

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

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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 with a broad-spectrum antibiotic 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,

These guidelines will be also published in *Infection and Chemotherapy* in the Korean language. This secondary publication has been allowed by the editors of both journals.

These guidelines were made by the committee "Guidelines for the empirical therapy of neutropenic fever patients based on literature in Korea" under the supervision of the National Evidence-based Healthcare Collaborating Agency. These could be different from those of Korean Society of Internal Medicine.

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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 "neutrop*nia," "granulocytopenia," and "leukopenia." The search entries for tumor were "cancer," "malignancy," "neoplasm," "leukemia," "lymphoma," "hematolog*" 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-bacteri*," "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

these recommendations was made by a consensus of the guideline development committee.

Strength of recommendations and quality of evidence

For strength of recommendations and quality of evidence, the methods used in the latest guidelines of IDSA were accepted (Table 1) [28].

Evaluation by external specialists

Questionnaire survey

To evaluate the key questions and recommended answers given by a consensus of the committee for the development of these guidelines, a questionnaire survey on the guidelines was performed. The questionnaire asked whether each recommendation could be accepted in Korea and whether the strength of each recommendation was graded appropriately.

The subjects of the questionnaire survey were infectious diseases physicians and hematology-oncology physicians to enhance its specialty, and physicians in general hospitals operating HSCT centers around the nation to ensure representativeness.

Symposia of related academic societies

The final treatment guidelines, which reflected opinions from the internal review and the questionnaire survey, were presented in symposia of major related societies through 2010. Additionally, its revision and spread are planned after acceptance of opinions of and evaluations by

various specialist groups.

DEFINITION OF NEUTROPENIA AND FEVER

Fever is defined as an increase in body temperature to over 38.0°C, using a tympanic thermometer, or to over 37.5°C, using an axillary thermometer. If the tympanic or axillary temperature is thought to be inaccurate or the oral temperature is mainly measured, fever is defined as an increase in a single oral temperature to over 38.3°C or to over 38.0°C for more than 1 hour.

Neutropenia is defined as an absolute neutrophil count less than 500/mm³ or expected to be less than 500/mm³ within 2-3 days.

Major foreign guidelines, including those of IDSA and NCCN, define fever as an increase in oral temperature to over 38.3°C once or to 38.0°C for more than 1 hour [2,3,11,19,22]. In the questionnaire survey conducted with 33 medical staff members in 28 hospitals in Korea, 79% of the respondents answered that fever was defined as an increase in body temperature in two locations to over 38.0°C or an increase in body temperature to over 38.0°C for 1-2 hours [29]. Only two respondents (6%) measured oral temperature, and 31 (94%) said that they measured axillary or tympanic temperature [29]. Thus, the definition of fever using tympanic or axillary temperature, as stated in the guidelines developed by a consensus of specialists in Asia-Pacific countries, is more pragmatic in Korea [19].

Table 1. Definition of strength of recommendation and quality of evidence

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial.
II	Evidence from ≥ 1 well-designed clinical trial, without randomization, from cohort or case-controlled analytic studies (preferably from > 1 center), from multiple time-series, or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Adapted from the Canadian Task Force on the Periodic Health Examination [28].

The correlation between tympanic and core temperatures has been well studied [30,31], and a correlation in febrile neutropenic patients has also been reported [32]. Notably, even in patients with no or only mild fever, the oral temperature may read higher than the actual temperature in the presence of oral mucositis [33].

When the neutrophil count is reduced to less than 500/mm³, the risk of infection is increased [34]. In a study on the neutrophil count, measured at the time of fever, and the frequency of infection in leukemia patients undergoing chemotherapy, over 70% of febrile patients showed a neutrophil count of less than 500/mm³; furthermore, fever with a lower neutrophil count was caused by infection in more cases [35]. A questionnaire survey involving Korean medical institutions also revealed that 31 (94%) of the respondents used the same aforementioned definition [29].

INITIAL EVALUATION

Fever in neutropenic patients can be caused not only by bacterial or fungal infection, but also by non-infectious causes, such as drugs, blood transfusions, and the use of granulocyte colony stimulating factor. Because infection in neutropenic patients proceeds rapidly and symptoms or signs of an inflammatory response are rarely observed even in cases of infection, a close initial evaluation is necessary [36].

The initial evaluation of suspected febrile neutropenic patients should focus on determining possible causative sites or microorganisms. As soon as a patient is admitted to a hospital, a history should be taken, a physical examination should be conducted, and blood and other specimens should be collected for bacterial and fungal cultures.

A thorough history should include information on associated disease (s), currently used drug (s), the latest anticancer therapy, and whether a family member currently has an infectious disease. Decisions should be made regarding whether to hospitalize the patient and/or to use prophylactic antibiotics.

The physical examination should evaluate common sites of infection, such as the oral mucosa, paranasal sinuses, ear, chest, abdomen, skin, nails, groin, anal and vaginal areas, vascular catheter insertion sites, and bone marrow biopsy sites [2,3]. It is important to pay attention to even small symptoms and signs, including mild pain

or tenderness at these sites [2]. Initial blood tests should include a complete blood cell count, differential blood count, blood urea nitrogen, creatinine, electrolytes, total bilirubin, and a liver function test. If necessary, based on symptoms, an arterial blood gas analysis or urinalysis should also be conducted.

Microbiological cultures should be performed before the administration of antibiotics. At least two pairs of blood cultures should be conducted. When a central venous catheter is present, culture of blood collected through the catheter is recommended. Some specialists insist that unless the differential time to positivity is calculated, specimens from a central venous catheter alone can be cultured without peripheral venous samples because catheter-related infection may occur [3].

In cases with no sign or symptom of infection, specimens from the nasal cavity, oropharynx, urine, stool, and rectum do not need to be cultured, except for the purpose of hospital-related infection control [2,3]. However, stool cultures and *Clostridium difficile* toxin assays can be conducted for patients with diarrhea, and rotavirus or norovirus infections can be checked in the winter and during epidemic periods. Urine culture is recommended when there are symptoms of urinary tract infection, when a urethral catheter has been inserted, or when a urinalysis reveals abnormal findings. Although a colony-stimulating factor (CSF) examination is not absolutely necessary, it should be conducted in cases with symptoms of central nervous system infection. The presence of hemorrhagic tendencies and thrombocytopenia should be evaluated and, if necessary, appropriate interventions, such as transfusions, should be performed before the examination. For newly observed skin lesions or those of unknown causes, biopsies should be conducted and the results of microbiological cultures and histopathological findings should be evaluated. In cases with bullous lesions on the mucous membranes or skin, the presence of herpes simplex virus (HSV) infection should be determined. If a respiratory manifestation is present, a chest X-ray should be taken. Additionally, even with no symptoms, basal chest X-rays are recommended for comparison with future images when respiratory symptoms are present. Although there may be no abnormality on chest X-rays because there is no inflammatory response in neutropenic patients, approximately half of these patients can show evidence of pulmonary infiltration on chest computed tomography (CT) images [2,37].

RISK OF INFECTION

To determine the risk of serious infectious diseases in febrile neutropenic patients, the risk index of the Multinational Association for Supportive Care in Cancer (MASCC) can be used. A patient with a total score of 21 points or above is classified as low-risk [38]. Since the 1980s, many studies identifying patients who can be treated with oral antibiotics or as outpatients have been conducted by classifying their risk [38-41]. The MASCC risk index was developed through a prospective study by scoring weights based on factors influencing the prognosis of neutropenic fever using various factors, such as age, gender, underlying disease (s), the therapeutic condition of a cancer, associated disease (s), history of treatments for previous infectious diseases, and blood test results, in 1,139 subjects from 15 countries [38]. When the MASCC risk index score of 21 points or above was classified as the low-risk group, the positive and negative predictive values of no serious complications of neutropenic fever were 94% and 39%, respectively. NCCN differentiates between low- and high-risk groups by adding clinically important factors not included in the MASCC risk index [3]. A study analyzing the risk of severe complications or death caused by infection in Koreans has also been reported. Among the factors that could be initially assessed in febrile neutropenic patients visiting the emergency department, the risk factors of a continuous fever lasting 3 or more days were a visit within 10 days after the last anticancer therapy and newly observed pulmonary infiltration. Risk

factors of septic shock were a change in consciousness and a creatinine clearance of less than 75 mL/min, and those of death were tachycardia, reduced creatinine clearance, a change in consciousness, and an associated pathogenic condition. Additionally, duration of neutropenia was significantly related with the mortality rate and incidence rate of septic shock [42]. The risk factor of death due to acute leukemia during a hospital stay in patients undergoing anticancer therapy was a previous or current fungal infection [43].

ANTIBIOTIC PROPHYLAXIS

Is antibiotic prophylaxis necessary for expected febrile neutropenic patients?

1. Antibiotic prophylaxis is recommended for patients at intermediate-to-high risk of infection (A-I).
2. Fluoroquinolones are recommended as prophylactic antibacterial agents (A-I).

Because neutropenic patients have a high risk of infection, antibiotic prophylaxis can be helpful. However, if antibiotic prophylaxis is applied to all neutropenic patients, including those at a relatively low risk of infection who do not need it, antibiotic-resistant bacteria may emerge and excessive medical costs may be incurred. Thus, it is important to determine which patients will be most helped by antibiotic prophylaxis and the appropriate period for

Table 2. Overall infection risk in cancer patients by type of disease or therapy

Overall infection risk	Disease or therapy examples	Antimicrobial prophylaxis
Low risk of infection	Anticipated neutropenia < 7 days Standard chemotherapy regimens for most solid tumors	Bacterial: none Fungal: none Viral: none, unless prior HSV episode
Intermediate risk of infection	Anticipated neutropenia 7-10 days Autologous HSCT Lymphoma Multiple myeloma Chronic lymphocytic leukemia Purine analog therapy: fludarabine, clofarabine, nelarabine, 2-CdA	Bacterial: consider fluoroquinolone prophylaxis Fungal: consider prophylaxis Viral: during neutropenia, at least 30 days after HSCT
High risk of infection	Anticipated neutropenia greater than 10 days Allogeneic HSCT Acute leukemia: induction, consolidation Alemtuzumab therapy	Bacterial: consider fluoroquinolone prophylaxis Fungal: consider prophylaxis Viral: during neutropenia, at least 30 days after HSCT

HSV, herpes simplex virus; HSCT, hematopoietic stem cell transplantation; 2-CdA, 2-chlordexoyadenosine (also known as cladribine).

prophylaxis. Patients for whom prophylactic antibacterial, antifungal, or antiviral treatment is recommended are shown in Table 2 [3].

While past studies on antibiotic prophylaxis mainly used sulfamethoxazole/trimethoprim, many studies conducted since the late 1990s have used fluoroquinolones. According to a meta-analysis on the use of prophylactic antibacterial agents [44], the group using prophylactic antibacterial agents showed a lower mortality rate following infection and a lower total mortality rate compared with those not using prophylactic antibiotics or using placebo; the effects in the fluoroquinolones group were particularly evident. Another meta-analysis reported that fever, infection caused by Gram-negative bacteria, microbiologically documented infection, and total infection occurred less in patients using prophylactic fluoroquinolones than in those using sulfamethoxazole/trimethoprim or placebo. However, even prophylaxis using fluoroquinolones did not reduce Gram-positive bacterial infection, fungal infection, or the mortality rate [45]. Additionally, although there was concern about the emergence of antibiotic-resistant bacteria in the group using prophylactic antibacterial agents, resistance was not increased in the fluoroquinolone group. However, some reports have stated that resistant Gram-negative bacteria increased during fluoroquinolone prophylaxis, and this tendency improved after discontinuation of the prophylaxis; close attention to this is necessary [46]. That is, evidence for the use of prophylactic antibacterial agents such as fluoroquinolones exist in intermediate-to-high risk groups, but the long-term effects of antibiotic prophylaxis have not yet been fully determined; the emergence of resistant bacteria should be continuously monitored and antibiotic prophylaxis should be optimized in each hospital.

Ciprofloxacin or ofloxacin, which were widely used for prophylaxis in the past, had good antimicrobial activities against Gram-negative bacteria but relatively poor activities against Gram-positive bacteria. Studies using levofloxacin showed outstanding antimicrobial activity against Gram-positive bacteria as a prophylactic antibacterial agent for solid tumor and lymphoma patients [47] and solid tumor, lymphoma, and acute leukemia patients [48]. Both were large-scale studies that included over 300 subjects in each group. Infection caused by Gram-positive bacteria or bacteremia that was not prevented by fluoroquinolones decreased in the levofloxacin group. Although infection caused by Gram-negative bacteria was also significantly decreased, the

total mortality rate and the mortality rate due to infection were not significantly different between the two groups.

In Korea, a study was performed on the effects of prophylactic antibacterial agents in acute leukemia patients undergoing anticancer therapy [49]. The study used ciprofloxacin and roxithromycin for prophylaxis, and the patients using these prophylactic antibacterial agents showed fewer Gram-negative bacterial infections, but more Gram-positive bacterial infections. Additionally, the total infection rate and the mortality rate following infection did not differ between the two groups. As of 2010, the hospital does not use prophylactic roxithromycin.

Until when should antibiotic prophylaxis be used?

3. Antibacterial prophylaxis is administered until neutrophil recovery (absolute neutrophil count 500-1,000/mm³) (B-III).

Because there has been no prospective clinical study comparing the effect of the same drug for different periods to determine the proper administration period of prophylactic antibacterial agents, it is difficult to determine the appropriate end point of antibacterial prophylaxis. Most previous studies that showed effective outcomes of antibacterial prophylaxis used antibacterial agents from the beginning of anticancer therapy or within 48-72 hours after anticancer therapy until recovery of the absolute neutrophil count, and there was no difference in the preventive effects based on the administration period [48,50-53].

Is antifungal prophylaxis necessary?

4. Antifungal prophylaxis is recommended to prevent fungal infections in patients whose neutropenia is expected to last for more than 7 days. Appropriate antifungals for this purpose include posaconazole (A-I), fluconazole (B-I), itraconazole oral solution (B-I), low-dose amphotericin B deoxycholate (B-I), and low-dose liposomal amphotericin B (C-II).
5. Antifungal prophylaxis is recommended to prevent fungal infections in allogeneic HSCT recipients. Appropriate antifungals for this purpose include posaconazole (A-I), fluconazole (A-I), micafungin (B-I), and itraconazole intravenous injection followed by itraconazole oral solution (B-I).

When prolonged neutropenia is expected, such as

in patients undergoing remission induction therapy or maintenance/consolidation therapy due to a hematologic malignancy or those receiving allogeneic HSCT, antifungal prophylaxis is recommended [2,3]. Azoles have been widely used as prophylactic antifungal agents because of their favorable costs, adverse reaction profiles, and they allow the selection of other therapeutic antifungal agents for breakthrough fungal infections during antifungal prophylaxis.

A meta-analysis on antifungal prophylaxis revealed that the total mortality rate (relative risk [RR], 0.84; 95% confidence interval [CI], 0.74 to 0.95), fungus-related mortality rate (RR, 0.55; 95% CI, 0.41 to 0.74), invasive fungal infection, definite invasive fungal infection, definite invasive *Candida* infection, and the use of empirical antifungals decreased in the group using prophylactic antifungal agents compared with the groups not using prophylaxis or using a placebo [54]. Although fluconazole as a prophylactic antifungal agent tended to increase invasive aspergillosis, antifungal agents with specificity for filamentous fungi, such as itraconazole, resulted in less invasive aspergillosis infections [54].

Many studies have been performed on fluconazole, which has been shown to be very effective. Prophylaxis using 400 mg fluconazole per day reduced invasive fungal infections and the infection-related mortality rate in allogeneic HSCT recipients [55,56]. However, some reports stated that fluconazole did not significantly prevent invasive fungal infection in acute leukemia or autologous HSCT patients [57-59]. Additionally, studies using less than 400 mg prophylactic fluconazole per day did not find any significant difference in invasive fungal infections or mortality rates [60-62].

Itraconazole has antimicrobial activity against *Aspergillus* species and its preventive effect is thought to be superior to that of fluconazole; however, a study that directly compared fluconazole and itraconazole showed no significant differences in the all-cause mortality rate, fungus-related mortality rate, definite invasive fungal infection, invasive *Candida* infection, or superficial fungal infection [63-69]. When the efficacy of itraconazole was compared with that of fluconazole, limiting the studies to those using itraconazole oral solution, not the capsule, invasive fungal and *Candida* infections were decreased significantly [65-69]. The combination of itraconazole with vincristine or cyclophosphamide should be avoided because of the potential for drug interactions, and the administration of itraconazole should be performed

cautiously in patients with a history of heart failure or lower cardiac output because of its cardiotoxicity [70] (intravenous itraconazole is not approved as a prophylactic antifungal agent by the Korea Food and Drug Administration [KFDA] as of 2009).

Posaconazole oral solution has a wide range of antifungal activity against *Candida* and filamentous fungi [71,72]. An assessment of the effect of prophylactically administered posaconazole in acute myelogenous leukemia and myelodysplastic syndrome patients found that proven or probable invasive fungal infection and invasive aspergillosis were observed less and the survival rate was significantly higher in the posaconazole group than in the fluconazole or itraconazole groups. However, a higher frequency of adverse reactions was found, including increases in bilirubin and liver enzyme levels [73] (posaconazole is approved as a prophylactic antifungal agent for neutropenic fever by the KFDA, but is not on the market and is purchased through the Korea Orphan Drug Center as of 2009).

A study that compared micafungin and fluconazole as prophylactic agents in 882 allogeneic or autologous HSCT recipients reported that the success rate of prophylaxis (80.0% vs. 73.5%; 95% CI, 0.9 to 12) was higher and the frequency of invasive aspergillosis was lower in the micafungin group; however, the mortality rate was not significantly different between the two groups [74]. Moreover, no significant difference was found in the frequency of adverse reactions or the discontinuation rate between the two groups. However, a limitation of this study was that over 70% of the subjects were autologous HSCT or low-risk allogeneic HSCT recipients. A recent study insisted that the incidence of fungal infection was not significantly different between micafungin and fluconazole groups [75].

Although low-dose amphotericin B deoxycholate (0.2 mg/kg/day or 0.5 mg/kg 3 times per week) showed much better preventive effects than fluconazole, it is difficult to use in many cases because of its toxicity [76,77]. Because the amphotericin B lipid formulation has less toxicity than amphotericin B deoxycholate, studies on its use to prevent neutropenic fever have been conducted. Although a preventative effect of 50 mg (low-dose) liposomal amphotericin B was not observed in previous small-scale studies [78-80], recent large-scale studies found that it decreased invasive fungal infection and infection-related mortality rates [81]. Inhalation of amphotericin B deoxycholate has also been attempted to prevent

pulmonary fungal infection [82-84].

In Korea, a study investigated the effects of itraconazole oral solution and fluconazole as prophylactic agents and showed that the preventative effects of the two drugs were not significantly different [85]. However, administration compliance was lower due to gastrointestinal adverse reactions in the itraconazole group.

Until when should antifungal prophylaxis be used?

6. Use of prophylactic antifungal agents should be considered at least until neutrophil recovery (absolute neutrophil count 500-1,000/mm³) (B-III).
7. Use of prophylactic antifungal agents should be considered until the discontinuation of immunosuppressants if immunosuppressants are used after allogeneic HSCT (B-III).

Although it is difficult to find studies with reliable evidence for the determination of the end point of antifungal prophylaxis, they are generally administered until recovery of absolute neutrophil counts occurs [55,57,59,62,79,81,86-93]. However, allogeneic HSCT recipients may require antifungal prophylaxis even after neutrophil recovery, and NCCN recommends continuing prophylaxis until 75 days after HSCT [3]. Additionally, when graft versus host disease (GVHD) is observed, the period of antifungal prophylaxis can be extended. A recent large-scale study reported that an average of 112-day prophylactic posaconazole therapy effectively prevented invasive fungal infection in patients with GVHD [94].

Does *Pneumocystis jirovecii* need to be prevented?

8. Prophylaxis against *P. jirovecii* is recommended in allogeneic HSCT recipients (A-I).
9. Use of prophylaxis against *P. jirovecii* should be considered in cases of autologous HSCT, high-dose corticosteroid therapy (e.g., the equivalent of 20 mg/day or more of prednisone for 4 weeks or more), administration of T-cell-depleting agents, such as fludarabine (B-II) or anticancer therapy due to acute leukemia (e.g., acute lymphocytic leukemia) (B-III).
10. Use of sulfamethoxazole/trimethoprim (A-I) is recommended for prevention of *P. jirovecii*. If the patient is intolerant to the drug, consider using dapsone or aerosolized pentamidine (B-II).

Sulfamethoxazole/trimethoprim can be used to prevent *P. jirovecii* in acute leukemia patients and HSCT

recipients, and its preventive effect is excellent [95-97]. A meta-analysis on the prevention of *P. jirovecii* in immunocompromised patients (with the exception of human immunodeficiency virus [HIV] patients) showed that the *P. jirovecii*-related mortality rate was significantly reduced in the sulfamethoxazole/trimethoprim group (RR, 0.17; 95% CI, 0.03 to 0.94) [96,97]. Because *P. jirovecii* infection is known to increase in patients using alemtuzumab or fludarabine because of chronic lymphocytic leukemia or lymphoproliferative disorders [98-100], prevention of *P. jirovecii* can be considered. For this, 160/800 mg or 80/400 mg sulfamethoxazole/trimethoprim is administered, and if there is a concern about adverse events, such as bone marrow suppression, 160/800 mg is administered every other day. When the drug was used every other day, its preventive effect did not differ from that of daily administration (RR of pneumonia, 0.82; 95% CI, 0.61 to 1.09). Significantly more patients who took the drug daily discontinued it due to adverse reactions (RR, 2.14; 95% CI, 1.73 to 2.66) [101]. However, these results should be interpreted carefully because the study was performed not with neutropenic patients, but with HIV infection patients. If sulfamethoxazole/trimethoprim is difficult to administer because of leukopenia, dapsone or aerosolized pentamidine can be used [102]. However, dapsone and aerosolized pentamidine produce a weaker preventive effect against *P. jirovecii* than sulfamethoxazole/trimethoprim and can lead to additional infections and a higher mortality rate following infection [103].

Is antiviral prophylaxis necessary?

11. Antiviral prophylaxis against HSV is advised in HSV-seropositive patients in the case of allogeneic HSCT (A-I), autologous HSCT at high risk for mucositis (A-II), induction or re-induction therapy for acute leukemia (B-I), or the use of T-cell-depleting monoclonal antibodies (e.g., alemtuzumab) (B-II).
12. Consider using prophylactic antiviral agents in consecutive chemotherapy if HSV was reactivated in the previous chemotherapy (B-III).
13. Acyclovir or valacyclovir is recommended for the prevention of HSV (A-I).

If antiviral prophylaxis against HSV is not conducted for allogeneic HSCT recipients, approximately 62-80% of HSV IgG-seropositive patients show reactivation of the virus, while only 1-1.5% of HSV IgG-seronegative patients

experience viral reactivation [104,105]. For autologous HSCT, a lack of antiviral prophylaxis leads to lesions caused by HSV in approximately 2-6% of cases [106-108]. Thus, antiviral prophylaxis is recommended for HSV-seropositive patients among allogeneic HSCT recipients and autologous HSCT recipients with a high risk of mucositis [3]. According to a study performed in the early 1990s, the antibody-positive rates of HSV type 1 were 100%, 91%, and 82% in populations aged over 30 years, in their 20s, and in their teens, respectively, in Korea. Antiviral prophylaxis is advised in most cases in this country [109].

A meta-analysis on studies using acyclovir to prevent reactivation of HSV revealed that lesions caused by HSV and its isolation rate were significantly decreased in the acyclovir group [110,111]. However, the mortality rate was reduced only when prophylactic antiviral agents were used during engraftment after allogeneic HSCT [111]. Recent studies using valaciclovir, which is more easily administered than acyclovir, reported that the development of HSV lesions was not significantly different between acyclovir and valaciclovir groups [112,113]. Antiviral prophylaxis is generally used until the completion of engraftment or the improvement of mucositis (approximately 30 days in most cases) [114,115].

Although varicella-zoster virus is frequently observed in patients undergoing anticancer therapy, it is not mentioned in these guidelines because it is beyond the scope of empirical therapy for neutropenic fever.

INITIAL ANTIBIOTIC THERAPY

Because infection proceeds rapidly and discrimination between the early stages of bacterial infection and noninfectious fever is difficult in neutropenic patients, empirical antibiotics should be initiated immediately after the development of fever in all neutropenic patients. Even when a fever is not present, symptoms and signs causing a reasonable suspicion of infection require empirical antibiotics, as in febrile patients.

What are the major etiological agents of neutropenic fever in Korea?

14. In contrast to western countries, Gram-negative bacteria are the prevailing etiological agents of infections in neutropenic fever patients in Korea.

15. Adjustment of empirical antibiotics may be necessary depending on the resistance patterns in each hospital because the reported antimicrobial resistance rates of the bacteria causing neutropenic fever vary widely by hospital.

The distribution of etiological agents of neutropenic fever in studies published in Korea over the last 10 years is shown in Table 3. While Gram-positive bacteria account for 60-70% of microbiologically documented infection in Europe and America, Gram-negative bacteria were more frequently observed in studies in Korea until the early 2000s. This is a general characteristic in the Asia-Pacific region, including China, Taiwan, Thailand, and Malaysia [19]. Among Gram-positive bacteria, *Streptococcus* and coagulase-negative *Staphylococcus* are the most frequently observed, and *Staphylococcus aureus* and *Enterococcus* are next. Among Gram-negative bacteria, *Escherichia coli* is found most frequently, and *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* follow it.

Little data regarding antimicrobial susceptibility to etiological agents has been reported in Korea, and the reported resistance rates vary. The rate of methicillin-resistant *S. aureus* (MRSA) and those of fluoroquinolone-resistant and third-generation cephalosporin-resistant *E. coli* were 38-77%, 16-93%, and 0-7.0%, respectively [116-118]. Thus, each hospital needs to choose early empirical antibacterial agents by considering the types of frequently detected bacteria and their susceptibilities. For example, ciprofloxacin combination therapy is difficult to use as an early empirical antibacterial agent in hospitals showing a high fluoroquinolone resistance rate. Additionally, these guidelines do not recommend glycopeptides as early empirical antibacterial agents, but their partial use can be considered in hospitals with high MRSA rates. These guidelines describe general recommendations, and antibacterial agents not mentioned in these guidelines can also be empirically used according to types of detected bacteria and their susceptibilities in each hospital.

Table 3. Distribution of bacterial organisms in patients with neutropenic fever in Korea

Reference	Rho et al. [119]	Rhee et al. [120]	Choi et al. [116]	Kim et al. [121]	Park et al. [118]
Period	1996-2001	1996-2003	1998-1999	1999-2000	2001-2002
Hospital	A	B	C	D	C
Patients	Leukemia	Allo-HSCT	Acute leukemia	Cancer	HSCT
Prophylaxis	NA	Cotrimoxazole, nystatin gargle	Ciprofloxacin, roxithromycin, fluconazole	NA	Ciprofloxacin, fluconazole/ itraconazole, SMX/TMP
No. of MDI	27 (100)	78 (100)	158 (100)	42 (100)	72 (100)
Gram (+) bacteria	11 (40.7)	36 (46.2)	75 (47.5)	11 (26.2)	25 (34.7)
<i>Streptococcus</i>	1 (3.7)	-	24 (15.2)	2 (4.8)	9 (12.5)
CoNS	4 (14.8)	15 (19.2)	20 (12.7)	4 (9.5)	7 (9.7)
<i>Staphylococcus aureus</i>	4 (14.8)	-	13 (8.2)	3 (7.1)	2 (2.8)
<i>Enterococcus</i>	2 (7.4)	-	14 (8.9)	2 (4.8)	6 (8.3)
Gram (-) bacteria	16 (59.3)	42 (53.8)	83 (52.5)	31 (73.8)	47 (65.3)
<i>Escherichia coli</i>	4 (14.8)	-	43 (27.2)	2 (4.8)	32 (44.4)
<i>Pseudomonas aeruginosa</i>	1 (3.7)	-	12 (7.6)	5 (11.9)	4 (5.6)
<i>Klebsiella pneumoniae</i>	6 (22.2)	-	12 (7.6)	8 (19.0)	4 (5.6)
<i>Enterobacter</i>	-	-	5 (3.2)	4 (9.5)	3 (4.2)
<i>Acinetobacter baumannii</i>	2 (7.4)	-	-	2 (4.8)	2 (2.8)
<i>Aeromonas hydrophila</i>	1 (3.7)	-	6 (3.8)	-	-
<i>Citrobacter freundii</i>	-	-	-	2 (4.8)	1 (1.4)
Salmonella	-	-	-	4 (9.5)	-

Values are presented as number (%).

HSCT, hematopoietic stem cell transplantation; NA, not available; SMX/TMP, sulfamethoxazole/trimethoprim; MDI, microbiologically defined infection; CoNS, coagulase-negative *Staphylococcus*.

Outpatient oral antibiotics

When should oral antibiotics be used as the initial treatment for febrile neutropenic patients?

16. Oral antibiotics may be used for the initial treatment of febrile neutropenic patients if the risk of infectious complications is low (A-I).

Many randomized controlled studies have demonstrated that febrile neutropenic patients with low risks of complications may be treated with oral antibiotics [122-125]. Thus, if the risk of infectious complications is low, based on the risk index, oral antibiotics can be used for treatment. However, a survey conducted in Korea from 2005 to 2006 found that oral antibiotics were rarely used for the treatment of febrile neutropenic patients in Korea [29].

Outpatient treatments can be considered when febrile

neutropenic patients meet the following conditions: a fever does not begin during the hospital stay, acute diseases are not associated, neutropenia is expected to improve within 7 days, the general condition is good (ECOG 0-1), the serum creatinine level is less than 2.0 mg/dL, the liver function level is within 3 times the normal range, and the MASCC risk index is 21 points or more [3]. Additionally, access to a medical institution needs to be secured for patients to ensure early outpatient treatment.

Which oral antibiotics can be used empirically for the initial treatment of febrile neutropenic patients?

17. The combination of ciprofloxacin and amoxicillin/clavulanic acid is recommended as oral antibiotics for febrile neutropenic patients (A-I).
18. The combination of ciprofloxacin and clindamycin is an acceptable alternative as oral antibiotics for penicillin-allergic patients (A-II).

19. However, ciprofloxacin-based oral antibiotic regimens are not recommended for patients recently treated with fluoroquinolone prophylaxis (B-II).

Well-designed randomized studies have demonstrated that the combination of ciprofloxacin and amoxicillin/clavulanic acid was effective as empirical oral antibiotic therapy in febrile neutropenic patients in the low-risk group [122,124]. Penicillin-allergic patients can be treated with a combination of ciprofloxacin and clindamycin [126]. A randomized study found that ofloxacin was also effective in low-risk febrile neutropenic patients [125]. Levofloxacin was also estimated to have similar effects. Additionally, there are some reports that moxifloxacin can be effective in low-risk patients [127].

Although some small studies reported that ciprofloxacin monotherapy was acceptable [128,129], it has also been associated with the risk of serious infection caused by viridans streptococci and thus should be used carefully [130]. Fluoroquinolone-based oral antibiotic therapy is not recommended if fluoroquinolones have been used for antibiotic prophylaxis.

There are almost no studies on other oral antibiotics, such as cephalosporins, for the initial treatment of neutropenic fever, but they can be used according to frequently reported etiological bacteria and their susceptibilities. If the etiological bacteria are determined, various oral antibiotics can be appropriately used, based on their antimicrobial susceptibilities.

Intravenous antibiotics

Empirical antibiotics as initial therapy should be chosen by considering the susceptibilities of the bacteria detected in each hospital. For hospitals with high rates of resistant bacteria, such as MRSA and multiple-drug-resistant Gram-negative bacteria, appropriate antibiotics should be used based on the circumstances in each hospital. Additionally, these guidelines suggest generally recommended antibiotics, and antibiotics not mentioned in these guidelines can also be used properly if their effects are demonstrated.

Use of antibiotics against *Pseudomonas* is commonly recommended as an initial empirical antibiotic therapy. Other factors that should be considered in choosing initial empirical antibiotics for febrile neutropenic patients include the infection site (s), history of MRSA infection or colonization, organ dysfunction, history of the use of

antibiotics, and bactericidal effects of antibiotics.

Which intravenous antibiotics can be used as the initial monotherapy for febrile neutropenic patients?

20. Cefepime, imipenem/cilastatin, meropenem, or piperacillin/tazobactam is recommended as empirical monotherapy if the febrile neutropenic patient has no complications of infection (A-I).

21. Ceftazidime can be considered as empiric monotherapy if the febrile neutropenic patient has no complications of infection, but clinicians should be aware of the possibility of breakthrough infections (from Gram-positive bacteria or drug-resistant Gram-negative bacteria) (B-II).

No significant difference between antibiotic monotherapy and antibiotic combination therapy has been observed in febrile neutropenic patients without complications of infection in many randomized studies [131-140]. Antibiotics recommended for antibiotic monotherapy are cefepime, ceftazidime, imipenem/cilastatin, meropenem, and piperacillin/tazobactam [141,142]. Because ceftazidime is not effective against Gram-positive bacteria, such as viridans streptococci or pneumococci, and is vulnerable to extended-spectrum β -lactamase and type 1 β -lactamase, it should be used carefully [143]. Additionally, a clinical study found that the clinical effect of ceftazidime was lower than that of meropenem in cancer patients with neutropenic fever [144,145]. Thus, some professionals recommended the addition of cefazolin to ceftazidime to enhance the antibacterial activity against Gram-positive bacteria [146].

In a nationwide survey from 2005 to 2006, cefepime was used most frequently as a single antibacterial agent for neutropenic patients in Korea [29]. A recent meta-analysis revealed that cefepime could increase the mortality rate in neutropenic patients [147,148]. However, the US FDA found that the mortality rate of cefepime was not significantly different from that of the control group in an additional analysis. In Korea, a study compared cefepime monotherapy and ceftazidime + tobramycin combination therapy in 90 solid cancer patients with neutropenic fever; no significant difference was found in effects or complications between the two groups [149]. Moreover, a comparison between cefepime and ceftazidime monotherapy in 40 Koreans with cancer associated with neutropenic fever found no significant difference in the treatment success rate [150].

Because cefepime and ceftazidime can be used without dose adjustment in cases of mild or intermediate renal inadequacy, they are relatively safe for patients taking other drugs to treat renal toxicity. Aminoglycoside monotherapy is not generally recommended as an initial antibacterial monotherapy for febrile neutropenic patients [2].

Other antibiotics can be added to antibacterial monotherapy regimens according to clinical outcomes; thus, clinical responses to antibiotics, secondary infection, adverse reactions, and resistant bacteria should be evaluated carefully.

Which intravenous antibiotics (with the exception of glycopeptides) can be used as the initial combination therapy for febrile neutropenic patients?

22. An aminoglycoside + anti-pseudomonal penicillin (\pm β -lactamase inhibitor), or ciprofloxacin + anti-pseudomonal penicillin are recommended as the initial intravenous combination therapy for febrile neutropenic patients (A-I).
23. An aminoglycoside + an extended-spectrum cephalosporin (cefepime or ceftazidime) is also recommended as the initial intravenous combination therapy for febrile neutropenic patients (A-II).

Empirical combination therapy using an aminoglycoside and anti-pseudomonal β -lactam antibiotic (ticarcillin/clavulanic acid, piperacillin/tazobactam, ceftazidime, or cefepime), with the exception of glycopeptides, is recommended. A combination of a fluoroquinolone and anti-pseudomonal β -lactam antibiotic can be administered to patients not treated with prophylactic fluoroquinolones [151-155].

According to a survey in Korea, the most common antibiotic combination therapy for neutropenic patients was the combination of a third- or fourth-generation cephalosporin (ceftazidime or cefepime) and an aminoglycoside [29]. However, inclusion of an aminoglycoside can increase adverse reactions, such as renal toxicity, ototoxicity, and hypokalemia. Taking an aminoglycoside once daily is an alternative to maintain its therapeutic effect and to help reduce these adverse events [156,157]. However, for treatment of meningoencephalitis or endocarditis, administration of an aminoglycoside once per day is not recommended. When a patient has poor renal function, it is necessary to measure the blood aminoglycoside level and maintain it at an appropriate therapeutic level.

In cases associated with resistant bacteria or complications,

such as hypotension, combination therapy, rather than monotherapy, is recommended. In particular, clinically unstable febrile neutropenic patients with hypotension, tachypnea, newly developed or deteriorating tachycardia, changes in consciousness, decreased urine amounts, or organ dysfunction may require a combination of broad-spectrum β -lactam antibiotics (imipenem/cilastatin, meropenem, or piperacillin/tazobactam) and an aminoglycoside to extend the antibacterial spectrum and to obtain a synergistic effect against some Gram-negative bacteria. A study in Korea found that in 35 febrile neutropenic patients with shock, the most frequently observed etiological microorganism was Gram-negative bacteria (27 subjects, 77%); of these, *E. coli* was the most common [158]. Fig. 1 presents the algorithm for the initial management of febrile neutropenic patients.

RE-EVALUATION AFTER 3-5 DAYS AND CHANGE OF ANTIBIOTICS

To evaluate the effect of initial antibiotics, 3-5 days are needed [159]. At this time, future treatments are determined according to whether the patient has bacteremia or pneumonia, whether fever has improved, or whether the condition of the patient has deteriorated. If a patient's condition deteriorates within 3 days, the evaluation of empirical antibiotics can be advanced. However, because many studies have suggested that the period to defervescence in febrile neutropenic patients is 2-7 days (median 5 days), we can wait until 5 days have passed without changing the initial antibiotics if a bacterium is not grown in cultures and fever continues to be observed.

Patients without fever in 3-5 days

What should be done when initial empirical antibiotics are effective within 3-5 days?

24. If the causative organism is not found and initial empirical antibiotics seem to be effective after 3-5 days, the initial empirical antibiotics should be maintained until neutrophil recovery (A-II).

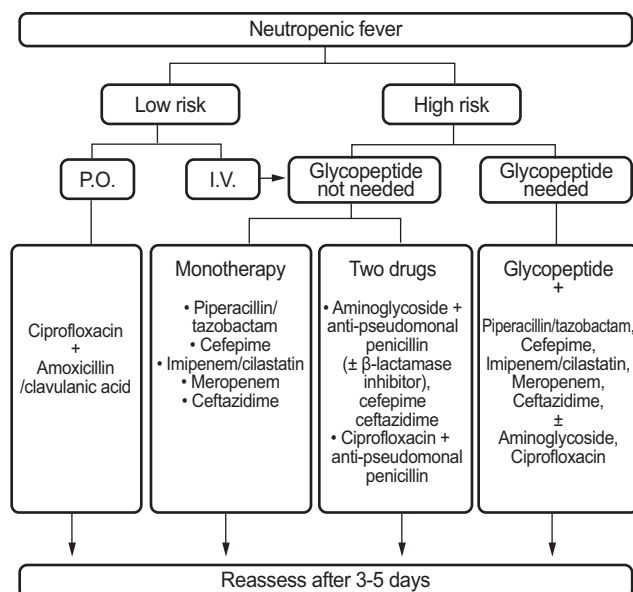


Figure 1. Algorithm for initial management of febrile neutropenic patients.

25. Maintain intravenous antibiotics until absolute neutrophil count recovery for patients who were in the high-risk group at the beginning of the administration of empirical antibiotics. For those in the low-risk group, consider changing to oral antibiotics (B-II).

When a patient's fever improves, symptoms and signs of infection are stable or improved, and hemodynamic levels such as blood pressure or pulse rates are stable, the initial antibiotics are considered to be effective [3]. Under the circumstances, if a causative organism is identified, more appropriate antibiotics can be used to decrease adverse reactions and treatment costs. However, to prevent newly developed bacteremia, it is recommended to maintain a broad antibacterial spectrum [2]. Antibiotics should be maintained for at least 7 days, and it is recommended to continue treatment until the causative organism is removed in cultures, until infections of all sites are cured, or until symptoms and signs in the patient are eliminated. Changing to oral antibiotics after intravenous antibiotics for the first 72 hours can be considered. A study in Korea reported that when ciprofloxacin was orally administered to 40 patients showing no clear evidence of infection, an increasing absolute neutrophil count and defervescence in 72 hours indicated successful treatment in 39 cases (98%) [160].

Although it is desirable to discontinue antibiotics after

the recovery of neutrophils to an absolute count of $> 500/\text{mm}^3$, the discontinuance of antibiotics can be considered even in the cases of absolute neutrophil counts of $< 500/\text{mm}^3$ if neutropenia is maintained without symptoms or signs of infection. However, this approach is available only when a patient can be monitored carefully, the mucous membranes and skin are normal (no inflammation of the mucous membranes, ulcers, evidence of catheter site infections, or hemorrhage), and neither invasive intervention nor anticancer therapy has been planned [2].

If fever is eliminated after 3-5 days but etiological bacteria are not identified, it is generally recommended to maintain the initial antibiotics until the recovery of neutrophils to an absolute count of $> 500/\text{mm}^3$. In cases with specific infection sites, the administration of antibiotics for an appropriate period based on the site is recommended. However, if there is no clear infection (pneumonia, enteritis, endocarditis, catheter-related infection, or skin or soft tissues infection) or no cultured bacteria, and if a patient is in the low-risk group at the beginning of the therapy, intravenous antibiotics for over 2 days can be replaced with oral antibiotics if clinically necessary [122,124]. However, patients in the high-risk group should continue intravenous antibiotics (Fig. 2).

Patients with fever in 3-5 days

When fever persists even after 3-5 days of antibiotic therapy and neither infection sites nor causative organisms are detected, reasons shown in Table 4 can be considered. Re-evaluation of the following is necessary: complete blood cell count, general chemistry, electrolyte test, C-reactive protein (CRP), urinalysis, results of all cultures, a close physical examination, chest X-ray, evaluation of any vascular catheter, additional cultures of blood and specimens from specific infection site (s), imaging studies on sites suspected to have infection (if possible), blood antibiotic levels (particularly aminoglycosides), and ultrasonography or CT for patients with pneumonia, paranasal sinusitis, or enteritis.

The current blood culture system can detect 90-100% of bacteria in blood within 48 hours of blood culture. Thus, it is recommended to repeat blood cultures at 48-hour intervals, as necessary.

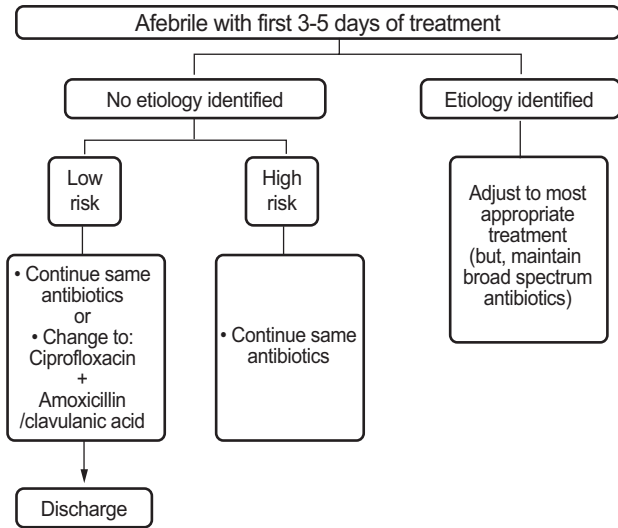


Figure 2. Algorithm for management of patients who become febrile in the first 3-5 days of initial antibiotic therapy.

What should be done if fever persists after 3-5 days?

- 26. If fever persists after 3-5 days of antibiotic therapy and reassessment does not yield a cause, continue administration of the same antibiotics when the patient’s condition is clinically stable (B-II).
- 27. However, if the patient is in an unstable condition, consider expanding the antibacterial spectrum to cover anaerobes, drug-resistant Gram-negative bacteria, or drug-resistant Gram-positive bacteria (B-II).
- 28. If the fever persists even after the use of empirical antibacterials, consider using antifungal agents, depending on the risk of infection (A-II).

If fever persists even after 3-5 days of the initial antibiotic therapy and its cause is not identified, one of following three measures can be taken (Fig. 3). First, if the condition of a patient is not unstable and no additional relevant information is obtained from re-evaluation, the initial antibiotics can continue to be administered. In particular, for patients who are expected to show recovery of neutrophils within 5 days, it may be appropriate to maintain the initial antibiotics. It is not recommended to change antibiotics when fever persists in a patient in stable condition.

Second, antibiotics can be changed or added. When a disease proceeds or complications or adverse drug reactions are observed with newly found or deteriorating abdominal pain or lesions of the mucous membranes, infection around

Table 4. Reasons for persistent fever 3-5 days after initiating antibiotic therapy

Reason
Nonbacterial infection (fungal, viral, or mycobacterial infection)
Resistance to antibiotics
Inadequate drug concentration
Drug fever
Bacteremia due to cell wall-deficient bacteria
Infection at an avascular site (such as an abscess)
Fever related to underlying malignancy
Intravascular catheter-related fever

a catheter, or changed mucous membrane flora, changing the initial antibiotics or adding another antibiotic should be considered. For these cases, cooperation with the infectious diseases specialists is recommended [3].

Third, antifungal agents can be added while changing or maintaining antibacterials. Generally, if fever persists after several days of empirical antibacterial use, it is necessary to consider the use of antifungal agents (see EMPIRICAL ANTIFUNGAL THERAPY section for details).

USE OF GLYCOPEPTIDES

Should glycopeptides be included in an empirical antibiotic regimen?

- 29. Glycopeptides should not be routinely added to an initial empirical antibiotic regimen (A-I).

Eighteen randomized studies have investigated whether glycopeptides should be added to an initial empirical antibiotic regimen. Of them, only two were double-blind randomized trials [17]. The largest was a multi-center study that included 747 subjects [161], and the smallest had only 46 subjects [162]. When the 747 neutropenic patients in the largest study were randomly divided into addition of vancomycin to ceftazidime + amikacin and no-addition groups, the vancomycin addition group showed faster responses in patients who were found to have bacteremia caused by Gram-positive bacteria; however, the addition group was not significantly different in terms of defervescence and mortality rate compared with the no-addition group. Furthermore, no patient died in the first 3 days among the patients with bacteremia caused by Gram-positive bacteria. However, renal toxicity following

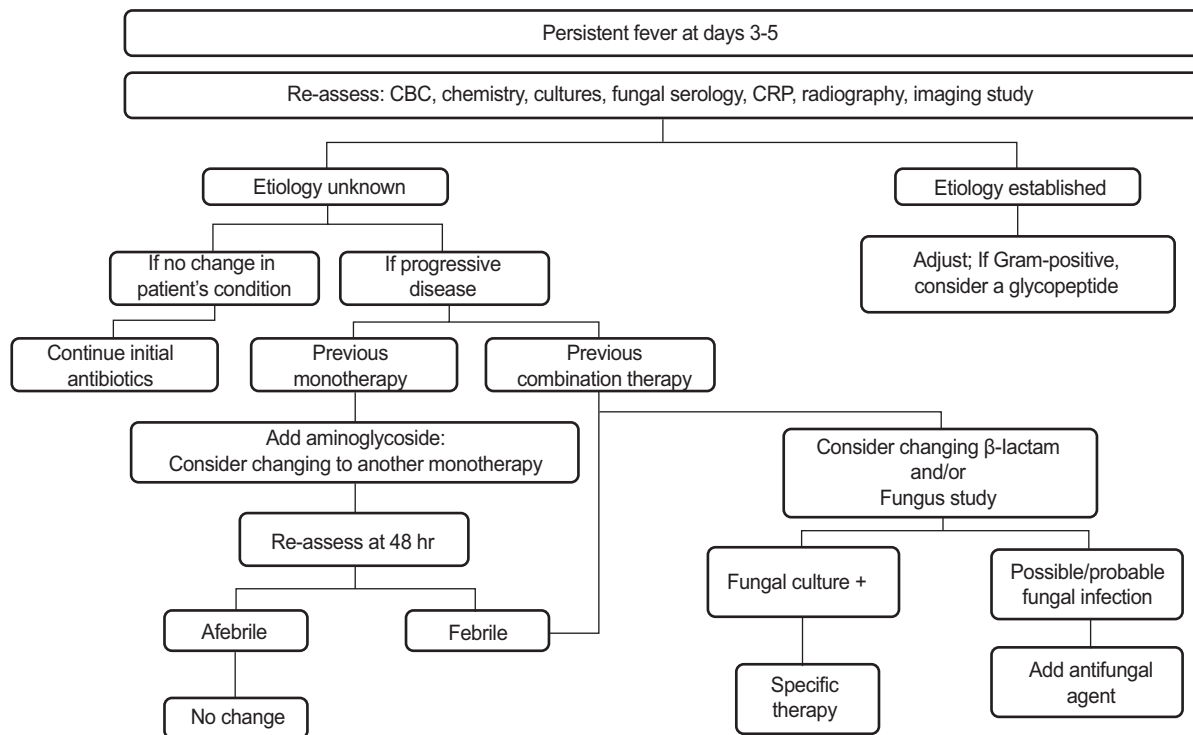


Figure 3. Algorithm for management of patients who have a persistent fever after 3-5 days of initial antibiotic therapy. CBC, complete blood count; CRP, C-reactive protein.

the use of antibiotics occurred in 2% of patients in the no-vancomycin group, but was significantly higher (6%) in the vancomycin group ($p = 0.02$) [161]. Recently, the results of two meta-analyses on the need for the administration of vancomycin as an initial empirical antibiotic regimen were reported [163,164]. One meta-analysis examined a total of 2413 patients by including 14 of 18 randomized studies [163]. It revealed that the addition of a glycopeptide did not significantly reduce the total mortality rate (odds ratio [OR], 0.67; 95% CI, 0.42 to 1.05). In particular, an analysis of 405 patients that included only six studies using the same broad-spectrum antibiotic showed the same finding (OR, 1.05; 95% CI, 0.52 to 2.00). The other meta-analysis investigated a total of 2392 patients by including 13 randomized studies [164]. It also found that the additional administration of a glycopeptide did not significantly decrease the total mortality rate (RR, 0.96; 95% CI, 0.58 to 1.26). For breakthrough infection, the first meta-analysis did not show any significant association with the use of glycopeptides with an OR of 1.18 (95% CI, 0.81 to 1.98) [163], while the second one found that breakthrough infection caused by Gram-positive bacteria was reduced, with a RR of 0.28 (95% CI, 0.11 to 0.37) [164]. However,

these findings should be interpreted carefully. All of the studies in the analysis were conducted from 1985 to 1993, before the emergence of vancomycin-resistant enterococci (VRE); thus, VRE breakthrough infection during the administration of vancomycin was not reflected [17]. Moreover, because viridans streptococci bacteremia can deteriorate rapidly, to streptococcal toxic shock syndrome, in neutropenic patients, there is a suggestion that the addition of vancomycin to an initial antibiotic regimen is favorable in hospitals with high penicillin resistance of viridans streptococci [165]. However, most β -lactam antibiotics (e.g., cefepime, imipenem/cilastatin, meropenem, piperacillin/tazobactam), except ceftazidime, have good antibacterial activity against viridans streptococci, so vancomycin is not likely to be of additional help unless ceftazidime monotherapy is used [166].

Although the frequencies of MRSA and VRE are high in Korea, there has been no randomized study on this issue. Only one retrospective study on MRSA bacteremia in not only neutropenic patients, but also others, reported that the addition of vancomycin to an initial antibiotic regimen did not significantly affect the prognosis [167]. According to data from an analysis of 457

febrile neutropenic patients in a university hospital for 10 years [158], *S. aureus* was identified in 10 (6%) of 172 patients with proven bacteremia, and 77% of them had MRSA. Although data on the rate of viridans streptococci bacteremia in febrile neutropenic patients are insufficient in Korea, approximately 5-7% of the total bacteremia was reported to show viridans streptococci [117,158]. The data on penicillin-resistance of viridans streptococci are also insufficient. One study reported that with the exception of pneumococcus isolated from neutropenic patients, 7 (36%) of 19 streptococci strains were penicillin-resistant [116]. While some researchers have reported that the antimicrobial susceptibility tests of 103 strains of viridans streptococci isolated from various clinical specimens in a university hospital found no penicillin resistance (although they were not from neutropenic patients) [158,168], others have insisted that of 45 strains isolated from blood, 27% were not susceptible to penicillin [169].

However, *S. aureus* bacteremia is rarely found as a causative organism of bacteremia for the first fever in neutropenic cancer patients after cytotoxic chemotherapy. Its rate was reportedly 1-2% in large-scale clinical studies [132,138,144]. Furthermore, the frequency of resistant bacteria, such as MRSA, is low for the first fever; bacteremia caused by Gram-positive bacteria does not deteriorate rapidly in cases of late initial treatment, unlike bacteremia caused by Gram-negative bacteria, and indiscriminate use of glycopeptides can lead to the emergence of resistant bacteria and nephrotoxicity. Thus, there is insufficient evidence to support the routine inclusion of glycopeptides in the initial antibiotic therapy for febrile neutropenic patients in Korea. Based on these findings, it is recommended not to routinely add vancomycin to the treatment regimen for febrile neutropenic patients in whom the cause has not been clearly determined (A-I).

30. When fever persists or recurs 3-5 days after the initiation of the empirical treatment, glycopeptides should not be routinely added to the empirical treatment (B-I).

Two randomized studies investigated whether the addition of a glycopeptide was effective if fever persisted for 3-4 days after beginning initial antibiotic therapy [170,171]. One study randomly administered vancomycin or placebo to 165 of 763 patients whose fever had not

improved within 3-4 days after the empirical use of piperacillin/tazobactam. The two groups were not significantly different in terms of defervescence, mortality rate, breakthrough infection, or the frequency of the use of amphotericin B deoxycholate [170]. This result was consistent with that of a recent meta-analysis (RR of treatment failure, 0.61; 95% CI, 0.18 to 2.09) [164]. Based on these findings, it is recommended not to routinely add glycopeptides when fever persists or recurs after 3-5 days (B-I).

31. The use of glycopeptides as empirical antimicrobial therapy is recommended if the patient's blood cultures are positive for Gram-positive bacteria, a catheter-related infection is suspected, there is colonization with MRSA or a history of MRSA infection, the patient has severe sepsis or shock pending the results of cultures, or the patient has a skin or soft tissue infection (A-II).

Studies on the detailed indications of glycopeptides as an initial empirical antibiotic regimen are not sufficient, but the indications consistently suggested by most specialists, including those who contributed to the IDSA and NCCN guidelines, are as follows:

1. Positive for Gram-positive bacteria in blood culture (A-II)
2. Suspected catheter-related infection (A-II)
3. History of MRSA and penicillin-resistant *S. pneumoniae* colonization or infection (A-II)
4. Severe sepsis or shock following sepsis (A-II)
5. Skin or soft tissue infection (A-II)

The following indications remain controversial among specialists:

1. Risk of viridans streptococci bacteremia (B-III)
2. Severe damage to the mucous membrane due to anticancer therapy (B-III)
3. Prophylaxis using sulfamethoxazole/trimethoprim or fluoroquinolone (B-III)

However, even after glycopeptides are administered according to the indications, the discontinuance of glycopeptides is recommended if bacteremia caused by resistant Gram-positive bacteria is not observed in blood cultures (A-I).

Are the efficacy and the adverse reactions of teicoplanin identical to those of vancomycin when a glycopeptide is used as an empirical antibiotic regimen for neutropenic patients?

32. The use of teicoplanin can be considered as empirical antibiotic therapy for neutropenic patients because it has equivalent efficacy and lower adverse reactions, such as nephrotoxicity, compared with vancomycin (B-I).

As of 2009, 18 randomized studies comparing the efficacy and adverse reactions of teicoplanin and vancomycin had been reported. Of these studies, 13 were performed with neutropenic patients. A meta-analysis on these randomized studies revealed that the mortality rates (RR, 0.95; 95% CI, 0.74 to 1.21) and clinical failures (RR, 0.92; 95% CI, 0.81 to 1.05) were not significantly different between teicoplanin and vancomycin [172]. Additionally, an analysis limited to the studies conducted in neutropenic patients found no statistically significant difference in the mortality rates (RR, 0.95; 95% CI, 0.68 to 1.34) or clinical failures (RR, 0.98; 95% CI, 0.83 to 1.16) between teicoplanin and vancomycin [172]. However, fewer adverse reactions were observed in the teicoplanin group compared with the vancomycin group (RR, 0.61; 95% CI, 0.50 to 0.74). In particular, nephrotoxicity was lower in the teicoplanin group than in the vancomycin group (RR, 0.44; 95% CI, 0.32 to 0.61) [172]. However, teicoplanin is not yet approved by the US FDA as an empirical antibiotic for MRSA infection and neutropenia, and clinical experience and research data on it in severe infections (e.g., endocarditis and encephal meningitis) are not sufficient compared with those for vancomycin. Moreover, previous randomized studies did not include many patients with MRSA infection itself [172]. As the minimum inhibitory concentration (MIC) of vancomycin against *S. aureus* has risen, treatment failures have been reported [173], and the vancomycin MIC and levels need to be measured in some cases. Data regarding the association between teicoplanin MIC and treatment failure are insufficient, and levels are difficult to examine; thus, it should be used carefully. Additionally, most studies have stated that the efficacy of teicoplanin was identical to that of vancomycin by taking it once daily after a loading dose [172], but some researchers recommend administering a high dose for infections with complications. Thus, the appropriate dose remains controversial [174].

DISCONTINUATION OF ANTIBIOTICS

When can antibiotic therapy be discontinued?

33. If the origin of the fever is unclear, it is recommended to continue antimicrobials until the absolute neutrophil count reaches 500/mm³ or higher (A-II).
34. If the causative organism or infection site has been identified, treatment duration is adjusted to the specific infectious disease in line with the recovery of neutrophils (A-II).

Duration of antibiotic therapy should be determined by considering the infection site, causative organism, general condition of the patient, treatment response, and neutrophil recovery [3]. If the origin of fever is unclear, antimicrobials should be maintained until the absolute neutrophil count reaches 500/mm³ or higher [3]. When the causative organism or the infection site has been identified, treatment duration should be adjusted to the specific infectious disease by considering the neutrophil recovery [3]. Because there is insufficient evidence regarding treatment duration for these clinical circumstances, this committee suggests general recommendations.

If the cause of fever is unclear

When the absolute neutrophil count is over 500/mm³, the fever has improved, and the patient is in a clinically stable condition, empirical antibiotic therapy should be discontinued (A-II). If the absolute neutrophil count is over 500/mm³, fever is persistent, and the patient is clinically stable, then the patient should be monitored for approximately 5 days and empirical antibiotic therapy should be discontinued for a differential diagnosis (e.g., drug fever, hepatosplenic candidiasis). If the absolute neutrophil count is less than 500/mm³ but the fever has improved and the patient is in a clinically stable condition, antibiotic therapy should be continued until neutrophil recovery (A-II). Patients in the low-risk group can be changed to oral antibiotics and therapy can be maintained until recovery of the absolute neutrophil count to over 500/mm³ occurs (A-II). However, some experts say that for a clinically stable patient whose absolute neutrophil count is expected not to recover, the cause of fever is not clear, and the fever does not persist for more than 7-14 days, empirical antibiotic therapy can be discontinued carefully (B-III).

If the cause of infection is identified microbiologically or clinically

For a microbiologically or clinically documented infection, antibiotic therapy for the treatment duration of a specific infection should be conducted as shown in Table 5.

CATHETER-RELATED INFECTIONS

Which examination is useful in the diagnosis of catheter-related infection?

35. If a catheter-related infection is suspected, a skin swab for culture from the exit site of the catheter and blood cultures from the catheter may be obtained (B-II).
36. The differential time to positivity is a useful diagnostic tool for detecting catheter-related infection (A-II).

Catheter-related infection is a common complication frequently observed in neutropenic patients [3]. Exit-site infection is defined as a local flare or induration within 2 cm of the exit of a catheter and tunnel infection is defined as a local flare or induration > 2 cm from the exit of a catheter, pus from the exit, or a local flare or induration along the tunnel [175]. If catheter-related infection is suspected, a skin swab for culture from the exit of the catheter should be obtained, and blood cultures from the catheter itself should be conducted [3]. Because the skin swab culture from the exit site has a low specificity for

catheter-related infection, but shows a high sensitivity, it can be useful for the exclusion of certain diagnoses [176]. Additionally, a study reported that blood cultures from both central venous catheters and peripheral blood, when performed by the automated blood culture systems used by many hospitals, could also measure the time for bacteria to grow initially. Furthermore, the differential time to positivity (DTP) or the difference between the two times was helpful for the diagnosis of catheter-related infection [3]. That is, when > 120 min of DTP was designated as a cutoff value, its sensitivity and specificity were high for the diagnosis of long-term catheter-related infection in recent studies [177-181]. However, because the studies were not performed with long-term catheters, such as the Hickman catheter, and because the specificity of the examination was lower for patients already treated with antibiotics, the results should be interpreted carefully.

Most catheter-related infections are caused by Gram-positive bacteria, and coagulase-negative *Staphylococcus* is most frequently isolated [182]. Thus, if catheter-related infection is clinically suspected, a glycopeptide, such as vancomycin, can be used (A-II). Because linezolid was found to increase the mortality rate when it was routinely administered to patients with suspected catheter-related infection in a randomized trial [183], it is not routinely recommended for the treatment of suspected catheter-related infection except in patients with catheter-related infection confirmed to have been caused by Gram-positive bacteria (A-I).

Table 5. Suggested duration of therapy for documented infection

Microbiologic or clinically documented infection
Skin and soft tissue infection: 7-14 days (if Gram-negative sepsis, consider 10-14 days)
Bacteremia
Gram-positive bacteria: 7-14 days
Gram-negative bacteria: 10-14 days
<i>Staphylococcus aureus</i> : at least 2 weeks after first negative blood culture or 4-6 weeks
Yeast: at least 2 weeks after first negative blood culture
Sinusitis: 10-21 days
Bacterial pneumonia: 10-21 days
Intra-abdominal infection (i.e., typhlitis): until no evidence of symptoms or signs of infection and neutrophil recovery
HSV/VZV: 7-10 days
HSV, herpes simplex virus; VZV, varicella-zoster virus.

When should a catheter be removed?

37. Catheter removal is recommended for patients with bloodstream infections caused by fungi, non-tuberculous mycobacteria, *Bacillus* spp., *Corynebacterium jeikeium*, *S. aureus*, *Acinetobacter*, *P. aeruginosa*, *Stenotrophomonas maltophilia*, and vancomycin-resistant *Enterococcus* (A-II).
38. If the catheter has not been removed because the presence of a catheter-related infection is clinically uncertain, catheter removal may be considered if the same bacteria are identified in the consecutive blood culture at 48-72 hours after beginning appropriate antibacterial agents (B-II). However, immediate removal of the catheter is necessary if a catheter-related infection is suspected and the patient is clinically unstable (A-II).

Most catheter-related infections can be improved by

antibiotic therapy without removal of the catheter [3]. In particular, the catheter salvage rate of coagulase-negative *Staphylococcus* reaches 70-80% with intravenous antibiotics alone; thus, the use of antibiotics without catheter removal is generally recommended [182,184] (A-II). However, for catheter-related infection caused by fungi (yeasts or molds) or non-tuberculous mycobacteria (e.g., *Mycobacterium chelonae*, *M. abscessus*, or *M. fortuitum*), the catheter should be removed immediately [3]. *Bacillus* spp., *C. jeikeium*, *S. aureus*, *Acinetobacter*, *P. aeruginosa*, *S. maltophilia*, and VRE can be difficult to treat with antibiotic therapy alone [3]. Thus, catheter-related infections caused by these microorganisms also require initial catheter removal (A-II). In cases with severe inflammation of the mucous membranes, intestinal bacteria flora, such as VRE and *Candida*, can cause infection through the blood; DTP is helpful in discriminating these cases from those of catheter-related infection [3]. Moreover, when the catheter is not removed because the presence of catheter-related infection is unclear, but the same bacteria are identified in consecutive blood cultures 48-72 hours after beginning appropriate antibiotics, catheter removal should be considered [3,182] (B-II). However, if catheter-related infection is suspected and a patient is clinically unstable, the catheter requires immediate removal [3] (A-II). In cases of bacteremia caused by *S. aureus*, when catheter-related infection is suspected, catheter removal is generally recommended, because the success rate is low [185] (A-II). However, if the fever of a patient with a catheter and unclear cause of infection improves in 48-72 hours after beginning proper antibiotics and the blood culture result is negative, the process can be closely monitored while maintaining the catheter [184] (B-II). General indications for catheter removal are presented in Table 6.

Table 6. Suggested indication for catheter removal

1.	Tunnel infection
2.	Septic phlebitis
3.	Catheter-related infection caused by <i>Candida</i> spp.
4.	Mycobacterial catheter-related infection
5.	Suspected catheter-related infection and clinically unstable
6.	Persistent bacteremia or clinically deteriorating 72 hr after the initiation of appropriate therapy
7.	Catheter-related infection caused by <i>Staphylococcus aureus</i> (B-II)
8.	Other Gram-positive organisms: <i>Bacillus</i> spp., <i>Corynebacterium jeikeium</i> , vancomycin-resistant enterococci
9.	Gram-negative organisms such as <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> , <i>Stenotrophomonas maltophilia</i>

All of the recommendations are level A-II with the exception of recommendation 7.

EMPIRICAL ANTIFUNGAL THERAPY

When should empirical antifungal therapy be considered if empirical antibacterial agents are not effective?

39. Empirical antifungal therapy is recommended in patients who are expected to maintain neutropenia for a longer period (> 10 days), when the fever does not resolve within 3-5 days of initial empirical administration of antibacterial agents (A-II).
40. Regardless of fever, empirical antifungal therapy is recommended in patients who have a history of invasive fungal infection, fungal colonization with neutropenia, symptoms (pleuritic chest pain, blood tinged sputum, or hemoptysis) or signs that suggest newly developed pneumonia, tenderness, or edema around the paranasal sinuses or orbital area, ulcerating lesions or eschar in the nose (A-II).

Empirical antifungal therapy is a standard treatment when broad-spectrum antibacterials are not effective in neutropenic fever patients, based on clinical studies conducted in the 1980s [2,3,11,14,186-190]. Although characteristics of the patients, medications, and epidemiology of fungi may differ compared with those of 20-30 years ago, a lack of antifungal therapy for continuous neutropenic fever can increase invasive fungal infection (IFI) and lead to a higher mortality rate following IFI. Thus, empirical antifungal therapy is recommended in these cases (A-II) [3,14,191].

Currently, 40-50% of neutropenic patients classified as high-risk are known to take empirical antifungal agents [190]. According to a study that analyzed patients after HSCT and anticancer therapy in a single center in Korea from March 2000 to February 2001, 122 of 318 (38.4%) patients used empirical antifungal agents, and 74 (23.8%)

among them had IFIs that were caused by *Aspergillus* and *Candida* species in most cases (6, 46, and 22 proven, probable, and possible IFIs, respectively) [192]. A foreign study also stated that approximately 15-45% of patients with a continuous neutropenic fever were estimated to have IFI [190]. Other reasons that antifungal therapy is used before a definitive diagnosis of infection are 1) because IFI is difficult to diagnose during the neutropenic period, 2) the delay of antifungal therapy to definitive diagnosis can easily provoke disseminated infection, and 3) in the autopsy of patients who died of neutropenic fever, IFI (*Candida* or *Aspergillus* species in most cases) that had not been clinically documented was found, and a continuous fever was the only initial sign of IFI [14,188-190].

If fever persists or recurs even after the administration of antibacterials, empirical antifungal therapy should be conducted [2]. When to begin the empirical antifungal therapy can differ according to the degree of risk. Patients in the low-risk group do not need to start antifungal therapy before diagnosis, while those in the intermediate-risk group are recommended to begin antifungal therapy when fever persists after 6-8 days of beginning broad-spectrum antibacterials due to continuous neutropenic fever and neutropenia. For patients in the high-risk group with over 10 days of neutropenia, empirical antifungal therapy should be started quickly when neutropenic fever persists or recurs after 3-5 days of beginning broad-spectrum antibacterials or when the clinical condition deteriorates [11,193]. When neutropenia is expected to persist for a relatively short period (< 10 days) or estimated to have been resolved for several days from the decision of whether to use empirical antifungal therapy, empirical antifungal therapy is not routinely considered, unless there is a symptom or sign causing suspicion of invasive fungal infection or a history of invasive fungal infection (B-III).

Which antifungal agents can be used empirically?

41. The following antifungal agents are recommended or can be considered for empirical antifungal therapy: caspofungin (A-I), liposomal amphotericin B (A-I), amphotericin B deoxycholate (B-I), itraconazole (B-I), and voriconazole (B-II). Amphotericin B deoxycholate should not be considered in the presence of risk factors for nephrotoxicity (B-I).
42. Azoles may not be considered as empirical antifungals if prophylaxis with fluconazole or itraconazole has already been administered (B-II).

Because many types of antifungal agents have been developed over the last 10 years and antifungal prophylaxis has been widely conducted in the high-risk group, filamentous fungi, as opposed to yeasts, such as *Candida*, have been found more frequently in IFIs of febrile neutropenic patients. Moreover, the rate of non-albicans species in candidiasis has increased, and fluconazole resistance has become a problem [193-196]. Thus, empirical antifungal agents need to meet the following conditions: 1) appropriate antifungal activity (having susceptibility to prevalent fungi in a region and in a hospital, or at least to *Candida* and *Aspergillus* species), 2) acceptable results in randomized controlled studies, 3) recommendations in currently published guidelines, 4) superior tolerance and less adverse reactions, and 5) a reasonable price [197].

To assess the effect of empirical antifungal therapy, the following five composite endpoints are comprehensively considered: 1) resolution of fever during neutropenia, 2) successful treatment of any baseline fungal infection, 3) absence of any breakthrough fungal infection during therapy or within 7 days after completion of therapy, 4) no premature discontinuation of therapy because of drug-related toxicity or lack of efficacy, and 5) survival for 7 days after the completion of therapy. If the therapy does not satisfy any of these endpoints, it is considered to be ineffective [198-200]. When toxicity is observed after initial empirical antifungal therapy, other antifungal agents can be used early in treatment. However, the time to determine whether it is effective remains a controversial issue. For amphotericin B deoxycholate, which is still widely used in Korea, it is recommended to change to other antifungal agents if there is no effect within 3-5 days. When an empirical antifungal agent is changed, a different class of antifungals should be considered first (B-III).

Because amphotericin B deoxycholate has been used as an empirical antifungal for decades and various antifungal agents have since been developed, their efficacy, safety, and adverse reactions have been compared. In Europe and the US, fluconazole, itraconazole, liposomal amphotericin B (not amphotericin B deoxycholate), caspofungin, and voriconazole have been administered empirically (voriconazole is not used as an empirical antifungal agent without the approval of KFDA as of 2009) [14,29,195,201].

Recommended empirical antifungal agents are summarized in Table 7, including doses and characteristics.

Although amphotericin B deoxycholate has been widely used in Korea due to the accumulated experience with

its use and its broad antifungal spectrum, the rate of adverse reactions, such as infusion-related toxicity and nephrotoxicity, which is reportedly as high as 50%, is a limitation. ECIL-1 does not recommend amphotericin B deoxycholate in patients 1) with underlying renal impairment, 2) taking co-medications with nephrotoxicity (e.g., taking an immunosuppressant, such as cyclosporin or tacrolimus after allogeneic HSCT, or antibiotics with nephrotoxic potential, such as aminoglycosides), and 3) with a previous history of toxicity. Additionally, current guidelines and reports do not recommend amphotericin B deoxycholate as an empirical agent because of its low efficacy and frequent and severe adverse events [3,14,190,193,195,197,201]. Therefore, although considering the accumulated experiences with its use, broad-spectrum activity, and low price, this committee does not suggest amphotericin B deoxycholate for patients with underlying renal impairment, taking co-medications with nephrotoxicity after allogeneic HSCT, or with a risk of renal failure, such as the elderly (B-I).

Liposomal amphotericin B produces an effect similar to that of amphotericin B deoxycholate (50% vs. 49%), but the frequencies of proven breakthrough fungal infection and adverse reactions (infusion-related toxicity and nephrotoxicity) of the five composite endpoints were significantly lower for liposomal amphotericin B [3,14,190,198,202]. In particular, the frequencies of infusion-related toxicity (17% vs. 44%) and nephrotoxicity (19% vs. 34%) were significantly lower [198]. This committee recommends liposomal amphotericin B for antifungal therapy as A-I.

The overall success rate of caspofungin does not differ from that of liposomal amphotericin B (33.9% vs. 33.7%), but its survival rate for > 7 days after the end of therapy was higher and the mortality rate in underlying fungal infection patients was significantly lower. Moreover, discontinuation of a drug due to drug-related toxicity and adverse reactions was observed less frequently for caspofungin [3,14,190,200]. Thus, this committee recommends caspofungin and liposomal amphotericin B of the same strength (A-I). However, only the intravenous type is available, and it is not effective against *Zygomycetes* or *Cryptococcus* species.

Itraconazole in capsule form shows a different absorption rate according to patients, and its absorption rate is improved in the oral and intravenous forms when combined with cyclodextrin. When intravenous itraconazole and amphotericin B deoxycholate were

compared, they had similar efficacies and the toxicity of intravenous itraconazole was lower [3,14,190,203,204]. In a recent study, itraconazole provoked fewer adverse reactions and its efficacy was superior to that of amphotericin B deoxycholate, but the time to response and the length of fever were longer [205]. However, its potential for drug interaction should be monitored carefully, and it should be particularly avoided in patients with congestive heart failure.

Although voriconazole shows less breakthrough invasive fungal infection compared with liposomal amphotericin B in neutropenic fever patients ($p = 0.02$), its overall success rate is lower (26% vs. 31%), “non-inferiority” has not been proven, and it is not approved as an empirical antifungal agent by the FDA [3,14,190,199]. However, it is recommended as a primary therapeutic agent for aspergillosis, with a recommendation strength of A-I, and is used for off-label indications as an empirical antifungal agent due to low rates of breakthrough fungal infection and nephrotoxicity in the US and other countries [193,195,201,206]. Thus, this committee suggests the use of voriconazole as an empirical antifungal agent only in the high-risk group with a high risk of invasive aspergillosis.

Although fluconazole has been reported not to differ from amphotericin B deoxycholate, it has limitations as an empirical antifungal agent because it is not effective against filamentous fungi, such as *Aspergillus* species, and is used prophylactically [3,14,190,195,207]. A questionnaire survey conducted in HSCT centers of Korea reported that antifungal prophylaxis was administered to 57.6% of anticancer therapy and 90.9% of HSCT patients [29]; thus, fluconazole can be used as an initial empirical antifungal agent for patients not undergoing antifungal prophylaxis and in hospitals with a high rate of *Candida* infection.

The current trend of prophylaxis with antifungal agents effective against filamentous fungi is thought to largely influence the choice of empirical antifungal agents. When fluconazole or itraconazole is included in antifungal prophylaxis, there is an opinion that it should not be considered an empirical antifungal agent [195]. Future clinical studies to determine which empirical antifungal agents are appropriate according to types of antifungal prophylaxis are expected to be performed.

Table 7. Recommendation of empirical antifungal agents in neutropenic fever

Antifungal agents	Daily dose	Recommendation level	Comments/cautions
Caspofungin	70 mg IV × 1 dose, then 50 mg IV q24h 70 mg IV × 1 dose, then 35 mg IV q24h for patients with moderate liver disease	A-I	Only echinocandin is approved as empirical therapy in febrile neutropenia Similar efficacy, but less toxic compared with liposomal amphotericin B as empirical antifungal therapy for persistent neutropenic fever Rarely hepatotoxic, not nephrotoxic Available only in IV formulation Not active against <i>Zygomycetes</i> , <i>Cryptococcus</i>
Liposomal amphotericin B	3 mg/kg IV q24h	A-I	Reduced infusion-related toxicity and nephrotoxicity compared with amphotericin B deoxycholate At least as effective and safer than amphotericin B deoxycholate as empirical antifungal therapy in neutropenic fever
Amphotericin B deoxycholate	0.5-1.5 mg/kg IV q24h	B-I ^a	Broad spectrum of activity including <i>Candida</i> , <i>Aspergillus</i> , <i>Zygomycetes</i> , <i>Cryptococcus</i> , and other rare molds Substantial infusion-related toxicity and nephrotoxicity including electrolyte wasting
Itraconazole	200 mg IV q12h × 4 doses, then 200 mg IV q24h	B-I	Negative inotropic effects; contraindicated in patients with congestive heart failure Increases cyclophosphamide metabolites; associated with hyperbilirubinemia and nephrotoxicity Potent inhibitor of the cytochrome P450, with regard to drug interaction Not active against <i>Zygomycetes</i> IV formulation should be used with caution in patients with significant renal impairment Therapeutic drug monitoring is necessary
Voriconazole	6 mg/kg IV q12h × 2 doses, then 4 mg/kg IV q12h; oral 200 mg PO bid daily (in case of aspergillosis)	B-II	Not approved by KFDA as an empirical antifungal agent for neutropenic fever Most panel members consider to be an acceptable option empirically in patients at high risk for invasive mold infection Consider drug interaction (rifampin, phenobarbital, etc.) In Asian population, 10-20% of patients are poor metabolizers of voriconazole Not active against <i>Zygomycetes</i> IV formulation should be used with caution in patients with significant renal impairment Therapeutic drug monitoring is necessary
Fluconazole	400 mg IV q24h	C-II	Active against <i>Candida</i> <i>C. glabrata</i> is associated with variable resistance and <i>C. krusei</i> is always resistant Not active against molds (e.g., <i>Aspergillus</i> spp., <i>Zygomycetes</i>)

KFDA, Korea Food and Drug Administration.

^aPanels do not recommend amphotericin B deoxycholate in the presence of risk factors for renal toxicity (B-I) (e.g., impaired renal function at baseline, nephrotoxic co-medication including cyclosporin or tacrolimus in allogeneic hematopoietic stem cell transplantation recipients, aminoglycosides antibiotics, old age, or history of previous toxicity).

Which additional examination(s) can be conducted to diagnose fungal infection after examinations have been performed in the early stages of fever?

43. Periodic radiological examinations such as chest X-rays and CT, fungal cultures, non-culture based microbiological tests, such as galactomannan and β -D-glucan, and sputum or nasal swab surveillance are useful for the early diagnosis of fungal infections (B-I).
44. Active efforts, such as bronchoscopy, bronchoalveolar lavage, tissue biopsy, and culture, are necessary (B-II).

The Mycoses Study Group of the European Organization for Research and Treatment of Cancer (EORTC/MSG) revised the definition of invasive fungal infection in 2008 to include various methods [208]. However, the definitions were made for communication between clinical researchers, researchers of epidemiological studies, and clinicians, and were not an actual standard practice applied to patients clinically. That is, even when a case does not meet the definition, it does not mean every IFI can be excluded. As clinical characteristics and radiological and laboratory markers have been developed and repeatedly tested, they have been used to identify IFIs and to treat them early. These efforts enhance the survival rate of IFI by treating it early with only a small number of antifungals and reduce unnecessary use, adverse reactions, and medical costs by administering antifungals only to patients in need of them [209]. Additionally, regarding beginning empirical antifungal therapy, there are many efforts to diagnose and treat IFI early and to determine the treatment duration by using one or a combination of repeated fungal cultures, simple X-ray, CT, and non-culture-based diagnostic tests, even when IFI is not clinically suspected [209-211].

In patients with a sustained neutropenic fever, CT is helpful to diagnose IFI, especially invasive aspergillosis. The halo sign or haziness around a nodule or infiltration is a characteristic chest CT finding of infection caused by angio-invasive microorganisms, and it is useful for the suspicion of invasive aspergillosis observed in long-term neutropenic patients; however, it is not found in all patients. Although there is no disease-specific radiological finding characteristic of IFI, empirical antifungal therapy (mold-active therapy) should begin when severe neutropenia persists with symptoms such as fever, cough, and chest pain and pulmonary nodules or infiltration are newly observed on CT images. Additionally, the results of

radiological examinations (e.g., CT, MRI) of the abdomen, paranasal sinuses, and head and neck are considered in combination with patients' symptoms and signs and laboratory findings. If there are any abnormalities in the examinations, active efforts, such as bronchoscopy and biopsy, are made to lead to confirmation of the diagnosis and to determine the appropriate use of antifungals through targeted therapy [2,3,12,209].

Galactomannan (GM) is a component of the cell wall of fungi and is used for double-sandwich enzyme-linked immunosorbent assays. It is examined in the plasma, serum, bronchoalveolar lavage fluid, and cerebrospinal fluid, and is known to be helpful for the diagnosis of invasive aspergillosis. Its sensitivity and specificity differ according to the study, and its cutoff value varies according to the type of underlying disease and antifungal prophylaxis [209,212-214]. When antibiotics such as piperacillin/tazobactam or amoxicillin/clavulanic acid are used, a false-positive result may be observed, and antifungals that are currently effective against filamentous fungi can provoke a false-negative result [195,213,215]. Except as an auxiliary measure for diagnosis, GM is used for surveillance in the high-risk group (for early diagnosis before symptoms) and monitoring of responses after antifungal therapy. A recent meta-analysis reported that the sensitivity and specificity of GM analysis were 71% (95% CI, 68 to 74) and 89% (95% CI, 88 to 90), respectively [216], but a study using it clinically found that its sensitivity was < 50% [217]. In particular, because false-negative results can be observed when using antifungals, results should be interpreted carefully.

Moreover, another component of the cell wall of fungi, (1 \rightarrow 3)- β -D-glucan, is currently used as an auxiliary measure to diagnose IFI. Unlike GM, it is detected in not only *Aspergillus*, but also *Candida*, *Fusarium*, *Trichosporon*, *P. jirovecii*, *Acremonium*, and *Saccharomyces*; however, it has not been identified in *Zygomycetes* [213,215].

Although the polymerase chain reaction (PCR) method has been developed, it has not been standardized and results on clinical validity do not exist. Thus, EORTC/MSG does not recommend it as an auxiliary measure for diagnosis. Despite this, real-time quantitative PCR has been attempted for many genera and species of fungi [208,213,215]. Nucleic acid sequence-based amplification (NASBA) that manufactures a primer with a preserved 18S rRNA base sequence and nucleic acid and performs isothermal amplification has also been developed [218].

Antifungal therapy using described surrogate markers is

called “preemptive therapy” and has been recently studied [211], but this committee believes that it is too early to recommend it for routine preemptive therapy in Korea.

Until when should empirical antifungal therapy be used?

45. Treatment duration is usually determined by defervescence, recovery of the absolute neutrophil count, and a clinically stable condition. Empirical antifungals may be discontinued early if defervescence is achieved, neutropenia has recovered, and fungi have not been identified. However, if invasive fungal infection is identified during empirical therapy, the proper treatment duration for the respective disease should be followed (B-III).

When fungal infection is confirmed during the use of empirical antifungal therapy, the treatment duration is determined by any underlying disease(s) and the type and spectrum of fungal infection [2,193,194]. If fungal infection is not confirmed, there is no accurate standard by which to determine the empirical treatment duration, but in previous studies, the duration was an average of 7-14 days (range, 1 to 113) [198-200,203-205]. The treatment duration was limited mainly to experience with amphotericin B deoxycholate. Amphotericin B deoxycholate may be discontinued when neutropenia is improved, the patient’s condition is stable, and there are no abnormalities on chest and abdominal CT. If neutropenia persists but the patient’s condition is clinically stable, amphotericin B deoxycholate can be discontinued when it has been used for 2 weeks and there are neither suspicious lesions on physical examination nor abnormalities on CT. For stable patients in the high-risk group, continuation of amphotericin B deoxycholate is considered during the period of neutropenia [2]. GM can be helpful to determine the discontinuation of antifungal therapy with no evidence of fungal infection in clinical or radiological examinations despite continuous neutropenia because its negative predictive value is high. On the contrary, when the level is positive, additional examinations, such as CT, are necessary [209,210,213,215]. Moreover, if fever persists even after the recovery of neutropenia, active efforts, such as radiological examinations, biopsy, and cultures, are needed to determine the cause of the fever.

CLOSING REMARKS

These guidelines represent an approximately 6-month effort. There were more studies in Korea than expected, but most were retrospective surveys conducted at a single hospital. These guidelines suggest drugs actually used as of December 2009 and their evidence, and if related Korean literature exists, it is also described. Although most questionnaire surveys performed in hospitals in Korea focused on clinical experiences based on the standard of reimbursement benefits, these guidelines attempt to provide an academic background for antibiotic therapy for febrile neutropenic patients. Thus, the contents of these guidelines may differ from the current notification of the Ministry of Health and Welfare and the standards of review of HIRA. In particular, the use and doses of antibiotics and the use of empirical antifungal therapy differ. Regarding the assessment of this guideline by specialists, the manuscript was revised by accepting opinions after presentations at five academic conferences in early 2010 and after the questionnaire survey had been conducted with related physicians in Korea. Of 40 recommendations, 36 indicated appropriateness and 11 indicated the need for adjustment in over 10% of the respondents. Among them, seven were related to antibiotic prophylaxis. With the exception of these, there were opinions that some oral antibiotics, the use of glycopeptides, catheter-related infections, and empirical antifungal therapy need to be modified. This is believed to be because therapeutic strategies, including experiences, prophylaxis, distribution of causative organisms, and the current situation of resistance, differ according to hospitals. In future, we hope that clinical experiences in Korea help patients and are consistent with international standards through much discussion.

This committee has attempted to develop guidelines that are helpful for clinicians who examine and have concern for patients. However, the current guidelines do not mention tuberculosis or chronic hepatitis, the incidence rates of which are expected to be characteristically high in Korea. Moreover, various guidelines for the diagnosis and treatment of common diseases (e.g., invasive aspergillosis) in febrile neutropenic patients and prevention of infectious complications in specific groups (e.g., HSCT recipients) are considered necessary. We hope that many researchers obtain the necessary additional data through prospective studies and suggest future directions. Finally, we hope that these guidelines are widely used and periodically revised

every few years by related societies to provide the latest treatment information based on literature from Korea and other countries.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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