COMMITTEE REPORT

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Clinical evaluation methods for new antimicrobial agents to treat respiratory infections: Report of the Committee for the Respiratory System, Japan Society of Chemotherapy

Abstract
The present report constitutes an attempt to improve and modify the existing clinical evaluation method for new antimicrobial agents to treat respiratory infections. One year ago, a general guideline on the clinical evaluation of antimicrobial agents to treat respiratory infections was drafted in Japanese, leaving scope for critical discussion, and this has been translated into English, as there were no major changes. In this report, respiratory infections have been discussed under the headings "acute respiratory tract infection" and pneumonia and acute exacerbation of chronic pulmonary diseases. Standardized criteria were set for the assessment of severity of infection and effectiveness of the antimicrobial agent in question. Severity was evaluated on the basis of a combined assessment of the severity of infection and severity of the clinical condition of the patients. Clinical effectiveness of the antimicrobial agent used was evaluated on the basis of clinical outcome as well as microbiological outcome of the trial. Body temperature, local pain, cough, change in sputum quality, peripheral white blood cell count, C-reactive protein level, and chest radiograph were used as the parameters for the evaluation. To maintain the quality of specimens to be examined, Geckler's classification of specimens was used. This report was constructed based on the analysis of large amounts of material collected over the years, incorporating internal and external factors concerning the present evaluation methods. The newly suggested standardized criteria for clinical evaluation of the new antimicrobial drugs are expected to be practiced properly hereupon and subjected to further improvement if necessary.

Key words Committee report · Clinical evaluation method · Antimicrobial agents · Respiratory infection

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Introduction

The committee for Clinical Evaluation Methods for New Antimicrobial Agents was established in 1993 after the 41st general meeting of the Japan Society of Chemotherapy (June 1993) was concluded. A special meeting was held, with the aim being international harmonization between Japan, the United States, and Europe in the area of clinical evaluation of antimicrobial agents. The guidelines for USA[1] and Europe,[2] which were presented at the meeting, showed 95% conformity with each other. Before that, in 1991, the first International Conference on Harmonization (ICH) was held in Brussels, Belgium. However, Japan had its own guidelines issued by the Ministry of Health and Welfare, known as Good Clinical Practice (GCP), and this went into effect from February 1990.[3,4] Against this background at home and abroad, the Director of the Japan Society of Chemotherapy, Masatoshi Konno, established the Committee for Clinical Evaluation Methods for New Antimicrobial Agents as a special committee of the Society. One of the reasons for the establishment of this special committee was that despite the advanced level of technical development in

producing antimicrobial agents in Japan, the clinical evaluation of these new antimicrobial agents has not necessarily been accepted by the rest of the world. So, it was high time for Japan to establish its own clinical evaluation methods for antimicrobial agents which incorporated the viewpoints on international harmonization. The Committee for Clinical Evaluation Methods for New Antimicrobial Agents consisted of three separate committees: Committee for the Respiratory System, Committee for the Urinary System, and Committee for Preventing Postoperative Infections. An international meeting was held in 1995 during the 43rd General Meeting of the Japanese Society of Chemotherapy, with the aim being international harmonization of the clinical evaluation of antimicrobial therapy. Mr. S. Ragnar Norrby of Sweden, representing the Committee for European Guidelines, Mr. Murray M. Lumpkin of the Food and Drug Administration (FDA), United States, and Mr. William R. Darrow of the Schering Plough Research Institute, United States, were guest speakers.[5–7] On behalf of Japan, the three Subcommittee Chairmen of the Committee for Clinical Evaluation Methods for New Antimicrobial Agents announced the committee reports at that meeting.[8–10] The authors of this report belong to the Committee for the Respiratory System.[8]

The Committee for the Respiratory system, guided by the principles of international harmonization, had organized regular meetings and drafted the general guidelines for the clinical evaluation of antimicrobial agents in the light of those issued by the FDA in the USA and the Infectious Diseases Society of America (IDSA).[11] The next step was to investigate various viewpoints in order to establish the guidelines for Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections. In this report, we have attempted to describe and discuss all the relevant details of the methods that should be adapted for the clinical evaluation of antimicrobial agents used to treat respiratory infections.

Clinical evaluation methods in brief

Basic concepts and range of indications

The Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infection was outlined on the basis of need for international harmonization and also in conformity with the Japanese good clinical practice (GCP) standards.[12–14]

The guidelines of the IDSA involved bacterial infections of the five respiratory organs, which are, precisely, streptococcal pharyngitis and tonsillitis, otitis media, paranasal sinusitis, bronchitis, and pneumonia.[1] However, in Japan, otitis media and paranasal sinusitis are commonly dealt with in the field of ear, nose, and throat (ENT) rather than being considered as respiratory disease.[12,13] Taking this into consideration, respiratory infections were classified into three groups: (1) Acute upper respiratory tract infections, including acute tonsillitis, acute pharyngitis, acute bronchi-

tis, peritonsillar abscess, and retropharyngeal abscess; (2) pneumonia; and (3) acute exacerbation of chronic pulmonary diseases. This classification is appropriate for the clinical evaluation of antimicrobial agents, particularly during phase II and III trials and it can also be applied for phase IV trials.

In infections other than those mentioned above, in particular, suppurative pulmonary disease, such as lung abscess and empyema, trials should be undertaken after the respective standards are established.

Inclusion and exclusion criteria

The criteria for selecting patients for clinical trials were set with the objective of having better evaluation of the effects of the trial drug. In this regard, the severity of the patient's clinical condition and the severity of the infection itself were considered carefully. Each particular disease entity has an individual pattern and, likewise, they have different standards for selection.

In some patients with acute upper respiratory tract infection there are some underlying diseases which could impair the clinical effects of the trial drug. Thus, the standard was made for this group only on the basis of severity of the infection itself, without considering the underlying disease, if any.

So far as other groups, e.g., pneumonia and acute exacerbation of chronic pulmonary diseases, are concerned, the severity of the clinical condition was determined by combining the severity of the infection itself and that of any underlying diseases or complications. In general, the severity of the patient's clinical condition is largely influenced by the underlying disease severity, which makes it difficult to properly evaluate the antimicrobial drug under trial. Therefore, it has been suggested to exclude any patient considered as "severe" from the clinical evaluation.

Effectiveness of antimicrobial agent

The effectiveness of an antimicrobial agent under trial is evaluated on the basis of its microbiological effects and clinical effects. The parameters used are the course of the etiologic agent and the speed of improvement in signs and symptoms. The evaluation should be done at two time points, after 3 and 7 days of treatment. Conventionally, a trial drug used to be administered for 14 days, but it has been recognized now that any patient requiring 14 days of treatment is an exception. According to present standardization, drug administration should be discontinued if an etiologic agent is considered as eradicated by the 3rd day of treatment on the basis of clinical and microbiological evaluation. But a subsequent follow-up is necessary. The degree of leeway allowed regarding the test performance should be predetermined in the protocol.

The evaluation of microbiological effects is conducted as per the *General guidelines on clinical evaluation of antimicrobial drugs*, 1996.[15] The standards should be recorded in the protocol in advance. The clinical effects are evaluated as

an objective standard and divided into two categories: "effective" and "not effective" instead of extremely effective and slightly effective. In addition, when the clinical effects cannot be evaluated for some reason, the remark "evaluation not possible" is to be recorded.

Further, a comprehensive evaluation is conducted on the basis of clinical effects, microbiological effects, and the safety (objective and subjective adverse effects and any test abnormalities). The evaluation methods and standards should be determined for any particular disease and they must be prerecorded in the protocol. The evaluation of safety is conducted in accordance with the *General guidelines on the clinical evaluation of anti-infective drugs*, 1996[15] and the evaluation standards for adverse reactions and clinical test result abnormalities in clinical trial patients treated with antimicrobial agents.[16]

In general, evaluation of the effectiveness of an antimicrobial agent is done at the end of treatment (EOT), but the infection may flare up again and may recur after the EOT, even though the trial drug was thought to be effective initially.[1] For this reason, physical examination and laboratory tests should be performed at a defined time period after the EOT for a final evaluation which indicates the end of study (EOS). For respiratory infection, the appropriate time period is suggested to be about 1 week.

Clinical evaluation of new antimicrobial agents in acute respiratory tract infections

Concept of the disease and indications for clinical evaluation of antimicrobial agents

Acute upper respiratory tract infections cover range of illness from common cold to acute bronchitis. Acute bronchitis is an infective inflammation of the respiratory tract extending downwards from the glottis. It is a lower respiratory tract infection, but also shares some characteristics which should be included in the pathophysiology of upper respiratory tract infections. Clinical evaluation of oral antimicrobial agents was undertaken in patients with acute tonsillitis, acute pharyngitis, acute laryngopharyngitis, and acute bronchitis. Peritonsillar abscess (including severe crypttonsillitis and peritonsillar inflammation) and retropharyngeal abscess were subject to trial with injectible antimicrobial agents. Infections accompanied by some underlying chronic respiratory diseases are classified separately.

Most upper respiratory tract infections start initially as a common cold and frequently the infection descends, involving the lower respiratory tract. The primary etiologic agents encountered in common cold are often viruses, as some viral pathogens, such as rhinovirus, coronavirus, influenza virus, adenovirus, coxackievirus, and respiratory syncytial virus, have a particular predilection for the respiratory tract.[17,18] A secondary bacterial infection may result in the involvement of lower respiratory tract. However, the distribution of the infectious pathogens varies according to the site of involvement. In acute tonsillitis and peritonsillar abscess, the pathogens are β-*hemolytic streptococcus*, *Haemophillus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, in order of frequency.[19–21] In acute pharyngitis,[22,23] the most commonly encountered bacteria are *S. pneumoniae* and *H. influenzae* and then β-h*emolytic streptococcus* and *S. aureus*. Among the etiologic agents of acute bronchitis,[24] *S. pneumoniae* and *H. influenzae* are frequently seen, followed by *Moraxella* (*Branhamella*). Other organisms are S. aureus and β-*hemolytic streptococcus* with a lower frequency of occurrence. *Mycoplasma* upper respiratory tract infections are common during the prevalence period.[25] In addition, *Chlamydia* (*Chlamydia psittaci* and *Chlamydia pneumoniae*) is also involved in acute respiratory tract infection.[26]

Patients infected by one of the above pathogens, as diagnosed by bacteriological examination, or those who are highly suspected to be infected but still not confirmed are appropriate subjects to include in a clinical trial of new antimicrobial agents. Patients with insignificant microbiological test results, but having signs and symptoms of acute respiratory tract infection, such as high WBC count or productive cough of purulent nature are also suitable for inclusion in the trial.

In *Mycoplasma* and *Chlamydia* infections the host response, as well as the physical evidence, is mild and, interestingly, recovery is also slow even after treatment with an antimicrobial agent. In these patients, standards for inclusion in and evaluation of the trial should be set out separately.

Diagnostic standards

Microbiological diagnostic standards

It is very important to determine the etiologic agents in patients with respiratory infection who are selected as subjects for a trial for clinical evaluation of a new antimicrobial agent. The most important and commonly used methods for identifying an infectious pathogen, are microscopic examination of smears and culture of specimens in appropriate media. The sample should be collected with a sterile cotton swab before administration of the antimicrobial agent is commenced. The swab should be scratched along the posterior pharyngeal wall and uvula, and the surface of the suppurating tonsils in patients with pharyngitis and tonsillitis, respectively, to collect a sample. The sample is then cultured in an appropriate medium, e.g., blood agar medium, for 16–18h at 37°C. In acute bronchitis, the sample is obtained from the purulent area of the sputum and is cultured as described above. Samples that may be contaminated with normal flora in the upper respiratory tract should be excluded to avoid the probability of error in evaluation. A specimen with 25 or more leucocytes and 10 or less epithelial cells per visual field (100 × magnification) is extremely likely to be expectorated from a lesion and the probability of identification of the etiologic agent is also extremely high. If the specimen does not satisfy the above conditions identification of the etiologic pathogen will be less likely. There-

Table 1. Geckler's [27] classification of specimens for quality control

Group	WBC count/visual field[a]	Squamous epithelial cells/visual field[a]
1	<10	>25
2	10–25	>25
3	>25	>25
4	>25	10–25
5	>25	<10
6[b]	<25	<25

[a] Observed at 100 × magnification
[b] Transtracheal aspiration method used in patients with granulocytopenia

fore, quality control of the specimen is very important, and some references such as Geckler et al.[27] (Table 1) and Ogihara's classification[28] should be used as guidance. Demonstration of bacteria within phagocytic cells (neutrophils or macrophages) in a particular specimen is the best evidence to establish diagnosis and such samples should be stored for future re-evaluation.

Various methods are used for culture tests of sputum, including the washing culture method and the quantitative culture method, and a combination of one of these methods with another procedure yields a higher probability of detecting an etiologic agent. Detection by the quantitative culture method of a microbial pathogen at 10^7 CFU/ml or more in a specimen is indicative of that organism being the etiologic agent. But an organism present in numbers lower than 10^7/ml in a specimen obtained following the standard procedure with a minimal amount of normal oral flora contamination may also be the etiologic agent. The culture should be continued for 24 h in case of absence of any visible colony. Some cultures demand special condition; for example, carbon dioxide gas culture yields a higher detection frequency of β-hemolytic streptococcus. Even though diagnosis by quick diagnostic kit is performed for some pathogens, the culture test method is still the most dependable and must be performed to confirm a diagnosis. Similarly, in *Mycoplasma* and *Chlamydia* infection, diagnosis can be done by serological tests,[29,30] but it is better to confirm the findings by culture test during an ongoing trial of antimicrobial agents.

Clinical diagnostic standards

The most common signs and symptoms of acute bacterial upper respiratory tract infection are fever, purulent productive cough, and pustules or abscess in the upper respiratory tract. It can be reasonably concluded that a suppurative inflammatory condition is present when the white blood cell count rises to 8000/mm^3 or higher, there is migration of nuclei to the left, and there is an increase in C-reactive protein (CRP) to 0.7 mg/dl or higher. It can be discriminated from a viral condition, in which fever is accompanied by mucoid exudate and sputum, no or mild increase in CRP, and leukopenia in many patients. The characteristic features of individual diseases may be summarized as listed below:

Acute tonsillitis. Reddening and swelling of tonsils with pustules on the surface.

Acute pharyngitis. Local pain, reddening and swelling of the uvula and throat and a purulent exudation. Many patients do not exhibit these typical features.

Acute bronchitis. Chest pain and cough, often productive and purulent, are the cardinal features.[31]

Diagnosis of acute upper respiratory tract infection depends on the isolation of a pathogenic bacteria in a suitable specimen from a patient having some of the characteristic features appropriate for the site of involvement. In case of failure to identify any significant bacteria by microbiological testing, other clinical and pathological findings should be considered collectively for the diagnosis. If the leukocyte count is 8000/mm^3 or higher, CRP is 0.7 mg/dl or higher, and a purulent-productive cough or-exudate is present, then it is obvious that the pathology is of bacterial and not viral origin. Sometimes the erythrocyte sedimentation rate (ESR) is of accessory value, although it is increased in many other conditions and therefore should be performed with other diagnostic tests.

Diagnosis of acute respiratory tract infection by *Mycoplasma* and *Chlamydia* is relatively difficult, in contrast to that of pneumonia, in which a fairly reliable diagnosis can be made with the help of a chest X-ray. Laboratory tests reveal a reduced WBC count in many patients, which leads to confusion with viral infection. As culture methods are not well practiced, a reliable diagnosis needs the detection of the antibody titer for a specific antigen or DNA of the pathogen in the serum. Precisely, a fourfold or higher increase in *Mycoplasma* antibody titers is observed between blood samples taken during the onset of the disease and during the convalescent period (usually after 2 weeks), or a rise of 64 times or higher and 320 times or higher in complement fixation (CF) and indirect hemagglutination (IHA) antibody titers, respectively, in a single sample is diagnostic of *Mycoplasma* infection. Similarly, in *Chlamydia* infection, a fourfold or higher rise in the CF antibody in paired serum samples or a 16-fold or higher increase in a single sample is diagnostic of *Chlamydia* infection. Detection of antibodies or DNA in the serum by fluorescence antibody technique, enzyme antibody technique, DNA probes, or the polymerase chain reaction (PCR) technique can also be used as alternative diagnostic tests for *Mycoplasma* and *Chlamydia* infection.

Inclusion criteria for the target population

Bacteriological infection

Target subjects for clinical evaluation of antimicrobial agents should satisfy criterion (1) and at least any two criteria from (2) to (5), as described below.

(1) The suspected etiologic agent is isolated from a suitable specimen or there is a strong possibility of its presence. Patients from whom a good sample has been obtained

(pustules/ purulent exudate/ purulent sputum) even though the etiologic agent is not confirmed.

(2) A white blood cell count of $\geq 8000/\text{mm}^3$.
(3) Stab leukocytes of $\geq 10\%$.
(4) CRP $\geq 0.7\,\text{mg/dl}$ (or a value which exceeds the maximum value at the facility).
(5) Body temperature, $\geq 37°\text{C}$.

Mycoplasma *and* Chlamydia *infection*

Target subjects for clinical evaluation of antimicrobial drugs with *Mycoplasma* and *Chlamydia* infection should have the signs and symptoms described in the previous section for acute bacterial upper respiratory tract infection and must satisfy criterion (1) and at least three of the remaining six criteria as described below:

(1) A fourfold or higher increase in *Mycoplasma* antibody titers in paired serum samples, or 64 times or higher increase in CF antibody titers, or 320 times or higher increase in HA titers in a single serum sample. Patients exhibiting a fourfold or higher increase in *Chlamydia* antibody titers in paired serum samples, or 16 times or higher increase in CF antibody titers in a single sample. Patients tested positive for *Mycoplasma* or *Chlamydia* by antigen or gene detection techniques as described before.
(2) A white blood cell count of $\geq 8000/\text{mm}^3$.
(3) Stab leukocytes of $\geq 10\%$.
(4) CRP of $\geq 0.7\,\text{mg/dl}$ (or a value which exceeds the maximum value at the facility).
(5) Body temperature of $\geq 37°\text{C}$.
(6) A persistent cough.
(7) Pain at the local site of inflammation.

However, in many patients the results related to criterion (1) are available 1–2 weeks after commencement of treatment, and thus some patients who do not satisfy the standard criteria are also included in the trial. Such patients should be excluded immediately and should be treated with another suitable antimicrobial agent. Furthermore, care should be taken to avoid misinterpretation of the antibody titer test due to cross reaction between different genuses of *Chlamydia*, with particular attention to *C. trachomatis* which frequently complicates urinary tract infections.

Standards for severity evaluation

Acute upper respiratory tract infections are mostly mild or moderate in severity, although a few may become severe. To categorize the degree of severity, indicators have been determined and they are interpreted as shown in Table 2. The indicators are body temperature, white blood cell count, and CRP value. Ideally, the indicators should be assessed on the day of and 1 day prior to commencing the clinical trial for the antimicrobial agent and the highest values for the indicators between these 2 days should be selected.

Table 2. Standardized criteria for evaluation of severity in patients with acute upper respiratory tract infection

Parameters	Severity of disease		
	Mild[a]	Moderate[b]	Severe[c]
Body temperature (°C)	<37.5		≥ 38.6
Peripheral white blood cell count (/mm³)	<10000/mm		≥ 15000
CRP (mg/dl)	<4.0		≥ 10.0

[a] Satisfies two or more of the defined criteria
[b] Cases which are neither mild nor severe
[c] Satisfies two or more of the defined criteria

Standards for efficacy evaluation

It is difficult to set standards for evaluation of efficacy. However, this is done on the basis of clinical and microbiological test findings. Usually, administration of antimicrobial agents for 4–7 days is sufficient for mild and moderate acute upper respiratory tract infection of bacterial origin. But in severe infections or in *Mycoplasma* or *Chlamydia* infections the drug may be continued for as long as 14 days. In general, clinical improvement is observed by subsiding fever and lowering of white blood cell count and CRP value. The ESR may also be used as an indicator for evaluating drug efficacy, although it is affected by conditions other than infection alone. The speed of recovery should be assessed for the evaluation of drug efficacy. Precisely, a 3-day and a 7-day evaluation should be conducted. The evaluation is made on the basis of the clinical and microbiological assessment. When the microbiological effects are equivocal, the evaluation is made on the priority basis of clinical assessment. In severe bacterial infections or *Mycoplasma* or *Chlamydia* infections a final day evaluation is conducted after a maximum of 14 days, in addition to the 3-day and 7-day evaluation.

Standards for evaluation of microbiological outcome

Patients meeting the inclusion criteria and compliant with the regimen are submitted to 3-day and 7-day evaluation (on-therapy evaluation) after the regimen has started and a final evaluation after the etiologic agent is determined and the drug regime is over (end-of-therapy evaluation). To assess further, a post-therapy evaluation is done at least 7 days after the completion of the therapy (test-of-cure evaluation). The following concepts are used for the evaluation:

(a) *Presumed eradication.* A bacterial outcome should be extrapolated from a clinical outcome in this condition.

(b) *Documented eradication.* Absence of the etiologic agent from the cultured specimen after the regimen.

(c) *Persistence.* Presence of the etiologic pathogen even after the complete course of antimicrobial agent therapy. The MIC of the trial drug as well as that of standard drugs

should be assessed to determine the resistance of the concerned pathogen.

(d) *Recurrence.* Isolation of the original pathogens from a culture after the test-of-cure culture while previous culture was negative. The originality of the pathogen should be carefully verified and if necessary, in-vivo sensitivity should be assessed to compare the patterns.

(e) *Reduction.* Quantitative reduction of the original pathogen as verified by a quantitative culture technique.

(f) *Partial eradication.* Disappearance of one or more microbes after treatment in an infection involving multiple pathogens. It is very important to confirm the involvement of multiple pathogens for evaluation.

(g) *Superinfection.* Isolation of a pathogen other than the original pathogen from a specimen taken while the patient is on therapy in a patient who has signs and symptoms of infection.

(h) *Apparent new infection.* Isolation of a new pathogen from a site of infection without clear signs and symptoms while the original pathogen is eradicated by antimicrobial treatment.

(i) *New infection.* Isolation of a new pathogen from a site with clear signs and symptoms of infection while the original pathogen is eradicated by antimicrobial treatment.

(j) *Evaluation not possible.* When a patient is not in conformity with any of the above conditions for various reasons.

Standards for evaluation of clinical outcome

The patients should be evaluated clinically for the effectiveness of the trial antimicrobial agent 3 days and 7 days after initiation of the therapy. The outcome may be categorized as "effective" or "ineffective" on the basis of the standardized criteria shown in Tables 3 and 4. Acute upper respiratory tract infection may be of bacterial or nonbacterial origin and hence they have been evaluated by different standards.

(a) Acute bacterial upper respiratory tract infections. A drug may be evaluated as effective when all or two of three criteria (Table 3) are satisfied and the third one has not worsened. The drug is usually given for 7 days initially. If

after 3-day and 7-day evaluations at least two of the three criteria are fulfilled, the drug may be continued for another 7 days at maximum. Fulfillment of the standards during this period indicates the effectiveness of treatment. On the contrary, failure to achieve the standards at any time point indicates that the treatment is ineffective. The drug should be discontinued and another appropriate antimicrobial drug should be started without delay. Failure to pursue an evaluation for any reason leads to a conclusion of "evaluation not possible".

(b) Acute nonbacterial upper respiratory tract infections (*Mycoplasma* and *Chlamydia*). The evaluation of acute nonbacterial upper respiratory tract infections is done on the basis of the standardized criteria as shown in Table 4. A drug may be evaluated as effective when all of the five, or three or four of the five criteria are satisfied and the others are not worsened. Evaluation time and procedure are the same as those used for acute bacterial upper respiratory tract infections.

Final evaluation

The clinical evaluation of an antimicrobial agent should be conducted during and after the completion of therapy, as described in the section clinical evaluation methods in brief, subsection, Effectiveness of antimicrobial agent. However, sometimes a post-therapy evaluation is conducted after a defined time period depending on the pathology and the pathogen involved. In some instances of acute bacterial or *Mycoplasma* or *Chlamydia* infections, initial therapy is proved to be effective but is followed by a recurrence. Thus, final evaluation of an antimicrobial agent is quite difficult and it is therefore important to continue the follow-up examinations and laboratory testing for a defined time period. In acute upper respiratory tract infections, a 7-day post-therapy follow-up is considered to be appropriate and this should be described in the protocol in advance.

Clinical evaluation of new antimicrobial agents in pneumonia

Pneumonia is frequently subjected to clinical evaluation for new antimicrobial agents. This section deals with determin-

Table 3. Evaluation of effectiveness of new antimicrobial agents in patients with acute bacterial upper respiratory tract infections

Parameters	Criteria of effectiveness
Body temperature	Improvement to <37°C
White blood cell count	Improvement to <8000/mm^3 or to the facility's normal range
CRP	Improvement to 30% or less of the previous value

Table 4. Evaluation of effectiveness of new antimicrobial agents in patients with acute nonbacterial upper respiratory tract infections

Parameter	Criteria of effectiveness
Body temperature	Improvement to <37°C
White blood cell count	Improvement to <8000/mm^3 or to the facility's normal range
CRP	Improvement to 30% or less of the previous value
Persistent cough	Disappeared
Throat pain	Relieved

ing the inclusion criteria to select patients appropriate for evaluation, to set evaluation standards for severity of the disease and efficacy of the antimicrobial drug. Moreover, the parameters used to assess the above determinants are also set down.

Disease concept and indications for clinical evaluation of antimicrobial drugs

Pneumonia is defined as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection and accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales). The infectious agents involved cover a wide range from aerobic to anaerobic bacteria, *Mycoplasma*, *Chlamydia*, and acid fast bacilli, as well as viruses and fungi.[32–35] The frequency of an etiologic agent varies on host factors (such as age, underlying disease prevalence), agent factors (types of species), and environmental factors (whether infection acquired in community or hospital setting).

The pathogenic microbes discussed under this guidance include general bacteria (such as *S. pneumoniae*, *S. aureus*, *H. influenzae*, *K. pneumoniae*, *P. aeruginosa*, and *Moraxella*), *Legionella*, *Mycoplasma*, and *Chlamydia*. Pneumonia which is caused by pathogens such as viruses, fungus, or acid-fast bacilli needs to be evaluated by completely different diagnostic standards and the standardized criteria for evaluation of the effectiveness of new agents also need to be set down.

It is not easy to identify the etiologic pathogens for pneumonia, particularly before commencing an antimicrobial drug, and previous reports indicate that this identification rate is less than 50%. Therefore it is important that the concerned drug should cover the probable etiologic pathogens. However, a comparatively reliable prediction is possible on the basis of careful examination of the aforementioned host, agent, and environmental factors, close monitoring of the clinical conditions (prevalence, age, purulent sputum) and performing appropriate tests (peripheral white blood cell count, chest X-ray, and gram staining of a smear specimen of the purulent sputum). When a drug under trial (such as a macrolide or a new fluoroquinolone) reasonably covers the spectrum of pathogens (*H. influenzae* and *K. pneumoniae*, as well as *Mycoplasma* and *Chlamydia*) which are involved in community-acquired infections, it is not necessary to identify the etiologic pathogen at the beginning of treatment. This identification is important with drugs such as β-lactams which target only bacterial infections. Of course, the importance of various culture tests and serodiagnosis can not be surpassed. In some cases a quick diagnosis is now also possible by employing molecular biology techniques such as the PCR method. Above all, collecting an appropriate specimen, selection of its culture methods, and, finally, proper evaluation is of utmost importance.[36–38]

Inclusion criteria for patients

The diagnosis of pneumonia should be based on standardized clinical, radiographic and microbiologic criteria.[39] Patients should satisfy at least the following criteria to be included in an evaluation trial for the clinical effectiveness of a new antimicrobial agent.

(1) Confirmation of the presence of a new infiltrate(s) on a chest X-ray or computed tomography (CT) scan.
(2) Confirmation of an existing inflammatory condition, as evidenced by an increased white blood cell count (WBC > 10000/mm^3), migration of the nucleus to the left in 10% or more of stab leukocytes, a raised CRP (1.0mg/dl or more), and an increased ESR.

Once the above two criteria are satisfied, then two of the four following conditions should be met.

(1) Fever.
(2) Cough, sputum (purulent in nature), chest pain, and dyspnea.
(3) Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony).
(4) A microorganism should be isolated from a specimen of respiratory secretion after Gram staining and semiquantitative culture. Supply of a quality specimen raises the possibility of correctly determining the etiologic agent. Specimens of respiratory secretion may be obtained by any of the following means:
 • Deep expectoration
 • Nasotracheal aspiration
 • Bronchoscopy with bronchoalveolar lavage or protected brush sampling
 • Transtracheal aspiration.

Exclusion criteria

In addition to complying with the general exclusion criteria applicable to other trials, patients enrolled in pneumonia trials should be excluded for the following reasons:

(1) Patients with known bronchial obstruction or a history of postobstructive pneumonia. (This does not exclude patients who have chronic obstructive pulmonary disease.)
(2) Patients with primary lung cancer or another malignancy metastatic to the lungs.
(3) Unless the study is specifically designed for such a patient population, patients with cystic fibrosis, AIDS, known or suspected *Pneumocystis carinii* pneumonia, or known or suspected active tuberculosis.

Table 5. Evaluation of severity of infection in pneumonia

Parameters	Severity of disease		
	Mild[a]	Moderate[b]	Severe[c]
Body temperature	<37.5°C		≥38.6°C
Number of infiltrates on chest radiograph	<4		≥6
White blood cell count	<10000/mm³		≥15000/mm³
CRP	<4.0mg/dl		≥10.0mg/dl

[a] Satisfies three or more of the defined criteria
[b] Cases which are neither mild nor severe
[c] Satisfies three or more of the defined criteria

Table 6. Scoring criteria for pneumonia on the basis of chest radiograph findings of area of involvement

Pneumonia score	Area of involvement
0	No abnormal infiltrate
1	Very small infiltrate which is limited to one intercostal site
2	Between 1 and 3
3	Infiltrate involving 1/10 of one lung
4	Between 3 and 5
5	Infiltrate involving 1/3 of one lung
6	Between 5 and 7
7	Infiltrate involving 2/3 of one lung
8	Infiltrate involving almost one entire lung
9	Between 8 and 10
10	Infiltrate involving almost completely both lungs

Severity evaluation standards

The clinical effect of the trial drug is largely influenced by the severity of the pneumonia, and the patient's condition is evaluated on the basis of the severity of the infection itself and the severity of underlying diseases and/or complications.

Severity of infection

The severity of pneumonia may be evaluated on the basis of the standardized criteria such as body temperature, chest X-ray findings, peripheral white blood cell count, and CRP, as shown in Table 5. The criteria for evaluating the severity of infection are assessed on the day of and the day before commencing therapy and the higher values of the two are selected.

It is difficult to rigidly restrict the criteria for mild, moderate, or severe infection. Even when the white blood cell count is less than 10000/ml³, but the nucleus in 80% or more of neutrophils and in 20% or more of stab leukocytes has migrated to the left, the case is evaluated as exceeding the mild standards. In addition to this, underlying disease factors such as hematological disorders or liver diseases also affect the white blood cell count and these should also be taken into consideration.

To evaluate the severity of pneumonia, chest X-ray is the most important tool and therefore a precise interpretation of the finding is also necessary. A scoring system has been developed on the basis of the number of infiltrating shadows on the chest X-ray, as shown in Table 6 and Fig. 1. Any pre-existing stromal dysfunction will affect the score and it is not included in the evaluation.

Severity of underlying diseases and complications

The onset and course of pneumonia is greatly influenced by the presence of any underlying disease and its extent. Therefore, to conduct a proper evaluation of the clinical effect of a new antimicrobial agent, these factors should be critically monitored on the basis of some standardized criteria, as listed below:

Mild. No effect on the onset of pneumonia and its course (such as high blood pressure, hyperlipidemia, or mild liver dysfunction).
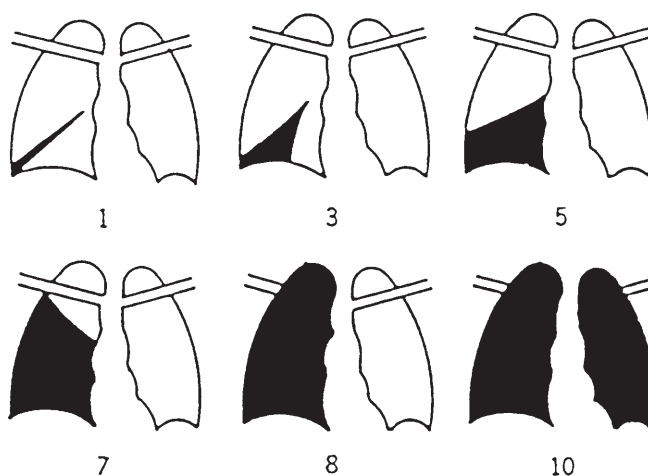

Fig. 1. Pneumonia score on the basis of involvement of lung area by infiltrates. The *black are* as in each lung represent the area of involvement by the infiltrates. *Numerals below the sketches of the lungs* indicate the respective scores. *See Table 6* for explanation of the score

Moderate. Possibility of affecting the onset and course of pneumonia but the magnitude is not expected to be severe (such as mild chronic obstructive pulmonary diseases, well controlled diabetes, or chronic nephritis).

Severe. Affecting the onset and course of pneumonia significantly, as well as the effects of treatment (such as connective tissue diseases, leukemia, malignant diseases particularly in advanced stages, congestive heart failure, and chronic airway diseases with respiratory insufficiency).

Severity of patient's condition

The severity of the pneumonia itself and the severity of underlying diseases or complications are evaluated in combination to conduct a proper evaluation of the severity of the patient's condition. The clinical effect of an atimicrobial agent may be affected considerably by the severity of the patient's condition and thus a careful analysis of this factor is mandatory. Even though the severity of an

infection itself is of mild or moderate degree the patient's condition may be evaluated as severe, provided a parallel severe underlying disease conditions or complications exist. These patients are not included in the usual trials for evaluation of antimicrobial drugs and they should be studied under special trial settings (bold entries in Table 7).

Efficacy evaluation of a new antimicrobial drug

The efficacy of a new antimicrobial drug is evaluated on the basis of microbiological and clinical outcome.

Standards for evaluation of microbiological outcome

Determining an etiologic agent in pneumonia patients is quite difficult, particularly in those patients from whom a good sample of respiratory secretion is not available. In many patients, and, in particular, during the early stages of pneumonia, expectoration of purulent sputum is inefficient and isolation of an etiologic agent is not possible. But it is very important to identify and follow the course of the causative pathogen in order to evaluate the clinical effect of a new antimicrobial agent. Therefore, efforts should be made to facilitate expectoration through measures such as the infusion of physiological saline. In some cases of pneumonia, a blood culture is useful to identify the etiologic agent (such as *S. pneumoniae* and *S. aureus*). Another factor which makes isolation of etiologic agents of pneumonia difficult during trials is pretreatment with some form of antimicrobial drug. Therefore, patients who have not received any antimicrobial drug since the onset of the disease should be included in the trial.

Special attention should be given to those specific pathogens, such as *Legionella*, *Mycoplasma*, and *Chlamydia*, which cannot be detected in general bacterial culture.[29–40] These pathogens are encountered quite often in trials targeting pneumonia. It is therefore important to identify them using special media and selection media, or by serological tests. The evaluation criteria for serological tests should be set down beforehand. So far as *Mycoplasma* detection is concerned, antibody titers in a paired test sample taken at the onset of the disease and during the convalescence stage should show a fourfold or higher increase. And when a single sample titer is estimated, CF antibody titers and HA antibody titers should be 64 times and 320 times higher, respectively. Similarly, a diagnosis of *Chlamydia* pneumonia may be made if the CF antibody titers show a fourfold or higher increase in a paired test sample or it is 64 times or higher in a single test sample.[41–43] Cold agglutination titers rise simultaneously but are of limited value as they are also increased due to other factors.

Pneumonia patients in whom the etiologic agent has been isolated and identified should be examined 3 days and 7 days after the onset and on the day of completion of treatment (maximum 14 days). The evaluation is conducted on the basis of the standardized criteria as described in the section "Clinical evaluation of new antimicrobial agents in acute respiratory tract infection, subsection Standards for efficacy evaluation; Standards for evaluation of microbiological outcome."

Standards for evaluation of clinical outcome

The clinical outcome after treatment with a new antimicrobial drug is evaluated on the basis of a comparison of the patient's baseline signs and symptoms and other laboratory parameters with those at a later stage. Results of evaluation may be expressed as "effective", "ineffective", and "evaluation not possible", as described in Table 8.

The evaluation is undertaken 3 days and 7 days after the beginning of the antimicrobial drug therapy and usually the drug is discontinued after 7 days of treatment. However, the results of the assessment of the standard criteria may not be available within 7 days, particularly in severe pneumonia or pneumonia accompanied by underlying diseases, or moderate or severe complications. In this situation, the drug may be continued for as long as 14 days, provided a trend of improvement is observed, as indicated by an improvement in chest X-ray and CRP value. The drug may be considered as effective if there is resolution of all signs and

Table 7. Evaluation of severity of patients with pneumonia

Severity of underlying diseases and complications	Severity of infection		
	Mild	Moderate	Severe
None	Mild	Moderate	Severe
Mild	Mild	Moderate	Severe
Moderate	Moderate	Moderate	**Severe**
Severe	**Severe**	**Severe**	**Severe**

Bold entries indicate patients who should be studied under special trial settings

Table 8. Evaluation standards for efficacy of antimicrobial agents in pneumonia

Parameters	Evaluation		
	Effective[a]	Ineffective	Evaluation not possible
Body temperature	Lowered to 37°C		
Chest radiograph score	Lowered to 70% or less of the previous value	Does not satisfy the efficacy standards	Not possible to evaluate the efficacy for any reason
White blood cell count	Reduced to <9000/mm^3		
CRP	CRP		

[a] Satisfies three or more of the defined criteria

symptoms of pneumonia and improvement or lack of progression of all abnormalities on chest radiograph.

In patients with accompanying underlying disease or complications, complete resolution is not achieved, and the standardized criteria are not satisfied (in particular, CRP value and body temperature) during this 14 days. In such patients, it is necessary to provide objective proof of improvement after treatment to evaluate the drug as "effective", such as comparable records prior to onset of pneumonia and after the treatment. The clinical effect of the study drug should be evaluated as early as 3 days after the commencing of treatment, and the speed of clinical recovery should also be considered in combination. When a trend of improvement in the standard criteria is absent, the next evaluation after 7 days is not necessary; instead, the drug should be discontinued and the administration of an appropriate antimicrobial agent should be initiated.

Final evaluation

Evaluation of the clinical effect of a new antimicrobial agent is usually completed along with the completion of the treatment regime. However, a post-therapy follow-up observation may be necessary in particular patients depending on the pathology and pathogenic organism concerned. For example, a drug may be evaluated as effective initially in some patients with severe pneumonia with underlying diseases, or *Mycoplasma* pneumonia, or *Chlamydia* pneumonia, but the infection may recar by the same pathogen at a subsequent stage. Therefore, follow-up observations for a defined period of time are important to rule out such possibilities. A 1-week period is considered to be adequate for the follow-up evaluation of pneumonia, and this time the evaluation is final. During the evaluation of a new antimicrobial agent, the economic aspects of the drug should also be assessed, in conjunction with its efficacy and safety. If a trial drug exhibits equal efficacy to a similar existing drug(s) with a fewer adverse reactions and, moreover, is economical, it is evaluated as superior to the existing drug(s). However, the standardized criteria and specific methods for evaluation must be mentioned in the protocol in advance.

Clinical evaluation of new antimicrobial agents in acute exacerbation of chronic pulmonary diseases

Acute exacerbation of chronic pulmonary diseases is almost always attributable to an infection, and the pathogens are often bacteria treatable with antimicrobial agents.[44,45] This section deals with defining the guidelines for the selection of patients, evaluation of the severity of the patient's condition, and evaluation of the efficacy of the trial drug.

Disease concept and indications for clinical evaluation of antimicrobial agents

Symptoms are acutely aggravated when an infection occurs in patients with chronic pulmonary diseases with impaired airway protectivity, such as chronic bronchitis, chronic pulmonary emphysema, bronchiectasis, and diffuse pan-bronchiolitis. Administration of antimicrobials should be initiated at the earliest possible time. Sometimes, an acute exacerbation is due more to an underlying disease or complication rather than the infection itself. Acute exacerbation due to bacterial causes is characterized by increased cough, sputum production, and dyspnea, in addition to development of sputum purulence. The amount of sputum and the degree of purulence (purulent, muco-purulent, and mucoid) are good indicators for clinical assessment. A suitable specimen of respiratory secretion is essential for identification of the etiologic pathogens. Isolation of the causative organism is necessary for a proper evaluation of the efficacy of the study drug. The commonly encountered microorganisms in acute exacerbation of chronic pulmonary diseases are *H. influenzae*, *S. pneumoniae*, including other streptococci, *Moraxella (Branhamella) catarrhalis*, and *S. aureus*, as well as *K. pneumoniae*, *Pseudomonas*, and anaerobic bacteria.[44,45] Many of these microbes are established to be involved in community-acquired infection, except for methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram negative bacteria such as *Pseudomonas*. In contrast, MRSA and *Pseudomonas* have been isolated in patients with a long history of persistent infection and comparatively severe underlying respiratory diseases.[46,47]

Improvements in the symptoms and signs have mainly been considered in the design of conventional evaluation standards for the clinical effects of an antimicrobial agent, whereas the effects of the drug on the etiologic agent have not been given importance. Even though deterioration in clinical condition can be assessed by increased body temperature, peripheral white blood cell count, and CRP values, the absence of fever and increased white blood cell count do not rule out the possibility of acute exacerbation. Analysis of conventional evaluation data has shown that 30%–40% of such patients did not have fever and an increase in white blood cell count was observed in only 40% of patients. Therefore, it is important to conduct the evaluation of microbiological effects along with the clinical effects for a better outcome. The ESR, chest X-ray, and arterial blood gas analysis may also be useful additional tools.

Inclusion criteria for selection of patients

Patients enrolled in the study to evaluate the clinical effects of a new antimicrobial agent should have a clinical diagnosis of chronic pulmonary disease based on history, physical examination, and radiographic examination. It is also necessary to exclude the presence of chronic bronchitis and pneumonia. The standardized criteria for selection of patients are as follows:

(a) Onset of cough and sputum or an increase in the volume of sputum and/or worsening in the degree of purulence.
(b) Increase in CRP (≥ 0.7 mg/dl or a value which exceeds the facility's maximum value).

The following criteria are also to be satisfied while the above two criteria are fulfilled.

(c) Microbiologic confirmation of an etiologic pathogen by Gram's stain examination, and isolation on culture in a suitable specimen. The specimen is considered to be adequate when it contains <10 squamous epithelial cells and >25 WBC per field at 100 × magnification.
(d) Fever (>37°C).
(e) An increase in the peripheral white blood cell count (≥8000/mm or a value which exceeds the facility's maximum value).

Standards for severity evaluation

The severity of the patient's condition in acute exacerbation of chronic pulmonary disease is affected by the severity of underlying diseases and complications, as well as the severity of the infection itself. Respiratory function reserve is already compromised in these patients, even in the absence of infection, and therefore, microbial invasion worsens the functional ability due to inflammation of the airway. The underlying diseases and complications range from mild to severe form, having very little to major effects, respectively, on the onset and course of infection. Special attention should be given to those patients with respiratory and cardiac insufficiency, as they are prone to worsen easily.

The common indicators for assessment of severity of infection include fever, peripheral white blood cell count, and CRP values. But in some instances, cases such as aggravation of persistent *Pseudomonas* infection in patients with severe underlying lung diseases (such as severe diffuse panbronchiolitis, bronchiectasis, old lung tuberculosis, and tracheostomy) these indicators do not show significant changes, while dyspnea may become severe.

Severity of infection

Severity of infection in acute exacerbation of chronic pulmonary diseases may be evaluated on the basis of fever, peripheral white blood cell count, and CRP values, as shown in Table 9. These three criteria are assessed on the day of and 1 day prior to onset of treatment and the higher values of the two are selected for evaluation. However, it is presumed that these indicators for ev-

aluation are not caused by any underlying disease or complication.

Severity of underlying diseases or complications

Underlying diseases and complications may be categorized as mild, moderate, and severe.

Mild. Patients with a mild chronic pulmonary disease (such as chronic bronchitis, chronic pulmonary emphysema, or diffuse panbronchiolitis) and uncomplicated heart disease, or with complications which do not affect the course of an infection (such as mild hypertension, hyperlipidemia or liver dysfunction).

Moderate. Patients with moderate chronic pulmonary diseases and mild (latent) cardiac insufficiency, or with complications which are expected not to have a major effect on infection (such as controlled diabetes and chronic nephritis).

Severe. Patients with chronic pulmonary disease accompanied by respiratory insufficiency or cardiac insufficiency, or with complications which affect the course of infection seriously (such as uncontrolled diabetes, including ketoacidosis, connective tissue disease, tracheostomy, artificial respiration, or advanced malignancy).

Severity of infection becomes intractable in patients with severe underlying lung diseases and/or complications. If the majority of the study population belong to this category, appropriate evaluation of the trial drug may not be possible.

Severity of patient's condition

Severity of the patient's condition is evaluated on the basis of a combined evaluation of severity of the infection and severity of the underlying diseases and complications, as shown in Table 10. As the severity of the patients condition largely affects the course of infection, an appropriate analysis is necessary for a better outcome of the trial. According to the standardized criteria for the assessment of severity of the patient's condition, a patient with mild or moderate infection may be evaluated as "severe" when the infection is accompanied by severe underlying disease or complications. These subjects are usually not appropriate for clinical evaluation of antimicrobial agents.

Table 9. Standardized criteria for evaluation of severity of disease in patients with acute exacerbation of chronic pulmonary diseases

Parameters	Severity of disease		
	Mild[a]	Moderate[b]	Severe[c]
Body temperature (°C)	<37.5		≥39.0
Peripheral white blood cell count (/mm^3)	<10000		≥15000
CRP (mg/dl)	<5.0		≥10.0

[a] Satisfies all of the defined criteria
[b] Cases which are neither mild nor severe
[c] Satisfies all of the defined criteria

Table 10. Evaluation of severity of patients with acute exacerbation of chronic pulmonary diseases

Severity of underlying diseases and complications	Severity of infection		
	Mild	Moderate	Severe
Mild	Mild	Moderate	Severe
Moderate	Moderate	Moderate	**Severe**
Severe	**Severe**	**Severe**	**Severe**

Bold entries indicate patients who should be studied under special trial settings

Efficacy evaluation standard

Determining the etiologic agent is necessary, as evaluation of the characteristics of the antiinfective drug is premised on the understanding that the etiologic agent is known. The clinical findings, in combination with the change in the course of an etiologic agent, should be investigated as evaluation criteria in order to determine the extent to which the in-vitro antimicrobial activity is reflected in the actual treatment of an infection. Thus, evaluation of microbiological effects, as well as clinical effects, is conducted 3 days after commencement of the treatment and after the treatment is complete (usually 7 days or a maximum of 14 days). The first evaluation after 3 days give an impression of the trend of effectiveness of the study drug and speed of recovery, and helps to decide whether to continue the drug.

Standards for evaluation of microbiological outcome

Identification of the microbe by Gram staining of the smear specimen is particularly useful before commencement of the antimicrobial agent treatment. Isolation of the etiologic agent from a specimen of respiratory secretion largely depends on the quality of the specimen. A purulent sputum specimen containing >25 WBC per field and <10 squamous epithelial cells at ×100 magnification may provide a good opportunity to determine the causative pathogen by Gram staining and culture. In gross appearance, the sputum should contain yellow or green portions which should be used for tests. Care should be taken to avoid a false-negative result often obtained by examining mucoid sputum containing a lot of saliva. Mucoid sputum may be expectorated even under stable conditions without infection in patients with chronic bronchitis and chronic pulmonary emphysema. An increase in the sputum volume is a sign of exacerbation of infection, but if the sputum is mucoid, the infection is viral in origin, and is not a target infection for evaluation of antimicrobial agent therapy and, therefore, should not be included in the evaluation study. When there are inadequate and inefficient supplies of specimen, transtracheal aspiration or bronchoscopy may help in obtaining a quality sample of respiratory exudate.

Selection of the appropriate culture medium is also important for the correct identification of the causative agent. Usually, almost all aerobic bacteria can be isolated on a blood agar or chocolate agar medium. Serological diagnostic methods are not helpful in patients with acute exacerbation of chronic lung diseases, in contrast to pneumonia. Evaluation of the microbiological outcome may be conducted using a similar standard procedure to that described in the section. "Clinical evaluation of new antimicrobial agents in acute respiratory tract infection", subsection "Standards for efficacy evaluation; standards for evaluation of microbiological outcome."

Further, to evaluate the efficacy of an antimicrobial agent, in-vitro MIC (minimum inhibitory concentration) and MBC (minimum bacterial concentration) may be examined. The MBC also provides information on the speed of microbiologic recovery of the lesion. For example, a specimen (such as sputum) collected from a patient before and 3 days after commencement of a trial antimicrobial agent and subjected to MBC investigation will give comparable information on the effectiveness of the trial drug as well as on the speed of elimination of the causative pathogen. Thus, quantitative information on the microbe, along with the results of Gram staining and culture, will help in the understanding of the nature and kinetics of infection. In addition, useful information may also be obtained by measuring the concentration of the trial drug in blood and in the lesion.

Standards for evaluation of clinical outcome

The effectiveness of a new antimicrobial agent may be shown by observation of the following improvements:

- An improvement in the cough.
- A reduction in the sputum volume to as low as almost half of that before adiminstration of the antimicrobial agent.
- A change in the sputum from purulent to mucopurulent or mucoid, or from mucopurulent to mucoid.
- A return of body temperature to normal if there was fever before treatment (fever is not observed in all patients, and a previous clinical trial study of antimicrobial drugs in acute exacerbation of chronic lung diseases reported that 40% of the patients had a body temperature of 37°C or lower).

In addition to the above determinants, the peripheral white blood cell count and CRP are also important indicators for evaluation. The CRP is a very sensitive indicator for tracking the effects of chemotherapy. A trial drug may be evaluated as "effective" when the CRP value shows an improvement or becomes negative. But there are exceptions to this observation. Even though peripheral white blood cell count is an important indicator for evaluation of the clinical effects of a new antimicrobial agent, previous trials have shown that WBC count does not increase ($>8000/mm^3$) in some patients (approximately 40%) with chronic pulmonary diseases. Similarly, certain patients did not show a clear-cut increase in CRP value (0.7mg/dl in approximately 5% of the patients). In such patients, therefore, careful attention should be paid to clinical criteria, such as cough and sputum, for evaluation. In addition, peripheral WBC count and CRP values may fluctuate due to underlying conditions such as connective tissue diseases, and the evaluation of the trial drug in such patients must be conducted with great care. The standardized criteria for evaluation of the clinical effects of a new antimicrobial drug in patients with chronic pulmonary disease are summarized in Table 11. As shown in Table 11, a drug would be considered "effective" when there is improvement in cough and sputum condition and in addition, two out of the remaining three criteria are satisfied and the other one is not worsened. A failure to meet the above standardized criteria would evaluate the trial drug as "ineffective". Further, the remark "evaluation not possible" is applied when the standardized criteria are beyond the scope of evaluation for any reason. Efficacy evaluation of the trial drug is conducted 3

Table 11. Evaluation of effectiveness of new antimicrobial agents in patients with acute exacerbation of chronic pulmonary diseases

Parameters	Criteria for effectiveness
Cough	Improved in terms of severity
Sputum	Improvement in degree of purulence[a] Reduction in amount[b]
CRP	Improvement to 30% or less of the previous value
Body temperature	Improvement to <37°C
White blood cell count	Improvement to <8000/mm^3 or to the facility's normal range

[a] Change from purulent to muco-purulent or mucoid, or change from muco-purulent to mucoid
[b] Reduction to 50% or less by quantitative measurement

days (72 h) and 7 days after commencement of drug administration. Evaluation of the clinical effects after the drug has been administered for 3 days, based on the standardized criteria may help to assess the speed of improvement in the clinical and microbiological status. In patients satisfying the efficacy criteria after 3 days' administration of the antimicrobial agent, the agent may be evaluated as "extremely effective". In general, evaluation after 7 days', treatment provides reasonably sufficient information to justify defermination of the efficacy of the trial drug. If the drug is effective, the etiologic agent would be eradicated after this time and the residual signs and symptoms, if any, would reach the baseline level of the particular patient during the stable state (i.e., before the exacerbation of the chronic pulmonary disease). Sometimes the treatment is extended for another 7 days as there is improvement in the signs and symptoms but not enough to discontinue the drug. But particular attention should be paid in patients who receive long term antimicrobial therapy, in terms of microbial substitution and development of resistance. If the drug is suspected to be ineffective, it should be discontinued immediately and the switch over to a suitable drug should not be delayed.

Final evaluation

Administration of a new antimicrobial drug for evaluating the clinical effects in patients with acute exacerbation of chronic pulmonary diseases may result in eradication of the etiologic agent and hence the drug may be evaluated as "effective". But sometimes recurrence or reinfection may follow termination of the treatment. Therefore, it is important to conduct follow-up examinations for a defined time period after cessation of the drug. The precise schedule should be mentioned in the protocol in advance. Usually, a post-therapy follow-up for 1 week is considered adequate to rule out the possibility of recurrence or reinfection. Laboratory tests such as microscopy of the stained smear, culture, and, particularly, quantitative assessment of the microbes in the respiratory secretions are very useful for a precise evaluation of the recurrence and reinfection during the post-therapy period.

Closing remarks

The present report constitutes an attempt to improve and modify the existing clinical evaluation methods for new antimicrobial agents to treat respiratory infections. This draft was constructed on the basis of analyzing large amounts of material collected over years and incorporating internal and external factors concerning the present evaluation methods. The newly suggested standardized criteria for clinical evaluation of the new antimicrobial drugs are expected to be practiced properly hereupon and subjected to further improvement if necessary.

The volume of the fundamental material upon which the evaluation standards have been set down is enormous and should be discussed elsewhere, as it is beyond the scope of this report. This information should be published in the Journal of the Society by the respective concerned committees.[48]

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