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Management of febrile neutropaenia: ESMO Clinical Practice Guidelines†

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definition of febrile neutropaenia

Febrile neutropaenia (FN) is defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l.

incidence, morbidity, mortality and microorganisms

Despite major advances in prevention and treatment, FN remains one of the most frequent and serious complications of cancer chemotherapy (ChT). It is a major cause of morbidity, healthcare resource use and compromised treatment efficacy resulting from delays and dose reductions of ChT. Mortality from FN has diminished steadily, but remains significant.

Most standard-dose ChT regimens are associated with 6–8 days of neutropaenia, and FN is observed in ∼8 cases per 1000 patients receiving cancer ChT. FN is responsible for considerable morbidity as 20%–30% of patients present complications that require in-hospital management, with an overall in-hospital mortality of ∼10%. The mean cost per hospitalisation in Western countries is ∼13 500€ (15 000 US$).

There is a clear relationship between the severity of neutropaenia (which directly influences the incidence of FN) and the intensity of ChT. Currently, the different regimens are classified as producing a high risk (>20%), an intermediate risk (10%–20%) or a low risk (<10%) of FN.

It has been shown that several factors, other than ChT itself, are responsible for increasing the risk of FN and its complications. Among them, age plays a major role [II, III] with older patients having a higher risk of FN following ChT, with worse morbidity and mortality rates. Other factors having a similar role are as follows:

- advanced disease,
- history of prior FN,
- no antibiotic prophylaxis or granulocyte colony-stimulating factor (G-CSF) use [III, IV],
- mucositis,
- poor performance status and/or
- cardiovascular disease [III, IV].

The risk of FN and its complications increases when one or several co-morbidities are present in the patient. These considerations will be instrumental in deciding whether a ChT-treated patient should receive primary prophylaxis to decrease the potential risk of FN.

In the case of FN, prognosis is worst in patients with proven bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia [for bacteraemias due to coagulase-negative *Staphylococcus* (CNS) only, no attributable mortality has been reported] [1]. The presence of a focal site of presumed infection (e.g. pneumonia, abscess, cellulitis) also makes the outcome worse. Mortality varies according to the Multinational Association of Supportive Care in Cancer (MASCC) prognostic index (Table 1): lower than 5% if the MASCC score is ≥21, but possibly as high as 40% if the MASCC score is <15 [2].

Positive microbiological detection rates by standard blood cultures vary depending on whether or not patients have received prophylactic antibiotics. Overall, bacteraemia can be detected in ∼20% of patients with FN; this obviously helps to further adjust antibiotic therapy.

It is crucial to understand that different centres experience different patterns of frequency of causative pathogens. Consequently, these guidelines are intended for use alongside appropriate local antimicrobial policies adapted to the epidemiology of the centre.

Over the last few decades, a shift has occurred from FN associated mainly with Gram-negative bacteria to FN associated with Gram-positive organisms. At the present time, most centres report Gram-positive and Gram-negative bacteraemia in

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Table 1. MASCC febrile neutropaenia risk index

Characteristics	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 tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with 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 [2]. Reprinted with permission. © 2000 American Society of Clinical Oncology. All rights reserved.
BP, blood pressure.

50% of patients with FN, although centres that do not use fluoroquinolone prophylaxis report a predominance of Gram-negative bacteria. An increase in antibiotic-resistant strains has been noted, such as extended spectrum β-lactamase (ESBL)—producing Gram-negative bacteria, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). Increasing numbers of infections with fluconazole-resistant *Candida* strains (e.g. *Candida krusei* and *Candida glabrata*) have also been reported [3].

chemoprophylaxis

Antimicrobials (first non-absorbable antibiotics and later, co-trimoxazole) have been used for a long time for the prevention of episodes of FN in ChT-treated patients. This approach has been somewhat successful, but has also led to the emergence of resistant strains, limiting its efficacy. Since the 1990s, fluoroquinolones have been used extensively for chemoprophylaxis. Most studies have shown that fluoroquinolones reduce the incidence of infection and, in some studies, also the infection-related mortality, but at the expense of the emergence of quinolone-resistant strains. This should, in the end, render the prophylaxis useless; moreover, these strains jeopardise the use of fluoroquinolones as a therapy of FN in low-risk patients, as will be discussed elsewhere. For all of these reasons, the use of antimicrobials, including fluoroquinolones, should be discouraged. Guidelines from the EORTC (European Organisation for Research and Treatment of Cancer) and American Society of Clinical Oncology (ASCO) recommend that clinicians limit the use of antibacterial prophylaxis to patients at high risk for FN; others recommend the mere avoidance of such practices for the prevention of FN. The most recent update of the Cochrane meta-analysis still recommended the use of ciprofloxacin or levofloxacin in cancer patients undergoing intensive ChT [4].

indications for primary prophylaxis of FN with G-CSF

Several meta-analyses indicate that primary prophylaxis with G-CSF (i.e. G-CSF administered immediately after cycle 1 of ChT) reduces the risk of FN by at least 50% in patients with solid tumours without significantly affecting tumour response or overall survival [I] [5–7].

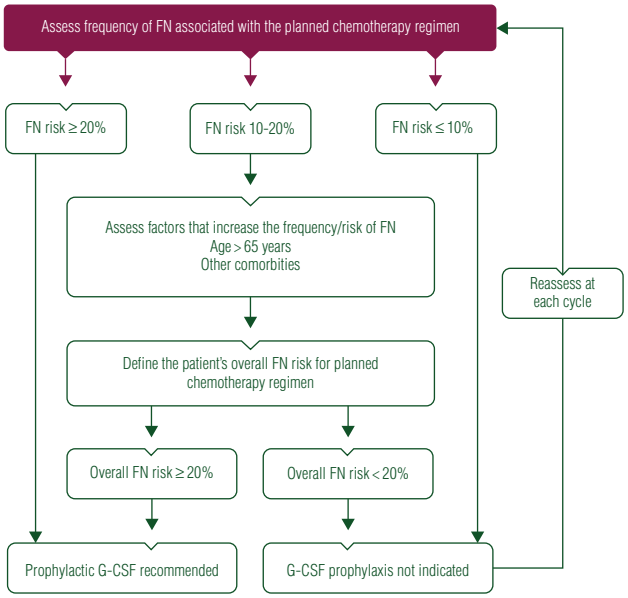

Figure 1. Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage, adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropaenia; G-CSF, granulocyte colony-stimulating factor. Reprinted from [8], with permission from Elsevier.

Most guidelines recommend that G-CSF be administered prophylactically if the risk of FN is >20% for all planned cycles of treatment [I, A]. Classifications of the risk according to the type of ChT have been published and updated [8]. For patients with an intermediate risk (10%–20%), it is important to consider the patient's age and particularly any coexisting morbidities, as already mentioned [8–10].

An algorithm for the decisions about primary prophylactic G-CSF use is presented in Figure 1.

Besides this approach, G-CSF can be considered in patients with reduced bone marrow reserve due to extensive radiotherapy [III] or patients who are neutropaenic in the context of HIV infection [II].

Recent meta-analysis of randomised, controlled trials [11] and experience in real-world settings [12] confirm the outstanding (>50% success) of primary prophylaxis with filgrastim or pegfilgrastim.

With most ChT used for the treatment of common tumours, the risk of FN is maximal during the first course; thus, it makes sense to recommend primary prophylaxis for the patients at risk rather than to systematically resort to secondary prophylaxis. Secondary prophylaxis (i.e. G-CSF given for a course of ChT following a course with FN) is indicated if dose reduction below threshold or delay of ChT is not desirable (e.g. treatment with a curative intent).

There are few complications associated with G-CSF administration; the most common adverse effect is minor or moderate bone pain that can usually be handled with standard analgesics.

dose schedule, route of application of G-CSF and pegfilgrastim

Use 5 μg/kg/day of G-CSF subcutaneously (s.c.) 24–72 h after the last day of ChT until sufficient/stable post-nadir ANC

recovery (achieving a target ANC of >10–10^9/l is not necessary). Pegfilgrastim, injected s.c. as a single dose of either 100 μg/kg (individualised) or of a total dose of 6 mg (general approach), is considered equally effective [I, A]. The equivalent dose of filgrastim is 5 μg/kg/day for ∼10 days. There are no adequate data for reduced numbers or days or alternate days of G-CSF instead of standard, neither for use on day 1 instead of on day 2. EMA/FDA approved biosimilars can be considered.

use of G-CSF in high-risk situations

The therapy of acute leukaemias, autologous and allogeneic stem cell transplantations (TPLs) leads to higher risks of FN and potentially lethal complications [13].

The incidence of FN in high-risk situations is as follows:

- common during autologous and allogeneic peripheral blood stem-cell (PBSC) TPLs and bone marrow TPL, during graft failure,
- in 35%–48% of acute myeloid leukaemia (AML) cases at diagnosis and
- in 13%–30% during acute lymphoblastic leukaemia (ALL) induction ChT.

FN-related mortality is described as follows:

- 0%–10% in autologous TPL,
- highly variable in allogenic TPL,
- 80% during graft failure,
- 20%–26% during the first 2 months in AML and
- 2%–10% during induction ChT of ALL.

management of FN: patient education and local policies

Success in FN management requires prompt recognition of, and reaction to, potential infection. It is vital to educate outpatients to monitor their symptoms, including body temperature, and to provide 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 at the Emergency Department, and in this situation, clear protocols must again be in place to manage these patients appropriately. The first administration of therapy should be given in the hospital within 1 h from the admission of a patient with FN. Delay in antibiotic administration has been associated with significant prolongation of the hospital stay and increased mortality.

As already mentioned, the spectrum of infection in cancer patients is different from place to place and changes over time; therefore, paying attention to local epidemiology is crucial [14].

initial assessment and investigations

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

Table 2. Initial assessment and investigations

1	Note the 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[a]
	Sputum microscopy and culture[a]
	Stool microscopy and culture[a]
	Skin lesion (aspirate/biopsy/swab)
	Chest radiograph
5	Further investigations (profound/prolonger neutropaenia/following allografts)
	High-resolution chest CT (if pyrexial despite 72 h of appropriate antibiotics)
	Bronchoalveolar lavage

i.v., intravenous; CT, computed tomography.
[a]Urinalysis, sputum and stool cultures only in case of suspected focus of infection at these sites.

An initial assessment (Table 2) 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 neutropaenic patients can be minimal, particularly in those receiving corticosteroids, or in elderly patients who often may present with a confusional state.

Vigilance is required in patients at risk for FN who present unwell, are hypotensive (compared with the known previous blood pressure readings), with a low-grade temperature or afebrile, as they may be developing Gram-negative septicaemia, requiring prompt treatment.

Urgent full blood counts, to ascertain the ANC along with other investigations listed in Table 2, are crucial in guiding early management.

Two sets of blood cultures from a peripheral vein and any indwelling venous catheters should be taken as well as specimens for microbiological testing from any suspected sites of infection, before the prompt institution of empirical broad-spectrum antimicrobial therapy. Urinary tract infections have to be suspected even in asymptomatic patients with a past history of such infections.

outcome risk assessment

The vast majority of FN cases, as managed according to the algorithm set out in Figure 2, respond promptly to empirical

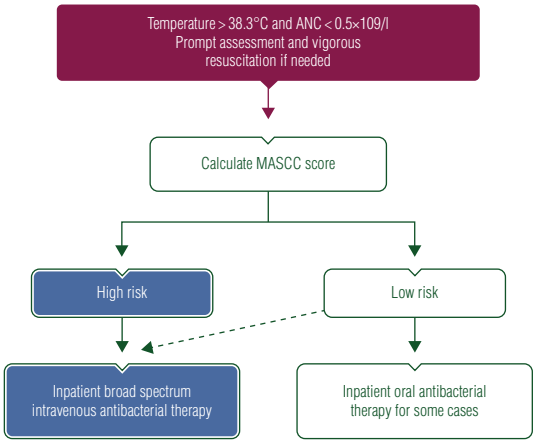

Figure 2. Initial management of febrile neutropaenia. ANC, absolute neutrophil count; MASCC, Multinational Association of Supportive Care in Cancer.

therapy, suffering no major complications. A number of instruments have been developed in attempts to predict these low-risk cases where complications are not likely. The most widely used instrument, the MASCC index, allows the clinician to rapidly assess, on just a clinical basis, the risk of a patient with FN. The MASCC score has been prospectively validated in several studies. The criteria and weighting scores are listed in Table 1. Low-risk cases are those scoring ≥21. The serious medical complication rate in low-risk cases is estimated to be 6% and the mortality rate to be below 1%. If an obvious focus of infection is apparent, antibacterials should be tailored accordingly.

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,
- do not have acute leukaemia or evidence of organ failure and
- do not have pneumonia, an indwelling venous catheter or severe soft tissue infection [I, A].

Precise criteria were not defined as they varied between the trials reviewed. Single-agent quinolones (moxifloxacin) 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 afebrile patients after 48 h on i.v. therapy is supported in the review and preferred by many physicians. Some low-risk patients may be treated with outpatient parenteral regimens.

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 the patient's convenience, economy [15] and reduction in the incidence of nosocomial infections. There is also 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 [II, B], and provided that there is an adequate understanding of the risks and that patient surveillance is available [16–19].

Table 3. Key recommendations for the management of FN

- FN is observed in ±1% of patients receiving ChT; it is associated with considerable morbidity (20%–30%) and mortality (10%)
- FN can be effectively prevented by the use of G-CSFs; it is recommended to use these agents in patients receiving chemotherapies with a >20% risk of developing FN and in those having serious co-morbidities and/or aged >60 years [I, A]
- Patients with FN should be assessed for the risk of complications using a validated predictive tool, such as the MASCC score [I, A]
- Patients with FN at a low risk of complications can often be treated with oral antibiotics and possibly as outpatients, if adequate follow-up is available [I, A]
- Patients with FN at a high risk of complications should be hospitalised and treated without delay with broad spectrum antibiotics; these patients should be closely monitored for instability (pre-shock) [I, A]

FN, febrile neutropaenia; ChT, chemotherapy; G-CSF, granulocyte colony-stimulating factor; MASCC, Multinational Association of Supportive Care in Cancer.

high-risk patients

Patients with FN who are at high risk as assessed by the MASCC criteria (<21), or have high-risk features as judged by the admitting doctor, should be admitted and commenced on broad-spectrum i.v. antibiotics, since the risk of bacterial sepsis is very high [20].

choice of i.v. antibacterial

Local epidemiological bacterial isolate and resistance patterns are crucially important in determining the first-choice empirical therapy, since coverage for MRSA or resistant Gram-negative bacteria may be required [21]. A meta-analysis comparing monotherapy (e.g. an anti-pseudomonal cephalosporin like ceftazidime or cefepime, imipenem, meropenem or piperacillin–tazobactam) with combination therapy found equivalent efficacy [I, A] [22, 23]. This is less clear in the subsets at high risk of prolonged neutropaenia and those with bacteraemia, where the bactericidal activity and synergistic effect of a β-lactam antibiotic in combination with an aminoglycoside might be preferable; namely, in case of *Pseudomonas aeruginosa* sepsis or in centres with known intermediate susceptibility of Gram-negative bacilli to β-lactams [3].

Key recommendations about the management of febrile neutropenia are summarised in Table 3.

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 a patient has an i.v. catheter, catheter-related infection (CRI) should be suspected, and blood must be cultured from the catheter and peripherally 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] [24].

All cases of 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 [25].

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 CNS, an attempt at preserving the catheter can be made if the patient is stable [III, B]. Catheter retention does not have an impact on the resolution of CNS bacteraemia but is a significant risk factor for recurrence in those patients in whom the catheter was 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. 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, while recognising 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 in an outpatient is diagnosed either on clinical grounds and/or on the basis of radiological imaging, antibiotic cover may be extended to treat atypical organisms such as *Legionella* and *Mycoplasma* by adding a macrolide or a fluoroquinolone antibiotic to a β-lactam antibiotic [V, D]. Consideration for infection with *Pneumocystis jirovecii* 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 TPL and exposure to purine analogues, as well as lack of reliable chemoprophylaxis with co-trimoxazole [26]. In high-risk patients with profound prolonged neutropaenia and lung infiltrates, early treatment with a mould-active antifungal agent is recommended.

lung infiltrates. Patients with AML during remission induction ChT and those undergoing allogeneic haematopoietic stem cell TPL with prior conditioning ChT are at risk of invasive fungal infections (namely aspergillosis) due to prolonged and profound neutropaenia [27]. 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 computed tomography (CT) scan should be carried out on the same day, looking for typical features such as nodules with halos or ground-glass change, and galactomannan should be measured in serum. If any infiltrate is found, bronchoalveolar lavage should be undertaken if possible.

Advice from an infectious diseases (ID) specialist or clinical microbiologist is recommended, and an appropriate therapy against infection with fungi or *Pneumocystis* species should be instituted. The choice of antifungal agents will depend on centres, individual patients and use of prior prophylactic therapy [28].

Therapy for presumed aspergillosis (for cases with typical infiltrates on CT) could consist of either voriconazole or liposomal amphotericin B [I, A] [29, 30]. These antifungals can be combined with an echinocandin in unresponsive disease [IV, B]. A precise microbiological diagnosis is highly desirable in patients suspected of invasive fungal infection, as the sensitivity to various antifungal agents is variable among different species.

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

vesicular lesions/suspected viral infection. After appropriate samples are taken, therapy with aciclovir should be initiated [I, A]. Ganciclovir (or foscarnet) should be substituted only when there is a high suspicion of invasive cytomegalovirus infection [I, A] [31, 32].

suspected meningitis or encephalitis. Lumbar puncture (if in any way possible before the institution of antibiotics) 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.

cellulitis. The addition of vancomycin broadens the cover against skin pathogens [V, D]. Linezolid and daptomycin are emerging alternatives to glycopeptides; however, more clinical experience is needed, especially in neutropaenic patients.

intra-abdominal or pelvic sepsis. If clinical or microbiological evidence of intra-abdominal or pelvic sepsis exists, metronidazole should be commenced [V, D], unless the patient is on a carbapenem or piperacillin–tazobactam, which have adequate anaerobic coverage.

diarrhoea. Assessment for *Clostridium difficile* is needed and, if suspected, oral vancomycin or metronidazole treatment should be administered [V, D].

candidiasis. Patients at risk of disseminated candidiasis are those with prolonged neutropaenia and especially those with haematological malignancies undergoing myeloablative therapy [33]. Candidaemia can be diagnosed on blood culture; however, cultures may take several days to become positive. Empirical initiation of antifungal therapy is recommended in patients whose fever fails to respond to broad-spectrum antibiotics after

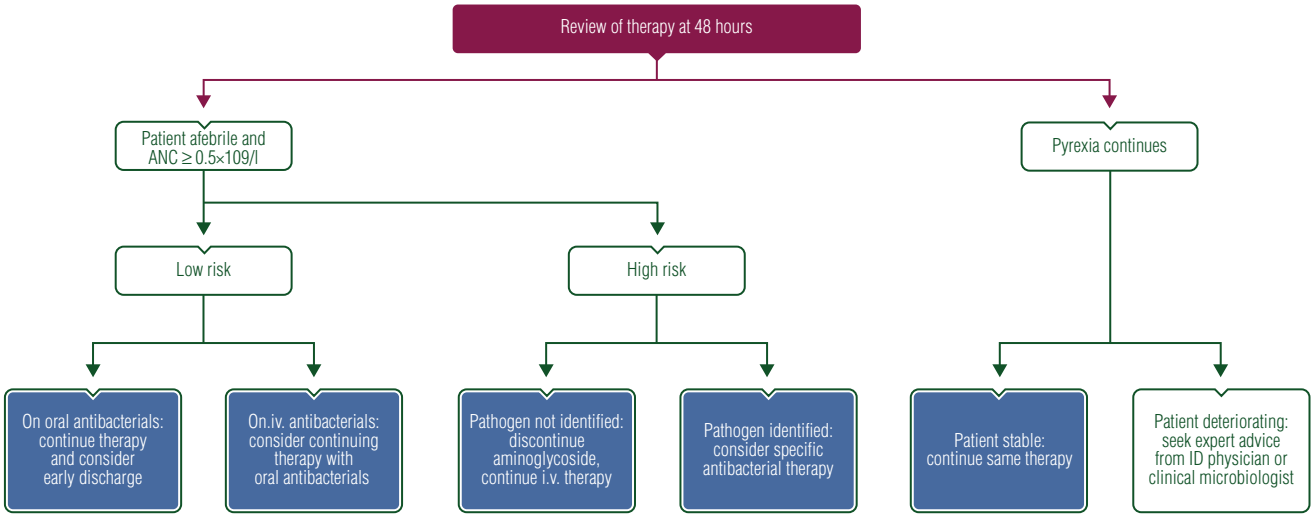

Figure 3. Assessment of response and subsequent management. ANC, absolute neutrophil count; i.v., intravenous; ID, infectious disease.

3–7 days of appropriate treatment [I, A]. A CT scan of the liver and spleen should be carried out before commencing anti-*Candida* treatment, looking for typical changes.

First-line empirical treatment depends on what is known about the patient. Liposomal amphotericin B and an echinocandin antifungal such as caspofungin are appropriate first-line treatments if the patient has already been exposed to an azole or if the patient is known to be colonised 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 neutropaenia has resolved, or for at least 14 days in patients with a demonstrated invasive Candida infection.

Specific needs for preventing other opportunistic infections are required in patients with haematological malignancies, namely those undergoing haematopoietic stem cell transplants [34].

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 afebrile and has an ANC of $\geq 0.5 \times 10^9$/l (Figure 3) for 24 h. Repeated imaging may be required in patients with persistent pyrexia.

If the patient is afebrile and has an ANC of $\geq 0.5 \times 10^9$/l at 48 h, has low risk and no cause of infection has been found, consider changing to oral antibiotics [II, A]. If the patient is at high risk with no cause found and is on dual therapy, aminoglycoside may be discontinued [V, D]. When the cause is found, continue on appropriate specific therapy [II, A].

If the patient is still febrile at 48 h, but clinically stable, initial antibacterial therapy should be continued. If the patient is clinically unstable, antibacterial therapy should be rotated or broadened if clinical developments justify this. Some haematology units will add a glycopeptide to the regimen, while other centres will change the regimen to imipenem or meropenem and a glycopeptide. This group of patients with persistent fever 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 in the context of a rising C-reactive protein, 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

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [34].

for >4–6 days, empirical initiation of antifungal therapy may be needed [I, A].

duration of therapy

If the ANC 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 ANC 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 ChT when antibacterials are often continued for up to 10 days, or until the ANC 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].

An overall algorithm for the assessment of response and subsequent management is proposed in Figure 3.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified as standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

JK has declared speaker's fees and consulting fees from TEVA. JdN has declared no potential conflicts of interest. KR has reported research support from Merck, Allergan, and JMI Laboratories and participation in an advisory board for Allergan. BR has reported advisory boards for Sandoz/Hexal, Amgen and Roche, research support from Sandoz/Hexal and speaker's bureau for Teva, Amgen and Roche. GM has reported personal fees (outside the submitted work) from Merck/MSD, Astellas, Gilead, Pfizer, F2G, Roche and Basilea. MA has reported consultancy for Amgen, Hospira, Pfizer, Pierre Fabre, Roche, Sandoz, Teva and honoraria for lectures at symposia for Amgen, Chugai, Hospira, Kyowa Hakko Kirin, Pierre Fabre, Roche, Sandoz, Sanofi, Taiho and Teva. JH has declared that he is a member of the rolapitant advisory board for Tesaro.

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