CHAPTER 11

Strategies for non-responders

The committee for The Japanese Respiratory Society guidelines in management of respiratory infections

*The Japanese Respiratory Society*

**Strategies for non-responders**


**HOW TO TREAT NON-RESPONDERS**

When a patient does not respond to antimicrobial agents (hereinafter, antibacterial agents), the drugs should not be changed before an attempt is made to discover the reason for ineffectiveness.¹ First, it is more practical to imagine the possibility that pneumonia-like infiltration may have occurred by a cause other than pathogenic microorganisms. In other words, a differential diagnosis such as heart failure, pulmonary oedema, carcinoma of the lung and a variety of diffuse pulmonary infiltrations must be distinguished from pneumonia. If these disorders are ruled out, proceed to isolating and identifying the causative microorganisms based on the assumption that the patient may have contracted pneumonia caused by pathogenic microorganisms.

It is necessary to determine whether the causative microorganisms are sensitive to the medications. Since unique microorganisms have been isolated from patients who have unique risk factors in hospital-acquired pneumonia (HAP), we should postulate causative microorganisms based on the differential diagnosis. Characteristic risk factors are neutropenia, immunosuppression induced by myelosuppressive anticancer drugs, immunosuppressants, adrenocortical steroid administrations, the use of a ventilator and aspiration. In addition, a variety of underlying diseases, insertion of IVH catheters, long-term admission in the ICU, AIDS, bone marrow and organ transplantation are important in the aetiology of HAP. Thus, it is necessary to identify the causative microorganisms based on the patient’s characteristics or background factors. Next, if the patient does not respond to antimicrobial therapy despite administration of appropriate antibacterial agents, the validity of antimicrobial therapy itself must be evaluated. In such situations microbial factors, host factors (complications and underlying diseases), medication-related factors, and the timing of assessment of the clinical efficacy of the antibacterial agents should be evaluated in the above order. If this approach to the treatment of patients with HAP is used, the antibacterial agents should be effective. However, if the patient’s condition remains unchanged or worsens, re-evaluation of the efficacy of the antibacterial agents based on the procedures outlined above is required. In summary, the following procedures should be carried out:

1. Check to see whether the patient has actually contracted HAP or not.
2. Check to see whether the prescribed antibacterial agents are appropriate for eradicating the causative bacteria.
3. Check to see whether the patient has been treated with reasonable medications.
4. Evaluate the validity of antimicrobial therapy, taking into account:
   (a) Microbial factors
   (b) Host’s factors
   (c) Drug-related factors
   (d) Timing of the efficacy assessment

**DIFFERENTIAL DIAGNOSIS OF ‘PNEUMONIA’ IN ITS BROAD SENSE (I.E. PNEUMONIA CAUSED BY CAUSATIVE AGENTS OTHER THAN PATHOLOGICAL MICROORGANISMS)**

If antibacterial therapy is ineffective despite the fact that the chest X-ray shows 'pneumonia-like' infiltration, 'respiratory disorders caused by agents other than pathological microorganisms' should be suspected first.²,³

1. Pulmonary infiltrates caused by congestive heart failure and pulmonary oedema (occasionally complicated by pneumonia caused by microorganisms)
2 Obstructive pulmonary infiltrates induced by carcinoma of the lung and other malignancies, and atelectasis (often complicated by pneumonia caused by microorganisms)

3 Diffuse pulmonary disorders (a number of underlying diseases are linked to diffuse pulmonary infiltrates that are occasionally complicated by pneumonia caused by microorganisms)

(a) Drug-induced pneumonitis
(b) BOOP (bronchiolitis obliterans-organizing pneumonia)
(c) Eosinophilic pneumonia
(d) Aggravation of idiopathic interstitial pneumonia (IIP)
(e) Hypersensitive pneumonitis
(f) Sarcoidosis
(g) Autoimmune-disease-induced pulmonary lesions (collagen-disease-induced pulmonary lesions)
(h) Others

4 Pulmonary thrombosis
5 Alveolar proteinosis
6 Foreign bodies in the trachea and bronchus
7 Radiation-induced pneumonitis
8 Acute respiratory distress syndrome (ARDS)
9 Others

When any one of these disorders is complicated by ‘pneumonia caused by pathogenic microorganisms’, it becomes difficult to diagnose the primary disease, and the pneumonia often progresses rapidly. The three major associations with pneumonia among the disorders listed above are (i) drug-induced pneumonitis; (ii) BOOP; and (iii) eosinophilic pneumonia.

If all of the causative factors other than pathogenic microorganisms have been ruled out, the following examinations should be performed on suspicion of ‘pneumonia caused by microorganisms’.

HOW TO PROCEED WITH DIFFERENTIAL DIAGNOSIS OF ‘PNEUMONIA CAUSED BY MICROORGANISMS’?

Basic concepts for the differential diagnosis of ‘pneumonia caused by microorganisms’

If antibacterial agents are ineffective even though pathogenic microorganisms are the cause of the pneumonia, a slightly different approach from that for community-acquired pneumonia (CAP) should be taken. The strategies for HAP are outlined below.

A wider variety of pathogenic microorganisms cause HAP than cause CAP. Common bacteria and atypical bacteria as well as viruses, fungi, atypical mycobacterium, protozoa and other microorganisms may cause HAP. Even if the same type of microorganisms cause HAP their drug sensitivity may vary considerably because unlike CAP patients with a variety of underlying disorders and complications develop HAP. Moreover, the patients have usually been treated with a variety of medications and treatments, and they are often immunosuppressed. Nevertheless, as mentioned above, it is now clear that characteristic pathogenic microorganisms are linked to each unique risk factor, and by understanding the pathogenesis of each infectious disease it is possible to postulate the causative microorganisms with reasonably high probability. If initial therapy fails for HAP and an urgent decision is needed for treatment, it should be postulated as to which might be the causative microorganisms.

Aetiology of HAP and representative microorganisms

A variety of risk factors are associated with HAP. Representative risk factors are (a) neutropenia, (b) a mechanism for aspiration, and (c) the use of a ventilator. The following have also been listed as risk factors for HAP: (d) chronic respiratory disease, (e) diabetes mellitus, (f) renal failure, (g) use of adrenocortical steroid preparations and immunosuppressive agents, (h) insertion of an IVH catheter, (i) laparotomy and thoracic surgery, (j) long-term hospitalisation in the ICU, (k) head injury, (l) AIDS, (m) bone marrow transplantation and organ transplantation, (n) invasive examinations of the trachea and lungs.

Refer to Chapter 6 for (a) neutropenia, Chapter 8 for (b) mechanism for aspiration, and Chapter 7 for (c) the use of a ventilator.

(d) Patients with chronic respiratory disease occasionally develop pneumonia, and Streptococcus pneumoniae and H. influenzae are associated with mild to moderate pneumonia. However, Pseudomonas aeruginosa is a major causative microorganism, and Aspergillus and other fungi are also linked to pulmonary tuberculosis if residual cavities persist.

(e) Diabetic patients often develop pneumonia, and a variety of pathogens become causative microorganisms because of the reduced neutrophil activity. Streptococcus pneumoniae is often isolated from diabetic patients with CAP, whereas Staphylococcus aureus, anaerobic bacteria, gram-negative rods, fungi and Mycobacterium tuberculosis are commonly isolated from diabetic patients with HAP.

(f) Patients with renal failure often develop HAP. Staphylococcus aureus, anaerobic bacteria, gram-negative rods, fungi and Mycobacterium tuberculosis are frequent causative bacteria.

(g) Unlike the anticancer agents described in the previous section, adrenocortical steroid preparations and immunosuppressants have often been used to treat patients with malignancies and autoimmune diseases for long periods. Since myelosuppression and neutropenia persist for long time, cytomegalovirus (CMV) and Pneumocystis carinii (PC) could be the cause of pneumonia in patients with these conditions. Occasionally, Mycobacterium tuberculosis is also linked to pneumonia in patients with adrenocortical steroid preparations and immunosuppressants.

(h) Staphylococcus aureus and Staphylococcus epidermidis are often causative bacteria when an IVH catheter has been inserted. (Evaluation of pathogenicity should be advised carefully.) If such patients develop an infection, the IVH catheter must be removed or replaced immediately.
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(i) *Staphylococcus aureus*, enteric bacteria and anaerobic bacteria are often linked to HAP that occurs after laparotomy and open lung surgery.

(j) *Pseudomonas aeruginosa* and *Staphylococcus aureus* are often causative bacteria of HAP in patients hospitalised to the ICU for a long period.

(k) *Staphylococcus aureus* is often linked to HAP in patients with head trauma.

(l) *Pneumocystis carinii* and cytomegalovirus as well as *Mycobacterium tuberculosis*, non-tuberculosis Mycobacterium and fungi are linked to HAP in AIDS patients. Characteristically, a variety of other microorganisms can be isolated from AIDS patients.

(m) *Pneumocystis carinii*, cytomegalovirus, and fungi are often linked to HAP in patients who have undergone bone marrow or organ transplantation.

(n) Anaerobes in the oral cavity, *Staphylococcus aureus* and *Streptococcus pneumoniae* are often linked to HAP as a form of so-called ‘compressing infection’ in patients who have undergone invasive examinations of the respiratory tract and lungs.

How to proceed with differential diagnosis in clinical practice, and the selection of antimicrobial agents

The strategies for identification of causative microorganisms are outlined in Figure 1 (Differential Diagnosis). As shown in the flowchart, it is more practical to identify or rule out unique causative microorganisms first by taking advantage of their unique characteristics, than to postulate causative microorganism(s) in the order of their prevalence. For example, first, as shown in Figure 1 initially check whether the patient requires a ventilator, has a risk of aspiration disturbance or is bedridden and determine the duration of hospitalisation (as described in Sections 2 and 3). If the patient has at least one of these risk factors, anaerobic bacteria in the oral cavity or glucose non-fermenting gram-negative rods are often linked to HAP. Thus, carbapenem monotherapy may be adequate for patients with mild or moderate pneumonia. However, clindamycin (as a core antibacterial agent) should be used to treat patients with severe/intractable pneumonia in combination with carbapenems or fourth-generation cephems. Some physicians in Europe and the US recommend concomitant use of clindamycin and aminoglycosides. However, we should note that aminoglycosides are ineffective against anaerobic bacteria.

Next, underlying disorders (see Chapters 4, 5 and 6) must be determined. If patients have a chronic respiratory disorder, β-lactams with anti-*Pseudomonas aeruginosa* activity (penicillins, third or fourth-generation cephems, carbapenems and monobactams) or quinolones for injection (ciprofloxacin: CPFX) should be used as major antibacterial agents.

Representative causative microorganisms to suspect

- *Pseudomonas aeruginosa*, *Acinetobacter*, MRSA
- Anaerobic bacteria, *Staphylococcus aureus*
- *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, fungi
- *Staphylococcus aureus*, anaerobic bacteria, fungi, *Mycobacterium tuberculosis*
- *Cytomegalovirus*, *Pneumocystis carinii*, *Mycobacterium tuberculosis*, fungi
- *Pseudomonas aeruginosa*, *Staphylococcus aureus* (MRSA), fungi
- *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa* (*The catheter must be removed or replaced.*)
- Enteric bacteria, *Staphylococcus aureus*, and others

* Causative bacteria should be identified with caution.

**Figure 1** Flowchart for identification of causative microorganisms in non-responders.
In patients with severe/intractable pneumonia, concomitant use of aminoglycosides should be taken into consideration. If patients have diabetes mellitus, β-lactams (third or fourth-generation cephems, carbapenems and monobactams) should be used as initial therapy ruling out MRSA, fungi and *Mycobacterium tuberculosis*. If patients have renal failure, similar antibacterial agents may be selected, however, drugs with renal toxicity should be avoided. If patients have underlying disorders other than chronic respiratory disease, diabetes mellitus and renal failure (Chapters 4, 5 and 6), this must be examined to determine whether they have been treated with adrenocortical steroid preparations or immunosuppressive agents in the past.

If patients have been treated with adrenocortical steroid preparations or immunosuppressive agents and if the chest X-ray reveals diffuse pulmonary infiltrates, administration of ST-mixture ± pentamidine should be considered, while testing for PC (*Pneumocystis carinii*). In addition, the possibility of CMV (Cytomegalovirus) infection must be investigated. If the chest X-ray reveals localised pulmonary infiltrates, the presence of common bacteria and fungi, and *Mycobacterium tuberculosis* should be ruled out. If the patient has not been treated with adrenocortical steroid preparations or immunosuppressive agents, then check for neutropenia, next.

Since *Pseudomonas aeruginosa* and *Staphylococcus aureus* are often linked to HAP in patients with neutropenia, carbapenem monotherapy is adequate for the treatment of mild to moderate pneumonia. However, cases of severe/intractable pneumonia comprise most cases of HAP, and patients with severe/intractable pneumonia should be treated with carbapenems or the newly developed fourth-generation cephems in combination with aminoglycosides. Penicillins with anti-*Pseudomonas aeruginosa* activity are also often used concomitantly on a case-by-case basis, but the possibility of fungal infection should be ruled out at the same time.

Even if patients do not have neutropenia, β-lactams with anti-*Pseudomonas aeruginosa* activity (penicillins, third or fourth-generation cephems, carbapenems and monobactams) should be used as initial therapy during IVH catheter insertion. The possibility of MRSA infection, in particular, must be evaluated. In patients without IVH catheter, a variety of bacterial strains that are less drug-resistant are usually linked to HAP and thus β-lactam monotherapy (third-generation cephems, carbapenems and monobactams) is often effective in the management of HAP.

**Assessment of the validity of antimicrobial therapy**

Even if the causative microorganisms are sensitive to antibacterial drugs, satisfactory therapeutic efficacy may occasionally not be achieved, and whenever that happens, the adequacy and validity of therapy should be evaluated. A similar approach may be employed for the management of HAP in adults. The validity of antimicrobial therapy is evaluated according to the factors listed below.

**Microbial factors**

Even when antibacterial agents are indicated for the treatment of HAP, it may be difficult to achieve adequate antimicrobial efficacy for highly drug-resistant bacteria, such as MRSA, *Pseudomonas aeruginosa* or *Serratia*. Drug-sensitivity tests must be performed, and the most potent antibacterial agents selected based on the results of these tests. The antimicrobial effect of some agents may be inhibited by overproduction of drug-inactivating enzymes in patients with abscess-forming pneumonia. The antibacterial agents to which the bacteria are most sensitive should be used while employing physical means such as drainage of pus.

**Host factors (complications and underlying disorders)**

Care should be exercised in the management of complications and underlying disorders. In other words, even if antimicrobial therapy is adequate, the patient's condition may not be improved or the pneumonia may rapidly worsen if inadequate treatment is administered for complications or underlying disorders. (See above for a list of complications or underlying disorders.) It is necessary to treat complications and underlying disorders properly at the same time as the pneumonia. For example, lung cancer patients may develop pneumonia, and it is often too late if cancer chemotherapy and radiation therapy are initiated after a therapeutic effect is achieved against the pneumonia. Management of the pneumonia could be more effective if both the antimicrobial and cancer therapy are initiated simultaneously. Similarly, it is also important to start antimicrobial therapy simultaneously with the management of other underlying disorders. As with other diseases, management of the pneumonia requires careful monitoring of 'underlying diseases'. For example, rapid insulin dose escalation is needed for patients with diabetes mellitus at the acute phase of pneumonia, while rapid dose-reduction is needed as the pneumonia subsides. Pus formation and a diminished capacity to expel sputum from the lungs are physical factors that interfere the efficacy of antibacterial agents. When pus has formed, is sustained or temporary drainage of the pus is required, and when expectoration of sputum is impaired, postural drainage, tapping and other physical measures must be performed. In addition, when a foreign object such as an IVH catheter or a gastric tube is involved in inhibition of effectiveness of antimicrobial drugs, it may need to be removed or replaced.

**Factors related to antibacterial agents**

The validity of antibacterial therapy itself must be evaluated after assessment of microbial factors and
host factors. In other words, antibacterial chemotherapy itself may be problematic if satisfactory therapeutic efficacy has not been achieved despite adequate management of the pneumonia following correct diagnosis and accurate identification of the causative microorganisms.

In patients with 'common pneumonia', antibacterial agents should have adequate efficacy at the usual clinical doses. However, in most cases of HAP in which antimicrobial therapy fails, no antibacterial effect may be achieved at even twice the dose. The frequency and timing of administration must be evaluated in these cases instead. In Japan, antibacterial agents are customarily administered to pneumonia patients by intravenous drip infusion twice a day, but more frequent administration (three times a day or more) must be considered in severe cases of HAP or if the pneumonia rapidly progresses. Patients with severe pneumonia often exhibit bacteremia, and antibacterial agents should be administered frequently (three times a day or more) in accordance with the standard treatment protocol for bacteremia and sepsis. Moreover, clinicians should be familiar with the pharmacological characteristics of antibacterial agents, such as pharmacodynamics, pharmacokinetics and the interval of administration. It is essential to monitor the concentrations of some of antibacterial agents in the blood, such as anti-MRSA drugs (e.g. vancomycin and aminoglycosides) during the course of antibacterial therapy.

Next, the transferability of antibacterial agents to the site of infection should be re-evaluated. Since β-lactams are often poorly transferred to lung tissue, except at the peak of the inflammation, it is desirable to administer them by intravenous drip infusion in most patients with pneumonia. Because aminoglycosides are more poorly transferred to the respiratory tract compared to the alveoli, they are more effective when administered to patients with chronic respiratory disease by inhalation. Most macrolides, tetracyclines, and fluoroquinolones are efficiently transferred to lung tissue, but most of them are oral preparations. It is better to have injectable macrolides and fluoroquinolones.

Since several antibacterial agents are often administered concomitantly to patients with HAP, their antibacterial activity may be attenuated by drug interactions. For example, the antifungal agent itraconazole is often administered in combination with rifampicin and phenytoin, but since its blood level gets lower when administered concomitantly with these the dose of itraconazole must be increased. Similarly, concomitant use of metal ion (cation)-containing drug preparations interferes with the absorption of fluoroquinolones, making it necessary to administer fluoroquinolones without simultaneously administering cation-containing preparations.

Issues related to timing of the assessment of clinical efficacy

Finally, it should be evaluated whether the clinical efficacy of an antibacterial agent has been assessed in a timely manner. As a rule, the antibacterial effect of chemotherapy should be assessed on day 3 after the start of antibacterial therapy. In patients with HAP, however, more time may be required to assess the clinical efficacy of antibacterial agents, because patients with severe pneumonia often recover more slowly from the disease. Many patients with HAP enter a defervescent stage only after about a week of antibacterial therapy. On the other hand, severe HAP is often a fatal disease, and clinicians are therefore faced with a dilemma, because the wrong treatment must not be continued for a long time. Moreover, it should be noted that there are temporal differences (time lags) in the rates of improvement in a variety of parameters of pneumonia-related inflammatory responses. If pneumonia patients are treated with adequate antibacterial agents (i.e. to which the causative microorganisms are sensitive), defervescence occurs in many of them first, and is followed by decreases in the leucocyte count. The CRP level decreases slightly later. Resolution of pneumonia-related infiltrates occurs even later, and the erythrocyte sedimentation rate (ESR) normalises last. As an example, occasionally patients are encountered whose pulmonary infiltrates grow worse despite improvement in symptoms, but we can safely conclude that antibacterial efficacy has been achieved when patients definitely exhibit defervescence, normalisation of their leucocyte counts, and a reduction in CRP level. Moreover, because of underlying disorders the CRP levels of many patients with HAP do not convert to completely negative.

REFERENCES