Executive Summary

<Purpose>

This study intends to identify the epidemiology, resistance patterns, and antibiotic usage patterns for infectious diseases in febrile neutropenic patients based on Korean data, and to develop the guidelines for empirical treatment of febrile neutropenic patients in line with domestic circumstances through interdisciplinary joint research and a review of foreign literatures.

<Methods>

A treatment guideline development committee was organized under the initiative of the National Evidence-based Healthcare Collaborating Agency with methodology specialist and experts recommended by 8 academic societies: Korean Society of Infectious Diseases, Korean Society for immunocompromised Host Infections, Korean Cancer Association, Korean Society of Clinical Microbiology, Korean Society of Blood and Marrow Transplantation, Korean Society of Hematology, Korean Society for Chemotherapy, and Korean Association for Clinical Oncology.

The Key questions were selected in the areas of the definition of neutropenic fever, initial evaluation and infection risks, antibiotic prophylaxis, initial antibiotic therapy for febrile neutropenic patients, re-evaluation after 3-5 days and change of antibiotics, the use of glycopeptide, catheter-related infection in febrile neutropenic patients, and the use of antifungal agents. Agreement was reached through systematic review of the literatures and discussion in subcommittee.

Antibiotic prophylaxis

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).
3. Antibacterial prophylaxis is administered until neutrophil recovery (absolute neutrophil count: 500-1000/mm^3)(B-III).
4. Antifungal prophylaxis is recommended to prevent fungal infections in patients whose neutropenia is expected to last for more than 7 days: posaconazole (A-I), fluconazole (B-I), itraconazole oral solution (B-I), low-dose amphotericin B deoxycholate (B-I), or low-dose liposomal amphotericin B (C-II).
5. Antifungal prophylaxis is recommended to prevent fungal infections in allogeneic hematopoietic stem cell transplant recipients: posaconazole (A-I), fluconazole (A-I), micafungin (B-I), or itraconazole intravenous injection followed by itraconazole oral solution (B-I).
6. Consider using prophylactic antifungal agents at least until neutrophil recovery (absolute neutrophil count: 500-1000/mm^3)(B-III).
7. Consider using prophylactic antifungal agents until the discontinuation of immunosuppressant if immunosuppressant is used after allogeneic hematopoietic stem cell transplantation (B-III).
8. Prophylaxis against *Pneumocystis jirovecii* is recommended in allogeneic hematopoietic stem cell transplant recipients (A-I).
9. Consider using prophylaxis against *P.jirovecii* in the case of autologous hematopoietic stem cell transplantation, high-dose corticosteroid therapy (e.g., the equivalent of 20mg/day or more of prednisone for 4 weeks or more), administration of T-cell depleting agent such as fludarabine (B-II), or anticancer therapy due to acute leukemia (B-III).
10. The use of sulfamethoxazole/trimethoprim (A-I) is recommended for prevention of *P.jirovecii*. If the patients are

intolerant to the drug, consider using dapsone or aerosolized pentamidine(B-II).

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

Initial Antibiotic Therapy

14. In contrast to the 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.
16. Oral antibiotics may be used for the initial treatment of febrile neutropenic patients if the risk of infectious complications is low (A-I).
17. The combination of ciprofloxacin with amoxicillin/clavulanic acid is recommended for the oral antibiotics for febrile neutropenic patients (A-I).
18. The combination of ciprofloxacin with clindamycin is an acceptable alternative for the oral antibiotics for penicillin-allergic patients (A-II).

19. However, ciprofloxacin-based oral antibiotic regimens are not recommended if patients recently treated with fluoroquinolone prophylaxis (B-II).
20. Cefepime, imipenem/cilastatin, meropenem, or piperacillin/tazobactam is recommended as empiric monotherapy if the febrile neutropenic patient has no complications of infection (A-I).
21. Ceftazidime can be considered as the empiric monotherapy if the febrile neutropenic patient has no complications of infection, but beware of the possibility of breakthrough infections (either from Gram-positive bacteria or drug-resistant Gram negative bacteria) (B-II).
22. An aminoglycoside + anti-pseudomonal penicillin (± 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 + extended-spectrum cephalosporin (cefepime, ceftazidime) are also recommended as the initial intravenous combination therapy for febrile neutropenic patients (A-II).

Re-evaluation after 3-5 days and change of antibiotics

24. If the causative organism is not found and initial empirical antibiotics seem to be effective after 3-5 days, maintain the initial empirical antibiotics until neutrophil recovery (A-II).
25. Maintain the intravenous antibiotics until the absolute neutrophil count recovery for patients who were in the high risk group at the beginning of the administration of empirical antibiotics. In the low risk group, consider changing to oral antibiotics (B-II).
26. If the fever persists after 3-5 days of antibiotic therapy and reassessment dose 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 unstable condition, consider expanding the antibacterial spectrums to 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).

Use of glycopeptide

29. Glycopeptide should not be routinely added to an initial empirical antibiotic regimen (A-I).
30. Although fever persists or recurs after 3-5 days of empirical therapy, it is recommended not to add glycopeptide routinely (B-I).
31. The use of glycopeptide as empirical antimicrobial therapy is recommended if the patient's blood cultures are positive for Gram-positive bacteria, a catheter-related infection is suspected, known colonization with methicillin resistant *Staphylcoccus aureus* or history of MRSA infection, the patient has severe sepsis or shock pending the results of cultures, or the patient has a skin or soft tissues infection (A-II).
32. The use of teicoplanin can be considered as empirical antibiotic therapy for neutropenic patients because it has equivalent efficacy as well as lower adverse reactions such as nephrotoxicity compared to vancomycin (B-I).

Discontinuation of antibiotics

33. If the origin of fever is unclear, maintain antimicrobials until the absolute neutrophil count reaches at 500/mm^3 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).

Catheter-related infections in febrile neutropenic patients

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

Empirical antifungal therapy

39. Empirical antifungal therapy is recommended in patients who are expected to maintain neutropenia for a longer period (>10 days), if the fever does not settle 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 in neutropenic state, symptoms (pleuritic chest pain, blood tinged sputum, or hemoptysis) or signs that suggest newly developed pneumonia, tenderness or edema around paranasal sinuses or orbital area, ulcerating lesions or eschar in nose, etc. (A-II).

41. The following antifungal agents are recommended or can be considered as empirical antifungal therapy: caspofungin (A-I), liposomal amphotericin B (A-I), amphotericin B deoxycholate (B-I), itraconazole (B-I), 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).
43. Periodic radiological examinations such as chest X-rays and CT, fungal cultures and non-culture based microbiological tests (e.g., galactomannan, β-D-glucan), sputum or nasal swab surveillance are useful for early diagnosis of fungal infections (B-I).
45. Active efforts such as bronchoscopy, bronchoalveolar lavage, tissue biopsy and culture are necessary (B-II).
46. The treatment duration is usually determined by defervescence, recovery of absolute neutrophil counts, and clinically stable condition. The empirical antifungals may be discontinued early if the defervescence is achieved, the neutropenia recovered, and fungi have not been identified. However, if invasive fungal infection is identified during empirical therapy, proper treatment duration of the respective disease should be followed (B-III).