Pneumonia in immunosuppressed patients

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

The Japanese Respiratory Society

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WHAT IS IMMUNOSUPPRESSION?

‘Immunosuppression’ occurs as a result of a lack of either humoral (B-cell) immunity or cellular (T-cell) immunity, or both. While ‘immunosuppression’ plays a central role in susceptibility to infectious diseases in humans, neutropenia is another important contributing factor. In this chapter, ‘immunosuppression’ in its broad sense will be discussed, including lack of neutrophil-mediated immunity as well as lack of humoral (B-cell) immunity and cellular (T-cell) immunity. Patients develop a variety of infectious diseases as a result of immunosuppression, and the lung is one of the most susceptible vital organs.

TYPES OF IMMUNOSUPPRESSION AND FEATURES OF PNEUMONIA IN IMMUNODEFICIENT PATIENTS

Neutropenia

1 Neutropenic patients often have fevers but seldom exhibit pneumonia-related symptoms. The chest X-rays of neutropenic patients rarely show evidence of infiltration, and such patients seldom produce purulent sputum. The severity and duration of the neutropenia affects patients’ susceptibility to pneumonia and the prevalence of causative microorganisms.

(i) Severity of neutropenia

• Neutrophil count ≤ 1000/μL: Patients begin to show susceptibility to infection.
• Neutrophil count ≤ 500/μL: Patients show striking susceptibility to infection.

(ii) Duration of neutropenia

• No more than a few days: Susceptibility to infection low, seldom presents with clinical problems.
• Less than 3 weeks: Patients show increased risk of bacterial infection(s).
• More than 3 weeks: Patients show increased frequency of fungal infection as well as bacterial infection.

Neutrophil count ≤ 100/μL: Patients have almost completely lost neutrophil-mediated defence functions.

2 The major high risk factors for neutropenia are shown below

(i) Primary neutropenia: Genetically inherited neutropenia and periodic neutropenia are well-known, but their incidence is low.
(ii) Secondary neutropenia: Neutropenia associated with acute leukaemia and aplastic anaemia.
(iii) Iatrogenic neutropenia: Neutropenia associated with the use of myelosuppressive anticancer chemotherapy, radiation therapy, and bone marrow transplantation, as well as with drug-induced granulocytopenia.

Bacteria commonly associated with neutropenic patients and pneumonia

Most causative agents of pneumonia in neutropenic patients are bacteria that proliferate extracellularly (primarily pyogenic bacteria) and fungi (Aspergillus in particular). Other bacteria are rarely associated with pneumonia in neutropenic patients.

(i) Bacteria

• Gram-positive bacteria: including Staphylococcus aureus and Streptococcus pneumoniae.
• Gram-negative bacteria: including Pseudomonas aeruginosa, Klebsiella and E. coli.

(ii) Fungi: including Aspergillus and Mucor.

Humoral immunosuppression

1 Three types of humoral immunosuppression are known: lack of immunoglobulins as a whole, lack of a specific subclass of immunoglobulins, and defec-
tive immune response to specific antigens. Most humoral immunosuppression occurs as a result of impaired IgG synthesis in vivo. A
(i) Severity of the decreased IgG level
• More than 500 mg/dL: Patients seldom develop infection(s).
• 200–500 mg/dL: Patients begin to show susceptibility to infection.
• Less than 200 mg/dL: Patients show increased susceptibility to infection paralleling the decrease in serum immunoglobulin level.
2 The major high-risk factors for humoral immunosuppression are shown below.
(i) Primary humoral immunosuppression: Severe complex humoral immunodeficiency syndrome and X-chromosome linked agammaglobulinaemia are well-known forms of primary humoral immunodeficiency, but their incidence is low.
(ii) Secondary humoral immunosuppression: multiple myeloma, chronic lymphocytic leukaemia, some types of malignant lymphoma, some cases of HIV infection, severe nephrotic syndrome, burns, and protein-losing enteropathy.
(iii) Iatrogenic neutropenia: humoral immunosuppression associated with the use of myelosuppressive anticancer chemotherapy, radiation therapy, and bone marrow transplantation.
3 Bacteria commonly associated with humoral immunosuppression and pneumonia: Since opsonization via attachment of antibodies on the organisms, production of neutrophil chemotactic factor and complement activation are impaired, the host's defences against capsule-containing bacteria which correlate with opsonizing antibodies are primarily impaired. Other bacteria are rarely associated with hospital-associated pneumonia in patients with humoral immunosuppression.
Bacteria: includes Streptococcus pneumoniae, H. influenzae and Klebsiella.

Cellular immunosuppression

1 The CD4-positive lymphocyte counts of patients with cellular immunosuppression affect their susceptibility to pneumonia and the prevalence of causative microorganisms. Table 1 shows the correlation between CD4-positive lymphocyte counts and prevalent disorders among patients with HIV infection.

(i) Severity of lymphopenia (CD4-positive lymphocyte count)
• CD4-positive lymphocyte count ≥ 500/µL: Patients do not show any particular susceptibility to infection. Common bacterial pneumonia is seen.
• CD4-positive lymphocyte count < 500/µL: Patients develop tuberculosis and cryptococcosis more frequently than healthy individuals.
• CD4-positive lymphocyte count ≤ 200/µL: Patients are susceptible to opportunistic pneumonia caused by a variety of pathogenic microorganisms, including viruses and parasites.

Table 1 CD4-positive lymphocyte count and prevalent pulmonary lesions in HIV-positive patients

<table>
<thead>
<tr>
<th>CD4-positive lymphocyte count</th>
<th>Prevalent pulmonary lesions</th>
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<tbody>
<tr>
<td>CD4-positive lymphocytes ≤ 500/µL</td>
<td>Bacterial pneumonia (Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa) Tuberculosis (typical pathological conditions if CD4-positive lymphocytes ≥ 200/µL, atypical pathological conditions if CD4-positive lymphocytes &lt; 200/µL Kaposis sarcoma (preceded by dermatological lesions)</td>
</tr>
<tr>
<td>CD4-positive lymphocytes ≤ 200/µL</td>
<td>Pneumocystis carinii pneumonia Cryptococcosis (pulmonary lesion is part of systemic infection) Toxoplasmosis (pulmonary lesion is part of systemic infection) Malignant lymphoma (pulmonary lesion is part of systemic lesions)</td>
</tr>
<tr>
<td>CD4-positive lymphocytes ≤ 50/µL</td>
<td>Cytomegalovirus pneumonia (pulmonary lesion is part of systemic infection) Non-tuberculous atypical mycobacteriosis (rarely restricted to the pulmonary lesion)</td>
</tr>
</tbody>
</table>
of this, a variety of causative microorganisms have been isolated from pneumonia patients with cellular immunosuppression.

(i) Bacteria: *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Legionella*, *Nocardia* and *Mycobacterium*.

(ii) Viruses: Cytomegalovirus and herpes simplex virus.

(iii) Fungi: *Pneumocystis carinii*, *Aspergillus*, *Cryptococcus*, *Mucor* and *Candida*.

(iv) Protozoa and parasites: including *Toxoplasma* and *Strongyloides stercoralis*.

**DIAGNOSIS OF PNEUMONIA IN PATIENTS WITH IMMUNOSUPPRESSION (Fig. 1)**

**Primary examination**

1. If a patient is suspected of having pneumonia based on their presenting history, symptoms (cough, sputum, fever, dyspnoea, chest pain, etc.), leukocytosis, elevation of CRP, or infiltration on chest X-rays (as shown in Table 2), the primary examinations listed below should be performed, and immunosuppression should be assessed in accordance with the following criteria:

   (i) Neutropenia
   - Neutrophil count ≤ 500/µL.

   (ii) Humoral immunosuppression
   - IgG ≤ 500 mg/dL.

   (iii) Cellular immunosuppression
   - CD4-positive lymphocyte count ≤ 200/µL.

2. Primary examination

   Haematological examinations (with a haemocytometer): WBC counts (leukocyte counts), leukocyte fractions, CD4-positive lymphocyte counts, CD8-positive lymphocyte counts, CD4/CD8 ratio, and CRP (C-reactive protein).

   (i) Erythrocyte sedimentation rate (ESR): ESR at one hour.

   (ii) Immunoglobulins: IgG, IgA, and IgE.

   (iii) Blood gas analysis

   (iv) Chest X-ray: posteroanterior and lateral

   (v) Microbiological examinations

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**Figure 1** Flowchart for diagnosis, treatment and laboratory tests for hospital-acquired pneumonia among patients with immunosuppression.
• Sputum culture—general bacterial smear.
• Sputum culture—acid-fast bacterial smear.
• Sputum culture—fungal smear.
• Blood culture.

3 Secondary examinations
If a patient is diagnosed with immunosuppression (neutropenia, decreased IgG level and/or decreased CD4-positive lymphocyte count), empiric therapy should be instituted based upon the result of the primary examination. The following secondary assessments should be performed in parallel to isolate and identify the causative microorganisms.

Secondary examinations
1 Diagnostic imaging: CT (computed tomography).
2 Antigen tests
   (i) Bacteria: Urinary Legionella antigen level: sensitivity and specificity ≥ 90%.
   (ii) Fungi:
       • β-D-Glucan: If positive for β-D-glucan (≥ 20 pg/mL), fungal infection or Pneumocystis carinii infection should be suspected. However, false-positive responses are also noted for Cryptococcus.
       • Aspergillus antigen: high specificity but low sensitivity;
   (iii) Cryptococcus antigen: sensitivity = 90%, specificity = 90%.
   (iv) Candida antigen: Sensitivity and specificity are both poor.
   (v) Viruses: cytomegalovirus antigen (viraemia or antigenaemia assay).
   (vi) PCR:
       • cytomegalovirus;
       • Mycobacterium: Mycobacterium tuberculosis and atypical mycobacterium;
       • Pneumocystis carinii.
3 Skin reactions
   Tuberculin reaction: False-negative responses are often noted in patients with cellular immunosuppression, and the tuberculin test is not reliable.
4 Invasive examinations
   Bronchoscopy: Bronchoalveolar lavage (BAL), brushing, curettage, and lung biopsy (TBLB).

Problems associated with assessing immunosuppressed patients with pneumonia
1 When immunosuppressed patients develop pneumonia, there may be more than one microorganism involved. Since more than one microorganism can be simultaneously involved, always keep in mind that multiple microorganisms may cause pneumonia.
2 Colonisation by pathogenic microorganism is frequently noted in patients with immunosuppression. Consequently, in many patients with immunosuppression, the bacteria isolated are not necessarily the causative microorganism.
   (i) Microorganisms where there is little doubt that they are the causative agents.
       • Bacteria: Legionella, Mycobacterium tuberculosis;
       • Fungi: Pneumocystis carinii, Cryptococcus and Mucor.
   (ii) There is a possibility that the microorganisms isolated are not the causative agents.
       • Bacteria: MRSA, Pseudomonas aeruginosa and non-tuberculosis Mycobacterium (atypical mycobacterium).
       • Fungi: Candida.
       • Viruses: cytomegalovirus (particularly in AIDS).

EMPIRIC THERAPY FOR PNEUMONIA IN IMMUNOSUPPRESSED PATIENTS (I.E. TREATMENT BASED ON THE RESULTS OF PRIMARY EXAMINATION)

Neutropenia
1 Generally, common bacteria and fungi are often the causative microorganisms in hospital-acquired pneumonia in a setting of neutropenia, and since the pneumonia may very rapidly worsen, empiric therapy with the antibacterial agents listed below must be instituted immediately;
   (i) If the neutrophil count is between 500/μL and 1000/μL, one of the following should be used:
       • Third generation cephalosporin antibiotics;
       • Fourth generation cephalosporin antibiotics;
(ii) If the neutrophil count is below 500/µL, one of the following combinations should be used:

- Itraconazole + one of the following;
- Third generation cepham antibiotics + aminoglycosides;
- Fourth generation cepham antibiotics;
- Carbapenems;
- G-CSF facilitates improvement of pneumonia-related symptoms by shortening the duration of neutropenia.7

Humoral immunosuppression

1 In most patients with humoral immunosuppression, bacteria are the cause of the pneumonia. In addition, the prevalence of *H. influenzae* and *Streptococcus pneumoniae* is quite high. Approximately 10–20% of *H. influenzae* are β-lactamase-producing strains, and non-β-lactamase-producing ampicillin-resistant *H. influenzae* (BLNAR) strains constitute approximately 30% of the bacterial strains isolated from clinical specimens.8 It has been reported that approximately 50% of *Streptococcus pneumoniae* strains have poor sensitivity to penicillin (PISP) or are resistant to penicillin (PRSP).8 In view of the current situation, the following empiric therapy should be selected.

(i) If the IgG level is no more than 500 mg/dL, one of the following combinations should be used:

- Immunoglobulin + one of the following;
- Third generation cepham antibiotics;
- Fourth generation cepham antibiotics;
- Carbapenems;

Cellular immunosuppression

1 A wide variety of pathogenic microorganisms may cause pneumonia in patients with cellular immunosuppression, making it impossible to select empiric therapy that is effective against all of them. For this reason, empiric therapy should be instituted taking common bacteria as well as *Pneumocystis carinii* and *Legionella* (which cause rapidly progressive pneumonia) into consideration;

(i) If the CD4-positive lymphocyte count is between 200/µL and 500/µL, one of the following antibiotics should be used:

- Third generation cepham antibiotics;
- Fourth generation cepham antibiotics;

(ii) If the CD4-positive lymphocyte count is less than 200/µL or if bilateral infiltration is seen on the chest X-ray and/or PaO2 is ≤ 70 Torr, one of the following combinations should be used:

- ST mixture 12 tablets/day + Fluoroquinolone + Itraconazole + one of the following:
- Third generation cepham antibiotics;
- Fourth generation cepham antibiotics;
- Carbapenems;

(iii) If the above criteria are not applicable, one of the following combinations should be used:

- Itraconazole + one of the following:
- Third generation cepham antibiotics;
- Fourth generation cepham antibiotics;
- Carbapenems.

REFERENCES