Neutropenic Fever

35

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35.1 Introduction

Fever during neutropenia is almost universal after a HSCT. In neutropenic HSCT recipients, clinicians are faced with a unique combination of two issues: (1) high incidence of bacterial bloodstream infections and (2) high mortality in case of infections due to Gram-negative bacteria unless effective antibiotic treatment is provided promptly.

Additionally, in the absence of neutrophils which are responsible for most of clinical signs or symptoms during a localized bacterial infection (abscess formation, prominent lung infiltrates, pyuria, etc.), fever is frequently the only symptom present also in these cases. On the other hand, fever is a highly unspecific sign, and there are numerous causes of fever during neutropenia other than bacterial infections, including (a) viral infections, (b) fungal infections, (c) drug reactions (e.g. ATG), (d) transfusion reactions, (e) mucositis, (f) underlying disease, (g) engraftment syndrome, (h) GvHD, (i) cytokine release syndrome, (j) rejection and (k) haemophagocytosis.

However, since infection due to Gram-negative bacteria, including *Pseudomonas aeruginosa*, can result in rapid deterioration of clinical conditions and death, this possibility should be always considered and appropriate empirical antibiotic therapy started while awaiting the results pointing to the actual cause of fever. The issue of prevention of fever and infections during neutropenia through antibiotic prophylaxis with fluoroquinolones has been seriously challanged by a worldwide increase in antibiotic resistance (Mikulska et al. 2018).

35.2 Initial Management of Fever During Neutropenia

Initial management of fever during neutropenia should include all the following (Freifeld et al. 2011; Averbuch 2013; Lehrnbecher et al. 2017).

35.2.1 Diagnostic Procedures

(a). Two sets (1 set = 1 aerobic and 1 anaerobic bottle) of *blood cultures*
1. Including at least one set from the central venous catheter (CVC), if present
2. Using an aseptic methodology to reduce the risk of contamination
3. Providing adequate blood volume (20 ml in each bottle), since the volume of blood is essential to ensure optimal detection of bacteraemia or candidaemia
(b) *Clinical exam* with particular attention to subtle signs of a localized infection
4. Signs of infection of exit/entry of CVC

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E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_35

5. Perineal pain suggestive of an abscess
6. Skin or nail lesions suggestive of fungal infection
7. Abdominal defence or diarrhoea
8. Upper respiratory tract symptoms such as rhinorrhoea suggestive of viral respiratory infection
9. Mucosal lesions
10. CNS sings or symptoms (focal lesions, e.g. with fungal infection or bacteria abscess vs. being confused in severe systemic infection or viral encephalitis)

(c). Any *other microbiological exams* based on the clinical presentation (e.g. sputum culture, pharyngonasal swab for respiratory viruses, urinary antigen for *Legionella*, CMV DNA, *Clostridium difficile* toxin, etc)

(d). *Radiological exams* based on the clinical presentation (for suspected lung involvement, lung CT should be used since chest X-ray has too low sensitivity for detecting pneumonia in neutropenic patients)

35.2.2 Evaluation of the Risk of Clinically Severe Infection

Such an evaluation, based on comorbidities, current clinical presentation, etc. leads to the decision on hospital admission and the need for close monitoring for sings of further clinical deterioration.

35.2.3 Evaluation of the Risk of Infection Due to Resistant Bacteria

This risk is considered high in case of:

(a) Colonization with a resistant bacterial strain
(b) Previous infection caused by resistant bacterial strain
(c) Local epidemiology with high incidence of infections caused by resistant pathogens

35.2.4 Choice of the Appropriate Empirical Antibiotic Therapy

It comprised the choice between escalationa and de-escalation strategy (see Table 35.1) and the subsequent choice of antibiotic agent(s).

35.2.5 In High-Risk Patient's Assessment of the Need for Antifungal Therapy

(a) Assessing the risk of candidaemia in patients not receiving antifungal prophylaxis and presenting with septic shock
(b) Assessing the risk of invasive aspergillosis (IA) based on the incidence of IA (taking into account risk factors, mould-active prophylaxis, etc.) and the results of galactomannan (GM) screening or targeted testing.

Empirical antifungal therapy (adding antifungal agent in patients persistently febrile despite broad-spectrum antibiotics) could be replaced by diagnostic-driven strategy based on the use of diagnostic tools, such as a chest computed tomography scan, fungal serum markers (mainly GM, possibly also β-D-glucan or PCR) and targeted treatment following diagnosis (see Chap. 37).

35.3 Main Changes in the Last Decade and Empirical Therapy Modalities

The main change in the management of febrile neutropenia is due to an increasing rate of *multidrug-resistant (MDR) bacteria* in certain countries or centres, in particular Gram-negative rods resistant to almost all antibiotics available (e.g. *Enterobacteriaceae* resistant to third-generation cephalosporins ± piperacillin-tazobactam, i.e. producers of extended-spectrum β-lactamases [ESBLs]; *Enterobacteriaceae* or *Pseudomonas aeruginosa* or *Acinetobacter baumannii* resistant to carbapenems).

35.3.1 De-escalation Strategy

Thus, it might be no longer possible to imagine a single empirical antibiotic regimen which would be appropriate for all the patients and to use a traditional escalation approach, which means changing empirical antibiotic regimen in case of

Table 35.1 The main characteristics of escalation and de-escalation strategy

Strategy	Escalation	De-escalation
Definition	Empirical treatment active against susceptible *Enterobacteriaceae* and *P. aeruginosa*	Starting upfront an empirical coverage of *MDR* bacteria, particularly Gram-negatives, which is later (*72–96 h*) *reduced* (*de-escalated*) if a MDR pathogen is *not* isolated: • Susceptible strain isolated • No microbiological results
Antibiotics usually used	Monotherapy with anti-pseudomonal cephalosporin (cefepime, ceftazidime) or piperacillin-tazobactam	• Carbapenem or potentially a new β-lactam such as ceftolozane/tazobactam or ceftazidime/avibactam (although none of them studied in neutropenic patients yet), to cover ESBL-producers and some resistant *P. aeruginosa* *Combinations*, examples • β-lactam + aminoglycoside • β-lactam + coverage of resistant Gram-positives • Colistin-based combinations
Main advantages	Less induction or selection of resistant strains (carbapenem sparing). Less toxicity	Appropriate therapy before culture results are available > *lower mortality*
Main limitations	In case of infection due to a resistant Gram-negatives, prognosis is significantly worsened	*Overuse of broad-spectrum antibiotics/combinations > high antibiotic pressure, particularly in case of failure to de-escalate*
Who	All patients, unless criteria for de-escalation approach are present	Patients at risk for infections due to *resistant bacteria, such as*: • *Colonization with a resistant pathogen* • *Previous infection with a resistant pathogen* • *Centres in which resistant pathogens are frequently isolated* *Particularly* if presenting in *severe clinical conditions*

MDR multidrug resistant

persistent (48–72 h) fever. Indeed, patients who are at high risk of infections due to resistant bacteria, particularly if presenting in severe clinical conditions, should immediately receive agents targeting these strains since any delay in starting effective antimicrobial therapy has been associated with an increased mortality (Tumbarello et al. 2008). Therefore, a de-escalation strategy, typically used in critically ill patients in intensive care units, has been proposed also for neutropenic haematology patients (Averbuch et al. 2013).

Traditional *escalation empirical therapy* is defined as starting with piperacillin-tazobactam or ceftazidime or cefepime and then changing/adding antibiotics if necessary. This approach is still appropriate in most of cases, especially in countries or centres when resistance rates are low among pathogens commonly causing infections in neutropenia. With this approach, carbapenems are used as second-line therapy in patients either failing the initial therapy or in case of a documented infection, and adding an aminoglycoside to a β-lactam, which has been shown in numerous studies as associated with more toxicity and no clinical advantage, is avoided (Averbuch et al. 2013; Drgona et al. 2007). The empirical use of an antibiotic active against resistant Gram-positive bacteria (such as vancomycin) is not recommended neither as initial therapy nor in persistently febrile patients, unless the patient has signs or symptoms suggesting a Gram-positive aetiology (e.g. skin or CVC involvement or pneumonia) or a documented Gram-positive infection (Freifeld et al. 2011; Beyar-Katz et al. 2017).

De-escalation strategy consists of starting with a very broad initial empirical regimen, chosen due to on the severity of the patient's clinical presentation and the risk of infection due to resistant (mainly Gram-negative) bacteria based on individual factors for harbouring MDR bacteria and the local bacterial epidemiology.

The key issues of de-escalation approach are (1) providing immediately effective treatment of a potentially life-threatening MDR pathogen and (2) reducing as much as possible the unnecessary use of precious broad-spectrum drugs, such as carbapenems, colistin, novel beta-lactams or anti-MRSA agents. Data from neutropenic cancer patients in ICU, and more recently from neutropenic haematopoietic stem cell transplant recipients, showed that de-escalation approach is safe and feasible (Mokart et al. 2014; Snyder et al. 2017; Gustinetti et al. 2018). Main characteristics of escalation and de-escalation approach are reported in Table 35.1.

35.3.2 Antibiotic Discontinuation

Another issue of management of febrile neutropenia is the *length of antibiotic therapy*, particularly in the absence of clinically or microbiologically documented infection. Traditionally, antibiotic treatment was continued until neutrophil recovery, with the aim of avoiding infection relapse. In the last decade, this issue has been challenged by IDSA and ECIL guidelines, with the latter stating that antibiotics can be safely discontinued after ≥72 h of IV therapy in patients that are and have been haemodynamically stable since the onset of fever and are without fever for ≥48 h, irrespective of the granulocyte count and the expected duration of neutropenia. The rational for this recommendation was the fact that alteration of patient's microbiota leads to an increased risk of colonization/selection of resistant pathogens, which might subsequently cause life-threatening infections.

The safety of *discontinuation of empirical antibiotic* therapy after few days of treatment, provided the antibiotic treatment is restarted immediately if case of fever reappearance, has been reported and demonstrated in several studies (Orasch et al. 2015). Recently, the first randomized multicentre, open-label superiority trial was performed in 157 high-risk haematology patients with febrile neutropenia without etiological diagnosis. It showed that antimicrobial therapy can be safely discontinued after 72 h of apyrexia and clinical recovery, irrespective of the neutrophils count, and it saves exposure to antimicrobials (mean difference of 4.5 days of antibiotics in the per-protocol analyses). Of note, there were no differences in the number of total days of fever and the crude mortality, and the incidence of recurrent fever during neutropenia and secondary infections was also similar in both groups (Aguilar-Guisado et al. 2017).

35.4 Fever Persistent Despite Empirical Antibiotic Therapy

Fever persistent despite empirical antibiotic therapy is not an infrequent event. Patient's general clinical conditions are the most important factor to consider.

If no signs or symptoms of clinical deterioration (e.g. septic shock, confusion, worsening respiratory function) are present, slow response to antibiotic treatment should be considered, particularly if accompanied by improvement in inflammatory markers such as C-reactive protein, or procalcitonin (particularly for Gram-negative bloodstream infections). In alternative, nonbacterial infections (e.g. viral) or non-infectious causes, such as mucositis, should be considered. Usually, changes in antibiotic regimen are not necessary if clinical conditions are stable. Routine addition of antibiotics against resistant Gram-positives (glycopeptides) has not been shown effective (Beyar-Katz et al. 2017).

Results of GM or other non-invasive fungal tests, performed either in screening or at the onset of fever, should be available by day 2–3 of fever and should guide antifungal treatment. In selected patients at high risk of IA, lung CT scan may be performed to exclude pulmonary fungal disease. *Empirical antifungal treatment* has been introduced when non-invasive diagnostic tests were not available and CT scan availability was extremely limited. When these diagnostic measures became available, *pre-emptive approach* has been shown able to provide earlier treatment than empirical approach (Maertens et al. 2005) (see Chap. 37). Empirical antifungals might be

provided while awaiting the results of diagnostic tests or, in case of mould-active prophylaxis, the confirmation of adequate blood levels, but every effort should be made to confirm or exclude the presence of invasive fungal disease. Two meta-analyses in which empirical treatment was compared with no treatment or pre-emptive therapy confirmed that empirical antifungal treatment was associated with a lower rate of (diagnosed) invasive fungal diseases and higher exposure to antifungals but gave no significant advantage in terms of overall mortality (Goldberg et al. 2008; Fung et al. 2015). Similar results were provided by a randomized trial comparing empirical vs. pre-emptive antifungal treatment in which 30% of patient received autologous SCT (Cordonnier et al. 2009).

If clinical conditions deteriorate, usual management steps are:

1. *Aggressive diagnostic workup* (repeated blood cultures, CT scan, BAL lavage in case of pneumonia, lumbar puncture in case of CNS symptoms, etc.)
2. *Escalation* of antibacterial treatment
3. Starting an *antifungal therapy*

There is no universal scheme for antibiotic escalation therapy, but it usually covers resistant Gram-negatives (including those producing extended-spectrum beta-lactamases, ESBLs, e.g. with a carbapenem or an addition of aminoglycoside) and methicillin-resistant staphylococci or ampicillin-resistant enterococci (e.g. with a vancomycin or novel agents). Coverage of other resistant bacteria should be based on the local epidemiology, the epidemiology of a centre where the patient was cared for before transplant and on patient's past history of infections and colonization. Less frequent agents, such as legionella, mycobacteria, *Nocardia* and nonbacterial infections (viral, fungal and parasitic) should be considered in differential diagnosis and tested for, based on clinical presentation and patient's past exposure. Empirical antifungal treatment in this setting might be warranted while awaiting the results of all diagnostic workup.

Key Points

- Numerous causes of fever during neutropenia exist, but usually it should be managed as suspected bloodstream infection unless proven otherwise.
- The initial management includes diagnostics (mandatory blood cultures) and the assessment of the risk of (1) clinically severe infection and (2) infection due to resistant bacteria.
- In patients with severe presentation and the risk of resistant bacteria, de-escalation approach should be used in order to cover the most probable resistant strain(s).
- In other cases, escalation approach is appropriate, and the choice of the first-line empirical antibiotic therapy should be based on antibiotic susceptibility of Gram-negative bacteria most frequently isolated in a given centre.
- Empirical antifungal therapy could be replaced in most cases by diagnostic-driven (pre-emptive) strategy.
- In the absence of clinically or microbiologically documented infection, empirical antibiotic can be safely discontinued after 72 h of apyrexia and clinical recovery, irrespective of the neutrophils count, and it saves exposure to antimicrobials.
- In case of clinical worsening and persistence of fever, extensive diagnostic workup is mandatory.

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