CHAPTER 9

Treatment other than by antimicrobial therapy

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

In addition to antibacterial therapy, antipyretics; corticosteroids; granulocyte colony-stimulating factor (G-CSF) and immunoglobulins are available for the treatment of hospital-acquired pneumonia (HAP). Since none of these agents exert a direct effect on pathogenic bacteria and since their benefit is variable, their use should be left to the discretion of the treating physician. These agents should be used conventionally and in accordance with the manufacturer's 'Indications and Usage'. This chapter discusses the role of immunoglobulins, immunomodulators and G-CSF in treating pneumonia (Fig. 1).

IMMUNOGLOBULINS

When used as adjunct therapy for infectious diseases, the pharmacological effects of immunoglobulin preparations are mediated by their opsonin action, immunological bacteriolytic action, toxin-neutralising action and antibody-dependent-cell mediated cytotoxicity (ADCC). Gram-positive bacteria are eliminated from the host by the phagocytic action of neutrophils in the presence of antibody, and gram-negative bacteria are eliminated from the host by complement-mediated bacteriolysis. The phagocytic action of neutrophils is also stimulated by antibody binding to bacteria, which leads to complement activation. Antibody is also beneficial in neutralising bacterial toxins.

It takes some time for the host to produce antibody after being invaded by bacteria, and even if the host had been infected by the same bacteria in the past and retains antibody in the circulation, the antibody will be consumed by elimination of the bacteria from the host. Moreover, some patients have underlying disorders that may diminish their capacity to produce antibodies. There is also the possibility that antibody production will not be sufficient to eliminate the bacteria from the host because of the severity of the infection. Although many investigators have evaluated the clinical effects of immunoglobulin preparations on the outcome of patients with serious infectious disease and have reported the results in the literature, there is no consensus in regard to their efficacy. This issue is still a matter of controversy, but administration of immunoglobulins is of value in pneumonia patients with serious underlying disorders, patients with serious HAP, and patients with viral pneumonia, including cytomegalovirus pneumonia. (Refer to Chapter 6.) However, immunoglobulin preparations are ineffective for the treatment of pneumonia caused by parasitic and other microorganisms, including Legionella.

ANTI-INFLAMMATORY AGENTS

Glucocorticosteroids

There are two important factors in the pathogenesis of infectious diseases, such as direct factors (direct effects of bacteria on the host) and indirect factors (the inflammatory response that eliminates bacteria from the host). The host's response is usually beneficial for survival of the host, but is occasionally disadvantageous because of an overactive immune response. Administering steroids to patients with infectious diseases may be risky, because they may aggravate the infection or infections may develop concomitantly.

Glucocorticosteroids may also cause adverse reactions. Because of their inhibitory effect on inflammatory responses, steroids are often beneficial for patients with circulatory insufficiency or respiratory failure whose local inflammatory reactions are abnormally intense and whose prognosis is greatly influenced by local inflammatory reactions. Such pathological conditions include pneumonia complicated by sepsis, severe pneumonia and Pneumocystis carinii pneumonia. A number of investigators have
assessed the usefulness of steroids in patients with pneumonia in terms of the effect on patient outcome, and in general they were found to be effective in the management of AIDS patients with *Pneumocystis carinii* pneumonia, but ineffective in all other patients with pneumonia. Taken together, these findings indicate that it is better to avoid the use of glucocorticosteroids. If the use of steroids is unavoidable, concomitant use of effective antibacterial agents (i.e. antibacterial agents to which the causative bacteria are known to be sensitive based on sensitivity tests) is essential. In addition, care should be exercised when administering steroids, and patients should be monitored carefully especially in regard to adverse drug reactions. Particular care should be exercised in regard to dosage and administration, including the duration of administration. Since glucocorticosteroids exert conflicting pharmacological actions in the management of infectious diseases, their use is left to the discretion of the treating physician based on a careful clinical assessment of each case. (Refer to Chapter 6.)

**Nonsteroidal anti-inflammatory drugs**

Fever is one of the most important parameters for assessing the efficacy of antimicrobial agents, and it is one of the most objective parameters in the management of infectious diseases. Accordingly, as a rule the use of antipyretics is undesirable. However, if patients experience severe discomfort as a result of high fevers and develop secondary symptoms, the use of antipyretics may be allowed. If high fever induces adverse effects involving the cardiovascular system or respiratory dynamics, the use of antipyretics may also be allowed. While non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to elevate PaO\(_2\) through improvement of an intrapulmonary shunt, they do not improve patient outcome. Care should be exercised when administering NSAIDs in combination with antibacterial agents, and patients should be monitored for drug interactions, adverse drug reactions and possible gastrointestinal bleeding.

**Granulocyte colony-stimulating factor**

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein that acts on haematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation and activation of some phagocytic functions. For example, G-CSF stimulates the proliferation and differentiation commitment of precursor cells of the granulocyte lineage. G-CSF also prolongs the survival of mature neutrophils and induces activation of phagocytic functions, such as migration of mature neutrophils, enhanced phagocytic activity, production of activated oxygen and enhanced ADCC (antibody-dependent cytotoxicity). Granulocyte colony-stimulating factor stimulates the mobilisation of pluripotent stem cells from the bone marrow to peripheral blood and facilitates the entry of stem cells into the cell cycle. Compromised hosts with defective immune systems in relation to infection often develop HAP, and in such patients treatment with conventional antibacterial chemotherapy alone is often inadequate. Phagocytes, such as granulocytes, monocytes and macrophages, play major roles among the variety of host defence systems in eliminating bacteria from the host. Patients with HAP often have low levels of these cells in their peripheral blood. Granulocyte colony-stimulating factor should be administered to granulocytopenic patients with HAP. (Refer to Chapter 6.)

**REFERENCES**