clinical practice guidelines

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Management of febrile neutropenia: ESMO Clinical Practice Guidelines

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definition of febrile neutropenia

Febrile neutropenia (FN) is defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l.

incidence, morbidity, mortality and organisms

Despite major advances in prevention and treatment, FN remains one of the most concerning complications of cancer chemotherapy, and is a major cause of morbidity, healthcare resource use and compromised efficacy resulting from delays and dose reductions in chemotherapy. Mortality from FN has diminished steadily but remains significant. Overall mortality rates are ∼5% in patients with solid tumours (1% in low-risk patients) and as high as 11% in some haematological malignancies. Prognosis is worst in patients with proven bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia. Mortality varies according to the MASCC prognostic index (detailed further down): as low as 3% if the MASCC score is >21, but as high as 36% if the MASCC score is <15. Elderly patients are at a higher risk of febrile neutropenia following chemotherapy, with worse morbidity and mortality rates. However, good prospective trial data are lacking with respect to elderly cancer patients due to their relative exclusion from randomized clinical trials, which therefore limits specific recommendations relative to this patient group.

Positive microbiological detection rates by standard blood cultures vary depending on whether patients have had prophylactic antibiotics and whether they have a central venous catheter (CVC). One trial conducted in patients with solid tumours in which only a minority had CVCs (<10%) identified a rate of 7.2% in patients given antibiotic prophylaxis versus 14.6% in patients not given prophylaxis. Other trials in patients with haematological malignancies, with a higher proportion of patients with CVCs, report rates between 17% and 31%.

Different centres experience different patterns of principal causative pathogens. Consequently these guidelines are intended for use alongside local antimicrobial policies.

Over the last few decades a shift has occurred from FN associated mainly with Gram-negative bacteria to FN associated with Gram-positive organisms. Of those blood cultures that are positive in the setting of FN, typically 70% are reported to be Gram-positive organisms. An increase in antibiotic-resistant strains such as extended spectrum β-lactamase (ESBL)-producing Gram-negative bacteria, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) has been noted. Increasing numbers of infections with fluconazole-resistant *Candida* strains (e.g. *Candida krusei* and *Candida glabrata*) have also been reported.

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. Some patients may present with FN via the Emergency Department, and in this situation clear protocols must be in place to manage these patients appropriately.

initial assessment and investigations

A detailed history should be taken including the nature of the chemotherapy given, prior prophylactic antibiotic, concomitant steroid use, recent surgical procedure and presence of allergies. It is important to check the clinical record for past positive microbiology, in particular previous presence of antibiotic-resistant organisms or bacteraemia, in order to guide therapy.

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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. This is important because some infections (e.g. community-acquired pneumonia) may not be adequately covered by empirical antibiotics chosen for treating FN. Signs and symptoms of infection in neutropenic patients can be minimal particularly in those receiving corticosteroids. Vigilance is required in any patient at risk of FN who presents unwell, hypotensive, with a low grade temperature or afebrile, as they may be developing Gram-negative septicaemia, requiring prompt treatment.

Urgent full blood count to ascertain the neutrophil level along with other investigations listed in Table 1 are crucial in guiding early management.

Two sets of blood cultures from a peripheral vein and any indwelling venous catheters should be taken. In addition, sputum, urine, skin swabs and stool specimens where clinically indicated should be sampled, before the prompt institution of empirical broad-spectrum antimicrobial therapy.

outcome risk assessment

The vast majority of FN cases, as managed according to the algorithm set out in Figure 1, 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 likely. The most widely used instrument, the Multinational Association for Supportive Care (MASCC) index allows the clinician to rapidly assess risk before access to 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 even a small risk of treatment-related death. If an obvious focus of infection is apparent, antibacterials should be tailored accordingly.

Table 1. Initial assessment and investigations

1	Note presence of indwelling i.v. catheters
2	Symptoms or signs suggesting an infection focus
	Respiratory system
	Gastrointestinal tract
	Skin
	Perineal region/genitourinary discharges
	Oropharynx
	Central nervous system
3	Knowledge of previous positive microbiology results by checking clinical records
4	Routine investigations
	Urgent blood testing to assess bone marrow, renal and liver function
	Coagulation screen
	C-reactive protein
	Blood cultures (minimum of two sets) including cultures from indwelling i.v. catheter
	Urinalysis and culture
	Sputum microscopy and culture
	Stool microscopy and culture
	Skin lesion (aspirate/biopsy/swab)
	Chest radiograph
5	Further investigations (profound/prolonged neutropenia/following allografts)
	High-resolution chest CT (if pyrexial despite 72 h of appropriate antibiotics)
	Broncho-alveolar lavage

low-risk patients

oral therapy

A recent review has concluded that inpatient oral antibacterial therapy can be safely substituted for conventional intravenous (i.v.) treatment in some low-risk FN patients, namely those who are haemodynamically stable, who do not have acute leukaemia or evidence of organ failure, who do not have pneumonia, an indwelling venous catheter or severe soft tissue infection [I, A]. Precise criteria were not defined as they

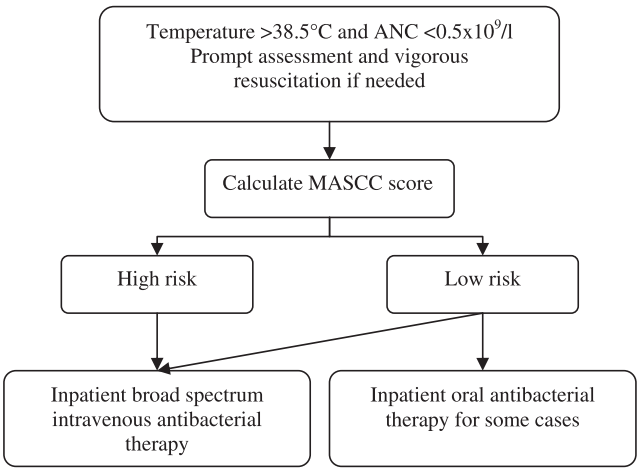

Figure 1. Initial management of febrile neutropenia.

Table 2. MASCC scoring index

Characteristic	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Scores ≥21 are at low risk of complications.
Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26.

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 have taken a quinolone antibacterial as prophylaxis. The safety of early change to oral combinations in apyrexial patients after 48 h on i.v. therapy is supported in the review and 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, only large series reported outcomes similar to those of patients treated conventionally but ~20% of cases required later re-admission. There is, however, evidence to support 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 [II, B].

high-risk patients

Patients with FN who are high risk as assessed by the MASCC criteria, or have high-risk features as judged by the admitting doctor, should be admitted and commenced on broad-spectrum i.v. antibiotics.

choice of i.v. antibacterial

Local epidemiological bacterial isolate and resistance patterns are crucially important in determining first-choice empirical therapy, since coverage for MRSA or resistant Gram-negative bacteria may be required. 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 bacteraemia, where the bactericidal activity and synergistic 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. The duration of treatment may vary and local antibacterial guidelines should be followed in these circumstances.

central i.v. catheters. If catheter-related infection is suspected, blood must be cultured from both the catheter and peripherally in order to measure the differential time to positivity (DTTP), which is the difference in time between positivity of results between catheter culture and peripheral blood culture. A DTTP of ≥2 h is a highly sensitive and specific indicator of catheter-related bacteraemia [I, A].

All cases of catheter-related infection (CRI) in the setting of FN require decision making on the choice and duration of i.v. antibiotics, and the need for catheter removal. When CRI is suspected, and the patient is stable, the catheter should not be removed without microbiological evidence of infection. A glycopeptide such as vancomycin should be administered through the line when possible to cover Gram-positive organisms [III, A]. Teicoplanin is a useful alternative as it can be administered once daily as a line lock. Success in treating CRI without removing the catheter depends on the pathogen isolated in the blood cultures.

In CRI due to coagulase-negative *Staphylococcus* (CNS), an attempt at preserving the catheter can be made if the patient is stable [III, B]. A prospective cohort study of antibiotic-treated CNS bacteraemia in neonates with CVCs found that retention of the line was successful in 46% of cases. A recent retrospective study in adults reported a 93% success rate in treating CRIs caused by CNS, with a re-infection rate over the following 4 months of only 8%. Catheter retention did not impact on the resolution of CNS bacteraemia but was a significant risk factor for recurrence in those patients who had the catheter retained.

Removal of the line is indicated in the context of tunnel infections, pocket infections (implanted port system) [III, B], persistent bacteraemia despite adequate treatment, atypical mycobacterial infection and candidaemia. With regard to line infections caused by *S. aureus*, the literature is divided. A recent German review recommends that line removal is mandatory whilst a retrospective Korean cohort study reported a 50% success rate in line salvage with anti-staphylococcal antibiotics. The desire to preserve the line must be balanced against the risk of metastatic spread by bloodstream seeding. The recommendation should be to remove the line if at all possible, whilst recognizing that with careful management it might be possible to maintain it for a short period. Persistent fever and bacteraemia despite appropriate antibiotics are indications for line removal.

pneumonia. If pneumonia is diagnosed either on clinical grounds and/or on the basis of radiological imaging, antibiotic cover must be extended to treat atypical organisms such as *Legionella* and *Mycoplasma* by adding a macrolide antibiotic to a β-lactam antibiotic [V, D]. Consideration for infection with *Pneumocystis jerovecii* should be given in patients who present with high respiratory rates and/or desaturate readily off oxygen or on minimal exertion. Predisposing factors include prior corticosteroid therapy, use of immune suppressants after organ transplantation and exposure to purine analogues.

High-dose co-trimoxazole is the treatment of choice for suspected *Pneumocystis* infection [I, A].

cellulitis. The addition of vancomycin broadens the cover against skin pathogens [V, D].

intra-abdominal or pelvic sepsis. If clinical or microbiological evidence of intra-abdominal or pelvic sepsis exists, metronidazole should be commenced [V, D].

diarrhoea. Assessment for *Clostridium difficile* is needed and treatment with metronidazole if suspected [V, D].

candidiasis. Patients at risk of disseminated candidiasis are those with prolonged neutropenia and therefore mostly those

with haematological malignancies undergoing myeloablative therapy. Candidaemia can be diagnosed on blood culture; however, cultures may take several days to become positive. Therefore treatment is usually started empirically in patients whose fever fails to respond to broad-spectrum antibiotics after 3–7 days of appropriate treatment. A chest computed tomography (CT) scan including liver and spleen should be performed before commencing anti-*Candida* treatment, looking for typical changes.

First-line empirical treatment depends on what is known about the patient. Liposomal amphotericin B or an echinocandin antifungal such as caspofungin are appropriate first-line treatment if the patient has already been exposed to an azole or if the patient is known to be colonized with non-albicans *Candida* [I, A]. Fluconazole can be given first line provided the patient is at low risk of invasive aspergillosis, local epidemiological data suggest low rates of azole-resistant isolates of *Candida* and the patient has not received an azole antifungal as prophylaxis. Once begun, antifungal treatment should be continued until neutropenia has resolved, or for at least 14 days in patients with a demonstrated fungal infection.

lung infiltrates. Patients with acute myeloid leukaemia during remission induction chemotherapy and those undergoing allogeneic haematopoietic stem cell transplantation with prior conditioning chemotherapy are at risk of invasive aspergillosis due to prolonged and profound neutropenia. Frequent assessment of initial response to antibacterial therapy is essential and in the absence of prompt improvement, further investigations are warranted. If invasive aspergillus is suspected, a high-resolution chest CT scan should be performed the same day, looking for typical features such as nodules with haloes or ground-glass change. If any infiltrate is found, bronchoalveolar lavage should be undertaken if possible. Advice from an infectious diseases (ID) specialist or clinical microbiologist is advised, and appropriate therapy against infection with fungi or *Pneumocystis* species should be instituted. Choices of antifungal agents will depend on centres, individual patients and use of prior prophylactic therapy. Therapy for presumed aspergillosis (for cases with typical infiltrates on CT) could consist of either voriconazole or liposomal amphotericin B [I, A]. These antifungals can be combined with an echinocandin in unresponsive disease [IV, B].

vesicular lesions/suspected viral infection. After appropriate samples are taken, therapy with aciclovir should be initiated [I, A]. Ganciclovir should be substituted only when there is a high suspicion of invasive cytomegalovirus infection [I, A].

suspected meningitis or encephalitis. Lumbar puncture is mandatory in these rare cases. Bacterial meningitis should be treated with ceftazidime plus ampicillin (to cover for *Listeria monocytogenes*) or meropenem [II, A]. Viral encephalitis is treated with a high dose of aciclovir.

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 $\geq 0.5 \times 10^9$/l (Figure 2). Repeated imaging may be required in patients with persistent pyrexia.

If apyrexial and ANC $\geq 0.5 \times 10^9$/l at 48 h.

- Low-risk and no cause found: consider changing to oral antibiotics [II, A].
- High-risk and no cause found: if on dual therapy, aminoglycoside may be discontinued [V, D].
- When cause found: continue on appropriate specific therapy [II, A].

If still pyrexial at 48 h.

- If clinically stable: continue with initial antibacterial therapy.
- If clinically unstable: antibacterial therapy should be rotated or cover broadened if clinical developments justify this. Some haematology units will add a glycopeptide to the regimen whilst other centres will change the regimen to a carbapenem and a glycopeptide. This group of patients is at a high risk of serious complications and prompt advice from an ID physician or clinical microbiologist should be sought. Unusual infections should be considered, particularly

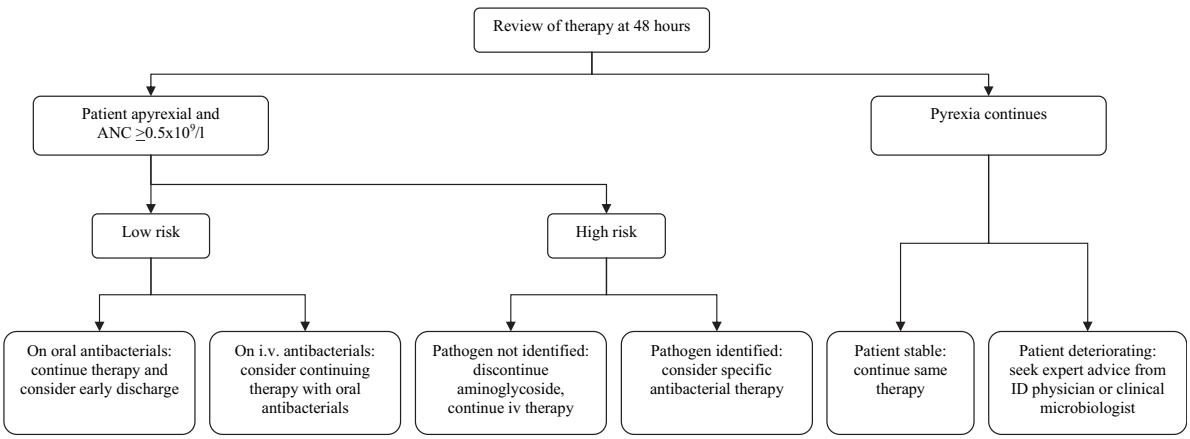

Figure 2. Assessment of response and subsequent management.

in the context of a rising CRP, with a view to proceeding to imaging of the chest and upper abdomen, to exclude probable fungal or yeast infection, or abscesses. When the pyrexia lasts for >4–6 days, initiation of antifungal therapy may be needed [I, A].

duration of therapy

If the neutrophil count is $\geq 0.5 \times 10^9$/l, the patient is asymptomatic and has been afebrile for 48 h and blood cultures are negative, antibacterials can be discontinued [II, A].

If the neutrophil count is $\leq 0.5 \times 10^9$/l, the patient has suffered no complications and has been afebrile for 5–7 days, antibacterials can be discontinued except in certain high-risk cases with acute leukaemia and following high-dose chemotherapy when antibacterials are often continued for up to 10 days, or until the neutrophil count is $\geq 0.5 \times 10^9$/l [II, A].

Patients with persistent fever despite neutrophil recovery should be assessed by an ID physician or clinical microbiologist and antifungal therapy considered [II, A].

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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