Note on evidence-based medicine (EBM)

These Guidelines have been compiled based on “evidence-based medicine (EBM)” methodology in conformity with the policies of the Committee for Preparation of Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP) of the Japanese Respiratory Society. The classification of the evidence levels and grades of recommendation are in accordance with the Medical Information Network Distribution Service (Minds). This guidelines was reviewed by clinical practice guidelines evaluation group in Minds by using the AGREE II (Appraisal of Guidelines for Research & Evaluation II) Instrument.

Classification of evidence levels

I. Evidence obtained from a systematic review and/or a meta-analysis of randomized controlled trials (RCTs)
II. Evidence obtained from more than one RCT
III. Evidence obtained from controlled trials without randomization
IVa. Evidence obtained from analytical epidemiological studies (cohort research)
IVb. Evidence obtained from analytical epidemiological studies (case-control studies, cross-sectional studies)
V. Evidence obtained from descriptive studies (case reports, accumulated cases)
VI. Evidence obtained from expert committee opinions and individual expert opinions without patient data

Grades of recommendation

A. Based on strong scientific evidence, and strongly recommended
B. Based on scientific evidence, and recommended
C1. No scientific evidence, but recommended
C2. No scientific evidence, and not recommended
D. Scientific evidence of ineffectiveness or harm, and not recommended

The grades of recommendation were determined on the basis of a comprehensive assessment that took the following factors into consideration:

Evidence level

This article is based on a guideline first published as Nursing- and Healthcare-associated Pneumonia (NHCAP) by the Japanese Respiratory Society in Japanese. Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2012.11.001.

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The amount of evidence and discrepancies between the conclusions
Degree of clinical efficacy
Clinical applicability
Evidence data in regard to harm and cost

Basic principles for preparing the “Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP)”

1. Objective: The objective of preparing the Guidelines was to improve the quality of NHCAP diagnosis, promote public health, and inform healthcare professionals engaged in its treatment.

2. Reliability: The Guidelines will be made available on the Japanese Respiratory Society website to collect opinions from the public and achieve greater reliability.

3. Clarity: The important information is listed in a clear and concise fashion, and commentary and annotations are provided below.

4. Applicability: A variety of clinical states of NHCAP patients are postulated to enable broad application.

5. Flexibility: Consideration is given to enable reasonable application of the content of the Guidelines. Recommendations are also made in regard to the handling of exceptions, alternative treatments, and unsuccessful cases.

6. These Guidelines are intended for use by healthcare providers who offer NHCAP clinical practice that is covered by Japanese National Health Insurance, and, when patients are admitted to “general beds” in Japanese hospitals.

7. The Guidelines should not cause any disadvantages to anyone. It should be noted that the Guidelines are not intended to limit clinical practice that is based on superior clinical experience. These Guidelines are intended to be references for clinical practice in relation to NHCAP and are not intended to obligate healthcare practitioners to follow them precisely in their healthcare practice.

8. Conformity: These Guidelines have been prepared in conformity with other guidelines for NHCAP and respiratory infection.

9. Recommended medications: Drug groups are recommended according to the nature of each treatment and the names of typical drugs are listed according to their pharmacological actions and actual manner in which they are used in medical practice.

10. Research plans: Information will be collected from surveys, studies, and papers that are relevant to these Guidelines.

11. Future plans: Revisions will be made as needed. In principle, revisions will be made every five years based on the results of nationwide surveys, etc. The Japanese Respiratory Society set up a committee for preparation of these Guidelines, to collect opinions in regard to these Guidelines from academic members of the Society, and to focus attention on international guidelines and their trends, as well as the intentions of the Society’s Guidelines Control Committee.

1. Forward-concepts of NHCAP and guideline principles

1.1. Concepts of NHCAP

The mortality rate of pneumonia is 1000 times higher among the elderly 85 years of age and over than among young adults irrespective of gender (Fig. 1) [1], and pneumonia is the first leading cause of death of males 90 years of age and over.


However, these earlier guidelines did not always play an adequate role as standards for clinical practice in regard to elderly patients, who have a high morbidity rate, because elderly pneumonia patients may be classified as having both CAP and HAP due to the fact that they are often admitted to healthcare-related facilities, such as nursing homes, that are intermediate between hospitals and communities, and because the outcome of pneumonia in the elderly population is worse than its outcome in the younger population.

The issues related to the handling of HAP and CAP are not limited to Japan. The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) made recommendations in regard to the treatment of such

Fig. 1 – Mortality from pneumonia by age and gender (per 100,000 patients) according to FY2005 vital statistics data.

However, the meaning of “HC” (healthcare) in the guidelines jointly published by the ATS and IDSA is not always the same as in Japan; the Japanese healthcare system is characterized by universal nursing-care insurance for those 65 years of age and over and by universal health insurance for the entire population, it is important to create a Japanese version of HCAP guidelines that includes both nursing-care-associated pneumonia and healthcare-associated pneumonia.

### 1.2. Objective and principles of the NHCAP guidelines

Ever since its preparation and publication of the clinical practice guidelines for CAP and HAP, the constant objective of the Japanese Respiratory Society in preparing clinical practice guidelines for pneumonia has been “to improve the quality of clinical practice in regard to pneumonia and to improve public health”.

Host factors play an important role in improving the quality of clinical practice in regard to pneumonia. In particular, the NHCAP population in Japan is quite varied, and it is not a uniform population because it includes patients who are in healthcare facilities for the elderly, patients who are receiving home care, and patients who have been admitted to long-term care facilities, and because the risks of aspiration pneumonia and underlying diseases change with age. In addition, since the NHCAP population also includes patients who are in their final years of life, such as patients with end-stage cancer, palliative care as well as long-term outcome is an important objective of treatment in the NHCAP population.

Strict priority in deciding where NHCAP patients are to be treated should be given to the judgments made by patients themselves, their physicians, and family members who provide their nursing care, and these Guidelines will not touch on this point. These Guidelines concern the treatment of pneumonia that is covered by health insurance and the treatment of pneumonia that is provided in beds in Japanese hospitals that are designated for “general patients”. If pneumonia that fulfills the definition of NHCAP at home or at a nursing care facility, the patients themselves and their families should consult with the medical institutions where treatment is possible and then decide where the patient will receive treatment.

In contrast to CAP and HAP, in which the patient populations exhibit relatively uniform features, it is difficult to assess the severity of NHCAP by considering only the condition of the pneumonia itself. These Guidelines place primary importance on the treatment that is required for a patient when the attending physician decides on the treatment category into which the patient falls, and have thus introduced the concept of “patient treatment category”.

Furthermore, the decision as to which treatment category the patient is assigned to should be made by the attending physician, who has the best knowledge of the individual patient’s condition, background, family relationships, and so forth. However, this strategy reveals a problem in regard to medical care for the elderly.

There is still controversy as to whether to continue treatment in cases in which it is impossible to achieve long-term improvement. The decision as to which treatment category the patient is assigned to is at the sole discretion of the attending physician.

The four principles of biomedical ethics discussed by Beauchamp and Childress are: (1) respect for autonomy, i.e., respecting the ability of individuals to make their own decisions; (2) nonmaleficence, i.e., not inflicting harm on others; (3) beneficence, i.e., preventing harm, offering benefit, and balancing benefit against risk and cost; and (4) justice, i.e., distributive justice for benefit, risk, and cost in regard to medical practice related to a patient [5]. The ethical aspects are especially important when considering medical care for the elderly. The antibiotics recommended in these Guidelines have been selected not only on the basis of the scientific evidence but also the ethical aspects.

The above were our objectives and principles in preparing these guidelines. We hope that these Guidelines will be widely used by physicians and other medical practitioners in the same way as the CAP, HAP, and respiratory infection guidelines published by Committee for the JRS Guidelines in Management of Respiratory Infections have already been, and that further progress will be made in the diagnosis and treatment of pneumonia in Japan as a result.

### 2. Definition of NHCAP

#### Summary

- HCAP is defined as pneumonia that overlaps both CAP and HAP (Level I).
- Since most cases of HCAP in Japan are diagnosed in elderly persons who are receiving nursing care, a separate diagnostic category, i.e., NHCAP, is needed (Minds recommendation grade C1).

#### 2.1. Clinical significance of HCAP in USA and other countries

The disease concept HCAP was publicly described for the first time in the HAP guidelines jointly published by the ATS and the IDSA in 2005 (Fig. 2) [4]. In Japan, it is more appropriate to use the term “NHCAP” instead of HCAP for the reasons stated below.

Internationally the term HCAP is generally used, and initially the HCAP population was defined as a group of CAP patients or HAP patients who had risk factors for involvement by drug-resistant pathogens (Level I) [4].

However, many reports on HCAP, mainly from the United States (U.S.) showed that the resistance of the causative agents and outcomes (mortality rates) in HCAP were similar to the resistance of the causative agents and outcomes (mortality rates) in HAP (Supplementary material Fig. S1) (Level IVa) [6,7]. In other words, it was found that some of the patients who had been admitted to a hospital with an initial diagnosis of CAP were older and had a poorer outcome than CAP patients, and the causative agents isolated from most of them were drug-resistant pathogens (methicillin-resistant Staphylococcus aureus (MRSA) and gram-negative bacteria such as Pseudomonas aeruginosa), in addition to the
pneumococci and *Haemophilus influenzae* that were the causative agents isolated from CAP patients.

HCAP patients are more likely to be diagnosed with CAP than with HAP. It is more appropriate to define HCAP as pneumonia that overlaps CAP and HAP and cannot be classified as either CAP or HAP (Level I) [4,6].

Furthermore, treatment for HCAP may be similar to the treatment for CAP or to the treatment for HAP, and it differs from hospital to hospital.

2.2. **NHCAP is Japanese version of HCAP: necessity of new terminology for HCAP in Japan**

There have been reports of data obtained from analyses of HCAP in Japan as well (Level IVb) [8,9]. Since these reports show that drug-resistant pathogens are a more common cause of HCAP than of CAP, and also in view of prognoses and other assessments, the treatment of HCAP in Japan should be based on the treatment of HAP. On the other hand, there is a report that most HCAP in Japan is similar to CAP, pneumonia with a poor outcome found largely in elderly patients, rather than HAP, which is drug-resistant pneumonia caused by gram-negative bacteria [10], and it is difficult to evaluate HCAP in Japan in a standardized manner (Fig. 3) (Level IVb). Reports in the U.S. and Europe have also pointed out that HCAP occurs in heterogeneous populations [6,11,12], and in view of its original definition, the true nature of HCAP can be described as a mixture of cases of pneumonia with a poor outcome in elderly patients that for the most part consists of aspiration pneumonia and drug-resistant pneumonia resulting from an advanced-medical-care environment (Fig. 4).

Furthermore, it has been pointed out that the differences in the healthcare environment between communities or countries are reflected in the incidence of HCAP and ratio of HCAP cases.
to HAP or CAP cases, and thus the data have sometimes varied significantly from report to report (Fig. 5) [Level I] [4,8,13].

In particular, the definition of “hospital” in Japan is very different from its definition in the U.S. This is largely because there are many more extended-care facilities, including “nursing homes” and “geriatric hospitals”, in the U.S., and many cases of pneumonia that have been diagnosed as HCAP in the U.S. would have been diagnosed as HAP in Japan [Fig. 6] [3,14].

On the other hand, when HCAP is viewed from a CAP perspective, if a bedridden patient residing at home developed aspiration pneumonia or a dialysis patient with risk factors for involvement by drug-resistant pathogens developed pneumonia and were transported to a nearby core hospital, the patient would be treated for CAP in Japan [2] whereas both would have been treated for HCAP in the U.S.

Because Japan has a unique nursing care insurance system and healthcare and nursing care system, caution is required when U.S. definitions are directly applied to the situation into Japan.

From this standpoint, the definitions of HCAP are suggested by the Committee for Preparation of Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP) of the Japanese Respiratory Society (Table 1). The definitions of NHCAP reflect the fact that there are many cases of aspiration pneumonia in the elderly in Japan on the background of the nursing care insurance system, and the Committee considers it appropriate to add the term “nursing care” and use the term “nursing- and healthcare-associated pneumonia (NHCAP)” to express HCAP in Japan (see Section 1). Naturally, the definition of NHCAP includes drug-resistant pneumonia that occurs during advanced medical care, dialysis and immunosuppressant therapy, and pneumonia caused by opportunistic pathogens. Furthermore, these Guidelines emphasize that the selection of treatment for NHCAP largely depends on the judgment of the attending physician and should not be selected in a routine manner. NHCAP can be viewed as “HCAP in Japan” or as “the Nippon version of HCAP”, and it is a highly original concept that reflects the unique conditions within Japan.

2.3. Pathogenic mechanism

It is important to take special note of aspiration pneumonia in regard to clinical practice related to NHCAP (see Section 8), because many of the cases of NHCAP are cases of pneumonia in the elderly (Table 2).

In addition to antibiotic therapy, preventive measures such as vaccination (see Section 9) are particularly important (Minds recommendation grade B).

We look forward to receiving many opinions and proposals from readers that will further reflect the particular state of healthcare in Japan.

3. The concept of patient treatment category

Summary

- Instead of classifying patients into categories based on the severity of their illness, these Guidelines suggest classifying patients into “patient treatment categories”, which take severity into account.
- Since the pathology, underlying diseases, and complications of NHCAP patients vary from case to case, it is impossible to make a prognosis based on the severity of the NHCAP and thus classifying patients with NHCAP according to the severity of their illness is inappropriate.
- An NHCAP patient’s treatment category should be determined based on an assessment of all of the following:

![Fig. 4 – Pneumonia that does not completely meet the definition of either CAP or HAP. There are two forms for such pneumonia.](image)

![Fig. 5 – Proportions of CAP cases and HCAP cases in Japan and abroad.](image)
whether drug-resistant pathogens are present, underlying diseases, complications, nutritional status, psychological and physical activity, and the state of support from other persons responsible for the patient’s care (Minds recommendation grade C1). The risk factors for involvement by drug-resistant pathogens are a history of antibiotic therapy within the preceding 90 days or current tube feeding (Level IVa).

Before determining the patient’s treatment category the attending physician should thoroughly discuss the objectives of treatment with the patient and the patient’s family.

3.1. Suggestion of “patient treatment categories” for NHCAP: why they are not “severity” categories

NHCAP occurs in the context of diverse pathology, underlying diseases, and complications in a variety of environments, and no two cases of NHCAP are the same (see Section 2). Thus, not only is it difficult to diagnose the severity of NHCAP in a simple, standardized manner, but doing so would be inappropriate, because it is impossible to make a prognosis based on the severity of NHCAP. After the topics of disease concept and definition, and choice of antibiotics, this was the topic that was most frequently discussed by the members of the guideline preparation committee. Although the pathology of CAP and pure HAP is similar, it is particularly evident in Japan that NHCAP occurs in the form of various pathologies in patients from a variety of residential environments who have different underlying diseases and complications, and it is difficult to stratify the cases according to severity or distinguish between different grades of severity. These Guidelines propose giving priority to the treatment required by the individual patient instead of severity when classifying them, as described below (Fig. 7). Involvement by “high-risk” drug-resistant pathogens, such as P. aeruginosa, extended-spectrum β-lactamase (ESBL)-producing enteric bacteria, and MRSA (see Section 4 for details), has been adopted as a criterion for classifying patients according to treatment.

3.2. Basic concept of treatment categories

These Guidelines first classify NHCAP patients by initial treatment from the standpoint of the types of treatment that are required for NHCAP. If a physician examines a pneumonia patient and diagnoses the pneumonia as NHCAP and the

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**Table 1 – Definition of NHCAP.**

| 1. Pneumonia diagnosed in a resident of an extended care facility or nursing home |
| 2. Pneumonia diagnosed in a person who has been discharged from a hospital within the preceding 90 days |
| 3. Pneumonia diagnosed in an elderly or disabled person who is receiving nursing care |
| 4. Pneumonia diagnosed in a person who is receiving regular endovascular treatment as an outpatient (dialysis, antibiotic therapy, chemotherapy, immunosuppressant therapy) |

Standards for nursing care.

Patients whose performance status is PS 3 (capable of only limited self-care, confined to bed or a chair more than 50% of their waking hours) or more.

Item 1 includes patients on psychiatric wards.

**Table 2 – Main pathogenic mechanism of NHCAP.**

| 1. Aspiration pneumonia |
| 2. Bacterial pneumonia secondary to influenza |
| 3. Drug-resistant pneumonia (such as MRSA pneumonia) secondary to endovascular treatment, such as dialysis |
| 4. Pneumonia caused by opportunistic microorganism during treatment with an immunosuppressive agent or anticancer drug |

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Fig. 6 – Categories of HAP, HCAP, and CAP by type of facility and type of patient in Japan: realities in the “Nursing Care Insurance System”.

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patient's condition is considered severe enough to require intensive care in an intensive care unit (ICU) or mechanical ventilation, or both, the patient is classified as “treatment category D”. Patients who are determined to require inpatient treatment and have a risk of involvement by drug-resistant pathogens are classified as “treatment category C”. Patients who are determined to require inpatient treatment and have no risk factors for involvement by drug-resistant pathogens are classified as “treatment category B”. Patients for whom outpatient treatment is appropriate are classified as “treatment category A”. These NHCAP patient's treatment categories are determined not only on the basis of the severity of the pneumonia itself but on the basis of the patient's environment, and they are not simply severity categories. Furthermore involvement by drug-resistant pathogens must always be considered during the treatment of NHCAP patients.

### 3.3. Judging the need for hospitalization

The need for hospitalization is determined not only on the basis of the severity of the pneumonia itself but on the basis of the patient's underlying diseases and complications, nutritional status, psychological and physical activity, and support by the patient's family and other persons responsible for the patient's care, all of which are taken into consideration by the attending physician when making the final decision in regard to whether the patient requires hospitalization. While an overall evaluation becomes necessary to determine the “patient's treatment category”, there are three sets of criteria to help evaluate the severity of the pneumonia itself: (1) the A-DROP classification (Supplementary material Table S1) for evaluating the severity of pneumonia in the Japanese Respiratory Society's revised CAP guidelines [2]; (2) the I-ROAD classification (Supplementary material Fig. S2) for evaluating the severity of pneumonia in the Japanese Respiratory Society's revised HAP guidelines [3]; and (3) a more detailed classification, the Pneumonia Severity Index (PSI, Supplementary material Fig. S3) [15] cited in the IDSA's CAP guidelines [16–18]. The optimal set of criteria for each patient's condition should be selected from among these three sets of criteria to assess the severity of the pneumonia, and the patient's underlying diseases and complications, nutritional status, psychological and physical activity, and social situation, such as the patient's family situation, should then be taken into consideration to determine the treatment category and whether hospitalization is necessary.

### 3.4. Risk factors for involvement by drug-resistant pathogens

The patient's treatment category is decided in order to consider treatment options, which mainly consist of antibiotics. Involvement by drug-resistant pathogens is much greater in NHCAP than in CAP, and depending on the patient, involvement by drug-resistant pathogens may be greater than in HAP. Thus, patients assigned to the treatment category that requires hospitalization (but does not require ICU care or mechanical ventilation) should be classified separately based on the presence of risk factors for involvement by drug-resistant pathogens so that drug selection can be made based on this classification. Treatment category B consists of patients who have been assessed as having no risk factors for involvement by drug-resistant pathogens [8,19,20] and includes patients who have not received antibiotics within the preceding 90 days and who are not currently receiving tube feeding, and if the patient is positive in regard to either or both of these factors, the patient is classified into treatment category C.

A history of antibiotic therapy refers to treatment with any of a broad range of antibiotics (antipseudomonal penicillins, third-
or fourth-generation cephalosporins, carbapenems, quinolones) for 2 or more days within the preceding 90 days [8] (Level IVb). Patients with a history of MRSA isolation prior to the preceding 90 days should be assumed to be at risk of MRSA infection and are assigned to treatment category C.

3.5. Before the start of treatment

Because the pathology and background of NHCAP patients are varied, the views and judgments of the attending physician play a very large role in determining the treatment category and timing of the start of treatment. Thus, it is important that the attending physician hold thorough discussions with the patient’s family and other persons responsible for the patient in regard to the type of treatment that is most appropriate, including the choice between outpatient and inpatient treatment, and attempt to share the objectives of treatment with them.

4. Pathogens and risk factors for involvement by drug-resistant pathogens

Summary

- The most common causative agents isolated from Japanese NHCAP patients are pneumococcus, Staphylococcus aureus (including MRSA), Enterobacteriaceae, including Klebsiella and Escherichia coli, and Pseudomonas aeruginosa (Level IVa).
- Reports indicate that drug-resistant pathogens, including Pseudomonas aeruginosa, MRSA, and ESBL-producing Enterobacteriaceae, are the pathogens isolated in approximately 20% of NHCAP cases in Japan (Level IVa), but the data vary with the facility and region (Level IVa).
- Risk factors for involvement by drug-resistant pathogens, including, Pseudomonas aeruginosa, MRSA, and ESBL-producing Enterobacteriaceae, include “history of antibiotic therapy for 2 or more days in the preceding 90 days” or “current tube feeding” (Level IVa).
- When a patient does not have any risk factors for involvement by drug-resistant pathogens, drug-resistant pathogens are less likely to be isolated from that patient (the specificity and positive predictive value of being positive for any of the risk factors is low, but the sensitivity and negative predictive value are high) (Level IVa).
- Because the occurrence of drug-resistant pathogens and risk factors for involvement by them in NHCAP have been found to differ from facility to facility, serious consideration must be given to the actual data obtained at each facility, such as the results of local surveillance (Level IVa).

4.2. Pathogens in NHCAP

As shown in Table 3, the possible pathogens in NHCAP can be divided into two groups according to whether the patient has risk factors for drug-resistant pathogens.

<table>
<thead>
<tr>
<th>Table 3 – Possible pathogens isolated from NHCAP patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>When an NHCAP patient has no risk factors for involvement by drug-resistant pathogens</td>
</tr>
<tr>
<td>- Pneumococcus</td>
</tr>
<tr>
<td>- MSSA</td>
</tr>
<tr>
<td>- Gram-negative enteric bacteria (including Klebsiella and E. coli)</td>
</tr>
<tr>
<td>- Haemophilus influenzae</td>
</tr>
<tr>
<td>- Oral streptococci</td>
</tr>
<tr>
<td>- Atypical pathogens (particularly Chlamydia phila)</td>
</tr>
<tr>
<td>When an NHCAP patient has a risk factor for involvement by drug-resistant pathogens (the following will be considered in addition to the above-mentioned pathogens)</td>
</tr>
<tr>
<td>- Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>- MRSA</td>
</tr>
<tr>
<td>- Acinetobacter</td>
</tr>
<tr>
<td>- ESBL-producing enteric bacteria</td>
</tr>
</tbody>
</table>

4.1. Introduction

In contrast to the causative agents isolated from CAP patients, the causative agents isolated from NHCAP patients are likely to be drug-resistant pathogens (see Section 2). However, NHCAP patients come from a variety of backgrounds, and the composition and isolation rates of causative agents differ with the facility and region. Thus, in routine clinical practice, whenever possible it is desirable to consider therapeutic strategies in view of the actual data obtained at each facility, such as the results from local surveillance and antibiograms.

This section presents evidence related to pathogens and risk factors for involvement by drug-resistant pathogens in NHCAP patients. However, since no reports of studies in which the diagnostic category NHCAP was used (see Section 2) had been published at the time these Guidelines were being prepared, all descriptions in these Guidelines are based on reports in regard to patients with the following types of pneumonia to whom the various elements comprising the definition of NHCAP apply: HCAP (according to the definition used in the ATS-IDSA 2005 Guidelines); pneumonia in patients at nursing facilities and long-term care facilities (nursing home-acquired pneumonia, NHAP); pneumonia in patients with poor activities of daily living (ADL); pneumonia in dialysis patients; pneumonia in patients receiving chemotherapy for a malignant disease; and pneumonia in immunocompromised patients (final date of the literature search: January 31, 2011). Furthermore, because the scarcity of evidence on NHCAP is also a major issue from an international perspective, this section will also mention the challenges that need to be met going forward.
Haemophilus influenzae, which are known to be frequently isolated from CAP patients, and the isolation rates of MRSA, Pseudomonas aeruginosa, and gram-negative bacteria, which are known to be frequently isolated from HAP patients, differ from country to country [4,8,17,24] (Level IVa).

The results of epidemiologic studies conducted in Japan have shown that drug-resistant pathogens, including Pseudomonas aeruginosa, MRSA, and ESBL-producing Enterobacteriaceae, which may not be targeted for CAP therapy, have been isolated in approximately 20% of the cases in which the pathogen was known [8,9] (Level IVb). It is noteworthy that pneumococcus is the pathogen most frequently isolated in HCAP in Japan, the same as in CAP, whereas drug-resistant pathogens, including Pseudomonas aeruginosa, MRSA, and ESBL-producing Enterobacteriaceae, are isolated more frequently in HCAP than in CAP, but less frequently in HAP [8,24] (Level IVa).

3) Pneumonia in patients with poor ADL

There are three reports from Japan related to patients who meet the third requirement in the definition of NHCAP (NHCAP patients with poor ADL): “Elderly or disabled and requiring nursing care”, and all three reports state that the pathogens listed in Table 3, including pneumococci and other streptococci, MRSA, Klebsiella, Pseudomonas aeruginosa, and methicillin-susceptible Staphylococcus aureus (MSSA), are the pathogens that are most often isolated in patients with poor ADL, the same as in HCAP and NHAP [29–31] (Level IVa). In addition, there is a report of a study in which atypical pathogens (Chlamydophila and Mycoplasma pneumoniae) were isolated from a high proportion of patients with poor ADL, 44.7% [30] (Level IVa).

On the other hand, studies conducted on pneumonia in elderly patients abroad that included patients with poor ADL have reported that pneumococcus, Haemophilus influenzae, and gram-negative bacteria were the most frequently isolated pathogens [32,33,35]. Isolation of Legionella pneumophila has also been reported [32] (Level IVa).

4) Pneumonia in dialysis patients

It is well known that drug-resistant pathogens such as MRSA are more frequently isolated as pathogens from patients with healthcare-related bloodstream infections, including dialysis patients, than from patients with

<table>
<thead>
<tr>
<th>Causative agents (isolated)</th>
<th>Facility:</th>
<th>Study design:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteria</td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>–</td>
<td>2.1</td>
</tr>
<tr>
<td>ESBL-producing enteric bacteria</td>
<td>0</td>
<td>1.3</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>0</td>
<td>13.0</td>
</tr>
<tr>
<td>E. coli</td>
<td>3.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>17.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Other gram-negative bacteria</td>
<td>–</td>
<td>10.4</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>41.2</td>
<td>24.7</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3.5</td>
<td>18.2</td>
</tr>
<tr>
<td>MRSA</td>
<td>1.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Streptococci other than pneumococci</td>
<td>–</td>
<td>7.1</td>
</tr>
<tr>
<td>Other gram-positive bacteria</td>
<td>–</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Values shown are percentages (%).


* Cases in which the pathogens were unknown have been excluded.

Table 4 – Pathogens (isolated) in 5 epidemiological studies.

<table>
<thead>
<tr>
<th>Causative agents (isolated)</th>
<th>Facility:</th>
<th>Study design:</th>
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<td>Acinetobacter</td>
<td>–</td>
<td>2.1</td>
</tr>
<tr>
<td>ESBL-producing enteric bacteria</td>
<td>0</td>
<td>1.3</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>0</td>
<td>13.0</td>
</tr>
<tr>
<td>E. coli</td>
<td>3.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>17.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Other gram-negative bacteria</td>
<td>–</td>
<td>10.4</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>Single</td>
<td>Single</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>41.2</td>
<td>24.7</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3.5</td>
<td>18.2</td>
</tr>
<tr>
<td>MRSA</td>
<td>1.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Streptococci other than pneumococci</td>
<td>–</td>
<td>7.1</td>
</tr>
<tr>
<td>Other gram-positive bacteria</td>
<td>–</td>
<td>2.8</td>
</tr>
</tbody>
</table>


* Cases in which the pathogens were unknown have been excluded.
community-acquired bloodstream infections [34,35] (Level IVa). However, there have been few reports on causative agents isolated from pneumonia patients on dialysis. A report on hospitalized dialysis patients abroad showed that the most frequently causative agents were, in descending order, gram-negative bacteria, Pseudomonas aeruginosa, and MRSA, and the pneumonia isolation rate was 6% [36] (Level IVb). There have been studies on nosocomial pneumonia in dialysis patients in Japan that reported high isolation rates for Pseudomonas aeruginosa, MRSA, and gram-negative Enterobacteriaceae, although many cases appear not to have met the definition of NHCAP, because they included HAP patients [37] (Level IVb).

In prospective studies conducted abroad on the risks of infection by MRSA and multidrug-resistant gram-negative bacteria in pneumonia diagnosed in dialysis patients, 15–28% of outpatients were reported to be carriers of MRSA or multidrug-resistant gram-negative bacteria [38,39]. However, the isolation rate of multidrug-resistant bacteria from hemodialysis patients in Japan is unknown.

5) Pneumonia in patients receiving chemotherapy for a malignant disease

Chemotherapy for malignant diseases is known to lower immunocompetence and increase the risk of respiratory infection. Many different types of pathogens may be involved in respiratory infections. Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Nocardia are the types of bacteria that are most commonly isolated in patients who develop pneumonia while on chemotherapy for a malignant disease, and viruses, including RS virus, parainfluenza virus, influenza virus type A and type B, cytomegalovirus, fungi, including Aspergillus, Fusarium, and Mucor, and Pneumocystis jirovecii are also said to sometimes be involved [40] (Level IVa). However, because no reports have separated the data obtained from inpatients and outpatients, evidence on patient groups that meet the definition of NHCAP is scarce.

6) Pneumonia in immunocompromised patients

The list of possible causative agents of pneumonia in immunocompromised patients should include bacteria, acid-fast bacilli, fungi, Pneumocystis jirovecii, and viruses [41] (Level IVa). When attempting to identify causative agents at the time of diagnosis, it should be noted that their spectrum is affected by whether the type of immunodeficiency is a decrease in neutrophils, humoral immunodeficiency, or cellular immunodeficiency [3].

A comprehensive determination should be made by taking into account the clinical signs and course, information obtained from samples collected from respiratory organs, and the results of serodiagnosis, diagnostic imaging, e.g., by HRCT, urinary antigen tests, and other diagnostic studies [3,42] (Level IVa).

### 4.3. Risk factors for involvement by drug-resistant pathogens in NHCAP

Risk factors for involvement by drug-resistant pathogens in NHCAP include “history of antibiotic therapy for 2 or more days in the preceding 90 days” or “current tube feeding" (Table 5) [8,12,19,20] (Level IVa).

However, risk factors for involvement by drug-resistant pathogens in NHCAP may vary with the facility. When attempting to predict the isolation of drug-resistant pathogens based on the presence of these risk factors, it must be borne in mind that their specificity and negative predictive value are high, but their sensitivity and positive predictive value are low (Level IVa).

| Table 5 – Risk factors for involvement by drug-resistant pathogens* in NHCAP. |
|------------------|---------------------------------|
|                   |                                 |
|                   | History of antibiotic therapy for 2 or more days in the preceding 90 days |
|                   | Current tube feeding             |

*Drug-resistant pathogens include Pseudomonas aeruginosa, MRSA, Acinetobacter, ESBL-producing Enterobacteriaceae, and Stenotrophomonas maltophilia.

The risk of MRSA should be taken into account whenever there is past history of MRSA isolation. When attempting to predict the isolation of drug-resistant pathogens based on the presence of these risk factors, it should be borne in mind that their sensitivity and negative predictive value are high, but their specificity and positive predictive value are low.

1) Definition of drug-resistant pathogens

In NHCAP, “drug-resistant pathogens” include Pseudomonas aeruginosa, Acinetobacter, ESBL-producing Enterobacteriaceae, MRSA, and S. maltophilia [4,7,8,43–45].

2) Risk factors for involvement by drug-resistant pathogens

Two of the studies related to NHCAP, one in Japan and the other abroad, attempted to identify risk factors for involvement by drug-resistant pathogens [8]. In the study conducted in Japan, “history of treatment with a broad-spectrum antibiotic for 2 or more days in the preceding 90 days (anti-pseudomonal penicillins, third or fourth- generation cephalosporins, carbapenems, fluoroquinolone antibacterial agents)” and “current tube feeding” were shown to be significant risk factors for involvement by drug-resistant pathogens, and the odds ratio was 3.1 and 2.5, respectively [8] (Level IVb).

“History of antibiotic therapy for 2 or more days in the preceding 6 months” and “ADL scores [48] above 12.5 points” have been shown to be significant risk factors in the study of severe NHAP conducted abroad [19]. Furthermore, a combination of these two risk factors predicted isolation rates of drug-resistant pathogens (Pseudomonas aeruginosa and MRSA) with 100% sensitivity and 69.4% specificity.

In other words, they suggested that no drug-resistant pathogens would be isolated unless both of these risk factors were present (Level IVa).

There is a report indicating that current tube feeding is an independent risk factor for Pseudomonas aeruginosa infection (odds ratio: 13.9) [20] (Level IVa), and current tube feeding is viewed as a possible alternative to poor ADL as an indicator of the presence of drug-resistant pathogens [12] (Level IV).

The 2005 ATS-IDSA Guidelines mention risk factors for multidrug-resistant pathogens (Fig. 2) [4]. A report that praises...
the validity of the risk factors described in the 2005 ATS-IDSA Guidelines points to their high sensitivity and high negative predictive (96% and 97%, respectively) and their low specificity and positive predictive value (22% and 17%, respectively) [46] (Level IVa). Therefore, it suggests that their poor specificity for predicting isolation of drug-resistant pathogens is a problem, the same as in the study mentioned above [19].

3) The issues of drug-resistant pathogens—inauditory initial antibiotic therapy, relationship to the prognosis

NHCAP patients receive inappropriate initial antibiotic therapy (therapies in which drugs with low drug sensitivity are selected as initial antibiotic regimens) more often than CAP patients do, and receiving inappropriate initial antibiotic therapy adversely affects their prognosis. Thus, the initial antibiotic therapy for NHCAP patients should be selected more carefully than for CAP patients, by taking into account drug-resistant pathogens that are associated with inappropriate initial antibiotic therapy [4,6,8,11,13,17, 21-23,49-55] (Level IVa).

In a study conducted abroad Micek et al. reported finding that the mortality risk of inpatients was 2.2 times higher when inappropriate initial antibiotic therapy had been prescribed. The report said that inappropriate antibiotic therapy was prescribed for a higher proportion of HCAP patients than for CAP patients (30.9% vs. 13.6%, p = 0.002), and that there was a significant correlation between the inappropriate initial antibiotic therapy and involvement by drug-resistant pathogens [23] (Level IVb).

A study conducted in Japan reported finding that inappropriate initial antibiotic therapy was prescribed for a higher percentage of HCAP patients than for CAP patients (20.8% vs. 9.7%, p = 0.038), and that when drug-resistant pathogens were isolated from HCAP patients the odds ratio of inappropriate initial antibiotic therapy was 14.0 (95% CI: 4.5–43.6) [8] (Level IVb).

A study on NHAP conducted in Spain reported that when gram-negative bacteria or MRSA that had low drug sensitivity were isolated, the odds ratio of 1-month mortality was 16.4, and that there was a significant correlation between the drug-resistant pathogens and mortality [28] (Level IVa).

4) Relationship between isolation of drug-resistant pathogens and severity

A report on HCAP in Japan showed that there was little correlation between the severity of HCAP evaluated on the basis of the A-DROP classification [56] and isolation of drug-resistant pathogens [8] (Level IVb). However, there are several studies conducted abroad whose results suggest a correlation between the severity of HCAP and isolation of drug-resistant pathogens [19,52] (Level IVa) and a report that proposed initial antibiotic treatment strategies that take severity levels into account [11] (Level VI), and there is no consensus in regard to whether a correlation exists between the severity of HCAP and isolation of drug-resistant pathogens. The proposal of an initial antibiotic treatment strategy that takes severity levels into account is based on the results of studies which suggest that treatment with multiple broad-spectrum antibiotics, as recommended in the ATS-IDSA 2005 Guidelines, is unnecessary in patients whose condition is not severe [47,57,58] (Level II).

4.4. Discussion and future challenges

As shown in Table 4, there are differences from country to country in the causative agents isolated from NHCAP patients, and in Japan there are even differences between facilities. Thus, when considering initial antibiotic therapy, it is desirable to refer to as much data, such as local surveillance data and antibiograms obtained at each facility, as possible.

Drug-resistant pathogens such as gram-negative Enterobacteriaceae that have low drug sensitivity, including Pseudomonas aeruginosa, MRSA, and ESBL-producing Enterobacteriaceae, are often isolated from patients who meet the definition of NHCAP both in Japan and abroad. Pneumococcus, which is often isolated from CAP patients, is also isolated from NHCAP patients. Because there are also cases in which atypical pathogens (particularly Chlamydia phila) are assumed to be involved, treatment targeting them may be necessary. However, since there is insufficient evidence to support our predictions, it will be necessary to provide evidence through prospective immunology studies and clinical tests.

NHCAP patients are extremely diverse. There is little evidence as to the answers to the questions: “Are multiple broad-spectrum antibiotic regimens actually necessary in therapies targeting drug-resistant pathogens?”, “What are the risk factors for drug-resistant pathogens?” and “What are their evaluation methods with high sensitivity and high specificity?” At present, the following issues need to be classified [21,56]:

1) Essential risk factors for drug-resistant pathogens
2) Whether weighting (stratification, scoring) of each of the risk factors for drug-resistant pathogens is necessary
3) Whether there is a relationship between drug-resistant pathogens and severity (whether severity is a risk factor for drug-resistant pathogens or not)

The aging of Japanese society is predicted to accelerate, and the number of NHCAP patients as a proportion of all pneumonia patients is expected to continue to increase. Treatment strategies for NHCAP that are effective and efficient need to be discussed as crucial challenges, and high quality research and investigations must be conducted to elucidate the items above.

5. Diagnostic testing

Summary

- Expectorated sputum culture results do not directly mean the causative agents of pneumonia patients.
- Identification of the bacterial pathogens in pneumonia patients requires quantitative culture of sputum specimens that have been obtained from the lower respiratory tract by invasive methods in order to avoid contamination of oral bacteria (Level IVa).
- Drug-resistant pathogens are often detected in the sputum of NHCAP patients, but they are not always the causative agent (Level IVb).
- Expectorated sputum should not be used for cultures of anaerobic bacteria (Minds recommendation grade D).
• Quantitative or semiquantitative culture of sputum collected by tracheal suction might be reliable methods of identifying the causative agents in patients who have been intubated for management of mechanical ventilation (Level Iva).

5.1. Limitations of bacteriologic testing in NHCAP

Expectorated sputum is inadequate as a specimen for identifying the causative agents of pneumonia, because it is impossible to know whether an expectorated sputum specimen originated at the site of the pneumonia lesion and because sputum becomes contaminated by indigenous oral bacteria and colonized bacteria in the respiratory tract as it is expectorated, which makes it impossible to determine whether the bacteria that grow out in cultures are the pathogens that are causing the pneumonia, colonized bacteria in the respiratory tract, or indigenous oral bacteria.

It is reported to be possible to identify the causative agent in pneumonia patients by quantitatively culturing sputum specimens collected from the site of the infection by bronchialalveolar lavage (BAL), by a protected specimen brush (PSB), or, in patients who have been intubated, by tracheal aspiration (Level I) [4].

Since many NHCAP patients in Japan are elderly or bedridden and even collecting expectorated sputum specimens may be difficult, with the exception of a small number of facilities, invasive diagnostic procedures are rarely carried out promptly in Japan. Thus it is difficult to diagnose NHCAP based on bacteriological examinations. The results of bacteriological examinations should be used as one of the evidences for making decisions in regard to diagnosis and treatment, and empiric therapy should take priority in regard to antibiotic therapy (Minds recommendation grade C1).

5.2. Interpretation of causative agent in NHCAP

Studies conducted on NHCAP to date have reported that multidrug-resistant (MDR) pathogens are often isolated from NHCAP patients and that the rate of isolation of drug-resistant pathogens such as Pseudomonas aeruginosa and MRSA is significantly higher than in CAP (Level Iva) [7–9,13,22,23,48]. However, these studies on the causative agents isolated in NHCAP report the isolation rates of pathogens in bacteriological tests and do not specify the method used to collect the specimens, but most of them clearly use expectorated sputum as the specimens. Thus, it is uncertain whether the isolated bacteria are the actual causative agents [12].

5.3. Bacteriologic diagnostic testing methods

If expectorated sputum has been obtained before any antibiotics have been administered, bacteriological tests should be performed on the sputum.

Gram stain and cultures should be performed using expectorated sputum. Only aerobic culture is desirable. Because expectorated sputum is contaminated by indigenous oral bacteria, it is unsuitable for culturing anaerobic bacteria.

Since urinary antigen tests are a simple method of detecting pneumococci and Legionella pneumophila, they should be performed whenever possible, and now antigen tests for expectorated sputum itself have been approved for pneumococcus.

Culture tests are not standard procedure for identifying the pathogens in atypical pneumonia or viral pneumonia. Usually when a diagnosis of atypical pneumonia is made, titers of IgG antibodies against Mycoplasma and Chlamydia in paired sera and IgM antibody titers in the initial phase of the infection are measured. A rapid diagnostic test for influenza is one of the limited numbers of diagnostic methods that are available for viral pneumonia. Except influenza, a definitive diagnosis of viral pneumonia is usually made on the basis of antibody titers. Although PCR diagnosis is possible at some facilities, it is not generally used.

There is a report that when quantitative cultures of endotracheal aspirated sputum from patients with severe NHCAP who had been intubated for mechanical ventilation yielded a number of organisms greater than 10⁶ CFU/mL, it was the causative agent in a high percentage of the cases (90% sensitivity, 77% specificity) (Level Iva) [59]. On the other hand, there are also reports stating that for ventilator-associated pneumonia (VAP) patients, when the pathogen is not isolated by tracheal aspiration, the specificity that the pathogen is not the causative agent is 94% (Level Iva) [60].

When tuberculosis cannot be ruled out by chest X-rays, etc., specimens should always be collected from respiratory tract to stain for acid-fast bacteria and culture for mycobacteria. A PCR test of specimens collected from respiratory tract and a quantiFERON® test are also effective methods of diagnosing tuberculosis.

Please refer to other documents in the literature in regard to the diagnosis of fungal pneumonia or pneumocystis pneumonia.

5.4. Routine testing methods for the diagnosis of pneumonia

If a shadow is detected on a chest X-ray, and one or more of the following four findings is present: leukocytosis, fever, purulent sputum, high C-reactive protein (CRP) level, a diagnosis of pneumonia should be made and bacteriological tests should be performed.

When blood culture is possible, two or more sets of specimens should be taken for the bacteriological tests. If expectorated sputum specimens are collected, smear microscopy should be performed and, if it is evaluated to be of good quality, the microbiological result of culture is somewhat reliable. Urinary antigen tests for pneumococci should be performed whenever possible, and the Legionella urinary antigen test should be performed in severe cases or cases that are becoming more severe.

6. Antibiotic selection

Summary

• Treatment strategies should be decided from the standpoint of “respect for autonomy (of the patient)” by the attending physician, who has the best understanding of
the history of the patient and the patient’s family and their lives, and who will respect the wishes of the patient and the patient’s family (Minds recommendation grade C1).

- Because there is no risk of involvement by drug-resistant pathogens in patients in treatment category A or treatment category B, a narrow-spectrum antibiotic should be selected in the same manner as for the treatment of CAP pneumonia (Minds recommendation grade C1).

- Because they are at risk for involvement by drug-resistant pathogens, patients in treatment category C should be treated with one of the broad-spectrum antibiotics for which a low incidence of adverse reactions has been reported (Minds recommendation grade C1).

- A powerful broad-spectrum antibiotic, including an antibiotic for the treatment of drug-resistant pathogens and rare pathogens such as Legionella, should be selected for the treatment of patients in treatment category D, because of their poor prognosis (Minds recommendation grade C1).

### 6.1 Appropriate and inappropriate antibiotic therapy

There have been reports of patients who received inappropriate treatment having a significantly poorer outcome than patients who received appropriate treatment [7–9,13,22,23,48,50] (Level II). Moreover, even when the treatment of patients who received inappropriate treatment was changed to appropriate treatment with a broad-spectrum antibiotic, their outcomes failed to improve (Level IVa) [48], thereby demonstrating the importance of appropriate initial antibiotic selection. However, since these data include pathogens isolated by culturing expectorated sputum, it is uncertain whether the bacteria isolated were the actual causative agents. On the other hand, it is unclear whether selecting the most appropriate antibiotic for the patients from which drug-resistant pathogens had been isolated would have improved their outcome (Level IVa) [61,62].

Drug-resistant pathogens are involved in a high proportion of HCAP patients. However, since the pathogens isolated are not necessarily the causative agent, selecting an antibiotic targeting that pathogen alone may lead to overtreatment (Level I) [11,12].

The approach to the treatment of patients in whom drug-resistant pathogens may be involved that is recommended in the ATS/IDSA guidelines [4] (Level I) is to administer a broad-spectrum antibiotic immediately and allow streamlining or de-escalation whenever possible 48–72 h later, when the results of the cultures to identify the causative agent are available. The risk factors for involvement by drug-resistant pathogens in the ATS/IDSA guidelines have become the basis for the definitions for HCAP.

However, it was reported that the outcome of ICU patients in whom involvement by drug-resistant pathogens was suspected and who were treated with recommended drugs was significantly worse than that of those who were treated with non-recommended drugs, whether thorough bacteriological tests had been performed to identify the causative agent or not [63] (Level II). That finding suggested that appropriate treatment with an antibiotic targeting the causative agent does not necessarily improve the outcome of patients with involvement by drug-resistant pathogens, and patients’ baseline condition or adverse reactions of the antibacterial drugs may affect their outcome.

### 6.2 Basis for antibiotic selection and key points

In Japan, there are few opportunities to use invasive bronchoscopic techniques to collect sputum from HCAP patients, and there are few facilities where quantitative sputum cultures are performed. It is extremely difficult to identify causative agents based on information obtained from the results of bacteriologic screening of sputum specimens, and, as stated in Section 5, it is impossible to determine whether anaerobic bacteria and indigenous oral bacteria, which are frequently found in the elderly, are involved in aspiration pneumonia.

Thus, this Guideline recommends empiric treatment based on the data in regard to pathogens isolated in the past when selecting antibiotics, and that antibiotic streamlining and de-escalation be considered based on the results of attempts to isolate causative agents from blood or good quality of expectorated sputum specimens (Minds recommendation grade C1). However, from the standpoint of nonmaleficence toward patients who have complications and are in poor general condition or are in the terminal phase of their illness, it is recommended that adverse reactions be taken into account when selecting antibiotics.

### 6.3 Basic concepts in regard to antibiotic selection

NHCAP patients have a poorer outcome than CAP patients, and are more likely to have involvement by drug-resistant pathogens (Level I) [7–9,13,22,23,48,50]. Therefore, it is recommended that the antibiotic with activity against the possible causative agent be selected for initial treatment. The condition that should be considered first in NHCAP patients is aspiration pneumonia (Level IVa) [13,64,65]. The proportion of NHCAP patients with involvement by drug-resistant pathogens is higher among those who have received recent antibiotic therapy and those who have a history of hospitalization (within 3 months) (Level IVa). Thus, it is necessary to empirically select antibiotics for initial treatment that target these conditions and pathogens.

Needless to say, targeted therapy is ideal when the causative agent is known, but it is impossible to identify the causative agent of pneumonia by examinations of expectorated sputum alone.

Thus, from the standpoint of “respect for autonomy”, these guidelines entrust the final decision regarding the assignment of patients to a treatment category to the attending physician, who can investigate the way of life and family history of the patient and the patient’s family.

A narrow-spectrum antibiotic that targets, pneumococcus, Haemophilus influenzae, Klebsiella, Staphylococcus aureus, and anaerobic bacteria, or combination therapy is recommended for the treatment of patients assigned to treatment category A and treatment category B, who have no risk factors for involvement by drug-resistant pathogens (Minds recommendation grade C1).

Out of respect for the principle of nonmaleficence it is recommended that broad-spectrum antibiotics with a low incidence of adverse reactions be selected for the treatment
of the patients in treatment category C, who have risk factors for involvement by drug-resistant pathogens (Minds recommendation grade C1).

Out of respect for the principle of beneficence, selection of powerful broad-spectrum antibiotics, including antibiotics for drug-resistant pathogens and rare pathogens such as Legionella, is recommended for the treatment of the patients in treatment category D, who have been “determined to require intensive care, such as mechanical ventilation” (Minds recommendation grade C1).

These recommendations have been referred to as guidelines, and it is necessary for the attending physician to hold thorough discussions with the patient, the patient’s family, and the healthcare team in order to decide on treatment (Minds recommendation grade C1).

6.4. Recommendations of initial empiric antibiotic therapy (Fig. 8)

1) Outpatient treatment: patients with no risk factors for involvement by drug-resistant pathogens (treatment category A)

The main targets of the outpatient treatment of patients with no risk factors for involvement by drug-resistant pathogens (treatment category A) are pneumococcus, Haemophilus influenzae, Staphylococcus aureus, Klebsiella, and Chlamydia pneumoniae (Level IVa, Minds recommendation grade C1).

The antibiotics recommended for patients in treatment category A are β-lactamase inhibitor combined with penicillins (SBT/ABPC, CVA/AMPC), respiratory quinolones (GRNX, MFLX, LVFX), or macrolide antibiotics (CAM, CVA/AZM). Because β-lactamase inhibitor combined with penicillins are not effective against atypical pneumonia pathogens such as Chlamydia pneumoniae, they should be used concurrently with a macrolide. Since CTRX has a long half-life and high blood concentrations can be maintained with a single daily dose, it is suitable for outpatient therapy. CTRX is not effective against atypical pneumonia pathogens, so it should be used in combination with a macrolide. Since the activity of CTRX against anaerobic bacteria is insufficient, concomitant treatment with one of the macrolides, which have some degree of effectiveness against oral anaerobic bacteria, is thought to increase activity against anaerobic bacteria [66].

In addition, single-dose AZM-SR is currently available on the market and good compliance with AZM-SR therapy has been demonstrated. Because of its weak activity against anaerobic bacteria, selection of LVFX should be avoided if aspiration pneumonia is suspected.
2) Inpatient treatment: when no risk factors for involvement by drug-resistant pathogens are present (treatment category B)

The main targets of inpatient treatment of patients with no risk factors for involvement by drug-resistant pathogens (treatment category B) are pneumococcus, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Chlamyphila pneumoniae (Level IVa)* [8,9].

The recommended injectable antibiotics are the β-lactam-β-lactamase inhibitor combined with penicillin SBT/ABPC, cephalosporin antibiotics, such as CTRX, the carbapenem antibiotic PAM/PBP, and the respiratory quinoline LVFX. If a patient from a nursing facility for the elderly is admitted to a hospital for pneumonia and there is no risk factor of involvement by drug-resistant pathogens, the causative agents of common respiratory infections or aspiration should be suspected, and the antibiotics should be selected accordingly.

Because CTRX is mainly metabolized in the liver, it can be used to treat patients with impaired renal function. However, CTRX has weak activity against anaerobic bacteria. PAM/BP is one of carbapenem antibiotics, and although its antibacterial activity against *Pseudomonas aeruginosa* is weak, it is effective against pneumococcus and anaerobic bacteria. SBT/ABPC is useful against anaerobic bacteria and pneumococcus, *Staphylococcus aureus*, and *Moraxella*. β-lactamase-negative ABPC resistant (BLNAR) *Haemophilus influenzae* have recently increased, and SBT/ABPC is ineffective against *Haemophilus influenzae* (PIP is effective). The above-mentioned β-lactam antibiotics are ineffective against *Chlamydia pneumoniae*. LVFX injections are effective against a broad spectrum of causative agents in respiratory infections, from *Chlamydia pneumoniae* and *Haemophilus influenzae* to pneumococcus, but LVFX injections have little activity against anaerobic bacteria. Thus, CTRX and LVFX are inappropriate choices when aspiration pneumonia is suspected.

3) Inpatient treatment: when a risk factor for involvement by drug-resistant pathogens are present (treatment category C)

In addition to the causative respiratory pathogens mentioned above, the targeted microorganisms for inpatient treatment of patients who have risk factors for involvement by drug-resistant pathogens include, *Pseudomonas aeruginosa*, MRSA, and *Acinetobacter (Level IVa)* [8,9,65,66].

The antibiotics recommended for inpatient treatment of patients who have a risk factor for involvement by drug-resistant pathogens are present (treatment category C) are TAZ/PIPC, fourth generation cephalosporin, carbapenem, and new quinolones (CPFX, PZFX) which have activity against *Pseudomonas aeruginosa*. Because fourth-generation cephalosporin and new quinolone antibiotics have weak activity against anaerobic bacteria, they should be used concomitantly with MTZ, CLDM, or SBT/ABPC. If there is a risk of involvement by MRSA, for example, because of a history of hospitalization, VCM, TEIC, or LZD should be selected. ABK is also effective. Since none of the above antibiotics except the quinolones have any activity against atypical pneumonia pathogens such as *Chlamydia pneumoniae*, a quinolone or a macrolide is recommended for the treatment of patients suspected of having atypical pneumonia that occurs in epidemic outbreaks. TAZ/PIPC has been reported to exhibit activity that is equivalent to the activity of IPM/CS in NHAP patients [29].

4) Severe cases requiring intensive care (treatment category D)

In combination with antibacterial drugs recommended for the treatment of hospitalized patients who may have drug-resistant pathogens, injections of new quinolones such as CPFX or PZFX, or the macrolide AZM are recommended for the severe cases requiring intensive care as treatment for infection by *Legionella* and atypical pathogens, which are rarely isolated but may cause severe illness (Minds recommendation grade C1).

5) Modification of antibiotic recommendations according to the rates of isolation of drug-resistant pathogens

The effectiveness of antibiotics against community-acquired infections varies with the rates of isolation of drug-resistant pathogens. ESBL-producing enteric bacteria *Klebsiella* currently require particular attention. Klebsiella are a key group of bacteria that are isolated at a higher rate from NHAP patients than from CAP patients. With the exception of carbapenem, β-lactam antibiotics are ineffective against ESBL-producing *Klebsiella*. While the isolation rates of ESBL-producing *Klebsiella* have ranged from about 2% to 5% in a nationwide surveillance [67], since the rates were as high as 10% to 20% in some regions, penicillins and cephalosporins should be removed from the list of selections for empiric therapy (Level IVb, Minds recommendation grade C1). The clinical effects of TAZ/PIPC on ESBL-producing *Klebsiella* have not been confirmed.

6.5. Antibiotic dosage strategies

1) Antibiotic dosage and duration of therapy

The doses of antibiotics prescribed in Japan tend to be low from the view point of the PK-PD theory. Thus, for HAP in which there is a high isolation rate of drug-resistant pathogens, treatment with high doses of antibiotics has been recommended as initial treatment, when drug sensitivity is unknown [68]. Since elderly patients comprise the majority of NHAP patients, the antibiotic dosage should be adjusted as indicated in Section 7, “Antibiotic therapy and general management of the elderly pneumonia patients”.

Since there is no clear evidence concerning the duration of antibiotic therapy for NHAP, the most commonly prescribed 7- to 10-day regimen would appear to be most appropriate (Level IVb, Minds recommendation grade B) [67]. If the duration of treatment is prolonged beyond 7 to 10 days, an antibiotic with the same spectrum of activity or antibiotic de-escalation should be selected. Fever, the serum CRP level, and the leukocyte count are often used as indicators of the efficacy of antibiotic therapy. However aspiration can recur during effective antibiotic therapy for aspiration pneumonia, and it is necessary to determine whether the antibiotic is ineffective or aspiration has recurred.

2) Changes and modification of antibiotics

When a broad-spectrum antibiotic has been selected for initial treatment and the causative agent has subsequently been identified, it is desirable to make changes based on the causative agent that has been identified. However, since pathogens isolated from expectorated sputum are not...
necessarily the causative agent, there is no basis for assuming that therapy targeting the pathogen isolated is correct. The antibiotic regimen should be modified based on not only the results of bacteriological tests but a comprehensive assessment of the overall clinical course of the patient. If the patient’s general condition and oxygenation status are satisfactory, test results show a trend toward improvement, and possible causative agent have decreased, the antibiotic regimen should be modified to a narrow-spectrum antibiotic or concomitant treatment with more than one antibiotic should be discontinued (Fig. 9, Minds recommendation grade C1).

7. Antibiotic therapy and general management of the elderly pneumonia patients

7.1. Introduction

Many NHCAP patients are elderly and are in poor general condition due to underlying diseases. Because of reduced immunocompetence due to aging, poor nutritional status and immunodeficiency due to the presence and treatment of underlying diseases and, hypoactivity of the mucociliary transport system in the airways, a reduced cough reflex, and other factors, pneumonia in the elderly is often refractory. In addition, many patients receiving nursing care at home or in facility are subjected to medical procedures, such as catheterization that make them more susceptible to infection. Therefore, treatment of pneumonia in the elderly requires careful antibiotic therapy and general management.

7.2. Antibiotic therapy in elderly pneumonia patients

Because the renal function of many elderly patients is reduced, renally excreted drugs often have a prolonged half-life ($T_{1/2}$), a higher area under the blood concentration–time curve (AUC), and a lower urinary excretion rate. Assessment of the patient’s renal function is necessary before deciding on the dose of an antibiotic to prescribe, and creatinine clearance ($Ccr$) is widely used as an index of renal function in clinical practice. Because accurate $Ccr$ measurements require urine collection, estimated creatinine clearance ($eCcr$) values calculated from serum creatinine values by the Cockcroft–Gault formula have been used as an alternative.

Cockcroft–Gault formula:

$$eCcr \ (mL/dL) = \frac{(140 – \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85, \text{if female}$$

However, because the Cockcroft–Gault formula tends to underestimate $Ccr$ in the elderly in comparison with younger
subjects, a formula for estimating glomerular filtration rate (GFR) of Japanese has been proposed [69], and it is in widespread use (Level IVb).

- Formula for estimating the GFR of Japanese: eGFR (mL/min/1.73 m²) = 194 × serum creatinine⁻¹.094 × age⁻⁰.287 (× 0.739, if female)

The nomogram used to obtain the eGFR, which is the value obtained by using the formula devised for Japanese, is shown in Supplementary material Fig. S4.

Before prescribing drugs for elderly patients who do not have standard physique or who have reduced renal function, their renal function should be assessed based on their eGFR value without any correction for body surface area (BSA) [70].

Since most antibiotics are excreted renally, dose reduction is necessary in patients with a decreased GFR. The Guidelines' recommended administration and dosage of each drug according to the patient's renal function are shown in Supplementary material Table S2 (Note 1: The Ccr values calculated by means of the Cockcroft–Gault formula and eGFR values are estimated values. A 24-hour pooled urine specimen must be used to calculate the Ccr in order to obtain an accurate glomerular filtration rate. Note 2: The drug doses for patients with renal impairment specified in the Japanese Society of Nephrology guidelines [70] are based on the dosages covered by Japanese National Health Insurance, and as a result are lower than the doses prescribed for patients with renal impairment in Western countries.) Refer to the Sanford Guide to Antimicrobial Therapy 2000 [71] and other literature for the drug doses recommended for patients with renal impairment in Western countries.

Therapeutic drug monitoring (TDM) is recommended whenever the toxic range and therapeutic range of a drug are close to each other.

7.3. General management of pneumonia in elderly patients

Antibiotic therapy is the core of treatment for pneumonia. However, adjunctive therapies as well as general management become necessary in elderly patients with underlying diseases and whose general condition is poor. Attention should be paid to dehydration, nutritional status, circulatory function, and oxygenation status [69].

1) Fluid management

Dehydration is a problem that requires particular attention in elderly pneumonia patients. Sweating and hyperventilation due to a fever result in fluid loss, and fluid intake is sometimes inadequate because of patients' decreased level of consciousness. When that happens, adequate fluid therapy becomes necessary (Minds recommendation grade B) [72]. Dehydrated patients exhibit such clinical manifestations as impaired consciousness, dry skin, and dry tongue. The diagnosis should be made on the basis of such clinical findings together with the results of blood studies such as evidence of hemoconcentration (high hematocrit and high total protein level) and a high blood urea nitrogen (BUN) value.

Pneumonia in the elderly is usually accompanied by hypertonic or isotonic dehydration, and whenever it is, an isotonic solution should be administered according to the body fluid deficit [73]. Because elderly patients have little residual cardiac or renal function, care should be exercised to avoid overinfusion.

2) Nutritional management

Poor nutritional status is a risk factor for pneumonia in the elderly [74], and nutritional management is known to promote recovery from pneumonia (Level I) [75]. The quality of the diet of elderly patients is affected by factors such as poor oral hygiene, taste changes, decreased mobility, and oral medications, and mental factors such as depression, dementia, and hyponatremia lead to decreased oral intake. Social factors such as living in a facility, living alone, economic status, and inadequate cooking also affect oral intake.

It is important to monitor elderly patients for weight changes during treatment for pneumonia [76]. A decrease in body weight by more than 10% of their usual weight has been found to be associated with a high mortality rate and is considered serious, and a decrease by 5–10% is considered potentially serious. The serum albumin level is a useful index of nutritional status, and the serum albumin levels of patients with CAP are correlated with their mortality rates (Level IVb) [77].

Because most NHCAp patients have aspiration pneumonia, an adequate feeding method for elderly NHCAp patients with aspiration pneumonia should be selected based on an evaluation of their swallowing ability. Feeding methods for patients in whom oral intake is poor or impossible include peripheral venous nutrition, total parenteral nutrition (TPN) via a central vein, and enteral feeding via a nasogastric tube or a gastrostomy tube. The optimal method should be selected in view of the patient's condition and social background.

3) Respiratory management

The treatment of patients with severe pneumonia or pneumonia in patients with underlying lung diseases involves respiratory management that includes oxygen inhalation therapy and mechanical ventilation, because they tend to easily progress to respiratory failure. However, since the indications for endotracheal intubation and introduction of mechanical ventilation during the treatment of elderly patients and patients whose original general condition is poor depends on various factors, including the patient's social background, the physician should take the patient's condition, the wishes of the family, and the patient's wishes into account when considering intubation or the introduction of mechanical ventilation. NHCAp patients have a higher mortality rate than CAP patients, and some reports attribute their higher mortality rate to background factors, such as age, complications, and criteria for entering the ICU, rather than to their course of treatment [61].

8. Aspiration pneumonia

Summary

- Dysphagia and aspiration are significant risk factors for NHCAp (Level II)
• Central nerve system (CNS) disease and dementia are strongly associated with dysphagia, and they are common underlying diseases in HCAP patients (Level II)
• Aspiration pneumonia is more common among HCAP inpatients than among CAP inpatients (Level IVa).
• Vaccinations and oral health care are effective in preventing aspiration pneumonia (Level II, Minds recommendation grade B)
• Drugs that improve the swallowing reflex may be effective in preventing aspiration pneumonia (Level II, Minds recommendation grade B); however, percutaneous endoscopic gastrostomy (PEG) is not recommended (Level II, Minds recommendation grade C2)

8.1. Introduction

Pneumonia is the third or fourth highest cause of death in Japan, and most of the deaths from pneumonia occur in the elderly population. Japan is facing the advent of an unprecedented aging of society, and the field of nursing is rapidly expanding. In order to meet the demands of the rapidly aging of society in Japan, we are taking this opportunity to define and classify NHCAP.

The very old, the so-called old-older subjects of the population, now comprise a high percentage of home-care patients and patients residing in medical and nursing care facilities, who account for a large proportion of NHCAP patients, and they are at high risk of aspiration pneumonia. As the population requiring nursing care increases, the incidence of aspiration pneumonia is also expected to increase, and the significance of NHCAP in the healthcare and nursing care may be evident in future.

8.2. Aspiration as a risk factor for NHCAP

In overseas studies, no sufficient evidence for NHCAP has been reported. Nursing-home residents have been reported to be the population at highest risk of hospitalizations for pneumonia in the U.S., where 33.3 out of 1000 nursing-home residents per year have required hospitalization for the treatment of pneumonia, compared with 1.14 out of 1000 home residents per year. In Japan, 10% to 18% of all patients hospitalized for CAP in the U.S. are nursing home residents, and the percentage has been tending to increase [80]. The risk factors for NHAP in nursing homes residents include dysphagia and impossibility of oral intake (Table 6) [78–80]. It is also important to note pathological conditions that may increase patients’ susceptibility to aspiration (Table 7). More specifically, it has been pointed out that complications of CNS disease are an underlying disease in more than half of the cases, and lack of patient evaluations for aspiration is a cause of treatment inadequacy [28]. Many HCAP patients have cerebrovascular disease and impaired consciousness, both of which are strongly associated with dysphagia, and these disorders may affect the outcome [13,50] (Level II).

CNS disease and dementia, both of which are strongly associated with aspiration, are an underlying disease in many NHAP patients in Japan, and significant numbers of NHAP patients in Japan have undergone PEG [26]. Similarly, complications of CNS disease and tube feeding have been found in...
more than 40% and 10%, respectively, of HCAP patients, indicating strong possibility that aspiration, including silent aspiration such as un-witnessed aspiration during the night, is involved in the etiology of pneumonia in HCAP patients [8,81] Thus, difficulty in swallowing and dysphagia, both of which are strongly associated with aspiration, are the important risk factors for HCAP as defined by the ATS/IDSA, and for NHCAP in Japan (Level II).

8.3. Aspiration pneumonia cases as a proportion of NHCAP cases

Since pneumonia that results from aspiration is classified according to its etiology as “aspiration pneumonia”, it differs from pneumonia that is classified as NHCAP because of the facility where the pneumonia occurred, and because of this difference, some cases may be diagnosed as both NHCAP and aspiration pneumonia. There is insufficient evidence in either Japan or abroad in regard to the proportion of NHCAP cases that are cases of aspiration pneumonia. Data from Spain indicated that 20.6% of HCAP patients who require hospitalization have aspiration pneumonia, a clearly higher proportion than among CAP patients who require hospitalization (3.0%) [13].

Another study reported the presence of comorbidities that cause aspiration in more than 30% of HCAP patients, and a multicenter study of hospitalized pneumonia patients in Japan showed that more than 60% of the patients who had been hospitalized for CAP had aspiration pneumonia [64]. Thus, based on this comprehensive assessment, NHCAP cases in Japan are likely to include many cases of aspiration pneumonia (Level III).

Although the meaning of diagnosing aspiration pneumonia in NHCAP patients will require validation in the future, NHCAP is a type of pneumonia that occurs in elderly persons who have higher ADL disability levels than CAP patients. To clarify this potential association the detailed diagnosis of aspiration pneumonia is necessary [12].

8.4. Diagnosis of aspiration pneumonia

Since the only guidelines that clearly define aspiration pneumonia are the JRS Guidelines for the Management of Hospital-Acquired Pneumonia in Adults, these Guidelines will use their definition of

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Table 8 – Procedures for detection of functional dysphagia.

<table>
<thead>
<tr>
<th>1. Screening methods</th>
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<tbody>
<tr>
<td>Bedside assessment of swallowing function, arterial oxygen saturation monitoring during swallowing, repetitive saliva swallowing test, water swallowing test, simple swallowing provocation test, etc.</td>
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<table>
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<tr>
<th>2. Further swallowing assessment methods</th>
</tr>
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<tbody>
<tr>
<td>Water swallowing test, videofluoroscopic examination of swallowing, videoendoscopic examination of swallowing, laryngoscopic evaluation of swallowing, swallowing pressure measurement, simple swallowing provocation test, swallowing provocation test, examination of pulmonary uptake of a radioisotope, such as indium chloride, dissolved in the mouth the previous night</td>
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Fig. 10 – Diagnostic flow chart for aspiration pulmonary disorders.
aspiration pneumonia as being pneumonia that develops in patients in whom dysphagia and aspiration is known to occur (or is strongly suspected) [Fig. 10] [3]. It is important to conduct swallowing function tests as a means of detecting dysphagia and aspiration, and to determine whether aspiration has occurred during and after meals. Methods of testing for dysphagia range from bedside assessments to videofluoroscopic examinations of swallowing (Table 8). When performed on elderly patients who require a high level of nursing care, videofluoroscopic examinations of swallowing that are performed with the patient seated may result in aspiration during or after the examination, and priority should therefore be given to procedures such as bedside swallowing function assessments and simple swallowing provocation tests [82]. Further tests can be conducted while monitoring the patient’s condition (Minds recommendation grade B). Swallowing function assessments and examinations should be performed in accordance with the healthcare environment at each nursing care facility.

8.5. Treatment (Table 9)

Antibiotic treatment strategies for aspiration pneumonia do not differ greatly from treatment strategies for NHCAP. Since there is greater involvement by indigenous oral bacteria and anaerobic bacteria in patients with aspiration pneumonia than in pneumonia patients with no risk of aspiration, antibiotics that are effective against indigenous oral bacteria and anaerobic bacteria are given priority when selecting antibiotics to treat patients with aspiration pneumonia. However, a maximum effort should be made to identify the causative agents and select drugs with high activity against them. De-escalation procedures should be conducted when the causative agents have been identified and the clinical manifestations have improved. While the pneumonia of aspiration pneumonia patients may be cured, their dysphagia does not improve. Episodes of aspiration may recur during treatment for pneumonia, and pneumonia that has improved may become worse again as a result of recurring aspiration. Dysphagia rehabilitation needs to be provided in parallel with antibiotic treatment (Level III, Minds recommendation grade B).

There is evidence in Japan that pneumococcal polysaccharide vaccine (PPV) injections are effective in treating NHP. PPV injections are also recommended as a means of preventing aspiration pneumonia in NHCAP patients (Level II, Minds recommendation grade B) [83].

There is evidence for oral healthcare as another prevention for aspiration pneumonia (Level II, Minds recommendation grade B) [84]. Oral healthcare is expected to decrease the number of indigenous bacteria and can reduce the incidence of pneumonia due to unrecognized dysphagia.

PEG is sometimes performed as a means of preventing aspiration pneumonia, but there is no evidence that it prevents pneumonia, and the incidence of aspiration pneumonia in PEG patients is the same as in patients fed through a nasogastric tube. Thus, PEG is not recommended as a preventative measure for NHCAP (Level II, Minds recommendation grade C2) [85,86].

ACE inhibitors [87] and cilostazol [88] have been reported to be effective in preventing pneumonia in patients who have a history of cerebral infarction and are at high risk of aspiration. Unless the patient is bedridden and has a very low ADL level, these drugs can be expected to be effective in preventing aspiration pneumonia in NHCAP patients (however, they are not covered by Japanese National Health Insurance) (Level II, Minds recommendation grade B).

9. Vaccines

Summary

- Vaccination of nursing home residents with PPV is useful in preventing pneumococcal pneumonia and in decreasing the mortality rate (Level II, Minds recommendation grade B).
- Vaccination of residents of nursing care facilities for the elderly with a combination of influenza vaccine and PPV decreases their hospitalization rate for pneumonia (Level II, Minds recommendation grade B).

9.1. Introduction

NHCAP is often diagnosed in the elderly population, and vaccines play a vital role in preventing respiratory infections in elderly patients. The two types of vaccines that are being used to prevent pneumonia in the elderly are PPV and influenza vaccine. PPV contains the capsular polysaccharides of 23 serotypes of pneumococci and protects against about 85% of all pneumococcal pneumonia in adults. However, there has been little evidence regarding the usefulness of PPV or influenza vaccine in relation to NHCAP.

9.2. Pneumococcal polysaccharide vaccine (PPV)

A large part of the evidence for the usefulness of PPV is based on its efficacy in preventing invasive pneumococcal infections in large-scale cohort studies, case-control studies, and meta-
analyses [89–96], and there is no evidence to support its preventative effects against pneumonia based on large-scale prospective clinical studies. For example, the results of a meta-analysis have confirmed the usefulness of PPV against invasive pneumococcal infections, but the preventive efficacy of PPV against the development of pneumonia by all causative agents, including pneumococci, and its effectiveness in lowering mortality rates have not been clarified [96].

Pneumococci are also significant causative agents of NHCAP. The incidence of pneumococcal infection is reported to be particularly high among nursing home residents, among whom it has been reported to be approximately 14 times higher than among the elderly residing in the community [97]. The results of a randomized double-blind placebo controlled study of the usefulness of PPV in preventing pneumococcal pneumonia that had been conducted on nursing home residents in Japan were reported in 2010 [83]. The study revealed that the incidence of pneumococcal pneumonia and the incidence of pneumonia due to all causative agents were 63.8% lower and 44.8% lower, respectively, in the group vaccinated with PPV (502 cases) than in the group (504 cases) that was not vaccinated with PPV, and that mortality due to pneumococcal pneumonia was 0% in the PPV group as opposed to 35.1% in the placebo group (Supplementary material Table S3), indicating PPV was useful in preventing pneumococcal pneumonia and in decreasing the mortality rate from pneumococcal pneumonia [Level II]. That was Japan’s first prospective clinical study of PPV vaccination of nursing home residents, and it was significant in revealing the importance of PPV in NHCAP. More specifically, mass outbreaks of pneumococcal infection, including pneumococcal pneumonia, were found at nursing homes where 5% or less of the residents had been vaccinated [98–100], and the results showed that there were no new cases of pneumonia after the residents were vaccinated, and that the number of the residents who were infected with MDR pneumococci had decreased [100]. Based on the above findings, PPV vaccination is recommended for the prevention of NHCAP, particularly for residents of nursing homes (Minds recommendation grade B).

9.3. Influenza vaccine

The results of a meta-analysis of studies in regard to the usefulness of influenza vaccine in elderly patients 65 years of age and over did not demonstrate that it had the ability to prevent influenza-like symptoms, the hospitalization rate, complications, or the mortality rate [101]. However, in view of the fact that elderly patients and high-risk patients with underlying diseases who have influenza often have secondary bacterial pneumonia, vaccination of NHCAP patients is critical. Many reports indicate that combined vaccination with influenza vaccine and PPV is especially useful for elderly subjects 65 years of age and over. A decrease in the hospitalizations for influenza infection, pneumonia, pneumococcal pneumonia, and invasive pneumococcal infection as well as an approximately 40% decrease in mortality rate were observed in a group inoculated with both vaccines in comparison with a group that received neither vaccine, and these results indicate that inoculation with both vaccines had the added benefit of reducing hospitalizations for influenza or pneumonia by 10% to 20% and of decreasing hospital deaths by 20–40% [102,103] [Level III]. In addition, the hospitalization for chronic pulmonary diseases in elderly patients inoculated with either influenza vaccine or PPV alone fell to 52% and 27%, respectively, and mortality rates fell to 70% and 34%, respectively. However, if both vaccines are administered in combination, hospitalization and death are reduced to 63% and 81% [104] [Level III]. There have also been reports on the effects of combined use of both vaccines in Japan [105,106]. In one study related to NHCAP, 294 bedridden elderly patients (average age, 81 years; 224 females, 70 males) living at nursing home facilities received influenza vaccine each year. The subjects were randomly assigned to a group inoculated with PPV and a control group that was inoculated with the influenza vaccine alone, and the study compared the total number of febrile days, the number of febrile days attributable to an acute respiratory infection, and the number of days of hospitalization for pneumonia of each patient during the following year. The data for each parameter measured showed a decrease of approximately 50% in the group that received both vaccines in comparison with the control group inoculated with influenza vaccine alone [105] [Level II]. Consequently, combined inoculation with PPV and influenza vaccine is recommended for elderly who reside in nursing facilities (Minds recommendation grade B).

9.4. Conclusion

In Japan, which will continue to have one of the world’s most rapidly aging societies in the years to come, pneumonia among the elderly and the prevention of NHCAP are key challenges in the country’s strategy to cut medical costs. In the U.S., the Advisory Committee on Immunization Practices (ACIP) has recommended PPV vaccination of individuals aged 65 years of age and over, and the United States Centers for Disease Control and Prevention (CDC) proposed increasing the PPV and influenza vaccination rate of persons 65 years of age and over to 90% as one of the ten health goals to be met within the 10-year period starting in 2000 described in “Healthy People 2010” [107]. Pneumovax® NP is the only PPV that has been approved for use in Japan. As indicated in Supplementary material Table S4, recipients of the vaccine are covered by Japanese National Health Insurance only when it is used for the purpose of “preventing pneumococcal infections in post-splenectomy patients 2 years of age and over”. As of May 1, 2011, only 444 cities, wards, towns, and villages in Japan subsidized PPV vaccination (some no longer do), and the vaccination rate for those 65 years of age and over remains at 10.55%.

The safety measures investigation group of the pharmaceutical safety measures subcommittee of the Ministry of Health, Labor and Welfare took up the issue of PPV revaccination in Japan and on October 18, 2009 decided that “when the need of a particular patient to be revaccinated with PPV is recognized by a physician, the vaccine may be administered” (Supplementary material Table S5). The cost effectiveness ratio (CER) for extended life expectancy per 100,000 elderly 65 years of age and over, calculations have shown that combined vaccinations with influenza vaccine and PPV would reduce costs in comparison with vaccination with influenza vaccine alone [Level III] [108]. Furthermore, because vaccination of the very old, i.e., those 75 years of age and over, with
both vaccines would reduce the overall medical costs of treatment of pneumonia during the next 12-month period [106] (Level II), concurrent vaccination with both vaccines is also superior from the standpoint of cost effectiveness. For vaccination with PPV and influenza vaccine to become more widespread in the future, it will be necessary not only to rely on public funding by local municipalities but for the government to take measures as well.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2012.11.001.

References


