Evidence-Based Recommendations for Antimicrobial Use in Febrile Neutropenia in Japan: Executive Summary

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The recommendations for the management of febrile neutropenia that are summarized in the following algorithm were developed by experts from Japan in collaboration with consultants from the United States and Europe. They update those published in 1998 [1], especially with respect to the use of antimicrobial agents in the treatment of patients with neutropenia and unexplained fever.

DEFINITIONS OF FEBRILE NEUTROPENIA

1. Fever: A single axillary temperature of $\geqslant$37.5°C or a single oral temperature of $\geqslant$38.0°C
2. Neutropenia: A neutrophil count of <1000 cells/μL with a predicted decline to <500/μL

INITIAL EVALUATION

Stratification of patients in the low-risk or high-risk category for infectious complications should be based on the findings of following evaluations: a thorough history and physical examination, a complete blood cell count with differential count, blood chemistry profiles, C-reactive protein measurement, chest radiography, blood culture (2 sets, with the blood sample for 1 set obtained through the central catheter, if one is in place), urine culture, and Gram staining and/or culture of specimens from the potential infectious foci.

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INITIAL MANAGEMENT

The algorithm for the initial management of febrile neutropenic patients is summarized in figure 1. The antimicrobial agents should provide coverage against the most prevalent and life-threatening pathogens, such as viridans streptococci and gram-negative bacilli, including *Pseudomonas aeruginosa.*

1. Oral therapy for low-risk patients

Ciprofloxacin or levofloxacin with or without amoxicillin-clavulanate

2. Monotherapy

2.1. Cefepime or ceftazidime (depending on the drug-susceptibility profile of isolates from the institution) or a carbapenem. Add a glycopeptide if methicillin-resistant *Staphylococcus aureus* (MRSA) infection is documented.

2.2 Other fourth-generation cephalosporins or piperacillin-tazobactam are alternatives in institutions where the drug-susceptibility profile makes these agents acceptable.

3. Combination therapy for high-risk patients

One of the agents recommended for monotherapy (above) plus an aminoglycoside. Consider combination therapy especially for patients receiving remission induction therapy for treatment of acute leukemia or hematopoietic stem cell transplantation (HSCT).

MODIFICATION OF THERAPY DURING THE FIRST WEEK OF TREATMENT

1. Patients who become afebrile in 3–5 days (the treatment algorithm is summarized in figure 2)

1.2 Etiology not defined at days 3–5

Continue treatment for 4 days more; if the neutrophil count recovers and the patient's condition is stable, therapy can be discontinued at any time.

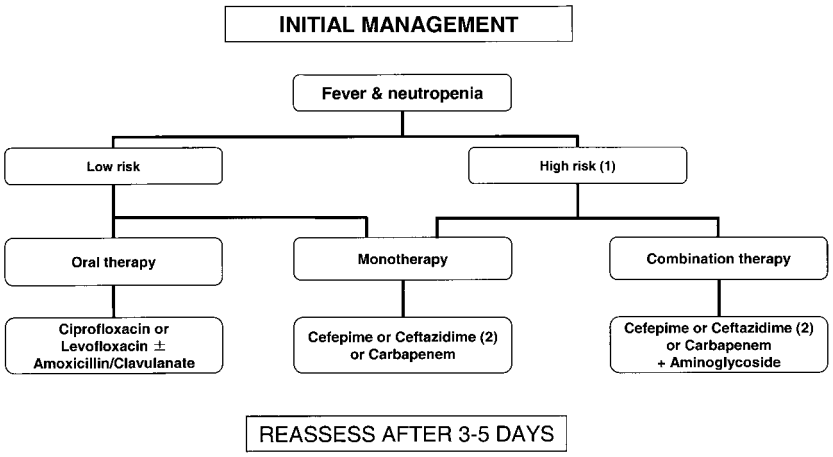

Figure 1. Diagram summarizing the treatment algorithm for initial management of febrile neutropenic patients. (1) If infection with methicillin-resistant *Stpahylococcus aureus* is documented, add a glycopeptide (vancomycin or teicoplanin) to the treatment regimen. (2) Ceftazidime resistance is increasing among gram-positive and gram-negative organisms in many parts of the world.

1.3 Etiologic agent identified

Consider adjusting the antimicrobial therapy; the same initial treatment can be continued for 4 days more, if the results of drug susceptibility tests are appropriate. Add a glycopeptide to the regimen if MRSA infection is documented.

2. Patients with persistent fever for 3–5 days or recurrence of fever after improvement with initial therapy (the treatment algorithm is summarized in figure 3).

Reassess the patient with the following evaluations: a thorough physical examination, blood cultures, Gram staining and/or culture of specimens from suspect lesions, a complete blood cell count with differential count, blood chemistry profiles, C-reactive protein measurement, radiography and other imaging studies if indicated; for fungal infection, include serologic testing or DNA studies.

Consider treatment with granulocyte colony-stimulating factor (G-CSF) for patients with documented infection or in a poor condition; G-CSF therapy can be withheld for patients who remain in a good, low-risk condition, with a predictable recovery of the neutrophil count in 1 week.

2.1 Etiology not defined

2.1.1 Clinically stable and no evidence of infection

Continue the initial therapy

2.1.2 Clinically unstable or progressive disease

2.1.2.1 Initial treatment with monotherapy

Add an aminoglycoside to the regimen or consider monotherapy with another β-lactam.

Consider changing cephalosporin/penicillin to a carbapenem or other β-lactam, or a carbapenem to another β-lactam when adding an aminoglycoside to the regimen .

2.1.2.2 Initial therapy with combination therapy

Consider changing cephalosporin/penicillin to a carbapenem or other β-lactam, or a carbapenem to a β-lactam.

Consider adding a quinolone (administered intravenously) to the regimen, if none was used as prophylaxis.

Reassess the patient 48 h after modification of therapy.

Consider use of antifungals if fever persists for >5 days during antibiotic treatment.

2.2 Etiologic agent identified

2.2.1 Bacteria

Adjust antibiotic therapy on the basis of susceptibility test results while maintaining treatment with broad-spectrum antibiotics; if a gram-positive organism is isolated, consider use of a glycopeptide.

2.2.2 Fungi

If a fungal infection is proven (i.e., culture for fungi yields positive results), add to the regimen an antifungal

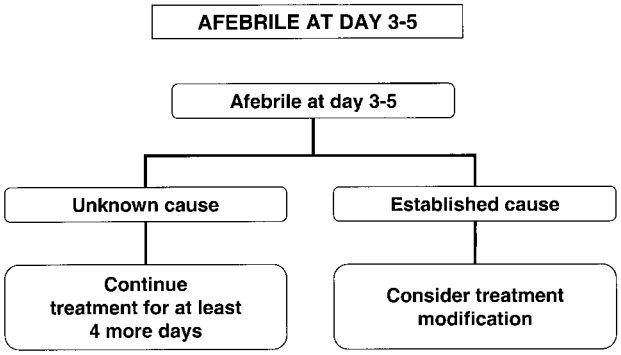

Figure 2. Diagram summarizing the treatment algorithm for febrile neutropenic patients who are afebrile at days 3–5 of therapy.

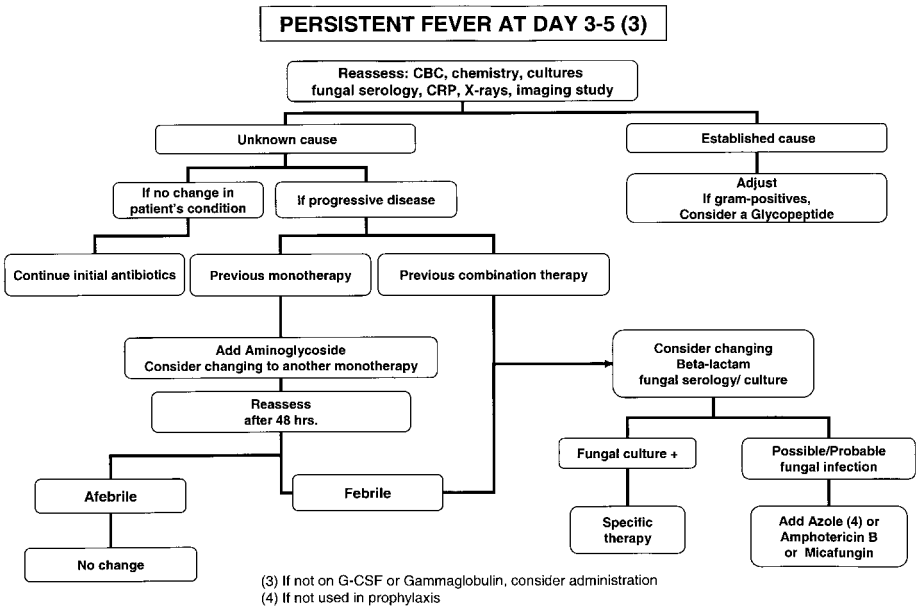

Figure 3. Diagram summarizing the treatment algorithm for initial management of febrile neutropenic patients who are have persistent fever at days 3–5 of therapy.

that is expected to be active against the documented fungal pathogen.

If a fungal infection is probable or possible (i.e., results of serologic or DNA testing for fungi are positive or imaging studies reveal characteristic features), add an azole to the regimen for patients who have not been taking an azole for prophylaxis, or add amphotericin B. Micafungin is an alternative in certain circumstances when drug-susceptible *Candida* or *Aspergillus* infection is suspected.

DURATION OF THERAPY

1. Afebrile by day 3–5

1.2 If the neutrophil count is ⩾500 cells/μL and the patient is in a stable condition and afebrile for ⩾48 h, therapy can be stopped after a total of 7 days of treatment has been completed.

1.3 If the patient is in a stable condition but still neutropenic (neutrophil count of <500 cells/μL) by day 7, therapy can be stopped when the patient has been afebrile for >5 days. If the patient was initially stratified as being at high risk, and no complications have occurred subsequently, it is safe to continue the antibiotic therapy.

2. Persistent fever

2.1 If the patient has a neutrophil count of ⩾500 cells/μL and is in stable condition, antibiotic therapy can be stopped 4–5 days after the neutrophil count has recovered to ⩾500 cells/μL.

2.2 If the neutrophil count is <500 cells/μL, continue antibiotic therapy for several weeks after appropriate reassessment; then reassess and consider discontinuation of therapy, if the patient's condition is stable.

G-CSF

1. Use of G-CSFs are considered if the patient remains febrile while taking antibiotics, has a documented infection, or is in a poor condition, or if neutropenia is predicted to persist for >10 days. G-CSF therapy can be withheld for patients who remain in a good, low-risk condition and whose neutrophil count is predicted to recover in 1 week.

2. For patients with acute myelogenous leukemia, control of the disease activity must be achieved with antileukemic agents.

γ-GLOBULINS

Therapy with γ-globulins are *not* recommended for routine use but can be considered for patients with persistent febrile neutropenia and a predictably worsening clinical course.

GRANULOCYTE TRANSFUSIONS

Granulocyte transfusions are not recommended for routine use in adults.

ANTIVIRALS

For herpes simplex virus infection, acyclovir is indicated as therapy for disease or as prophylaxis for seropositive patients (antibody titers of ⩾1:16) with hematological disease who have

undergone HSCT or chemotherapy. Acyclovir therapy should be considered for seropositive patients who are to receive induction therapy for acute leukemia.

ANTIMICROBIAL PROPHYLAXIS

1. Antibiotic prophylaxis should not be routinely given to patients who are predicted to develop profound neutropenia during the course of treatment for an underlying disease, because of the rapid emergence of antibiotic resistance; however, some Japanese hematologists use an oral quinolone or nonabsorbable antibiotic for patients with acute leukemia who have undergone HSCT.

2. An exception is administration of trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* infection in patients who have undergone HSCT, have neutropenia, and are receiving immunosuppressant agents, including receipt of glucocorticoids for a prolonged period.

3. Fluconazole is recommended as antifungal prophylaxis for patients who are to undergo HSCT, and this may be considered for patients with acute leukemia who are to receive intensive chemotherapy.

Reference

1. Masaoka T, Urabe A, Ohno R, et al. Evidence-based recommendations on antimicrobial use in febrile neutropenia in Japan. Int J Hematol **1998**; 68(Suppl 1):S5–6.