Evidence-Based Guidelines for Empirical Therapy of Neutropenic Fever in Korea

Dong-Gun Lee¹,², Sung-Han Kim³, Soo Young Kim¹⁴, Chung-Jong Kim¹, Wan Beom Park⁵, Young Goo Song⁶, and Jung-Hyun Choi²

1National Evidence-based Healthcare Collaborating Agency; 2Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea; 3Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine; 4Department of Family Medicine, Hallym University College of Medicine; 5Department of Internal Medicine, Seoul National University College of Medicine; 6Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

Neutrophils play an important role in immunological function. Neutropenic patients are vulnerable to infection, and except fever is present, inflammatory reactions are scarce in many cases. Additionally, because infections can worsen rapidly, early evaluation and treatments are especially important in febrile neutropenic patients. In cases in which febrile neutropenia is anticipated due to anticancer chemotherapy, antibiotic prophylaxis can be used, based on the risk of infection. Antifungal prophylaxis may also be considered if long-term neutropenia or mucosal damage is expected. When fever is observed in patients suspected to have neutropenia, an adequate physical examination and blood and sputum cultures should be performed. Initial antibiotics should be chosen by considering the risk of complications following the infection; if the risk is low, oral antibiotics can be used. For initial intravenous antibiotics, monotherapy or combination therapy with two antibiotics is recommended. At 3-5 days after beginning the initial antibiotic therapy, the condition of the patient is assessed again to determine whether the fever has subsided or symptoms have worsened. If the patient’s condition has improved, intravenous antibiotics can be replaced with oral antibiotics; if the condition has deteriorated, a change of antibiotics or addition of antifungal agents should be considered. If the causative microorganism is identified, initial antimicrobial or antifungal agents should be changed accordingly. When the cause is not detected, the initial agents should continue to be used until the neutrophil count recovers. (Korean J Intern Med 2011;26:220-252)

Keywords: Practice guideline; Neutropenia; Fever; Korea

INTRODUCTION

Background and purpose

The neutrophil is an important component of the innate immune system. Neutrophils primarily defend the body against microorganisms, and a low number of neutrophils indicates that a person is vulnerable to infection. Additionally, because neutropenic patients lack the leukocytes needed to develop an inflammatory response, common inflammatory manifestations that are observed in patients within the normal range of leukocytes are rarely found. Thus, except in the presence of a fever, an accurate diagnosis is difficult and the most appropriate time for treatment may be missed. Thus,
febrile neutropenic patients should be treated differently from other febrile non-neutropenic patients [1].

Many countries, including the US and Europe, have developed and reported guidelines on approaches to and treatments for febrile neutropenic patients. However, the pattern of neutropenic fever has changed over the last 20 years, and the distribution and resistance rate of causative microorganisms are known to differ by region, antibiotic prophylaxis, and the use of catheters [2].

The aim of this study was to investigate the epidemiology of infectious diseases and the patterns of resistance and antibiotic therapy in febrile neutropenic patients, and to develop and suggest empirical treatment guidelines for neutropenic fever that fit the circumstances in Korea through both a foreign literature review and a multidisciplinary study. These guidelines are for adults and refer to data published in Korea. These guidelines are also applicable to other diseases associated with neutropenia, anticancer therapy of malignant tumors, and hematopoietic stem cell transplantation (HSCT) recipients.

Organization of a guideline-development committee

In June 2009, the committee for the development of “Guidelines for the Empirical Therapy of Neutropenic Fever Patients based on Literature in Korea” was organized by receiving recommendations from committee members from eight academic societies under the supervision of the National Evidence-based Healthcare Collaborating Agency (NECA): the Korean Society of Infectious Diseases (KSID), the Korean Society for Immunocompromised Host Infections (KSIHI), the Korean Cancer Association (KCA), the Korean Society of Clinical Microbiology (KSCM), the Korean Society of Blood and Marrow Transplantation (KSBMT), the Korean Society of Hematology (KSH), the Korean Society for Chemotherapy (KSC), and the Korean Society of Clinical Oncology (KSCO). The committee consists of five infectious diseases physicians, four hematology-oncology physicians, one laboratory medicine physician, one NECA internist, and one methodologist.

Literature search

For a systematic literature review, the latest guidelines of Infectious Diseases Society of America (IDSA) [2], National Comprehensive Cancer Network (NCCN) [3], the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO) [4-13], the First European Conference on Infections in Leukaemia (ECIL-1) [14-18], Asia-Pacific [19], and Japan [20-27] were collected. To search the literature published after the publication of the IDSA guidelines (2002), which are relatively widely used, the PubMed (www.pubmed.gov) search engine was used. The search period was from January 2002 to October 2009. Search entries for neutropenia were “neutropenia,” “granulocytopenia,” and “leukopenia.” The search entries for tumor were “cancer,” “malignancy,” “neoplasm,” “leukemia,” “lymphoma,” “hematologic” and the combination of “stem or marrow” AND transplantation.” Literature regarding fever and antibiotic therapy were searched by combining “fever or febrile,” “anti-infect*,” “anti-bacter*,” “anti-microb*,” “anti-bio*,” “anti-fung*,” and “anti-vir*.” To find Korean studies published in foreign journals, the Korean literature was also searched through the PubMed engine.

Major reports published in Korea over the last 10 years were searched through the database of Korean Studies Information (http://kiss.kstudy.com) and KoreaMed (http://www.koreamed.org). Search entries were combination of “neutrophil” or “granulocyte,” “fever” and “infection” by Korean letters. Reports before 2000 were collected if they were considered to be related to the development of this treatment guideline. Related literature was added by searching references of the collected literature, manually if necessary. The searched Korean literature totaled 39 reports (4 review articles and 35 original articles). In total, 218 references are cited; 27 were from the Korean literature.

Formulation of key questions

To create empirical treatment guidelines for febrile neutropenic patients, the following major categories were selected: definition of neutropenia and fever, initial evaluation and risk of infection, antibiotic prophylaxis, initial antibiotic therapy for febrile neutropenic patients, re-evaluation after 3-5 days and change of antibiotics, use of glycopeptides, catheter-related infections, and antifungal therapy.

The subcommittee of infectious diseases specialists formulated key questions in each area. Key questions were determined by reviewing foreign treatment guidelines and recommendations that could cause problems in Korean circumstances.

Consensus

Recommended answers to the key questions were based on major guidelines and literature, and the final version of