Medical treatment

Diagnosis, treatment, and prevention of pneumonia

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Introduction

Pneumonia is recognized as a common disease with worldwide familiarity. It presents with a wide variety of pathological conditions, from a mild condition that can be cured within a week, to a severe condition that requires intensive care using an artificial respirator.

In other words, the characteristics of pneumonia greatly vary with reference to the infection setting and pathological conditions. It is largely classified into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and nursing and healthcare-associated pneumonia (NHCAP). This article discusses pneumonia with particular focus on CAP, which is a type of pneumonia that is relatively familiar to us.

Before World War II, pneumonia was the leading cause of death along with tuberculosis and gastroenteritis. With the advent of penicillin and other antibiotic drugs and with improvements in healthcare services and social health infrastructure, mortality risk from pneumonia dropped rapidly in the 1950s and has remained low, similar to mortality risk from tuberculosis. However, mortality risk from pneumonia started to increase 1980s onward and it is currently the third-leading cause of death, ahead of cerebrovascular diseases (Figure 1).

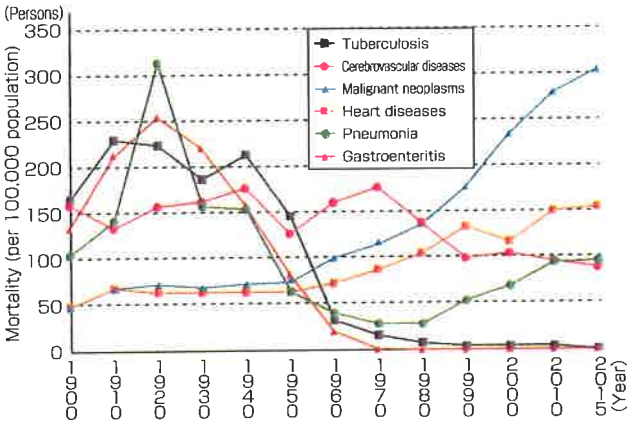


Figure 1. Trends in the cause of death of Japanese people

The analysis of mortality risk

from pneumonia by age groups shows that the elderly account for 96% or more of the mortality, indicating that aging in Japan is responsible for the increase in number of deaths from pneumonia (Figure 2).

The analysis of mortality data based on the classification of pneumonia into CAP, HAP, and NHCAP reveals that mortality is the highest in HAP, followed by that in NHCAP, with that in CAP being significantly lower compared with other types at 6.3% (Figure 3). Thus, CAP, the main focus of this article, does not necessarily contribute to the increase in the number of deaths caused by pneumonia. The reasons for focusing on CAP in this article include the gradual increase in its incidence rate, availability of the pneumococcal vaccine for elderly people at public expense, and most importantly, our relative familiarity with CAP, similar to bronchitis.

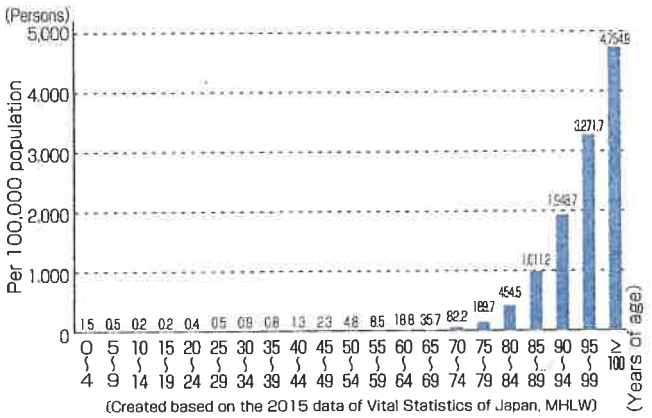


Figure 2. Mortality of pneumonia by age group

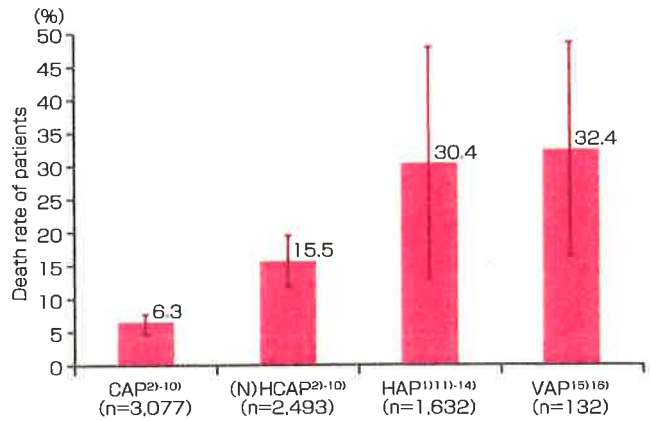


Figure 3. Comparison of death rate by pneumonia group (mean and 95% CI of each study)

1. Characteristics of community-acquired pneumonia

CAP is a type of pneumonia acquired by people who in principle do not have underlying diseases, which significantly differentiates it from HAP and NHCAP. In other words, CAP is the type of pneumonia that anyone could acquire in everyday life. Furthermore, CAP is different from the other types with reference to the causative microorganisms, and in particular, atypical pathogens (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila, and Coxiella) need to be considered. Among these, M. pneumoniae is the most frequently identified pathogen and the associated infections are mostly diagnosed as mild pneumonia which is treatable in an outpatient setting. One of the most significant

characteristics of CAP caused by atypical pathogens is that antibiotics effective against general bacteria are ineffective against CAP. Therefore, when CAP is suspected, antibiotics effective against both general bacteria and atypical pathogens should be administered. The details of treatment are discussed in a later section. In most cases, CAP patients respond well to treatment, and after recovery, they rarely suffer from complications such as deteriorated respiratory function; however, CAP leads to high mortality among elderly people with weakened immunity, and, therefore, remains a substantial threat.

It has been estimated that the number of patients aged 15 years or older with CAP in Japan is 1.88 million annually. Patients aged 65 years or older account for 70% of the total number of patients of whom 70% are hospitalized and 74,000 die in hospitals annually.

While there are many reports present on the causative pathogens of CAP, Streptococcus pneumoniae is consistently the most commonly identified pathogen, followed by Haemophilus influenzae (H. influenzae has no connection with influenza infections which gain public attention every winter; these infections are caused by the influenza virus which is a completely different pathogen, not to be confused with H. influenzae); Staphylococcus aureus; C. pneumoniae; M. pneumoniae; and so on .

2. Diagnosis of community-acquired pneumonia

Clinical conditions are the most important factor in the diagnosis of CAP. If symptoms such as cough, sputum, fever, difficulty in breathing, and chest pain are present, pneumonia can be suspected. Findings in physical examination such as breath sounds detected by auscultation, presentation with tachycardia, and tachypnea are important. The final definitive diagnosis is based on chest X-rays. If a chest CT scan can be performed at the same time, the accuracy of diagnosis is further enhanced. Recently, the effectiveness of lung ultrasound in CAP diagnosis has also been reported.

When pneumonia is diagnosed, it is extremely important to evaluate for sepsis, and severity of the pneumonia itself. Sepsis-related organ failure assessment score (SOFA score) and the A-DROP system shown in Tables 1 and 2, respectively, are recommended in the guidelines. Other inflammation markers used include CRP, white blood cell count, and more recently, procalcitonin (PCT).

The next important step in the diagnosis of pneumonia is to distinguish bacterial pneumonia from atypical pneumonia, which greatly influences treatment strategies to be discussed later. In general, patients with bacterial pneumonia are

likely to present with typical symptoms such as cough, sputum, and fever. It is not uncommon for patients with atypical pneumonia such as Mycoplasma pneumonia to not have sputum, and caution should therefore be exercised. In Europe and the US, because of differences in the philosophy of treatment, physicians do not focus on differentiating these two types of pneumonia at the initial stage of treatment; however, in Japan, it is common to initially differentiate Mycoplasma pneumonia from atypical pneumonia using six reference factors (Table 3). If the symptoms match four of the six factors, atypical pneumonia is suspected, and if the symptoms match three or less factors, bacterial pneumonia is suspected. Particularly for Mycoplasma pneumonia, recent advances in antigen detection methods allow quick

	0	1	2	3	4
Respiratory organ PaO_2/FiO_2 (mmHg)	≧400	<400	<300	<200 + Respiratory assist	<100 + Respiratory assist
Coagulation Platelet count ($\times 10^3/\mu L$)	≧150	<150	<100	<50	<20
Liver bilirubin (mg/dℓ)	<1.2	1.2～1.9	2.0～5.9	6.0～11.9	>12
Circulatory organs	MAP≧70mmHg	MAP<70mmHg	DOA<5 or DOB	DOA5.1～15 or Ad≦0.1 or NOA≦0.1	DOA>0.5 or Ad>0.1 or NOA>0.1
Central nervous system Glasgow Coma Scale	15	13～14	10～12	6～9	<6
Kidney creatinine (mg/dℓ) Urine volume (mℓ/day)	<1.2	1.2～1.9	2.0～3.4	3.5～4.9 <500	>5.0 <200

DOA: dopamine; DOB: dobutamine; Ad: adrenaline; NOA: noradrenaline

Table 1. SOFA score

A (**A**ge) : Men aged ≥70 years, and women aged ≥75 years
D (**D**ehydration) : BUN 21 mg/dL or more, or dehydrated
R (**R**espiration) : SpO_2 90% or less (PaO_2 60 torr or less)
O (**O**rientation) : Altered state of consciousness
P (Blood **P**ressure) : Systolic blood pressure: 90 mmHg or less

Mild: none of the above items is met.
Moderate: 1 or 2 of the above items are met.
Severe: 3 of the above items are met.
Extremely severe: 4 or 5 of the above items are met. If shock is present, classify as "extremely severe" even if only 1 of the above items is met.

Table 2. A-DROP system

diagnosis, and more accurate differential diagnosis will potentially become available in the future.

3. Treatment of community-acquired pneumonia

(1) Antibiotic treatment

The treatment of CAP is initiated following its diagnosis. It is imperative to determine whether an inpatient or an outpatient treatment setting is more appropriate. In general, outpatient treatment is selected for patients with mild symptoms, patients with moderate to severe symptoms are admitted to a hospital to receive care in a general ward, and intensive care in an ICU is selected for patients in an extremely severe condition or if sepsis has developed.

After the treatment setting is determined, the details of treatment are decided. The treatment of pneumonia is primarily based on antibiotic therapy, and selection of the appropriate medication is critical. However, this is difficult in actual medical practice. The antibiotic to be used for treatment is determined based on the causative pathogen; however, with the exception of M. pneumoniae for which a quick diagnosis method has been established, it is practically impossible to identify the pathogen at the time of diagnosis. Rather, it is not uncommon for pneumonia to be cured without identification of the causative pathogen.

Diagnostic tests are performed by staining sputum and sputum culture to detect and identify the causative bacterial pathogen; however, it takes several days at the least for obtaining results. Consequently, in actual practice, antibiotic drugs are determined based on past experience, known as empiric therapy.

In empiric therapy, antibiotic drugs targeting high-frequency microorganisms are used for patients with mild-to-moderate symptoms based on epidemiological information, clinical symptoms, and test findings. Further, if the causative microorganisms can be identified based on gram staining or quick diagnosis methods such as urinary antigen testing, it is possible to select more appropriate

1) Aged less than 60 years
2) No underlying diseases
3) Persistent cough
4) Weak findings by chest auscultation
5) No sputum, or causative pathogens could not be identified by the quick diagnosis method
6) White blood cell count in peripheral blood is less than 10,000/μL
Examined for Mycoplasma pneumonia and Chlamydia

Table 3. Items for differentiating bacterial pneumonia and atypical pneumonia

antibiotic drugs. Furthermore, if clear drug sensitivity test results are obtained using bacterial culture, targeted therapy is performed with a more selective antibiotic drug based on the results. In general empiric therapy, broad-spectrum drugs are selected; in contrast, in targeted therapy, sufficient dose levels of narrow-spectrum drugs are administered (Figure 4).

(2) Adjuvant therapy

In addition to antibiotic treatment, adjuvant therapy may be added especially in patients with severe pneumonia, and steroids are typically used for this purpose. The effect of steroids is most likely attributable to their anti-inflammatory action, and decreased mortality risk from the co-administration of steroids has been reported; however, management of systemic effects, including blood sugar control and impact on digestive organs, is required.

Oxygen is administered if hypoxemia occurs, and if the situation does not improve, respiratory care procedures are performed using an artificial respirator.

4. Prevention of community-acquired pneumonia

Prevention of CAP should be implemented in the same manner as prevention

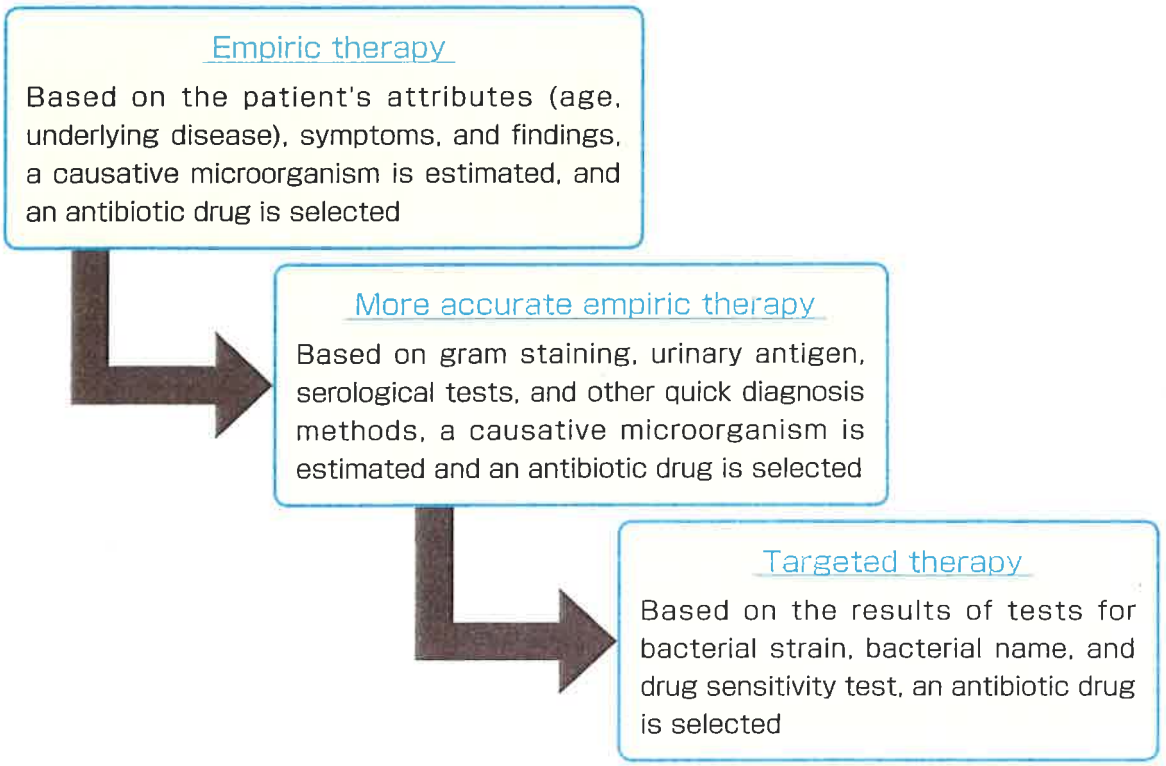


Figure 4. Basic concept of antibiotic drug selection using guidelines

of other infections. In the context of preventing infections via the oral route, gargling and hand washing are effective. Cough etiquette should also be promoted.

In addition to infection prevention measures, the importance of pneumococcal vaccination has been recognized, particularly in elderly people.

Two types of pneumonia vaccines are currently available in Japan: a 23-valent pneumococcal capsule polysaccharide vaccine (brand name: Pneumovax (supplier: MSD, Chiyoda-ku, Tokyo, Japan); hereinafter referred to as PPV23), and a 13-valent pneumococcal conjugated vaccine (brand name: Prevnar 13 (supplier: Pfizer, New York City, New York, USA); hereinafter referred to as PCV13), a protein conjugate vaccine.

PPV23 uses polysaccharides, which are antigenic capsule components of bacteria, to stimulate B-cells in the body promoting antibody production. However, the antibody titer gradually decreases over a period of years; therefore, a booster shot after approximately 5 years is considered essential.

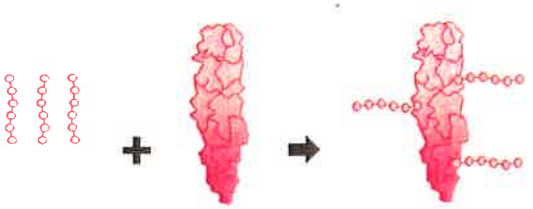
In PCV13, capsule polysaccharides are conjugated to a carrier protein such as a nontoxic mutant of diphtheria toxin (Figure 5). As a result, dendritic cells as well as T-cells are stimulated, improving memory function, and the effect is therefore considered to last for a long time after one dose of vaccination.

While rare, shock and anaphylactoid reaction (e.g., difficulty in breathing, rash, and sweating) have been reported as systemic adverse effects, similar to adverse effects of other vaccines. Relatively commonly reported adverse effects include localized reactions and in particular, reddening of the skin, swelling, and pain at the injection site seem more common. These symptoms disappear in several days at the latest.

With reference to the preventive effect of pneumococcal vaccines against pneumococcal pneumonia, some studies have reported no significant effect, while other studies have reported the vaccines as effective.

In the Netherlands, a trial (CAPiTA) of PCV13 was conducted in more than 80,000 subjects, and the preventive effect of PCV13 for CAP has been demonstrated (Table 4).

Enhanced effectiveness of pneumococcal vaccines in combination with the influenza vaccine has been reported in research studies overseas. In



Polysaccharide antigen (capsule polysaccharides) | Immunogenic carrier protein (non-toxic mutant of diphtheria toxin) | Conjugated vaccine

Figure 5. Structure of pneumococcal conjugated vaccine

Japan, the effectiveness of PPV23 in a group receiving the influenza vaccine has been reported.

There have been no reports of increased adverse reactions due to simultaneous influenza and pneumococcal vaccination, and no reports of decreased effectiveness. Therefore, simultaneous immunization with influenza and pneumococcal vaccines can be considered safe. Regarding combined vaccination with PPSV23 and PCV13 in people with no vaccination history, in the US, it is recommended that PCV13 be given first followed by PPSV23 after a minimum gap of one year. In Japan, the Japanese Respiratory Society guidelines for vaccination with PPSV23 and PCV13 are followed for elderly people (aged 65 years or older) (Figure 6). It is expected that the target population for vaccination is further expanded.

Conclusion

In summary, this article discussed the diagnosis and treatment of, and vaccination for, pneumonia. Some of the information presented may be relatively technical and may not be easy to understand for non-technical readers. As stated at the beginning, pneumonia is an infection that is familiar to us; however, it is a significant infection that may require inpatient treatment and in some cases, may result in death. The discussion in this article focused on the 2017 JRS Guidelines for the Management of Community-Acquired Pneumonia in Adults. While the guidelines were not discussed in detail because their focus is slightly different from the topic of CAP, the 2017 guidelines are clearly different from the conventional guidelines in that they suggest the possibility of considering ethical aspects of therapy in the terminal stage of pneumonia. Withholding treatment in end-of-life

	Number of persons who developed infections		Effects of vaccination (%)	(95% CI)
	Prevenar13 (n=42,240)	Placebo (n=42,256)		
Vaccine serotype community-acquired pneumococcal pneumonia	49	90	45.6	(21.8、62.5)
Vaccine serotype noninvasive community-acquired pneumococcal pneumonia	33	60	45.0	(14.2、65.3)
Vaccine serotype invasive pneumococcal infection	7	28	75.0	(41.4、90.8)

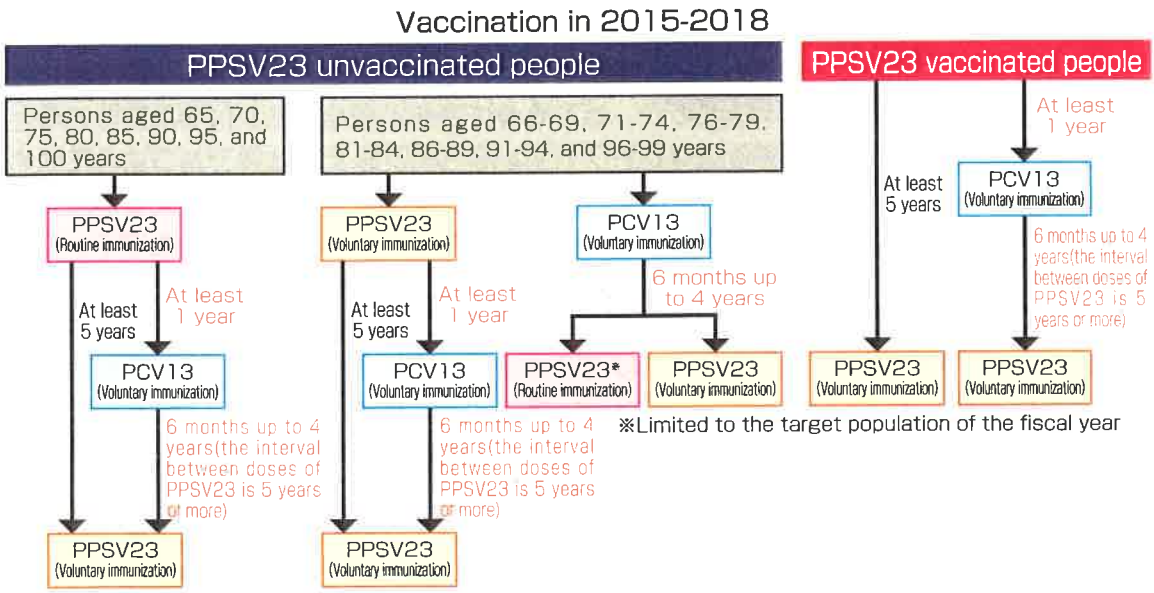
Table 4. Results of CAPiTA study (primary and secondary endpoints)

care, which is common in Europe and the US, has not penetrated Japan. There has been a trend of administering high doses of antibiotics to patients dying from old age or terminal cancer. This situation is expected to improve. I would also like to discuss the status of end-of-life care in Japan if there is future opportunity.

Finally, it would be my great delight if this article deepens the readers' understanding of pneumonia.

References

- JRS Guidelines for the Management of Community-Acquired Pneumonia in Adults, the Japanese Respiratory Society, 2017.
- The effects and adverse reactions of pneumococcal vaccine in elderly people, the Journal of Japan Physicians Association, vol. 32 No. 1, June 10, 2017.



Notes:

#1. This concept was created by referring to the PPSV23 routine immunization policy and ACIP Vaccine Recommendations.

#2. It is recommended that immunization schedule be decided so that the target population of routine immunization can receive routine PPSV23 vaccination.

#3. When both vaccines are given to PPSV23 unvaccinated persons, PCV13 may be given first, followed by PPSV23, while taking into consideration #2 above.

#4. Vaccinations of PCV13 followed by PPSV23 are based on the data of overseas studies. The efficacy and safety of vaccinations in Japanese population have not been evaluated.

#5. The routine immunization is in accordance with the transitional measures for the period from October 2014 to March 2019.

#6. This concept will be reviewed within 3 years.

Figure 6. The concept of pneumococcal vaccination in adults aged 65 years or older (January 2015)
(Joint Committee of the Japanese Respiratory Society and the Japanese Association for Infectious Diseases)