The studies on pathogenic microorganisms for community-acquired pneumonia and the validation of the guideline in hospitals with different characteristics, which were planned at the time of the proposal of the guideline, have been completed, and the results have already been reported. Attention to respiratory infection and the number of presentations and papers in academic conferences has been increasing. However, it is still too early to discuss improvement in treatment results as the original purpose.


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*Key words:* infectious diseases, antimicrobial chemotherapy, practical guideline, global standard, regional standard

**Introduction**

To date, clinical guidelines for the appropriate use of antimicrobial agents in the treatment of infectious diseases have been developed and updated by revisions in western countries (1–8). In Japan, Japanese Respiratory Society (JRS) published several practical guidelines: guideline for the treatment of community acquired pneumonia (9) in 2000 (to be revised in 2004), for the treatment of hospital acquired pneumonia in 2002 (10), and for the treatment of respiratory tract infections in 2003 (11). The guideline for the optimal usage of antimicrobial agents has been developed by the cooperation of the Japanese Society for Chemotherapy and the Japanese Association for Infectious Disease in 2001 (12), which will be revised in 2004.

The characteristics of guidelines published by Japanese societies and those published in the United States are reviewed here, which may show us the answer to whether we need “global standard” guidelines or “regional standard” guidelines where they are expected to be utilized. Health insurance systems are completely different in Japan and the U.S. The typical dosages and availability of the drugs also sometimes differ. These facts suggest that regional tailored guidelines are desired. In contrast, pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobials are the universal principles to be considered whenever discussing the optimal usage of antimicrobials. Furthermore, clinical evidence has been collected from all over the world. Hence, it is likely that the “global standard” guidelines which are based on the universal principles and a large quantity of evidence must be more reliable.

**Community-acquired pneumonia (CAP) guidelines in the United States as the “global standard”**

In the United States, CAP guidelines have been published by different societies, individually: One by American Thoracic Society (ATS) in 1993 (1), which was revised in 2001 (2); another by Infectious Diseases Society for America (IDSA) in 1998 (4). The latter was updated in 2000 (5) and in 2003 (6). These two guidelines are quite different in the strategies in diagnosis, the categorization of patients, and choice of antimicrobials and sometimes are confusing. Therefore, a CAP guideline is now being developed by cooperation of both ATS and IDSA, which should be a consensus guideline to represent both infectious disease physicians and pulmonary disease physicians and subsequently the guideline will be kind of “global standard”.

We need to imagine the “global standard” CAP guideline before it will come out. It is not easy because CAP itself is a very heterogeneous syndrome including various severities, various pathogens, and undetermined factors. However, we can say that the guideline should be based on the huge amount of evidence gathered worldwide. This evidence includes 1) double blinded random therapeutic studies comprised of a huge number of cases, 2) PK/PD indices based on large studies, and 3) the latest data on drug susceptibility of pathogens causing pulmonary infections.

**Factors influencing the clinical efficacies of antimicrobials**

The factors influencing the clinical efficacies of anti-
microbials should be considered in the guidelines. Some factors are homogeneous and the same in the worldwide and "global standard" guidelines. However, other factors are heterogeneous and quite different among the countries and even in the regions, which may require us to prepare a "regional standard" guideline (Table 1).

Table 1. Characterization of the Guidelines: “Global standard” and “Regional standard”

<table>
<thead>
<tr>
<th>Grade of evidence</th>
<th>“Global standard”</th>
<th>“Regional standard”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application of global agreement</td>
<td>Excellent</td>
<td>Fair</td>
</tr>
<tr>
<td>Individualization of antimicrobial chemotherapy</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Pathogens targeted</td>
<td>Not preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>Local frequency of antimicrobial resistance</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Local approved dosage of antimicrobials</td>
<td>Inaccurate</td>
<td>Accurate</td>
</tr>
<tr>
<td>Patient Categorization and Clinical evaluation of drugs</td>
<td>Not suitable</td>
<td>Suitable</td>
</tr>
<tr>
<td>Local health service system</td>
<td>Standardization required</td>
<td>Standardization required</td>
</tr>
<tr>
<td>Application of new strategies for prevention of emergence of antimicrobial resistance</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Figure 1. Pathogens isolated in community-acquired pneumonia.

Frequency of pathogens in CAP
Pathogens causing CAP are listed as frequency in Fig. 1 (13–15). Pneumococci is most frequently isolated from CAP patients: *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* follow. In general, *H. influenzae* is typically found in elderly patients with chronic pulmonary diseases. *M. pneumoniae* is in youngsters while *C. pneumoniae* affects both youngsters and the elderly. Reports differ
regarding the frequencies of these three pathogens, but the differences are widespread and they may reflect the difference of age distribution of the populations evaluated. The frequencies of pathogens isolated in hospital-acquired pneumonia and ventilator-associated pneumonia are almost the same in various studies.

**Frequency of drug resistance of pathogens**

The prevalence rates of drug resistance of CAP pathogens are very different among countries and even among regions. For example, fluoroquinolone-resistant pneumococci in several countries is very different. The rate of quinolone resistance among pneumococci in Hong Kong is ten times as much as that in Japan. In the U.S., quinolone resistant *S. pneumoniae* seems to be more prevalent, compared with the data from Japan (16). The rate of resistance varies when the pathogens are collected from different age populations. It is noteworthy that quinolone-resistant pneumococci is isolated much more frequently from the elderly (26%) than from children in Japan (17).

**Differences in officially approved dosage of antimicrobials**

The approved dosages of oral antimicrobials in Japan are similar to those in the United States. The efficacy of β-lactams and macrolides (other than azithromycin) are time dependent, and these drugs should be administered to keep the concentration constant above MIC. In contrast, quinolones, as well as aminoglycosides, show concentration-dependent killing of bacteria. The efficacy of quinolones is correlated with the ratio of area under the curve (AUC) and MIC, and quinolones are advised to be administered once a day.

Beta-lactams and macrolides are administered twice or thrice a day in two countries, and these regimens are reasonable when the PK/PD of these drugs is considered. In the case of fluoroquinolones, PK/PD analysis suggests that once-a-day administration of the drugs is desired (18, 19). The U. S. regimen is compatible with PK/PD profile, but the Japanese regimen is not. The approved dose of antimicrobials is usually less in Japan. Intravenous injection forms of levofloxacin and gatifloxacin are very useful in CAP treatment, but these forms are not available in Japan. Therefore, the dosages of antimicrobials in Japan are far from the "global standard" and the application of "gold standard" is not easy in Japan. We should be aware of the difference in dosages even when the same antimicrobials are used in Japan and in the western countries.

**Categorization of severity of infections and clinical background of patients**

As stated before, CAP is a heterogeneous syndrome, comprised of various severities and various clinical backgrounds of patients. To categorize the patients according to the severity of the disease and their clinical background is critical to develop a "global standard" CAP guideline. CAP guideline from IDSA, ATS, and JRS use different strategies to categorize the patients. When a different strategy is used, the patients will be categorized as a different severity. ATS and IDSA strategies show more than 70% identity in severity categorization while categorization using JRS strategy results in a more severe classification. Therefore, the categorization strategies should be more standardized globally. Endpoints in clinical evaluation of antimicrobials also need to be standardized.

**Factors influencing the guideline strategy**

Several factors should not influence the clinical efficacy of antimicrobial chemotherapy itself, but may influence strategies described in the guideline. Health insurance system is quite different in western countries and Japan. In Japan, all people are supported by the national health insurance system and patients are freely accessible to the clinical service without extraordinary expenses, while 16% of people in the U.S. are not supported by insurance. Medicaid and Medicare are the national health systems supporting only the poor and the elderly. Payment systems are also quite different in these countries. As a result, in the U.S., the costs and expenses is an important factor concerning antimicrobial chemotherapy, while Japanese physicians usually do not care about the cost of which they prescribe. The situations may change in the near future.

**New strategies for the prevention of emergence of antimicrobial resistance**

IDSA released a guideline for the prevention of emergence of antimicrobial resistance in 1997. Centers for Disease Control and Prevention has campaigned for the prevention of emergence of antimicrobial resistance and introduced cycling therapy and formulary change of the antimicrobial chemotherapy (20, 21). These strategies seem to be worthy to be included in the "global standard".

**Conclusion**

A “Global standard” guideline for the treatment of pulmonary infections has not yet been developed. To date, in many countries, CAP guidelines have been published, but those are no more than “regional standard” guidelines. These guidelines have been revised periodically, and some would say that a “global standard” guideline must be established by cooperation of professionals from several countries. Others would say that the usefulness of a "global standard" guideline seems to be limited considering the heterogeneity of CAP syndrome, drug resistance among pathogens, and national health systems. However, both the efforts to establish a "global standard" and to tailor it for the region will make the guideline more reliable and more satisfactory.

**References**


