CHAPTER 5

Antibacterial therapy of hospital-acquired pneumonia

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

The Japanese Respiratory Society

BASIC CONCEPTS FOR THE SELECTION OF ANTIBACTERIAL AGENTS

The pathogenesis of hospital-acquired pneumonia (HAP) is much more complex than that of community-acquired pneumonia (CAP), but the selection of antibacterial agents is rather limited. Most patients have some risk factors, and the physician is confronted with a situation in which antimicrobial therapy must be instituted without delay. In these guidelines we have stated the principles of treatment for CAP. In principle, antibacterial agents with a narrow spectrum should be chosen whenever the patient's condition allows it, thereby preventing resistance to broad-spectrum antimicrobials as long as possible. However, it is essential to first choose effective antibacterial agents for the management of patients with HAP, and then to administer adequate antibacterial agents promptly. For this reason, we are obliged to choose potent antibacterial agents with a broader spectrum when the causative bacteria have not been isolated or identified or if empiric therapy is employed. However, if potent antibacterial agents with a broad spectrum are used, there is a risk that resistant bacteria will emerge (i.e. with resistance to common antibiotics), especially in institutions or in certain areas. This then creates an extremely high risk of hospital-acquired infection caused by resistant bacteria. We have already learned this lesson in Japan, for example, by the nationwide prevalence of methicillin-resistant Staphylococcus aureus (MRSA). Because of this, we should strive to prevent the emergence of resistant bacteria through the proper use of antibiotics, as suggested by Bowton. However, there is still controversy as to whether 'antibiotic cycling' (i.e. routinely changing the types of antibiotics prescribed) is effective in preventing the emergence of resistant bacteria. These statements appear contradictory, because they recommend that we employ two conflicting methods of administration of antibacterial agents. However, in this guideline they are about 'the use of antibacterial agents', and can be rephrased as follows, taking this situation into consideration.

'An adequate dose of a potent antibiotic with a broad spectrum of action should be administered to patients with hospital-acquired pneumonia for a short period of time immediately after the onset of symptoms, and a wide variety of antimicrobial agents should be selected to minimize the risk of emergence of resistant bacteria at the institution concerned.'

In this respect, the following prerequisites or requirements are proposed concerning the use of antibacterial agents:
1. The prevention and treatment of HAP are directly linked to the management of HAP.
2. Although it is difficult to identify causative pathogens, always try to isolate the 'pathogen' as soon as possible.
3. Always attempt to identify trends in the prevalence of resistant bacteria in each institution or district or region (by a small unit) through epidemiological studies.

It is often difficult to isolate and identify the causative organism of HAP (by bacteriological examinations). It should be emphasised that MRSA infection can be ruled out by gram-staining of lower respiratory tract secretions (for example) even though we can not determine if it is a potent MRSA infection. If high-quality sputum specimens are acquired, the risk of overlooking Staphylococcus aureus is extremely low, and there is virtually no need to treat for MRSA infection. It is not always necessary to perform bacteriological studies to identify the causative bacteria of HAP. It is instead important to recognise that the use of drugs should be limited by ruling out the possibility of certain causative bacteria. It is also important to differentiate HAP from other disorders besides pneumonia, while paying
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attention to factors contributing to intractable pneumonia.\(^5\) Such care should be exercised in assessing the efficacy of antibacterial agents. An antibacterial agent should not be changed for no other reason than because the recovery process is prolonged, nor should long-term use of antibacterial agents be continued without a rationale. Clinicians need to know the patient's condition as well as the pathogenesis of respiratory infections. Consultation with specialists in infectious disease on a routine basis is recommended.

SEVERITY RATING OF PNEUMONIA AND SELECTION OF ANTIBACTERIAL AGENTS

The Guideline for hospital-acquired pneumonia in adults: diagnoses, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement by the American Thoracic Society (ATS)\(^6\) states that antibacterial agents should be selected based on the duration of hospitalisation (i.e. the initial period and thereafter). Conditions with regard to the length of hospital stay do not appear to be comparable in the US and Japan because of differences between their health care systems. For this reason, length of hospital stay ('short' vs. 'long') is not a parameter for the selection of antibacterial agents in this guideline. However, we should take the heading Changing pharyngeal bacterial flora of hospitalized patients: emergence of gram-negative bacilli into consideration.\(^7\) In other words, the longer the length of stay, the higher probability of pneumonia caused by gram-negative bacilli.

If treated by empiric therapy, it is more difficult to assess the severity rating of HAP than of CAP. The severity rating of HAP may be rated differently based on the condition of the individual patients, even when the severity of pneumonia is comparable. In other words, if the condition of the underlying diseases is severe, it is necessary to induce a remission reliably and quickly by potent antimicrobial therapy, even if the severity rating of the pneumonia is 'mild'.

Thus, the assessment of the severity rating of HAP is left to the discretion of the treating physician, because it is most likely to depend on the condition of the individual patient. We quoted the 'classification of the severity rating of pneumonia' as a reference in this guideline. Since the classification is based on the 'criteria for assessment of the efficacy of chemotherapy' established by the Japanese Chemotherapy Society,\(^8\) and the weight of factors other than pneumonia is relatively small, the range of applicability of these criteria for assessment is rather limited. Consequently, the criteria for the selection of antibacterial agents are as follows.

The severity rating of pneumonia affects selection of antibacterial agents in the following patients:
1. Patients with mild to moderate pneumonia who have no risk factors.
2. Patients diagnosed with mild pneumonia despite the presence of risk factors.

It is desirable to institute potent antimicrobial therapy to all other patients at the time of diagnosis. In other words, if patients have moderate or severe pneumonia and risk factors or severe pneumonia with or without risk factors (criteria #3), it is desirable to institute potent antimicrobial therapy at the time of diagnosis, while carefully examining for factors other than the severity rating of pneumonia. If factors other than pneumonia are involved, other disorders must be treated as well, while treating the pneumonia by alternative antimicrobial therapy (i.e. controlling the pneumonia by using alternative antibacterial agents).

The ATS proposed criteria for admission to the ICU for patients with severe HAP\(^8\) and clinicians are asked to institute antimicrobial therapy as appropriate in accordance with these criteria.

It is desirable to avoid mixed injections when antibacterial agents are used concomitantly. There are some articles in the literature that recommends administering concomitant antibacterial agents a certain number of hours apart, but no definitive instructions on this issue are set forth in this guideline.

ACTUAL EXAMPLES OF THE SELECTION OF ANTIBACTERIAL AGENTS

Empiric therapy (Fig. 1, Table 1)

Patients with mild to moderate pneumonia and no risk factors

1. Second-generation cephalosporins, or third-generation cephalosporins without anti-Pseudomonas activity.
2. Oral or intravenous fluoroquinolones
3. Clindamycin* + monobactam-derivative antibiotics.

Use of fluoroquinolone antibiotics or fluoroquinolone antibiotic preparations for intravenous injection is recommended if patients exhibit an allergic reaction to penicillin.

Care should be exercised when administering these antibiotics, other than oral fluoroquinolone derivatives that display potent antibacterial activity against *Streptococcus pneumoniae*, because they do not exert adequate antibacterial activity against *Streptococcus pneumoniae*, especially against penicillin-resistant *Streptococcus pneumoniae*. (see *Streptococcus pneumoniae* below.)

*Care should be exercised when injecting clindamycin, because it may induce cardiac arrest if rapidly injected intravenously. Administer clindamycin slowly by intravenous drip infusion over a period of 30 min to 1 hour.

Patients diagnosed with mild pneumonia despite having risk factors

When treating patients with mild pneumonia who have risk factors we recommend that the physician
Figure 1  Choice of antibiotics for empiric therapy of hospital-acquired pneumonia.

- **Group I**
  - Mild/moderate pneumonia with no risk factors
    - 1) Second-generation cephems, or third-generation cephems without activity against *P. aeruginosa*.
    - 2) Oral or injectable fluoroquinolones*
    - 3) Clindamycin + monobactams

- **Group II**
  - Mild pneumonia with a risk factor
    - 1) Third-generation cephems having activity against *P. aeruginosa* or fourth-generation cephems.
    - 2) Carbapenems*

- **Group III**
  - Moderate pneumonia with a risk factor or severe pneumonia
    - 1) β-lactams having activity against *P. aeruginosa* (third-generation cephems having activity against *P. aeruginosa*, fourth-generation cephems, or carbapenems) ± fluoroquinolones or aminoglycosides.
    - 2) Injectable fluoroquinolones* ± carbapenems
    - 3) When MRSA cannot be ruled out as the causative organism:
      - 1) or 2) + glycopeptides (such as teicoplanin and vancomycin) or arbekacin*.
    - 4) When *Legionella* pneumonia cannot be ruled out:
      - 1) with fluoroquinolones or 2), or β-lactams having activity against *P. aeruginosa* + macrolides or rifampicins.

- **Group IV**
  - Pneumonia with specific condition
    - **IV-1** Compromised immunity
      - 1) β-lactams having activity against *P. aeruginosa* (third-generation cephems having activity against *P. aeruginosa*, fourth-generation cephems, or carbapenems) ± aminoglycosides.**
      - 2) Injectable fluoroquinolones + clindamycin**
    - **IV-1-a** Neutropenia
    - **IV-1-b** Cellular immunosuppression
    - **IV-1-c** Humoral immunosuppression
      - Third- or fourth-generation cephems, carbapenems
    - **IV-2** Ventilation-associated pneumonia
      - 1) Early-stage VAP: β-lactams combined with a β-lactamase inhibitor or second- or third-generation cephems ± fluoroquinolones.
      - 2) Late-stage VAP: β-lactams, carbapenems, or fluoroquinolones having activity against *P. aeruginosa* ± aminoglycosides or minocycline ± glicopeptides.
    - **IV-3** Aspiration
      - Clindamycin, β-lactams combined with a β-lactamase inhibitor, carbapenems

* Refer to the text for the precautions for use (chapter 5).
** Non-bacterial causative organisms may be involved. Refer to the text (chapter 6).
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1. **Patients diagnosed with mild or moderate pneumonia who have any risk factors**
   
   1.1 Second generation cephems or third generation cephems without anti-pseudomonas activity
   
   1.2 Fluoroquinolones for oral or intravenous use
   
   1.3 Clindamycin + monobactams

   Fluoroquinolones are recommended for patients with a past history of allergic reaction to \( \beta \)-lactams. In addition, Clindamycin + Monobactams may be administered with caution. Care should be exercised when administering these agents except for some of the antibacterial agents, because their antibacterial activity against penicillin-resistant *S. pneumoniae* may be attenuated.

2. **Patients diagnosed with mild pneumonia who have any risk factors**

   Treatment options (1 or 3) are left to the discretion of the treating physician.

   - 2.1 Third and fourth generation cephems with anti-pseudomonas activity
   - 2.2 Carbapenems*

   * Option 2 should be chosen if aspiration pneumonia is suspected.

3. **Patients diagnosed with moderate or severe pneumonia who have any risk factors. Patients diagnosed with severe pneumonia with or without any risk factors**

   3.1 \( \beta \)-lactams (third and fourth generation cephems with anti-pseudomonas activities, and carbapenems) ± fluoroquinolones or aminoglycosides
   
   3.2 Fluoroquinolones for intravenous injection ± carbapenems*
   
   3.3 If MRSA cannot be ruled out as the causative bacteria, option 1 or 2 + glycopeptides (teicoplanin and vancomycin) or arbekacin** may be a treatment option.
   
   3.4 If Legionella pneumonia cannot be ruled out, fluoroquinolones should be chosen from options 1 and 2. Or, \( \beta \)-lactams with anti-pseudomonas activity ± macrolide or rifampicin may be a treatment option.

   * If patients have a past history of allergic reaction to penicillin and cephems, fluoroquinolones are the first choice.
   
   ** Care should be exercised when administering this drug if the patient has renal insufficiency. Therapeutic drug monitoring (TDM) should be performed as much as possible, and the occurrence of toxicity should be minimized while keeping the blood level of the drug within the therapeutic range.

4. **Patients in a special pathological state**

   Patients with Immunosuppressive conditions
   
   4.1 Neutropenia (induced by chemotherapy or radiation therapy, leukaemia, etc.)
   
   a. \( \beta \)-lactams with anti-pseudomonas activity (third and fourth generation cephems with anti-pseudomonas activity, and carbapenems) ± aminoglycosides
   
   b. Fluoroquinolones for intravenous injection ± clindamycin

   Anti-fungal therapy should be instituted promptly if aspergillosis or mucormycosis is suspected.
   
4.2 Cellular immunosuppression (organ transplantation, long-term use of steroid preparations, HIV infection, Hodgkin’s lymphoma and other malignancies)

   The concomitant use of macrolides or fluoroquinolones is recommended for the treatment of severe bacterial pneumonia, including Legionella pneumonia.

   The concomitant use of other antibiotics is also recommended as needed, taking other microorganisms (*Pneumocystis carinii*, cytomegalovirus, *Mycobacterium tuberculosis*, herpesvirus, Toxoplasma, etc.) into consideration.

4.3 Humoral immunosuppression (primary and secondary hypogammaglobulinaemia, multiple myeloma and other malignancies)

   Third and fourth generation cephems, and carbapenems

   Ventilator-associated pneumonia
   
   a. Early VAP: \( \beta \)-lactamase-inhibitor-containing \( \beta \)-lactams are recommended to use. Or, it is also recommended to use the second/third generation cephems or fluoroquinolones.
   
   b. Late VAP: \( \beta \)-lactams with anti-pseudomonas activity, or a fluoroquinolone or carbapenem ± aminoglycoside or minocyclin + glycopeptide.

   Aspiration pneumonia

   Clindamycin, \( \beta \)-lactamase-inhibitor-containing penicillins and carbapenems.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Empiric therapy</th>
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<tbody>
<tr>
<td>1. Patients diagnosed with mild or moderate pneumonia who have any risk factors</td>
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<tr>
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Fluoroquinolones are recommended for patients with a past history of allergic reaction to \( \beta \)-lactams. In addition, Clindamycin + Monobactams may be administered with caution. Care should be exercised when administering these agents except for some of the antibacterial agents, because their antibacterial activity against penicillin-resistant *S. pneumoniae* may be attenuated.

2. Patients diagnosed with mild pneumonia who have any risk factors

   Treatment options (1 or 3) are left to the discretion of the treating physician.

   - 2.1 Third and fourth generation cephems with anti-pseudomonas activity
   - 2.2 Carbapenems*

   * Option 2 should be chosen if aspiration pneumonia is suspected.

3. Patients diagnosed with moderate or severe pneumonia who have any risk factors. Patients diagnosed with severe pneumonia with or without any risk factors

   3.1 \( \beta \)-lactams (third and fourth generation cephems with anti-pseudomonas activities, and carbapenems) ± fluoroquinolones or aminoglycosides
   
   3.2 Fluoroquinolones for intravenous injection ± carbapenems*
   
   3.3 If MRSA cannot be ruled out as the causative bacteria, option 1 or 2 + glycopeptides (teicoplanin and vancomycin) or arbekacin** may be a treatment option.
   
   3.4 If Legionella pneumonia cannot be ruled out, fluoroquinolones should be chosen from options 1 and 2. Or, \( \beta \)-lactams with anti-pseudomonas activity ± macrolide or rifampicin may be a treatment option.

   * If patients have a past history of allergic reaction to penicillin and cephems, fluoroquinolones are the first choice.
   
   ** Care should be exercised when administering this drug if the patient has renal insufficiency. Therapeutic drug monitoring (TDM) should be performed as much as possible, and the occurrence of toxicity should be minimized while keeping the blood level of the drug within the therapeutic range.

4. Patients in a special pathological state

   Patients with Immunosuppressive conditions

   4.1 Neutropenia (induced by chemotherapy or radiation therapy, leukaemia, etc.)

   a. \( \beta \)-lactams with anti-pseudomonas activity (third and fourth generation cephems with anti-pseudomonas activity, and carbapenems) ± aminoglycosides
   
   b. Fluoroquinolones for intravenous injection ± clindamycin

   Anti-fungal therapy should be instituted promptly if aspergillosis or mucormycosis is suspected.

4.2 Cellular immunosuppression (organ transplantation, long-term use of steroid preparations, HIV infection, Hodgkin’s lymphoma and other malignancies)

   The concomitant use of macrolides or fluoroquinolones is recommended for the treatment of severe bacterial pneumonia, including Legionella pneumonia.

   The concomitant use of other antibiotics is also recommended as needed, taking other microorganisms (*Pneumocystis carinii*, cytomegalovirus, *Mycobacterium tuberculosis*, herpesvirus, Toxoplasma, etc.) into consideration.

4.3 Humoral immunosuppression (primary and secondary hypogammaglobulinaemia, multiple myeloma and other malignancies)

   Third and fourth generation cephems, and carbapenems

   Ventilator-associated pneumonia

   a. Early VAP: \( \beta \)-lactamase-inhibitor-containing \( \beta \)-lactams are recommended to use. Or, it is also recommended to use the second/third generation cephems or fluoroquinolones.
   
   b. Late VAP: \( \beta \)-lactams with anti-pseudomonas activity, or a fluoroquinolone or carbapenem ± aminoglycoside or minocyclin ± glycopeptide.

   Aspiration pneumonia

   Clindamycin, \( \beta \)-lactamase-inhibitor-containing penicillins and carbapenems.

select either option #1, second-generation cephem antibiotics, third-generation cephem antibiotics without anti-*Pseudomonas aeruginosa* activity, or option #3, clindamycin + monobactam antibiotics, based on an overall clinical assessment. For example, if the patient has pneumonia associated with chronic respiratory tract infection, sputum specimens can be collected easily. If a pneumococcal pneumonia is ruled out by gram-staining, oral fluoroquinolone antibiotics are indicated. Monotherapy with one of the following antibiotics is an alternative choice.

1. Third-generation cephem antibiotics, or fourth-generation cephem antibiotics with anti-*Pseudomonas aeruginosa* activity.

2. Carbapenem-derivative antibiotics.

   Treatment options 1 and 2 may be selected based on the likelihood of contracting aspiration pneumonia. In other words, by using the possibility of anaerobic bacterial infection as an indication for selecting the type of antibiotic. Selection of treatment option 2 is recommended if anaerobic bacterial infection cannot be ruled out.
Patients with risk factors who have been diagnosed with moderate pneumonia, and patients diagnosed with severe pneumonia regardless of risk factors

1. β-lactam antibiotics with anti-*Pseudomonas aeruginosa* activity (namely, third-generation cephalosporins with anti-*Pseudomonas aeruginosa* activity, or the fourth-generation cephalosporins, and carbapenem antibiotics) + fluoroquinolones or aminoglycosides.

2. Intravenous fluoroquinolones* + clindamycin*.

3. If MRSA cannot be ruled out as the causative bacteria, glycopeptide agents (teicoplanin and vancomycin) or arbekacin should be administered in addition to the antibiotics listed above. Care should be exercised when administering glycopeptide agents, because they may cause renal failure. Therapeutic drug monitoring (TDM) should be performed as much as possible to minimise the occurrence of toxicity while maintaining the blood level of glycopeptide agents within their therapeutic dose-range. The concomitant use of glycopeptide agents and aminoglycoside (or glycoside) antibiotics is contraindicated, as a rule.

4. If *Legionella* pneumonia cannot be ruled out, fluoroquinolones are preferable among treatment options 1 and 2. Or, β-lactam antibiotics with anti-*Pseudomonas aeruginosa* activity + intravenous macrolide and/or rifampicin (oral tablets) may be administered concomitantly.

*Intravenous fluoroquinolones are the first choice if patients have a history of an allergic reaction to penicillin and cephalosporin antibiotics.

Patients with specific underlying disorders

Patients with immunosuppressive conditions

Patients with neutropenia (myelosuppressive chemotherapy, radiation therapy, leukemia or other hematopoietic diseases):

1. Third-generation cephalosporin and the fourth-generation cephalosporin antibiotics with anti-*Pseudomonas aeruginosa* activity, or carbapenem antibiotics + aminoglycoside (or glycoside) antibiotics.

2. Monotherapy with fluoroquinolone antibiotics for intravenous injection + clindamycin.

If aspergillosis or mucormycosis is suspected, amphotericin B andazole antifungal agents should be promptly administered in combination with these antimicrobial agents to restore the neutrophil count.

Patients with cellular immunosuppression (organ transplantation, long-term use of steroid preparations, HIV infection, Hodgkin's lymphoma, and other hematopoietic diseases):

In addition to fluoroquinolone antibiotics, β-lactam antibiotics with anti-*Pseudomonas aeruginosa* activity and rifampicin (oral tablets) (i.e. antibacterial agents recommended for use in patients with severe pneumonia, including *Legionella pneumonia*), macrolide antibiotics for intravenous injection should be used concomitantly. Moreover, if *Pneumocystis carinii*, cytomegalovirus, *Mycobacterium tuberculosis*, *his*, herpes virus, toxoplasma or other pathogenic microorganisms are suspected, an effort should be made to isolate and identify the specific causative microorganism and treat pneumonia patients accordingly with adequate antibiotics.

Patients with humoral immunosuppression (primary and secondary hypogammaglobulinemia, multiple myeloma, and other malignancies): third-generation cephalosporin and the fourth-generation cephalosporin antibiotic preparations as well as carbapenem antibiotics. (Also, refer to Chapter 6 in regard to severe cases with underlying disorders.)

Ventilator-associated pneumonia Identify the causative bacteria at an early stage of the disease and administer adequate antibacterial agents promptly, because the mortality rate of ventilator-associated pneumonia (VAP) patients is quite high. The usefulness of bronchoscopic examinations has been well established, and bronchoscopy should be performed when possible. *Pseudomonas aeruginosa*, *Acinetobacter*, and MRSA are frequent causative bacteria of VAP. If *Pseudomonas aeruginosa* or *Acinetobacter* are the causative bacteria, fluoroquinolone for injection, third-generation cephalosporin antibiotics, carbapenem antibiotics and aminoglycoside agents are the first-line drugs. (Refer to Chapter 7.)

Aspiration pneumonia The elderly, patients with central nervous system disorders, bedridden patients and postoperative patients often develop aspiration pneumonia. Postoperative patients (after abdominal or thoracic surgery) often develop aspiration pneumonia, especially if they do not have an adequate cough reflex. Antimicrobial therapy should be instituted promptly, taking the possibility of 'pneumonia caused by anaerobes in the oral cavity' into consideration. Clindamycin, β-lactamase-inhibitor-containing penicillins and carbapenem antibiotics are effective in the treatment of aspiration pneumonia caused by anaerobic bacteria. Since the rate of colonisation by grammegative rod bacteria in the oral cavity is especially high among patients with a past history of treatment with antibacterial agents or who have been hospitalised for a long period, clindamycin is insufficient as a treatment for such patients. (Refer to Chapter 8.)

If causative microorganisms are suspected or identified, the following measures should be taken (Table 2)

*Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* is a frequent cause of opportunistic infection, and *Pseudomonas aeruginosa* is often isolated from patients with underlying disorders, including chronic respiratory diseases and malignant tumors. Carbapenem antibiotics, fluoroquinolone antibiotics, the third-generation cephalosporin antibiotics with anti-*Pseudomonas aeruginosa* activity, monobactam agents and penicillin derivatives
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Table 2  If it is feasible to identify the causative microorganisms, use of the following antibacterial agents is recommended

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Recommended Antibacterial Agents</th>
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<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Penicillins with anti-pseudomonas activity (high doses), third/fourth generation cephems, monobactams, carbapenems, and fluoroquinolones ± aminoglycosides</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>MRSA. If sensitive to penicillin, penicillins are recommended. For β-lactamase–producing Staphylococcus aureus, methicillin, oxacillin β-lactamase–inhibitor–containing penicillins or first generation cephems (are recommended)</td>
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<tr>
<td>Klebsiella</td>
<td>Third generation cephems, carbapenems, and fluoroquinolones (are recommended)</td>
</tr>
<tr>
<td>Extended spectrum β-lactamase (ESBL)–producing gram–negative rods</td>
<td>Carbapenems, fluoroquinolones, and cephemycins (are recommended)</td>
</tr>
<tr>
<td>Streptococcus Pneumoniae</td>
<td>Oral: Fluoroquinolones (choose a respiratory fluoroquinolone with excellent anti-pneumococcus activity)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Intravenous injection: Carbapenems and glycopeptides</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td>Clindamycin, β-lactamase–inhibitor–containing penicillins, and carbapenems</td>
</tr>
<tr>
<td>Legionella</td>
<td>Macrolides, fluoroquinolones, and rifampicin</td>
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<tr>
<td>Fungi</td>
<td>When a patient with severe neutropenia develops a fever, antibacterial agents are ineffective, and invasive aspergillosis is suspected, the following medications should be prescribed</td>
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<tr>
<td></td>
<td>1 Amphotericin B. The initial dose should be 1 mg, followed by gradual dose escalation. The maintenance dose should be between 1.0 and 1.5 mg/kg/day</td>
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<tr>
<td></td>
<td>2 Itraconazole: 200–400 mg in one or two divided doses (up to 200 mg/day indicated by Japanese health insurance coverage)</td>
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<tr>
<td>Mycobacterium tuberculosis</td>
<td>Tuberculosis therapy should be instituted and maintained for the first two months with the four agents listed below. Thereafter, tuberculosis therapy should be maintained with three agents, excluding pyrazinamide. The entire treatment period should be six months</td>
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<tr>
<td></td>
<td>Isoniazid: 400 mg in one dose</td>
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<td>Rifampicin: 450 mg in one dose</td>
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<td></td>
<td>Ethambutol: 750 mg in one dose or Streptomycin 0.5–0.75 g, intramuscular injection</td>
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<td></td>
<td>Pyrazinamide: 1.2 g in two divided doses</td>
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<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir: 10 mg/kg/day in two divided doses, intravenous drip infusion</td>
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<tr>
<td>Pneumocystis carinii</td>
<td>Sulfamethoxazole/trimechoprim mixture: 8–12 tablets in three divided doses, p.o.</td>
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</table>

(At high doses) are effective against Pseudomonas aeruginosa pneumonia. However, since Pseudomonas aeruginosa quickly acquires resistance to these antibiotics, and their antibacterial activity against mucoid-type Pseudomonas aeruginosa is often attenuated, antimicrobial therapy should be instituted with caution, making sure that the patient actually has an infection.

Concomitant use of aminoglycoside agents is particularly recommended for patients with severe pneumonia or serious underlying disorders. In addition, since metallo-β-lactamase–producing Pseudomonas aeruginosa also exist (metallo-β-lactamase degrades carbapenem antibiotics), care should be exercised when metallo-β-lactamase–producing Pseudomonas aeruginosa are the causative bacteria.

Staphylococcus aureus

The first-generation cephems and β-lactamase–inhibitor–containing penicillin derivatives should be chosen for the treatment of MRSA infections, taking β-lactamase production into consideration. Among oral preparations, fluoroquinolone antibiotics are effective in the treatment of MRSA infections. In addition to fluoroquinolone antibiotics, minocycline, carbapenem antibiotics, arbekacin, teicoplanin and vancomycin may also be used to treat patients with MRSA infections on a case-by-case basis. However, while arbekacin, teicoplanin and vancomycin have been approved for clinical use in MRSA infections, they are not covered by Japanese health insurance coverage for MRSA infections. Arbekacin, teicoplanin and vancomycin are effective for the treatment of MRSA infections. However, care should be exercised in isolating and identifying the causative bacteria to determine if MRSA is indeed the cause based on an overall assessment, including clinical findings as well as staining and culture results.

Klebsiella

Pneumonia caused by Klebsiella pneumoniae is common in patients with alcoholism (or alcohol-
dependency) and diabetes mellitus, and it is classified as 'lobar pneumonia'. The pneumonia caused by *Klebsiella pneumoniae* is characterised by discharge of viscous sputum. The third-generation cepham antibiotics are the drugs of first choice, because *Klebsiella* strains frequently produce β-lactamase. The third-generation cepham antibiotics have potent antibacterial activity and are ‘sharp’ antimicrobial agents, so to speak. Since it has recently been reported that some strains of *Klebsiella* produce β-lactamase enzymes that degrade a broad spectrum of β-lactam antibiotics, care should be exercised in this respect. Carbapenem antibiotics and fluoroquinolones have potent antibacterial activity against β-lactamase-producing *Klebsiella*.

Extended spectrum β-lactamase (ESBL)-producing gram-negative rods

Gram-negative rod bacteria, such as *Klebsiella* and *E. coli*, produce penicillinase, and some variant penicillinase enzymes acquire additional enzymatic activity by mutation that degrades third-generation cepham antibiotics. This type of variant penicillinase is called ‘ESBL’. Carbapenem antibiotics, fluoroquinolones and cephamicyn (or cephalaxin) antibiotics are effective against ESBL-producing gram-negative rods.

Anaerobes and *S. milleri* group

The elderly patients with central nervous system disorders, and bedridden patients are prone to develop aspiration pneumonia, and anaerobic bacterial infections should be suspected in such persons. Clindamycin, β-lactamase-inhibitor-containing penicillins, carbapenem antibiotics and minocycline are effective in the treatment of pneumonia caused by anaerobic bacteria.

*Streptococcus pneumoniae*

Oral fluoroquinolones have potent antimicrobial activity against *Streptococcus pneumoniae* if administered to patients with mild pneumonia who have no risk factors. Carbapenem antibiotics should be administered intravenously by drip infusion to patients with penicillin-resistant *Streptococcus pneumoniae* (PRSP). Vancomycin for injection and teicoplanin for injection are also effective against PRSP, although not covered by ‘the Japanese Insurance Medical Fee Payment System’ for PRSP infections.

If patients have a past history of allergic reaction to penicillin preparations, they should be treated with vancomycin by injection, or teicoplanin by injection, and fluoroquinolone antibiotics with potent anti-*Streptococcus* activity, depending on the severity rating of the clinical manifestations.

If bacterial sensitivity tests reveal PSSP or PRSP, antibacterial agents should be selected based on the results of the sensitivity tests.

*Haemophilus influenzae*

Approximately 10% to 20% of *H. influenzae* strains are known to produce β-lactamase, and non-β-lactamase-producing penicillin-resistant *H. influenzae* strains have been tending to increase in number. Oral fluoroquinolone antibiotics are very effective in patients with mild pneumonia without any risk factors. Third-generation and fourth-generation cepham for intravenous injection and carbapenems for intravenous injection are effective in the treatment of pneumonia caused by *H. influenzae*. Since some carbapenem antibiotics do not have potent antibacterial activity against *H. influenzae*, care should be exercised when selecting carbapenems.

*Moraxella catarrhalis*

Since 100% of *Moraxella catarrhalis* strains are known to produce β-lactamase, penicillins are ineffective. β-lactamase-inhibitor-containing penicillins, second-generation and third-generation cepham, and macrolides are effective in the treatment of pneumonia caused by *Moraxella catarrhalis*. Fluoroquinolones and carbapenems are very effective in the treatment of pneumonia caused by *Moraxella catarrhalis*.

*Legionella species*

*Legionella* spp. is occasionally found to be the causative bacteria of HAR when baths, heated-wire humidifiers and heaters are contaminated (i.e. water in these instruments is contaminated). *Legionella* pneumonia may occur as an epidemic at the institutions concerned, and care should be exercised in this regard. β-lactams are ineffective against *Legionella* spp., which is a parasitic microorganism in cells, and adequate therapy is required to eradicate *Legionella* spp. If β-lactams are ineffective in pneumonia patients. Macrolides and tetracyclines are effective in the treatment of pneumonia caused by *Legionella* spp. For adults, ciprofloxacin (600 mg/day divided in two) (a fluoroquinolone antibiotic for intravenous injection) and erythromycin (1500 mg/day divided in three) are the first-line medications. Concomitant rifampicin (oral, 450 mg x 1) or a fluoroquinolone antibiotic and azithromycin (500 mg x 1, for three days) is also effective in the treatment of *Legionella pneumoniae*.

*Fungi*

Invasive pulmonary aspergillosis (a type of pneumonia caused by *Aspergillus*) must be suspected whenever an extremely neutropenic patient develops fever and antibacterial agents are ineffective. It is important to institute adequate therapy in a timely manner. In other words, antifungal therapy must be started as soon as possible whenever invasive pulmonary
pneumocystis carinii pneumonia often occurs in patients with underlying diseases, such as haematological malignancies, and after organ transplantation. The prophylactic use of ST compounds in recent years has significantly lowered the incidence of Pneumocystis carinii pneumonia. The incidence of Pneumocystis carinii pneumonia is highest among AIDS patients with respiratory infections. Please refer to other chapters for details. The recommended treatment is:
- Sulfamethoxazole/trimethoprim compounds 8–12 g/day divided in three, oral administration;
- or, Sulfamethoxazole/trimethoprim compounds for intravenous injection (drip infusion): 6–12 vials/day divided in three or four.

If ST compounds are ineffective or patients develop severe Pneumocystis carinii pneumonia, the following drug may be used: pentamidine 4 mg/kg/day, by intravenous drip infusion.

**Mycobacterium tuberculosis**

The best treatment for Mycobacterium tuberculosis is intensified combination therapy consisting of four drugs (i.e. the conventional ‘standard therapy’ for Mycobacterium tuberculosis’ plus pyrazinamide (PZA) during the initial stage of the disease). The treatment period should be six months. If drug-resistant Mycobacterium tuberculosis is suspected be sure to consult a tuberculosis specialist because multidrug resistance may be induced if only one drug is substituted.

The following four drugs should be taken daily for the first two months of tuberculosis therapy.
- Isoniazid 400 mg x 1
- Rifampicin 450 mg x 1
- Ethambutol 750 mg x 1 (Streptomycin sulfate, 0.5–0.75 g intramuscularly daily, 2–3 times per week, may be substituted for ethambutol);
- Pyrazinamide 1.2 g/day divided by two.

The following three drugs should then be taken for the following four months.
- Isoniazid 400 mg x 1
- Rifampicin 450 mg x 1
- Ethambutol 750 mg x 1.

**Cytomegalovirus**

Patients with a severe cellular immunosuppression, such as occurs in haematological diseases, often develop cytomegalovirus infection, which is fatal. Postoperative organ transplantation patients often develop cytomegalovirus infections because of the immunosuppression that occurs after surgery. If patients develop acute hypoxemia or their chest X-ray reveals diffuse interstitial infiltration, cytomegalovirus infection must be suspected. Ganciclovir 10 mg/kg/day divided in two, by intravenous drip infusion is the treatment of choice.

**Pneumocystis carinii**

Pneumocystis carinii is a causative microorganism of HAP, and Pneumocystis carinii pneumonia often occurs in patients with underlying diseases, such as haematological malignancies, and after organ transplantation. The prophylactic use of ST compounds in recent years has significantly lowered the incidence of Pneumocystis carinii pneumonia. The incidence of Pneumocystis carinii pneumonia is highest among AIDS patients with respiratory infections. Please refer to other chapters for details. The recommended treatment is:
- Sulfamethoxazole/trimethoprim compounds 8–12 g/day divided in three, oral administration;
- or, Sulfamethoxazole/trimethoprim compounds for intravenous injection (drip infusion): 6–12 vials/day divided in three or four.

If ST compounds are ineffective or patients develop severe Pneumocystis carinii pneumonia, the following drug may be used: pentamidine 4 mg/kg/day, by intravenous drip infusion.

**REFERENCES**

APPENDIX 1

Supplementary Information

Definition of 'severe hospital-acquired pneumonia' to be treated in the ICU (ATS Guideline)

- Respiratory failure: Patients who require mechanical ventilation or inhalation of oxygen gas (≥35%) to maintain PaO₂ of 90% or more.
- Chest X-ray findings indicating rapid exacerbation, multilobular pneumonia, or cavity formation.
- Severe sepsis accompanied by hypotension or organ failure.
  - Shock (systolic blood pressure ≤ 90 mmHg and/or diastolic blood pressure ≤ 60 mmHg): requiring administration of a vasoconstrictor agent for four hours or longer.
  - Urine volume ≤ 20 mL/h or 4-h urinary volume ≤ 80 mL and the absence of any other cause (underlying disorder).
  - Patients with acute renal failure requiring haemodialysis.