

2.1. Exclusion Criteria

Patients should be excluded in accordance with the rules in Section 3.3 of the *General* section.

3. Dosing Methods and Treatment Duration

Doses, dosing interval, and treatment duration should be determined according to characteristics of the antibacterial drug to be developed. In principle, clinical evaluation should be able to be assessed after administrating them for at least the first 3 consecutive days. In addition, the desirable longest treatment duration is 7 days.

4. Timing of Evaluation and Observations

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

4.1.2. End of Treatment

The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated in response to cure or resolution within the specified number of days, observations applicable at this timing should be assessed.

4.1.3. Test of Cure

At this timing, whether the target disease is cured or not should be assessed. Culture specimens should be collected twice from patients with *Campylobacter* enteritis or shigellosis 2 to 7 days after the end of treatment and from those with *Salmonella* enteritis 7 to 10 days after the end of treatment, and these 2 culture should be separated by at least 24 hours.

4.2. Observations

Clinical symptoms (highest body temperature, stool description, number of bowl movements per day and abdominal pain, nausea, vomiting, and tenesmus, etc.) as well as hematology test (hematocrit, red blood cell count, white blood cell count, platelet count), blood biochemistry test (total bilirubin, liver enzymes, serum creatinine, CRP), urinalysis parameters, etc. should be followed up. Follow-up of clinical symptoms is not necessary for carriers.

5. Evaluation

5.1. Clinical Efficacy

Based on presence of clinical symptoms, the patient should be assessed as either “Success” or “Failure” by the investigator. If either assessment result is not applicable, the patient should be assessed as “Indeterminate.” Carriers, however, should be excluded from evaluation of the clinical effect.

5.2. Microbiological Efficacy

The microbiological efficacy should be assessed for each of the species isolated as causative bacteria in accordance with Table 1.

Table 1 Criteria for microbiological efficacy

	Definition
Success:	The result from microbial culture at the end of treatment is negative, and no subsequent relapse of causative bacteria occurs.
Failure:	− The result from microbial culture at the end of treatment is positive. − The result from microbial culture at the end of treatment is negative, but subsequent relapse of causative bacteria occurs.
Indeterminate:	− The result from microbial culture at the baseline is negative, and no subsequent shedding of causative bacteria occurs. − The other antibacterial drugs acting against the target species are used. − Any of the above assessments is not possible, for instance, microbiology test has not been performed for other reasons.

Guidance for the Clinical Evaluation of Ocular Infections

1. Object

1.1. Major Target Species

Streptococcus pneumoniae, *Haemophilus influenzae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Peptostreptococcus* sp., *Propionibacterium* sp., *Prevotella* sp., etc.

1.2. Target Diseases

Oral drugs: The following infections potentially caused by the above bacteria.
Blepharitis, hordeolum, and dacryocystitis

Injections: The following infections potentially caused by the above bacteria.
Orbital cellulitis (including eyelid abscess)
Keratitis, panophthalmitis (including endophthalmitis)

2. Inclusion Criteria/Exclusion Criteria

Patients should be excluded in accordance with the rules in Section 3.3 of the *General* section.

2.1. Diseases and Representative Causative Bacteria

- Blepharitis, hordeolum, and eyelid abscess: Bacterial infections in the eyelid skin, hair follicle, meibomian gland, etc. mostly caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*.
- Dacryocystitis: An acute or chronic bacterial infection in the lacrimal sac mostly caused by *Staphylococcus* sp., *Streptococcus pneumoniae*, and anaerobes.
- Keratitis: Infections triggered by corneal epithelial defect and associated with eye pain, ciliary hyperemia, and hypopyon. Mostly, ulcer forms at the corneal center. Frequently identified causative bacteria include *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella* sp., and *Serratia* sp.
- Orbital cellulitis: An intraorbital infection leading to eyelid swelling and proptosis. The most frequently identified causative bacteria is *Staphylococcus aureus*. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* may also cause the infection.
- Endophthalmitis: An intraocular infection that can develop through either exogenous or endogenous route. Exogenous endophthalmitis accounts for most of the cases. Gram-positive cocci such as *Staphylococcus* sp. and *Streptococcus* sp. are overwhelmingly major causative bacteria. The endogenous infection is mostly caused by Gram-negative bacilli such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa,* etc.

3. Dosing Methods and Treatment Durtaion

In principle, clinical evaluation should be made after administration for at least the first 3 consecutive days. The treatment duration should be 7 days, but may be extended to 14 days at the maximum.

4. Timing of Evaluation and Observations

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

4.1.2. Three Days after the First Dose (Days 3-4)

Observation during the treatment is critical in deciding whether to continue the treatment with the antibacterial drug or not. If signs and symptoms are not resolving, the investigators are required to make an appropriate decision, for instance, to discontinue the treatment with the antibacterial drug and switch to the other antibacterial drug, in due consideration of the subject's health.

4.1.3. End of Treatment (day of the end of treatment to 3 days after that)

The efficacy and safety at the end of treatment should be evaluated. When treatment is discontinued or terminated in response to cure or resolution within the specified number of days, observations applicable at this timing should be assessed.

4.1.4. Test of Cure (7 to 10 days after the end of treatment)

At this timing, whether the target disease is cured or not should be assessed. In foreign countries, this timing is deemed as the primary evaluation timepoint and thus critical for comparison with foreign data.

4.2. Observations

4.2.1. Symptoms and Findings

For each of the target diseases, two primary symptoms and findings and three secondary ones should be established.

Primary symptoms (in principle, they should be observed daily. For evaluation of an oral drug, they should be observed at the baseline, 3 days after the first dose, and at the end of treatment [at the time of discontinuation])

Blepharitis: Swelling, redness

Hordeolum: Swelling, pain

Dacryocystitis: Swelling, eye discharge

Orbital cellulitis (including eyelid abscess): Eyelid swelling, pain

Secondary symptoms and findings (only noteworthy symptoms and findings should be observed.)

Blepharitis: Eye discharge, hyperemia, foreign body sensation

Hordeolum: Eye discharge, hyperemia, foreign body sensation

Dacryocystitis: Redness, lacrimation, pain

Orbital cellulitis (including eyelid abscess): Exophthalmos, reduced visual acuity, eye discharge

To each symptom, 3 points (3+), 2 points (2+), 1 point (+), or 0 points (-) should be given.

4.2.2. Collection of Specimens for Microbiological Test

The microbiological test should be performed before starting treatment and at the end of treatment (or the time of discontinuation). Specimens for microbiological test should be eye discharge or eye secretion.

5. Evaluation

Severity assessment at the baseline

The total score on 5 symptoms and findings at the baseline should be calculated.

Severe: ≥ 10 points

Moderate: 5 to 9 points

Mild: ≤ 4 points

5.1. Clinical Efficacy at the End of Treatment (End of Treatment)

At the end of treatment, the clinical efficacy should be assessed as either "Success" or "Failure," or "Indeterminate" in accordance with the following definitions.

	Definition
Success:	The primary symptoms have resolved, or the symptom score is reduced to 1/4 of the initial within 1 week.
Failure:	The symptoms are not resolving.
Indeterminate:	Evaluation at the end of treatment is not possible due to dropout, exclusion, or other reasons.

5.2. Clinical efficacy at the Time of Test of Cure (Test of Cure)

Seven to 10 days after the end of treatment, the clinical efficacy should be assessed as either "Cure" or "Failure" or "Indeterminate" in accordance with the following definitions.

	Definition
Cure:	Signs and symptoms have resolved or are resolving, no longer requiring treatment with the antibacterial drug on the target disease.
Failure:	- Signs and symptoms persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease.
Indeterminate:	Information of symptoms and findings are missing, for reasons such as the non-attendance of subject at the date ecaluating End of Treatment. Cases where other antibacterial drugs have been administrated for a disease other than the target disease before the End of Treatment, even though the signs and symptoms attribute to the target disease had resolved or improved.

5.3. Microbiological Efficacy

The microbiological efficacy should be assessed in accordance with Appendix 15 "Guidance for Microbiological Evaluation" in this guideline.

For clinical evaluation of eye drops, see the guidance separately prepared by the Japanese Association for Ocular Infection.

Guidance for the Clinical Evaluation of Infections in Otorhinolaryngology

1. Object

1.1. Acute Otitis Media

1.1.1. Major Target Species

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella (Branhamella) catarrhalis

Group A *Streptococcus* (suppurative *Streptococcus*)

Staphylococcus sp. may be frequently detected in patients with spontaneous pus discharge, but presence of this genus is potentially attributable to contamination through the external auditory canal or microbial substitution from the other genus. To identify this genus as the causative bacteria, considerations should be given to the clinical symptom and situation of the detection.

1.1.2. Target Disease

Acute otitis media presumably caused by the above bacterial species.

Acute otitis media for clinical evaluation of antibacterial drugs may include recurrent otitis media and prolonged otitis media.

1.1.3. Inclusion Criteria/Exclusion Criteria

1.1.3.1. Inclusion Criteria

Patients who meet the diagnosis criteria for acute otitis media, are those who have ear pain, redness / protrusion of the tympanic membrane.In addition, it is desirable that the patients have fever.

1.1.3.2. Exclusion Criteria

1) Patients with otitis media with effusion, middle ear cholesteatoma, and adhesive otitis media as well as patients without intact tympanic mucosa due to prior surgery.
2) Patients with the following backgrounds and conditions that may affect clinical course of the infection:
   (a) Patients with severe infection for whom surgical treatment (except for tympanostomy or other dissection for microbiology test) is required to cure (for instance, patients who has facial swelling with systemic symptoms such as fever, those with middle ear mucosal edema or polypoid lesion associated with hyperplasia, opacity of the tympanic membrane, etc.).
   (b) Patients with severe complications such as acute mastoiditis, facial palsy, bacterial meningitis, cerebral abscess, etc.
   (c) Patients with congenital disorder such as maxillofacial dysplasia

1.1.4. Observations

For patients with bilateral symptoms, if the severity is similar on both sides, the right ear should be observed. If the severity is different between the right and left sides, the more severe side should be observed.

1.1.4.1. Symptoms and Findings

The following symptoms and findings should be followed up at all the Timing of Evaluation.

(a) Clinical symptoms

Ear pain and fever are main symptoms that must be obseved. It is recommended to grade the severity of symptoms with 3 levels, “None (normal)”, “Mild”, or “Severe”. For others, the additional symptoms suitable for clinical evaluation should be separately assessed if applicable.

(b) Tympanic membrane findings

Redness and protrusion are main findings that must be observed. It is recommended to assess the severity of the findings with 3 levels, “None (normal)”, “Mild”, or “Severe”. For others, the additional findings suitable for clinical evaluation should be separately assessed if applicable.

1.1.4.2. Collection of Specimens for Microbiology Test

It is not possible to collect of specimens in patients in whom clinical symptoms have resolved at the time of Test of Cure for microbiology test, because it is considered as an unethical and excessive intervention for the patient. Specimens for microbiology test should be collected before starting treatment and at the end of treatment or discontinuation.

If tympanostomy is possible, middle ear secretion should be collected by tympanostomy or puncture. If tympanostomy is contraindicated or unable to perform in the patient, (e.g pediatric patient), nasopharyngeal fluid may be collected by swabbing and used as a reference specimen for causative bacteria. If middle ear secretion is effluxed into the external auditory canal through tympanic membrane perforation, it should be removed by aspiration or debriding followed by disinfection on the external auditory canal, and then newly effluxed section should be collected. The causative bacteria should be isolated, cultured and identified. They also should be subjected to drug susceptibility test.

1.2. Acute Sinusitis

1.2.1. Major Target Species

Staphylococcus aureus

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella (Branhamella) catarrhalis

Oral anaerobes (*Peptostreptococcus* sp., *Porphyromonas* sp., *Prevotella* sp., etc.) may be as causative bacteria.

1.2.2. Target Diseases

Acute sinusitis supposed to be caused by the above mentioned bacterial strains

1.2.3. Inclusion Criteria/Exclusion Criteria

1.2.3.1. Inclusion Criteria

1) Patients who have the following symptoms and findings on day of the first dose of the antibacterial drug or one day before that, and have definitve inflammation findings caused by bacterial infection.
   (a) Redness is observed on the nasal mucosa.
   (b) Rhinorrhea or postnasal drip is purulent or mucopurulent.
   (c) Pathologic shadow in X-ray of the paranasal sinus should be used as a reference finding. Although

patients who have previous history of surgery should be excluded, those who have clearly intact maxillary sinus mucosa and in whom the last surgery was performed at least 365 days ago (for nasal polyp, patients in whom the removal procedure was performed at least 90 days ago) may be included.

1.2.3.2. Exclusion Criteria

Patients with the following factors and backgrounds that affect the infection:

1) Patients with severe infection for whom surgical treatment is required to cure (for instance, patients who have facial swelling with systemic symptoms such as fever, those with large nasal polyp that almost occludes the nasal cavity)
2) Patients with severe complications such as acute mastoiditis, facial palsy, bacterial meningitis, cerebral abscess, etc.
3) Patients with congenital disorder such as maxillofacial dysplasia

1.2.4. Observations

For patients with bilateral symptoms, if the severity is similar on both sides, the right side should be observed. If the severity is different between the right and left sides, the more severe side should be observed.

1.2.4.1. Symptoms and Findings

The following symptoms and findings should be observed at all the Timing of Evaluation.

(a) Clinical symptoms

Rhinorrhea and facial pain are main symptoms that must be observed. It is recommended to grade the severity of symptoms with 3 levels, “None (normal)”, “Mild”, or “Severe”. For others, the additional symptoms suitable for clinical evaluation should be separately assessed if applicable.

(b) Nasal cavity findings

Nasal discharge and postnasal drip are main findings that must be followed up. It is recommended to assess the severity of findings with 3 grades, “None (normal),” “Mild,” or “Severe.” For others, the secondary symptoms suitable for clinical evaluation should be separately assessed if applicable.

1.2.4.2. Collection of Specimens for Microbiology Test

It is not possible to collect of specimens for microbiology test in patients in whom clinical symptoms have resolved at the time of Test of Cure, because it is considered as an unethical and and excessive intervention for the patients. Specimens for microbiology test should be collected before starting treatment and at the end of treatment or discontinuation.

If possible, retained fluid should be collected by maxillary sinus stab. If maxillary sinus stab is unable to perform, the nasal discharge retained in the nasal cavity should be removed, and then secretion newly effluxed into the middle nasal meatus should be collected. Culture/detection for anaerobes (*Peptostreptococcus* sp., *Porphyromonas* sp., *Prevotella* sp., etc.) may be useful. The causative bacteria should be isolated, cultured, and identified. They should be also subjected to drug susceptibility test.

1.3. Acute Tonsillitis and Acute Laryngopharyngitis

1.3.1. Major Target Species

Group A *Streptococcus* (*Streptococcus pyogenes*)

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella (Branhamella) catarrhalis

Oral anaerobes (*Peptostreptococcus* sp., *Porphyromonas* sp., *Prevotella* sp., etc.) and others may act as causative bacteria.

1.3.2. Target Diseases

Acute tonsillitis and acute laryngopharyngitis potentially caused by the above bacterial strains

In addition, acute tonsillitis may include peritonsillitis and peritonsillar abscess in terms of the target disease. Acute laryngopharyngitis may include the cases with pharyngitis only.

1.3.3. Inclusion Criteria/Exclusion Criteria

1.3.3.1. Inclusion Criteria

1) Acute tonsillitis (including peritonsillitis and peritonsillar abscess)
   (a) Redness and pus plug, or pus laber are observed on the tonsil.
   (b) Peritonsillitis and peritonsillar abscess should be associated with peritonsillar swelling. In addition, peritonsillitis may not have to be associated with pus plug or pus laber, but peritonsillar abscess should be associated with pus.
2) Acute laryngopharyngitis (including pharyngitis only)
   (a) Pharyngeal pain (odynophagia) is recognized.
   (b) Redness or swelling is observed on the pharynx.
   (c) Pus, pus plug or pus laber is observed on the pharynx.
   (d) Laryngopharyngitis is associated with hoarseness.

1.3.3.2. Exclusion Criteria

Patients should be excluded in accordance with the rules in Section 3.3 of the *General* section.

1.3.4. Observations

For patients with bilateral symptoms, if the severity is similar on both sides, the right side should be observed, or if the severity is different between the right and left sides, the more severe side should be observed.

1.3.4.1. Symptoms and Findings

The following symptoms and findings should be observed at all the evaluation ttiming

The subjective symptoms of pharyngeal pain and odynophagia must be observed. It is recommended to assess the severity of symptoms with 3 levels, “None (normal)”, “Mild”, or “Severe”. As objective findings, the redness must be followed up, and symptoms characteristic to the target disease such as pus plug, pus laber, peritonsillar swelling (peritonsillitis), pus (peritonsillar abscess), and hoarseness (laryngopharyngitis) etc. should be additionally observed. It is recommended to assess the severity of the symptoms at 3 levels, “None (normal)”, “Mild”, or “Severe”. For others, the secondary symptoms suitable for clinical evaluation should be separately assessed if applicable.

1.3.4.2. Collection of Specimens for Microbiology Test

It is not possible to collect specimens for microbiology test at the time of Test of Cure is not possible in patients in whom clinical symptoms have resolved, because it is considered as an unethical and excessive intervention in the patient. Specimens for microbiology test should be collected before starting treatment and at the end of treatment or discontinuation.

From patients with acute tonsillitis (including peritonsillitis and peritonsillar abscess), pus plug and pus laber should be collected by scraping the tonsillar crypt. In addition, from patients with peritonsillar abscess, pus should be collected by stab or incision. The search for anaerobes (*Peptostreptococcus* sp., *Porphyromonas* sp., *Prevotella* sp., etc.) may be useful, if their involvement is suspected.

From patients with acute laryngopharyngitis (including pharyngitis only), specimens of purulent secretion (pus plug and pus laber on the lateral funiculus and posterior wall) should be collected.

The causative bacteria should be isolated, cultured and identified, and it should be subjected to drug susceptibility test.

2. Dosing Method and Treatment Duration

The dosing period should be 5 to 10 days in general, and patients who have received the drug for at least the first 3 consecutive days should be subjected to clinical evaluation.

In addition, the treatment duration and the shortest acceptable period for clinical evaluation should be determined according to characteristics of the antibacterial drug to be developed or an antibacterial drug.

3. Timing of Evaluation

Observation of symptoms and findings and laboratory test should be conducted on each day of observation based on the following criteria. In addition, Timing of Evaluation may be changed for individual studies based on these observation criteria.

3.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be screened to confirm that suitable subjects are included.

3.2. Three days after the First Dose (Day 2 to 4)

Observation on 3 days after the first dose is critical in deciding whether to continue the treatment with the antibacterial drug or not. If signs and symptoms are not resolving, the investigator should make an appropriate decision, for instance, to discontinue the clinical study and switch to the other antibacterial drug, in due consideration of the subject's health.

3.3. End of Treatment (0 to 3 days after the end of treatment)

At this timepoint, the microbiological efficacy should be specially evaluated.

3.4. Test of Cure (7 to 14 days after the end of treatment)

At this timepoint, the final clinical efficacy should be evaluated. The clinical efficacy should be evaluated based on the symptoms and findings specified for each disease.

3.5. At the Time of Discontinuation

At the time of discontinuation, the clinical and microbiological efficacy should be evaluated. The safety should be followed up wherever possible to ensure the health of subjects.

4. Evaluation

4.1. Severity Assessment

Severity should be assessed by giving appropriate scores to the clinical symptoms and objective responses on day of the first dose.

4.2. Clinical Efficacy Evaluation at the time of Test of Cure

The clinical efficacy should be assessed at the time of Test of Cure in accordance with the following criteria.

	Definition
Cure:	Signs and symptoms have resolved or are resolving, no longer requiring treatment with the antibacterial drug on the target disease.
Failure:	- Signs and symptoms persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease. - The patient died from the target disease.
Indeterminate:	Information about signs and symptoms are missing due to a lost of follow up at the time of Test of Cure, etc. Although symptoms and signs have resolved or are resolving, an antibacterial drug has been used (systemically) to treat a disease other than the target disease before Test of Cure.

4.3. Assessment of Microbiological Efficacy

The microbiological efficacy should be evaluated based on changes in amount of causative bacterium from the baseline to the end of treatment in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

The following considerations should be given to identification of causative bacteria.

4.3.1. Acute Otitis Media

If the microbiology test with middle ear secretion detects *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis*, and/or group A *Streptococcus* as the potential major causative bacterium (bacteria) of acute otitis media, such bacterium (bacteria) may be deemed as the actual causative bacterium (bacteria) irrespective of whether the infection is monomicrobial or polymicrobial. In addition, *Staphylococcus* sp. isolated from middle ear secretion may be deemed as the causative bacterium, if the bacterial amount is ≥ 2+, and the condition meeting either of the following i) or ii) is confirmed: i) the bacteria has been eradicated corresponding to changes in clinical symptoms; and ii) WBC phagocytosis is observed.

4.3.2. Acute Sinusitis

If the microbiology test with maxillary sinus stab or middle nasal secretion detects *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella (Branhamella) catarrhalis*, and/or anaerobes as the potential major causative bacterium (bacteria) of sinusitis, such bacterium (bacteria) may be deemed as the actual causative bacterium (bacteria).

5. Other Considerations

5.1. Target Diseases

Acute tonsillitis, acute laryngopharyngitis, and acute sinusitis are mostly caused by virus. The above inclusion and exclusion criteria of these diseases are mainly described for adult patients, but even in clinical studies in pediatric patients, patients applicable to antibacterial drugs should be included wherever possible.

In addition, acute otitis media more frequently occurs in pediatrics than in adults. In a study in pediatric patients with acute otitis media younger than 15 years, those without tympanic membrane tube placed, skull or facial malformation, or immunodeficiency should be included wherever possible. In principle, the same observations as those for adults should be used, but it is difficult for infants to report their symptoms such as ear pain, and thus signs like weeping or dysphoria should be alternatively used in the criteria.

To characterize the efficacy of an antibacterial drug, acute aggravation of chronicotitis media or chronicsinusitis may be included, but the clinical effect should be evaluated in subgroups divided according to stratification of these pathological conditions.

In this case, applicable acute exacerbation of chronicotitis media should be within 10 days after the exacerbation, and patients with middle ear cholesteatoma or those without intact tympanic mucosa due to prior surgery should be excluded. Applicable acute exacerbation of chronicsinusitis should be within 10 days after the exacervation, and patients without intact maxillary sinus due to prior surgery should be excluded.

Guidance for the Clinical Evaluation of Infections in Dentistry/Oral Surgery

1. Object

1.1. Major Target Species

Major causative bacteria in this field include *Staphylococcus* sp., *Streptococcus* sp., *Peptostreptococcus* sp., *Prevotella* sp., *Fusobacterium* sp., and *Porphyromonas* sp. The target bacteria should be determined according to characteristics of the antibacterial drug.

1.2. Target Diseases

Group I: Periodonititis (alveolar ostitis, alveolar periostitis, dental spportive tissue inflammation, periodontal abscess)

Group II: Pericoronitis (pericoronitis of the wisdom tooth)

Group III: Jaw inflammation (osteomyelitis of the jaw, periostitis of the jaw, jaw osteitis, perimaxillary inflammation)

Group IV: Cellulitis around the jawbone

2. Inclusion Criteria/Exclusion Criteria

2.1. Inclusion Criteria

1) Patients in whom causative bacteria can be identified (except for pericoronitis).
2) Age: Eligible age may be determined as appropriate for the antibacterial drug.
3) Of patients who received the other antibacterial drugs before the first dose of the antibacterial drug, those received the other one within 24 hours before the first dose or those who did not respond to the other one even given ≥ 24 hours before the first dose may be included.

2.2. Exclusion Criteria

Patients should be excluded in accordance with the rules in Section 3.3 of the *General* section.

3. Dosing Methods and Treatment Duration

Doses, dosing interval, and treatment duration should be determined according to characteristics of the antibacterial drug to be started. In principle, clinical response should be able to be assessed after administrating them for at least the first 3 consecutive days, and a treatment failure should be assessed after administration for at least 2 days. The treatment duration should be at least 3 days and may be extended up to 14 days according to characteristics of the drug.

4. Timing of Evaluation and Observations

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be adequately screened to confirm that suitable subjects are included.

4.1.2. Three Days after the First Dose (Days 3-4)

Observation during the treatment is critical in assessing the therapeutic efficacy of the antibacterial drug and deciding whether to continue the treatment or not. If signs and symptoms are not resolving, the clinical investigators are required to make an appropriate decision, for instance, to discontinue the clinical study and switch to the other antibacterial drug, in due consideration of the subject's health.

4.1.3. End of Treatment (day of the end of treatment or the following day)

It is a major evaluation timepoint in which the final clinical efficacy is assessed in the clinical study. In addition, when treatment is discontinued or terminated in response to cure or resolution within the specified number of days, observations applicable at this timing should be assessed.

4.1.4. Test of Cure (7 to 14 days after the end of treatment)

At this timing, whether the target disease is cured or not should be assessed.

4.2. Observations

4.2.1. Symptoms and Findings

General findings: Body temperature and others

Local findings: Severity of redness and heat sensation (intraoral, extraoral), swelling (intraoral, extraoral), pain (tenderness, spontaneous pain, odynophagia), the extent of trismus, etc. should be evaluated in accordance with the antibacterial drug efficacy criteria in the field of dentistry/oral surgery.[3)]

4.2.2. Collection of Sepcimens for Microbiological Test

In principle, specimens should be collected from obstructive abscess by fine-needle aspiration.

The collection of specimens should be evaluated as specified in Microbiological Test under 2. Inclusion Criteria/Exclusion Criteria, and the results should be assessed.

5. Evaluation

5.1. Clinical Efficacy

5.1.1. Clinical Efficacy at the End of Treatment (End of Treatment)

The clinical efficacy should be assessed based on the score ratio in accordance with the antibacterial drug efficacy criteria in the field of dentistry/oral surgery.[3)]

	Definition
Success:	Score ratio < 0.6
Failure:	Score ratio ≥ 0.6

5.1.2. Efficacy Evaluation at the time of Test of Cure

The efficacy should be assessed at the time of Test of Cure in accordance with the following criteria.

	Definition
Cure:	Signs and symptoms have resolved or are resolving, no longer requiring treatment with the antibacterial drug on the target disease.
Failure:	- Signs and symptoms persist or have deteriorated. - An additional antibacterialtherapy has been implemented to treat the target disease. - The patient died from the target disease.
Indeterminate:	Information of signs and symptoms are missing, for reasons such as the non-attendance of subject at the date evaluating Test of Cure. Cases where other antibacterial drugs have been administered (systemically) for a disease other than the target disease before the Test of Cure, even though the signs and symptoms attribute to the target disease had resolved or improved.

5.2. Microbiological Efficacy

The microbiological efficacy should be assessed based on the changing of causative bacterial load between baseline and the End of Treatment and Test of Cure in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

6. References

1) Kazuo Shiiki: I. Proposal of Antibacterial Drug Efficacy Criteria in the Field of Dentistry/Oral Surgery. Oral Therapeutics and Pharmacology 17:96-99, 1998
2) Kohsuke Ohono: II. Issues in Antibacterial Drug Efficacy Criteria.Oral Therapeutics and Pharmacology 17:100-102, 1998
3) Nobuo Yamane: III Antibacterial Drug Efficacy Criteria in the Field of Dentistry/Oral Surgery (new scoring method). Oral Therapeutics and Pharmacology 17:103-109, 1998
4) Akihiro Kaneko: IV. Quality of bacterial test materials and detection rate of dental infections. Oral Therapeutics and Pharmacology 17:110-113, 1998
5) Jiro Sasaki: VII. Clinical Study Guidance of Antibacterial Drugs in the Field of Dentistry/Oral Surgery. Oral Therapeutics and Pharmacology 17:121, 122, 1998

Guidance for the Clinical Evaluation of *Clostridium Difficile*-Associated colitis

1. Introduction

This section describes points to consider to obtain an approval for the indication of "infectious colitis (including pseudomembranous colitis)".

2. Object

2.1. Target Species

Clostridium difficile

2.2. Target Diseases

Guidance for the Clinical Evaluation of *Clostridium difficile*-Associated colitis

- *Clostridium difficile*-Associated colitis:

  This disease is classified into following three types by endospcopic findings; pseudomembranous colitis, nonspecific colitis, and diarrhea not associated with colitis. Pseudomembranous colitis is characterized by formation of circular yellowish-white pseudomembrane 1 to 2 cm in diameter on the colonic mucosa; non-specific colitis does not involve formation of pseudomembrane, but is associated mainly with redness, swelling, and edema on the mucosa; and diarrhea without colitis is associated with clinical symptoms of diarrhea but is characterized by normal appearance of the intestinal mucosa.

3. Inclusion Criteria/Exclusion Criteria

3.1. Inclusion Criteria

Adult patients with acute diarrhea in whom *Clostridium difficile* is isolated, or toxin is identified, and it is recommended to perform endoscopy for definitive diagnosis.

3.2. Exclusion Criteria

- Patients in whom the other enteric pathogen is isolated.
- Patients of whom stool results in massive isolation of *Staphylococcus aureus.*
- Patients who concomitantly receive vancomycin for injection and metronidazole.
- Patients who concomitantly take probiotic preparations.

4. Dosing Methods and Treatment Duration

In principle, clinical evaluation should be made after administration for at least the first 3 consecutive days.

5. Timing of Evaluation and Observations

The following observation of signs and symptoms and laboratory test should be performed on each observation day.

5.1. Timing of Evaluation

5.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be adequately screened to confirm that suitable subjects are included.

5.1.2. Three Days after the First Dose (Days 3-4)

Observation during the treatment is critical in deciding whether to continue the treatment with the antibacterial drug or not. If signs and symptoms are not resolving, the clinical investigators are required to make an appropriate decision, for instance, to discontinue the clinical study and switch to the other antibacterial drug, in due consideration of the subject's health.

5.1.3. End of Treatment (0 to 3 days after the end of treatment)

The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated in response to cure or resolution within the specified number of days, observations applicable at this timing should be assessed.

5.1.4. Test of Cure (21 to 28 days after the end of treatment)

At this timing, whether the target disease is cured or not should be assessed. In foreign countries, this timing is deemed as the primary evaluation timepoint and thus critical for comparison with foreign data.

5.2. Observations

5.2.1. Symptoms and Findings

Colitis symptoms such as diarrhea (frequency), abdominal pain, stool description (watery stool, mucous stool, bloody stool, muddy stool), abdominal bloating, nausea, vomiting, etc. and fever should be followed up. Of laboratory test parameters, white blood cell count should be determined, because leukocytosis is an important finding indicating the pathological condition.

In addition, detection status of exotoxins (cytotoxin, enterotoxin, and binary toxin) of *Clostridium difficile* should be checked.

Furthermore, it is desirable to make a definitive diagnosis of pseudomembranous colitis by endoscopically confirming formation of pseudomembrane on the intestinal mucosa.

5.2.2. Collection of Specimens for Microbiological Test

The microbiological test should be performed before starting treatment and at the end of treatment (the time of discontinuation).

Specimens for microbiological test should be stool collected.

6. Evaluation

6.1. Clinical Efficacy

6.1.1. Clinical Efficacy at the End of Treatment

The clinical efficacy should be assessed at the end of treatment in accordance with criteria on the following items.

The clinical efficacy should be assessed based on the clinical findings, and assessment results for the microbiological efficacy should be used as reference information.

Resolving of diarrhea symptoms: Daily loose stool, watery stool frequency of bowel movements, and frequency in the whole period

Improvement in stool form: Watery stool, loose stool, and solid stool

Duration of diarrhea: From the first dose to the first formed stool

Disappearance of pseudomembrane, edema, and colitis

The above items should be applied to the assessment.

6.1.2. Efficacy Evaluation at the Time of Test of Cure

The efficacy should be evaluated at the time of Test of Cure based on the clinical symptoms.

	Definition
Cure:	Signs and Symptoms have resolved or are resolving, no longer requiring treatment with the antibacterial drug on the target disease.
Failure:	- Signs and symptoms persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease.
Indeterminate:	Information of signs and symptoms are missing, for reason such as the non-attendance of subject at the date evaluating Test of Cure. Cases where other antibacterial drugs have been administrated (systemically) for a disease other than the target disease before the Test of Cure, even though the sings and symptoms attribute to the target disease had resolved or improved.

6.2. Microbiological Efficacy

The microbiological efficacy should be assessed based on the changing of causative bacteria load from baseline to the End of Treatment and Test of Cure in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline.

(Disappearance of *Clostridium difficile* and toxin should be used as supportive endpoints, but should not be used in the assessment of the clinical efficacy.)

Guidance for the Clinical Evaluation of Infections in pediatric population

1. Object

1.1. Major Target Strains

Basically, development of antibacterial drugs in the field of pediatrics should be implemented after the safety and efficacy are confirmed in adults. Many informations on target bacteria, therefore, may be acquired from previously conducted clinical trials in adult popluation.

For *Neisseria meningitidis, Bordetella pertussis*, and the like which are hardly isolated in clinical settings, the *in vitro* antibacterial activities should be mainly used to list these strains as applicable microorganism.

1.2. Target Diseases

- Acute tonsillitis, acute laryngopharyngitis, and scarlet fever

  If the substantial evidence suggests that the indications for tonsilititis and infections caused by *Streptococcus* sp. including Group A hemolytic *Streptococcus* are adequate, the indication for "scarlet fever"may also be warranted.
- Acute bronchitis and pneumonia

  Antibiotics are generally not indicated for treatment of acute bronchitis in adult populations, because most of the diseases caused by virus. Not a few acute bronchitis cases in pediatric population, however, are caused by bacteria including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Indications for pneumonia and acute bronchitis in pediatric population may be approved based on accumulated pediatric clinical cases of pneumonia and acute bronchitis if efficacy for pneumonia in adult population has been confirmed.
- Genital and Urinary Tract Infections (acute uncomplicated pyelonephritis, acute uncomplicated cystitis, complicated urinary tract infection, acute bacterial prostatitis, and acute epididymitis)
- Skin and soft tissue Infections (deep skin infection and infections secondary to injury, burn, and surgical wound)
- Infectious enteritis (limited to bacterial enteritis caused by *Shigella*, *Salmonella*, *Campylobacter*, etc.)
- Sepsis
- Suppurative meningitis
- Pertussis

For the following infections, which should be listed in the indications in pediatric populations as well, clinical studies should be conducted in accordance with guidance in the other specialties.

- Infections in otorhinolaryngology (acute otitis media, and acute sinusitis)
- Infections in orthopedics (suppurative osteomyelitis and suppurative arthritis)
- Intraabdominal infections (peritonitis and intraperitoneal abscess)
- Hepatobiliary infections (cholecystitis, cholangitis, and liver abscess)
- Infections in ophthalmology (blepharitis, hordeolum, dacryocystitis, orbital cellulitis [including eyelid abscess], keratitis, and endophthalmitis [including panophthalmitis])

- Infections in dentistry/oral surgery (periodontal inflammation and maxillary ostitis)
- Skin and soft tissue infections (infections secondary to injury, burn, and surgical wound)
- Obstetrical and Gynecological Infections (pelvic inflammatory disease, vulvitis, and bacterial vaginosis)

2. Inclusion Criteria

Diseases	Inclusion Criteria
Acute tonsillitis Acute laryngopharyngitis	- Symptoms such as fever, nasal discharge, cough, pharyngeal pain, and hoarseness are observed, and inflammatory findings such as redness are observed in the pharynx or larynx.
Scarlet fever	- Causative bacteria are locally detected in the infection site, or symptoms or findings suggestive of bacterial infections are observed.
Acute bronchitis	- Symptoms such as fever, cough, and sputum are observed; and continuous rales is recognized in chest auscultation; but no clear infiltrates in the lung field are observed in chest X-ray images. - Causative bacteria are detected in the respiratory tract, or symptoms or findings suggestive of bacterial infections are observed.
Pneumonia	- Symptoms such as fever, cough, and sputum are observed; and clear infiltrates in the lung field are observed in chest X-ray images. - Causative bacteria are detected in the respiratory tract or blood, or symptoms or findings suggestive of bacterial infections are observed.
Genital and Urinary Tract Infections	- Fever, pollakisuria, and miction pain are observed, and pyuria is observed in the urinalysis. - Causative bacteria are detected in the urine, or symptoms or findings suggestive of bacterial infections are observed.
Infectious Enteritis	- Fever, diarrhea, vomiting, and mucopurulent bloody stool are observed. - Causative bacteria are detected in the stool, or symptoms or findings suggestive of bacterial infections are observed.
Skin and soft tissue Infections	- Redness or blister is observed on the skin. - Causative bacteria are locally detected in the infection site, or symptoms or findings suggestive of bacterial infections are observed.
Sepsis	- Abnormal body temperature (hypothermia or fever) or general conditions suggestive of septicemia are observed. - Causative bacteria are detected in the blood, or symptoms or findings suggestive of sepsis are observed.
Suppurative meningitis	- Abnormal body temperature (hypothermia or fever), convulsion, consciousness disorder, and meningeal irritation are observed. - Causative bacteria are detected in the spinal fluid or blood, or symptoms or findings suggestive of bacterial infections are observed.
Pertussis	- Symptoms or findings suggestive of pertussis are observed. - *Bordetella pertussis* is detected in the respiratory tract, or pertussis is documented serologically.

3. Dosing Method and Treatment Duration

In principle, clinical evaluation should be made after administration for at least the first 3 consecutive days.

The treatment duration should be 7 days in general, but for severe diseases such as suppurative meningitis, treatment for at least 14 days is necessary.

Treatment duration and the shortest acceptable period for clinical evaluation should be determined according to characteristics of the antibacterial drug to be developed.

4. Timing of Evaluation and Observations

The following observation of signs and symptoms and laboratory test should be performed on visit. The evaluation period would be extended for patients in a severe condition, who may need long-term treatment.

4.1. Timing of Evaluation

4.1.1. Baseline (day of the first dose, Day 0)

During the baseline, patients should be adequately screened to confirm that suitable patients are included.

4.1.2. Three Days after the First Dose (Day 3)

Observation during the treatment is critical in deciding whether to continue the treatment with the antibacterial drug or not. If signs and symptoms are not resolving, the investigator should make an appropriate decision, for instance, to discontinue the clinical study and switch to the other antibacterial drug, in due consideration of the patient's health.

4.1.3. End of Treatment (day of the end of treatment to 3 days after that)

The efficacy and safety at the end of treatment should be evaluated. In addition, when treatment is discontinued or terminated in response to cure or resolution within the specified number of days, items applicable at this timing should be observed.

4.1.4. Test of Cure (7 to 10 days after the end of treatment)

At this timing, whether the target disease is cured or not should be assessed. In foreign countries, this timing is deemed as the primary Timing of Evaluation and thus important for comparison with foreign data.

4.2. Observations

4.2.1. Symptoms and Findings

Observations and examination items for each disease are shown below:

Diseases	Observation items (symptoms and findings)	Examination items
Acute tonsillitis, acute laryngopharyngitis, and scarlet fever	General condition, body temperature, and pharynx findings	Inflammatory findings, bacterial test
Acute bronchitis and pneumonia	General condition, body temperature, cough, and presence or absence of dyspnea	Inflammatory findings, bacterial test, chest X-ray (chest CT when necessary)
Genital and Urinary Tract	General condition, body temperature, pollakisuria, and miction pain	Inflammatory findings, urinalysis, and bacterial test
Infectious Enteritis	General condition, body temperature, description and frequency of diarrhea, and presence or absence of dehydration	Inflammatory findings, bacterial test
Skin and soft tissue Infections	General condition, body temperature, and local findings	Inflammatory findings, bacterial test
Sepsis	General condition and body temperature	Inflammatory findings, bacterial test
Suppurative meningitis	General condition, body temperature, presence or absence of meningeal irritation, presence or absence of consciousness disorder, presence or absence of convulsion, and presence or absence of anterior fontanelle, etc.	Inflammatory findings, spinal fluid findings, and bacterial test
Pertussis	General condition, cough, vomiting, cyanosis, apnea, and presence or absence of sleep disturance, etc.	Inflammatory findings, bacterial test, and anti-pertussis antibody

4.2.2. Collection of Specimens for Microbiology Test

The microbiology test is essential to evaluation of antibacterial drugs. There are potential risks that specimens are contaminated by indigenous bacteria other than causative bacteria if the sampling procedure is not appropriate, and thus considerations to avoid contamination must be given to ensure collecting appropriate specimens from the infection site. The microbiological test should be performed in accordance with Appendix 15 “Guidance for Microbiological Evaluation” in this guideline. The specimens and collection sites for microbiology test recommended for clinical trials for infections in pediatric populations are as follows:

Diseases	**Biological materials or collection sites**	**Notes**
Acute tonsillitis, acute laryngopharyngitis, and scarlet fever	Tonsil swab and pharyngeal swab	
Acute bronchitis and pneumonia	Sputum (nasopharyngeal swab) and blood (from patients with pneumonia)	Nasopharyngeal swab may be used depending on the collection condition.
Genital and Urinary Tract Infections	Urine	Urine through catheter should be aseptically collected.
Infectious Enteritis	Stool	Stool or anal swab should be used.
skin and soft tissue Infections	Infection site and pus by stab	
Sepsis	Blood	Venous or arterial blood
Suppurative meningitis	Spinal fluid and blood	
Pertussis	Nasopharyngeal swab	

5. Evaluation

5.1. Clinical Efficacy

5.1.1. Clinical efficacy at the End of Treatment (End of Treatment)

The clinical efficacy should be evaluated based on changes in symptoms and findings from the baseline to the end of treatment or discontinuation in accordance with the clinical efficacy criteria in "Criteria for Clinical Evaluation of Antibacterial Drugs in Pediatric Populations" by Japanese Society of Chemotherapy.

5.1.2. Efficacy Evaluation at the time of Test of Cure

The efficacy should be evaluated 7 to 10 days (at the time of Test of Cure) after the end of treatment or discontinuation in accordance with the following criteria.

	Definition
Cure:	Symptoms and signs have resolved or are resolving, no longer requiring treatment with the antibacterial drug on the target disease.
Failure:	- Symptoms and signs persist or have deteriorated. - An additional antibacterial therapy has been implemented to treat the target disease. - The patient died from the target disease.
Indeterminate:	- Information about symptoms and signs are missing due to a failure of office visit at the time of Test of Cure, etc. - Although symptoms and signs have resolved or are resolving, an antibacterial drug has been used (systemically) to treat a disease other than the target disease before Test of Cure.

5.2. Microbiological Efficacy

The microbiological efficacy should be evaluated at the end of treatment and at the time of Test of Cure in accordance with the microbiological efficacy evaluation in Appendix 15 "Guidance for Microbiological Evaluation" in this guideline.

5.3. Accetability for oral drug (only for oral drugs)

Acceptability of oral drug is an important issue for children.

The acceptability should be evaluated at the end of treatment in accordance with the following criteria. If a child refuses to take any drug, the assessment should be withheld, and the matter should be recorded in the case report form.

	Definition
Favorable:	When a patient is willing to take.
Easy:	When a patient takes the whole drug without any difficulty.
Moderate:	When a patient is reluctant to take the drug sometime, but finally takes the whole.
Hard:	When a patient is reluctant to take the drug, but finally takes most of the drug.
Not to take:	When a patient refuses to take the drug, or vomits after every dosing session.
Unknown:	When the taking status is unknown.

Guidance for Microbiological Evaluation

1. Introduction

In clinical studies of an antibacterial drug, the microbiology test result will be used as one of the important indeces in identification of causative bacteria that supports diagnosis of the infection and objective assessment of the efficacy of the antibacterial drug. The test may be performed using techniques such as culture, serological diagnosis, antigen detection, and genetic testing, etc., but an appropriate examination method should be selected in consideration of the disease, infection site, and target species. Especially, isolation and identification of causative bacteria by culture examination are important. By this examination, not only causative bacteria of the infection can be identified, but also the biological effect of the antibacterial drug can be directly evaluated based on subsequent changes in the amount of microorganism. The culture examination, however, requires appropriate collection of the specimens from the infection foci in advance. Highly reliable examination cannot be performed until appropriate specimens are properly stored and transported. The serological diagnosis, on the other hand, is performed to estimate causative bacteria based on antibody production in response to the infection, and thus is an indirect examination based on the biological response. In immunocompromised patients and those receiving immunosuppressive drugs or anticancer drugs, normal antibody production may not occur. In recent years, new microbiology test methods such as antigen detection of pathogen and genetic testing have been applied to infectious diseases. Although considerable advancements have been made on these methods in terms of susceptibility, specificity, and rapidity, it is important to use these methods based on adequate understanding of characteristics and precautions of each examination method. Although the examination methods other than culture and isolation may be often useful in diagnosis of the infection and estimation of causative bacteria, their use in the efficacy assessment have many issues, requiring careful considerations.

2. Facilities where microbiology test is performed

To perform a microbiology test for an antibacterial drug, a physician familiar with collecting appropriate specimens, microbiology laboratory with good quality control, and reliable microbiology laboratory technicians must be available. Concerning the above, the microbiology laboratory technicians must be trained for technical matters in microbiology tests for infections. Especially, microbiology tests require considerable skills in not only estimating causative bacteria by microscopic examination of smear preparations but also picking suspected colonies of causative bacteria, identifying, and performing drug susceptibility test. Since the microbiology laboratory technicians, therefore, play an important role in clinical studies of antibacterial drugs, if the test is performed in individual facilities, it is necessary to ensure their testing techniques and reliability as well as uncompromising quality control. As described below, it is desirable to perform test for susceptibility of causative bacteria to antibacterial drugs at one facility by collecting isolates from each of the participating facilities.

3. Actual Microbiology Test Practices and Points to Be Noted

The microbiology test in a clinical study differs depending on class and characteristics of the antibacterial drug, target diseases, and endpoints. For highly reliable results, it is recommended to prepare written procedures on the following items in details wherever possible.

3.1. Collection Method and Timing of Specimens

In culture examination, collection of appropriate specimens is critical. To ensure that specimens are collected from the infection site, the details should be specified in the protocol. Especially, if a specimen collected from the respiratory tract is macroscopically deemed to be saliva, re-collection of the specimen may have to be directed with results from microscopic examination of the smear preparation. For specimens in which contamination with indigenous bacteria is inevitable (sputum, urine, and stool), a written procedure should be prepared to reduce as much contaminating bacteria as possible (collection of sputum after oral washing and collection of midstream urine). In addition, if specimens are collected from an infant, which may be a special case, the specimen volume must be limited. Such a case may require an additional handling, for instance, diluting the specimen with a certain volume of liquid medium. Timepoints to collect specimens should be determined in consideration of the treatment duration of the antibacterial drug, basically including before treatment as well as timepoints during the treatment, at the end of treatment, and at the time of Test of Cure. Microbiology tests at the time of Test of Cure enables evaluation of development of drug-resistant bacteria and microbial substitution (phenomenon), etc. Because presence or absence of prior therapeutic drugs, their class, and time of their treatment considerably affect the microbiology test, especially the culture examination, these matters must be checked for each case.

3.2. Storage and Transportation of Specimens

The collected specimens must be transported to a microbiology testing facility, immediately. Especially, for specimens suspected of involving bacteria likely to die at low temperature or anaerobes, temperature and medium for transportation (such as transport system for anaerobes) should be appropriately specified. If it is inevitable to store specimens in a ward due to collection during night, a more specific storage method should be instructed, for instance, “specimens potentially contaminated with indigenous bacteria (stool and sputum) should be stored in a refrigerator, and aseptic specimens (spinal fluid and blood) should be placed in a culture bottle, and then stored in an incubator.” By setting acceptable hold time from collection of specimens to the microbiology test, reliable examinations will be ensured.

3.3. Qualitative and Quantitative Evaluation of Specimens and Estimation of Causative Bacteria by Microscopic Examination of Smear Preparations

It is necessary to evaluate not only whether the volume of a specimen is sufficient for microbiology test or not, but also whether it is qualitatively appropriate for the examination. Especially, a specimen of expectorated sputum can be evaluated in terms of whether it is appropriate for microbiology test by combination of macroscopic evaluation (Miller & Jones’ classification, etc.) and microscopic evaluation (Geckler’s classification, etc.). As described above, collection of appropriate specimens is the basis of microbiology test. If they are qualitatively insufficient, actions including re-collection of specimens will be required. Microscopic examination of the smear preparation is important not only in estimating identification of bacteria in the specimen, but also in determining whether the bacteria cause the infection or contaminate the specimen. Especially, findings such as bacteria phagocytized by white blood cells and bacterial clustering

consistent with the accumulation of white blood cells are considered to suggest that the observed bacteria cause the infection. Performance of the microscopic examination of the smear preparation largely depends on the skills of microbiology laboratory technicians, and from this viewpoint, it is desirable for such skilled technicians to work for the clinical study.

3.4. Culture and Identification Examination

To examine specimens by culture, conditions such as the pre-treatment method of the specimens, medium, and culture duration as well as the unified standards on the basis of semi-quantitative or quantitative culture system should be specified. Especially, picking of bacteria from grown colonies is a critical step that largely relies on the experience of the testing operator. If long-term observation is considered for anaerobes, auxotrophic mutants (HACEK group), bacteria only grown on a special medium (*Legionella* sp., etc.), or blood culture, a standard procedure should be prepared for the culture duration. Recently, isolates are frequently identified using an automatic analyzer, but it is known that the result differs depending on the analyzer in use to some extent. At this point, the microbiology test must be performed at a technically reliable facility, and quality control should be periodically recorded for each examination. If isolates are obtained from specimens contaminated with indigenous bacteria, it is often difficult to determine whether they are causative bacteria or contaminates. In this case, it should be comprehensively determined in consideration of changes in the amount of bacteria in the culture examination, results from microscopic examination of the smear preparations, clinical symptoms, and response to antibacterial drugs. If isolates are indigenous and low pathogenic bacteria (such as *Haemophilus parainfluenzae* in sputum), and microscopic examination of the smear preparations does not present findings suggesting that they may be causative bacteria, they should be determined to be contaminates. Bacteria isolated as causative bacteria should be stored for drug susceptibility tests and re-examinations for various parameters as described below. Because some bacteria are subject to be killed or to loss of drug-resistant factors during storage, due consideration should be given to selection of the storage method.

4. Microbiology Test other than Culture Examination

Important diagnosis methods to identify causes of the infection other than the culture examination include serum antibody examination, antigen detection of pathogen, and genetic testing. Especially, rapid diagnosis kits using immunochromatography have been recently developed, and their usefulness in clinical settings has been confirmed in terms of the sensitivity and specificity. Some of these diagnosis methods, on the other hand, are intended to be used in research settings. Microbiology test methods other than the culture method could be useful in diagnosis of the infection and estimation of causative bacteria, but their use in the efficacy assessment requires careful considerations.

In consideration of the target infection and causative pathogen, therefore, appropriate examination methods should be selected for each clinical study. Characteristics and precautions of each examination method are described below.

4.1. Serum Antibody Titer Assay

Basically, serum antibody titers (IgG, IgM) should be measured at 2 timepoints of the acute phase and recovery phase, and microorganisms against which the antibody titer increased at least 4 folds should be determined as causative ones. In some patients, however, the antibody titer remarkably increases already in

the acute phase, and thus inversely decreases in the recovery phase. In consideration of the above case, some examination methods sometimes use the remarkably high antibody titer in the acute phase as the criterion for definitive diagnosis. In addition, immunocompromised patients and those receiving immunosuppressive drugs or anticancer drugs may not adequately produce antibodies in response to the pathogen, and thus it should be noted that the serological diagnosis method gives a false negative result to these patients. If multiple serum antibody titer diagnosis kits are commercially available for particular causative bacteria, the same kit must be used to determine the antibody titer in one clinical study. The examination method to use should be carefully chosen based on the latest information about the sensitivity, specificity, simplicity, and reproducibility.

4.2. Antigen (Toxin) Detection of Pathogen

In recent years, antigen detection methods of pathogen using new technologies such as immunochromatography have been widely used in clinical settings. Table 1 shows representative antigen detection methods. Microbiological materials to be used as specimens include serum, pharynx and nasal cavity swabs, urine, stool, and spinal fluid. Frequently used antigen detection kits detect influenza virus antigen (nasal cavity swab), Group A hemolytic *streptococcus* antigen (pharynx swab), *Streptococcus pneumoniae* antigen (urine), and *Legionella* antigen (urine), etc. Kits that detect toxins produced by bacteria (verotoxin produced by enterohemorrhagic *Escherichia coli*, toxin and antigen produced by *Clostridium difficile*, etc.), which are not the microbial surface antigen, have been developed as well. It is necessary to pay attention not only to the sensitivity and specificity but also to the simplicity and reproducibility of the test, the duration of the positive result.

More specifically, it should be noted that the positive result in an examination for *Legionella* antigen in urine only indicates presence of antigen of *Legionella pneumophila* serogroup 1, and the negative result is given even if the other serogroup of *L. pneumophila* or the other *Legionella* strain is present. In addition, it has been known that patients positive for *Legionella* or *Streptococcus pneumoniae* shed the antigen into urine for several weeks once they become positive. In repeatedly infected hosts, whether this positive result reflects the current infection episode or a past history of the infection should be carefully determined.

It has been reported that a kit for Group A hemolytic *streptococcus* antigen (pharynx swab) responds to *Streptococcus* strains other than Group A hemolytic *streptococcus*, leading to agglutination.

In addition, it should be noted that detection of *Streptococcus pneumoniae* antigen in urine is not appropriate for children, because children, even healthy ones, have *Streptococcus pneumoniae* in the nasopharynx as indigenous bacterium, and thus a false positive result is often presented.

In patients with meningitis or infected with *Chlamydia*, on the other hand, the efficacy of an antibacterial drug can be evaluated using the clinical improvement and decrease in antigen of pathogen as indicators.

Table 1 Diagnosis of infection based on antigen detection of pathogen or toxin

Specimen	Target pathogen	Specimen	Target pathogen
Respiratory tract	Group A hemolytic *streptococcus*	Urine	*Legionella*
	Streptococcus pneumoniae, etc.		*Streptococcus pneumoniae*
Spinal fluid	*Streptococcus pneumoniae*	Blood	Lipopolysaccharide, etc.
	Haemophilus influenzae (type b)	Stool	*Escherichia coli* O157
	Escherichia coli		*Helicobacter pylori*
	Neisseria meningitidis		*Clostridium difficile*
	Group B hemolytic *streptococcus*	Genital secretion	*Chlamydia*

4.3. Genetic Testing

Amplification techniques such as PCR using gene sequences specific to pathogens are widely applied to diagnosis methods of infections. It should be noted, however, that some of these methods are intended to be used in research settings. Irrespective of the intended use, the gene amplification technique is widely used, because theoretically the specific gene can be detected even if only several copies of the gene are present. Some methods, however, are known to have sensitivity considerably compromised by inhibitors in specimens. Conventionally, this technique is applied to specimens of sputum from patients with pneumonia as a prompt diagnosis procedure in place of culture to search for causative bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. These bacteria, however, are frequently detected even in the healthy pharynx, and thus the pathogens cannot be identified only based on results from the genetic testing. This technique, on the other hand, is highly useful for identification of pathogens that are not indigenous in humans such as *Mycobacterium tuberculosis* and *Legionella* sp. In addition, the genetic testing basically cannot differentiate viable bacteria from dead ones. In patients in whom the treatment has been initiated in response to the positive result, genes derived from dead bacteria possibly lead to the persistent positive result. That is, the genetic testing is often useful for confirmation of causative bacteria of the infection because of the high sensitivity and specificity as well as rapidity, but to use this method for the efficacy evaluation, issues such as false positive due to detection of dead bacteria should be considered. There is, however, accumulation of cases where the culture indicates the negative result, but the causative bacteria are detected by the genetic testing, especially, in cases with the limited volume of specimens available, for instance, pediatric cases of acute otitis media.

Use of the genetic testing for identification of pathogens and evaluation in a clinical study should be adequately justified where applicable.

5. Drug Susceptibility Test

Strains isolated as causative bacteria should be subjected to drug susceptibility test to various antibacterial drugs. Results from the drug susceptibility test not only support the clinical effect of the antibacterial drug but also enable comprehensive efficacy evaluation of the antibacterial drug in combination with the

disposition data of the drug (PK/PD consideration). Usually, the drug susceptibility test is performed according to a broth microdilution method or agar plate dilution method as specified by the Japanese Society of Chemotherapy. In addition to the Japanese Society of Chemotherapy, the US Clinical and Laboratory Standards Institute (CLSI) also issued the guideline including the measurement method of drug susceptibility and criteria for sensitivity and drug resistance of various antibacterial drugs for each strain. In accordance with these guidelines, the test results should be interpreted. In a multicenter study, isolated and identified causative bacteria should be subjected to drug susceptibility test at the same facility wherever possible. Measurements of drug susceptibility of the causative bacteria before and after treatment with the antibacterial drug will provide useful information about a relationship between induction of drug-resistance and clinical efficacy.

6. Evaluation of Microbiological Effect

Evaluation of the efficacy from a microbiological viewpoint should be made based on the response of the causative bacteria at the End of Treatment and Test of Cure. If another evaluation system is necessary due to characteristics of the antibacterial drug, or the target infections or bacteria are special, appropriate evaluation criteria should be specified for each study protocol, including changes in antigen of pathogen described above. For instance, if special drug-resistant bacteria are targeted, the drug-resistant factors present in these bacteria should be genetically investigated, and using these factors as a marker of changes in the amount of bacteria may facilitate extensive investigations of not only effects against causative bacteria but also the trend of the microbial substitution phenomenon, or the manifestation of new drug-resistant bacteria. For such investigations, necessary examination procedures and appropriate evaluation criteria should be specified in advance. If multiple bacterial species are considered to cause the infection, not only the microbiological effect should be assessed for each subject, but also the effect should be evaluated for each causative bacteria. In such a case, utilizing genetic tests to each causative bacteria supplmentally may be useful to some extent to assessment of the microbiological effect of each subject as well as evaluation of dynamics of the bacteria involved in each pathological conditions. In addition, correlation between the microbiological effect on each of the causative bacteria and results from the corresponding drug susceptibility test should be discussed to evaluate the efficacy.

6.1. Microbiological Effect on each Causative Bacteria

For the microbiological effect, endpoints to be listed in the criteria should be specified for each of the target diseases. Assessment should be made on the each day of evaluation for each of the estimated causative bacteria (Table 2). Table 2 and Table 3 comprehensively cover microbiological events generally observed in clinical studies, but from a biostatistical viewpoint, the microbiological effect should be assessed as “Eradicated,“ “Presumably eradicated,“ “Persists,“ “Presumably persists,“ or “Indeterminate.“ According to characteristics of the disease such as skin infections, the effect may be assessed as “Colonization” or “Relapse, etc.”

Table 2 Assessment of Microbiological Effect on each of the Causative Bacteria

Assessment	Definition	Handling for analysis
Eradicated	Causative bacteria are not detected in specimens appropriately collected after treatment with the antibacterial drug.	Eradicated
Presumably eradicated	When clinical symptoms are resolving or have resolved in response to the treatment, and the initial infection foci no longer provides specimens appropriate for examination, the causative bacteria are estimated to have been eradicated.	
Colonization*	Obvious symptoms and signs of the infection have resolved in response to the treatment, but the initial causative bacteria are detected at the same site.	
Persist	Clinical symptoms are not resolving, and the initial causative bacteria are detected at the infection focus.	Persist
Presumably persist	When clinical symptoms are not resolving, and isolation from appropriately collected specimens is impossible or not conducted, the causative bacteria are estimated to persist.	
Relapse*	The causative bacteria are documented to have disappeared, but the same pathogenic bacteria are subsequently detected in specimens of the same infection site again. This result may be mainly applied to assessment for relapse at Test of Cure.	
Indeterminate	The microbiology test is performed, resulting in a failure of isolation or estimation of the causative bacteria. Or the microbiology test is not performed for other reasons.	Excluded

*, May be adopted where necessary.

6.2. Microbiological Effect of Each Subject

The microbiological effect is assessed for each subject. Where necessary, “microbial substitution” and “concomitant infection” may be adopted according to characteristics of the disease in consideration of the polymicrobial infection (see Table 3 on the following page).

In the analysis of the microbial eradication rate for each causative bacteria, the following assessment results should be handled as “Eradicated” in terms of the microbiological effect: “Eradicated” and “Presumably eradicated” as well as “Colonization” which is considered to be clinically effective, and “Microbial substitution” in which the pathogen susceptible to the antibacterial drug has been eradicated, and another pathogen not listed as proposed applicable microorganism newlymanifests. Patients with “Indeterminate” are not included in the denominator. To handle the response to polymicrobial infection as “Eradicated” in the analysis of the microbiological effect, all the causative bacteria are required to have been eradicated.

Table 3 Assessment of Microbiological Effect for Each Subject

Assessment	Definition	Handling for analysis
Eradicated	Causative bacteria are not detected in specimens appropriately collected after treatment with the antibacterial drug.	Eradicated
Presumably eradicated	When clinical symptoms are resolving or have resolved in response to the treatment, and the initial infection foci no longer provides specimens appropriate for examination, the causative bacteria are estimated to have been eradicated.	
Colonization*	Obvious symptoms and signs of the infection have resolved in response to the treatment, but the initial causative bacteria are detected at the same site.	
Persist	Clinical symptoms are not resolving, and the initial causative bacteria are detected at the infection focus.	Persist
Presumably persist	When clinical symptoms are not resolving, and isolation from appropriately collected specimens is impossible or not conducted, the causative bacteria are estimated to persist.	
Microbial substitution*	The initial causative bacteria have been eradicated in response to the treatment, and the other new pathogenic microorganisms are detected at the same site in association with obvious symptoms and signs of an infection.	
Concomitant infection*	While the initial causative bacteria are persisting, new different bacteria may manifest; and then in association with the above manifestation, clinical or laboratory findings related to the infection persist or are aggravated.	
Relapse*	The causative bacteria are documented to have been eradicated, but the same pathogen is subsequently detected in specimens of the same infection site again. This result may be mainly applied to assessment for relapse at Test of Cure.	
Indeterminate	Any of the above assessments is not possible, for instance, microbiology test has not been performed for other reasons.	Excluded

*, May be adopted where necessary.

6.3. Microbial eradication rate

Usually, the eradication rate of the causative bacteria is determined according to the following formula. If the causative bacteria are deemed to become indigenous bacteria according to characteristics of the disease such as skin infection, the assessment result for “Colonization” should be added.

$$\text{Microbial eradication rate (\%)} = \frac{\text{“Eradicated“ + “Presumably eradicated“ + “Colonization*“}}{\text{Patients subjected to assessment of the microbiological effect}} \times 100$$

*, May be adopted where necessary.

In the analysis of the microbioligical eradication rate for each of the causative bacteria, the following assessment results should be handled as “Eradicated” in terms of the microbiological effect: “Eradicated” and “Presumably eradicated” as well as “Colonization” which is considered to be clinically effective. Patients with “Indeterminate” are not included in the denominator.

To assess the effect on urinary tract infections (UTIs), the criteria for the corresponding disease should be used. For instance, the result is assessed as “Eradicated” or “Persist” based on the amount of bacteria in urine in accordance with the criteria for evaluation of clinical efficacy of antibacterial agents on UTIs.

Attachment

Applicable microorganism (genus, species, group) Examples

[Aerobic Gram-positive cocci]

Staphylococcus:	*Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*
Streptococcus:	Group A hemolytic *streptococcus*, *Streptococcus pneumoniae*, the other *Streptococcus*
Enterococcus:	*Enterococcus faecalis*, *Enterococcus faecium*, *Enterococcus avium*, vancomycin-resistant *Enterococcus faecium*, the other *Enterococcus*
Micrococcus	

[Aerobic Gram-negative cocci]

Neisseria:	*Neisseria gonorrhoeae*, *Neisseria meningitidis*
Moraxella:	*Moraxella (Branhamella) catarrhalis*

[Aerobic Gram- positive bacilli]

Listeria:	*Listeria monocytogenes*
Erysipelothrix:	*Erysipelothrix rhusiopathiae*
Corynebacterium:	*Corynebacterium diphtheriae*
Bacillus:	*Bacillus anthracis*, *Bacillus cereus*
Nocardia	

[*Enterobacteriaceae*]

Escherichia:	*Escherichia coli*
Shigella:	*Shigella dysenteriae*
Salmonella:	*Salmonella typhi*, S*almonella paratyphi*, *Salmonella* (except for *Salmonella typhi and* S*almonella paratyphi*)
Citrobacter	
Klebsiella:	*Klebsiella pneumoniae*, *Klebsiella oxytoca*
Enterobacter:	*Enterobacter cloacae*
Serratia:	*Serratia marcescens*
Proteus:	*Proteus mirabilis*, *Proteus vulgaris*
Morganella:	*Morganella morganii*
Providencia:	*Providencia rettgeri*, *Providencia inconstans*
Yersinia:	*Yersinia pestis*

[*Vibrionaceae*]

Vibrio:	*Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*, the other *Vibrio*
Aeromonas:	*Aeromonas hydrophila*, *Aeromonas sobria*, *Aeromonas caviae*

[Pasteurellaceae]

Pasteurella:	*Pasteurella multocida*
Haemophilus:	*Haemophilus influenzae*, *Haemophilus ducreyi*, *Haemophilus aegyptius* (Kochc-Weeks bacillus)
Aggregatibacter:	*Aggregatibacter actinomycetemcomitans*

Attachment

Applicable microorganism (genus, species, group) Examples

[Non-fermenting gram-negative bacilli]

Pseudomonas:	*Pseudomonas aeruginosa*, *Pseudomonas putida*, *Pseudomonas fluorescens*
Burkholderia:	*Burkholderia cepacia*, *Burkholderia pseudomallei*
Stenotrophomonas:	*Stenotrophomonas* (*Xanthomonas*) *maltophilia*
Acinetobacter:	*Acinetobacter baumannii*, *Acinetobacter calcoaceticus*
Flavobacterium:	*Flavobacterium meningosepticum*
Alcaligenes:	*Alcaligenes faecalis*

[*Legionellaceae*]

Legionella:	*Legionella pneumophila*, the other *Legionella*

[Aerobic Gram-negative coccobacilli]

Brucella:	*Brucella abortus*
Bordetella:	*Bordetella pertussis*
Francisella:	*Francisella tularensis*

[Microaerophilic Gram-negative bacteria]

Campylobacter:	*Campylobacter jejuni*, *Campylobacter coli*
Helicobacter:	*Helicobacter pylori*

[Anaerobic Gram-positive cocci]

Peptostreptococcus

[Anaerobic Gram-negative bacilli]

Bacteroides:	*Bacteroides fragilis*
Prevotella:	*Prevotella intermedia*, *Prevotella melaninogenica*, *Prevotella* (except for *Prevotella bivia*)
Porphyromonas:	*Porphyromonas gingivalis*
Fusobacterium:	*Fusobacterium nucleatum*

Capnocytophaga

[Anaerobic Gram- positive bacilli]

Clostridium:	*Clostridium tetani*, *Histotoxic clostridia*, *Clostridium difficile*
Actinomyces:	*Actinomycete*
Propionibacterium:	*Propionibacterium acnes*
Eubacterium:	*Eubacterium lentum*

[Others]

Mycobacterium:	*Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium avium complex* (MAC), *Mycobacterium kansasii*, *Mycobacterium intracellulare*
Gardnerella:	*Gardnerella vaginalis*

Attachment

Applicable microorganism (genus, species, group) Examples

[*Spirochaetaceae*]

Treponema:	*Treponema pallidum*
Borrelia:	*Borrelia recurrentis*

[*Leptospiraceae*]

Leptospira:	*Leptospira interrogans* serovar icterohaemorrhagiae

[*Rickettsiaceae*]

Rickettsia:	*Rickettsia* (*Orientia tsutsugamushi*)
Coxiella:	Q fever Rickettsiae (*Coxiella burnetii*)

[*Chlamydiaceae*]

Chlamydia:	*Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Chlamydia psittaci*

[*Mycoplasmataceae*]

Mycoplasma:	*Mycoplasma pneumoniae*, *Mycoplasma genitalium*
Ureaplasma:	*Ureaplasma urealyticum*