Management of febrile neutropenia: ESMO Clinical Recommendations

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Despite major advances in prevention and treatment, febrile neutropenia (FN) remains one of the most feared complications of cancer chemotherapy, and is a major cause of morbidity, healthcare resource use, and results in delays and dose reductions in chemotherapy which compromise efficacy. Mortality from FN has diminished steadily but remains significant. Overall mortality rates are ~5% in patients with solid tumors (1% in low-risk patients) and as high as 11% in some hematological malignancies.

A widely used definition of FN is an axillary temperature >38.5°C lasting >1 h in the context of an absolute neutrophil count (ANC) <0.5 x 10⁹/l. Different centers experience different patterns of principal causative pathogens and these guidelines are intended for use alongside local antimicrobial policies.

patient education and local policies

Success in FN management requires prompt recognition of, and reaction to, potential infection. Vital to this is educating outpatients to monitor symptoms including body temperature, and clear written instructions on when and how to contact the appropriate service in the event of concerns. In addition, effective, written local policies are essential to ensure a rapid response whenever FN is suspected.

initial assessment

An initial assessment (Table 1) of circulatory and respiratory function with vigorous resuscitation where necessary should be followed by careful examination for potential foci of infection. Signs and symptoms of infection in neutropenic patients can be minimal particularly in those receiving corticosteroids. Blood from a peripheral vein and any indwelling venous catheters plus sputum, urine and skin swabs where clinically indicated should be sampled for culture before the prompt institution of empirical broad-spectrum antimicrobial therapy.

outcome risk assessment

The vast majority of FN cases respond promptly to empirical therapy suffering no major complications. A number of instruments have been developed in attempts to predict those high-risk cases where complications are more likely. The most widely used instrument, the Multinational Association for Supportive Care in Cancer (MASCC) index allows the clinician to rapidly assess risk before access to the neutrophil count and without knowledge of the burden of underlying cancer, and has been prospectively validated. The criteria and weighting scores are listed in Table 2. Low-risk cases are those scoring ≥21. The serious medical complication rate in these is estimated to be 6% and mortality just 1%. However, some physicians are reluctant to use less vigorous management policies where there remains a small risk of treatment-related death.

choice of treatment

See Figure 1. Standard management of FN involves prompt administration of empiric broad-spectrum, i.v. antibacterial therapy with additional supportive care (i.v. fluid, oxygen, etc.) as indicated, as an inpatient until the patient has been afebrile and clinically stabilized for at least 24 h and the neutrophil count is ≥1.0 x 10⁹/l. Whilst this policy remains the safest approach, the development of tools for risk assessment and the availability of better antibacterials have broadened the treatment options.

low-risk patients

oral therapy

A recent review has concluded that inpatient oral antibacterial therapy can be safely substituted for conventional i.v. treatment in some low-risk FN patients, namely those who are hemodynamically stable, who do not have acute leukemia or
evidence of organ failure, who do not have pneumonia, an indwelling central venous catheter or severe soft tissue infection. Precise criteria were not defined as they varied between the trials reviewed. Single-agent quinolones were not inferior to combinations (quinolone with amoxicillin plus clavulanic acid) but the latter are preferred given the rise in Gram-positive FN episodes. Oral quinolone therapy should not be used in patients who had been taking a quinolone antibacterial as prophylaxis. The safety of an early change to oral combinations in apyrexial patients after 48 h on i.v. therapy is supported in the review and is preferred by many physicians.

outpatient and early discharge policies

The possibility of exclusive oral outpatient management for low-risk FN cases has become increasingly appealing on the grounds of patient convenience, economy and reduction in the incidence of nosocomial infections but is unsupported by high level evidence. Furthermore, one large series reported outcomes similar to those of patients treated conventionally but ~20% of cases required later readmission. There is, however, evidence to support an early discharge policy in these low-risk cases once they have become clinically stable, symptomatically better and there is evidence of fever lysis after a minimum of 24 h in hospital.

choice of i.v. antibacterial

Local bacterial isolate and resistance patterns are crucially important in determining first choice empirical i.v. therapy. However, a meta-analysis comparing monotherapy (e.g. an anti-pseudomonal cephalosporin like ceftazidime or a carbopenem) with combination therapy found equivalent efficacy [I, A]. This was less clear in the subsets at high risk of prolonged neutropenia and those with bacteremia, where the bactericidal activity and synergic effect of a β-lactam antibiotic in combination with an aminoglycoside is preferable.

specific indications for alternative therapy

Apart from the standard treatment with broad-spectrum antibacterial agents, there are a number of situations in clinical practice that require a specific regimen [II, A]. The duration of treatment may vary and local antibacterial guidelines should be followed in these circumstances.

central i.v. catheters

In most cases the infection can be successfully treated without removing the catheter. Removal of the line is indicated in the context of tunnel infections, persistent bacteremia despite adequate treatment, atypical mycobacteria infection and candidemia. Vancomycin should be added when infection of the line is suspected and should be administered through the line when possible.

cellulitis

The addition of vancomycin broadens the cover against skin pathogens.

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Table 1. Initial assessment and investigation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
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<tbody>
<tr>
<td>Burden of illness: no or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Burden of illness: moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient status (at onset of fever)</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt;20 years</td>
<td>2</td>
</tr>
</tbody>
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Scores >21 are at low risk of complications.

MASCC, Multinational Association for Supportive Care in Cancer.

Table 2. MASCC scoring index

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Figure 1. Initial management of febrile neutropenia.
**candidosis**
Antifungal treatment with fluconazole in the first instance is needed with early switch to an alternative antifungal if the response is inadequate.

**diarrhea**
Assessment for *Clostridium difficile* is needed and treatment with metronidazole if suspected.

**vesicular lesions/suspected viral infection**
After appropriate samples are taken, therapy with acyclovir should be initiated. Ganciclovir should be substituted only when there is a high clinical suspicion of invasive cytomegalovirus infection.

**lung infiltrates**
Frequent assessment of initial response to therapy is essential and in the absence of prompt improvement, CT scanning and bronchoalveolar lavage should be considered. Advice from an infectious diseases (ID) specialist or clinical microbiologist is advised. Appropriate therapy for infection with fungi/pneumocystis species, etc. should be instituted.

**suspected meningitis or encephalitis**
Lumbar puncture is mandatory in these rare cases. Bacterial meningitis should be treated with cefazidine or meropenem plus ampicillin and viral encephalitis with a high dose of acyclovir.

**daily follow-up and assessment of response**
The frequency of clinical assessment is determined by severity, but may be required every 2–4 h in cases needing resuscitation. Daily assessment of fever trends, bone marrow and renal function is indicated until the patient is apyrexial and ANC ≥ 0.5 × 10⁹/l (Figure 2) [II, B].

- **If apyrexial andANC ≥ 0.5 × 10⁹/l at 48 h**
  - Low-risk and no cause found: consider changing to oral antibacterials.
  - High-risk and no cause found: if on dual therapy, aminoglycoside may be discontinued.
  - When cause found: continue on appropriate specific therapy.

- **If still pyrexial at 48 h**
  - If clinically stable: continue initial antibacterial therapy.
  - If clinically unstable: antibacterial therapy should be rotated or cover broadened if there are significant clinical reasons to do that. This group of patients is at risk of serious complications and prompt advice from an ID physician or clinical microbiologist should be sought. When the pyrexia lasts for >4–6 days, initiation of antifungal therapy may be needed.

- **duration of therapy**
  - If the neutrophil count is ≥0.5 × 10⁹/l, the patient is asymptomatic and has been afibrile for 48 h and blood cultures are negative, antibacterials can be discontinued.
  - If the neutrophil count is <0.5 × 10⁹/l, the patient has suffered no complications and has been afibrile for 5–7 days, antibacterials can be discontinued except in certain high-risk cases with acute leukemia and following high-dose chemotherapy when antibacterials are often continued for up to 10 days, or until the neutrophil count is ≥0.5 × 10⁹/l.
  - Patients with persistent fever despite neutrophil recovery should be assessed by an ID physician or clinical microbiologist and antifungal therapy considered.

- **note**
  Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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**Figure 2.** Assessment of response and subsequent management.


