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Febrile Neutropenia in Immunocompromised Patients Part 1

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Introduction

Febrile neutropenia is an emergency condition, which, if not treated early, has a mortality rate of 70% (especially if the underlying disease is some type of blood malignancy). It is marked by fever (T > 37.8° C) in patients with a compromised immune system, manifested through very low white blood cell count (usually WBC < 2000/cc). The impact of febrile neutropenia may reach up to 18% in patients undergoing myelosuppressive chemotherapy.

Immunocompromised patients have been on a continuous rise in the last few years. The reasons for immunosuppression include:

- **Neoplasms:** Blood malignancies and solid tumours. These patients demonstrate deficiencies in terms of:
  - Drop in the number and function of neutrophils.
  - Disruption in innate humoral immunity, as is the case with multiple myeloma and chronic myeloid leukaemia.
  - Disruption in cell-mediated immunity, as is the case with lymphohyperplastic diseases.
  - Disruption in the mechanical barrier of the mucous membranes and skin, as is the case with mucositis following radiotherapy or placement of central and peripheral vein catheters, which are an entry point for bacteria.
  - The frequent underlying conditions, old age, bad nutrition of patients with cancer, population changes due to the natural flora, but also the frequently encountered thrombocytopenia in patients with malignancies provide the conditions for a compromised immune system.
- Acquired immune deficiency syndrome
- Patients suffering from chronic connective tissue disorders who receive corticosteroid, cytostatic and/or immunomodulatory medications.
- In general, potent antineoplastic therapies that include chemotherapy and radiotherapy regimens, expansion of the transplantation field and chronic administration of immunosuppressant therapies.

It has been clearly determined that neutropenia is the most significant risk factor for developing an infection. So mild neutropenia is when the number of neutrophils is 500-1000/cc, moderate when the number of neutrophils is 100-500/cc and severe when the number of neutrophils is less than 100/cc. The severity and duration of neutropenia and how quickly it spreads through the body are significant for the development and severity of the infection. Neutropenic patients with mild neutropenia and a duration that does not exceed 10 days run a lower risk. On the contrary, patients with severe neutropenia that lasts longer than two weeks run a high risk of developing severe infection.

The aetiology of neutropenia is depicted in the following tablet:

Medications	Peripheral damage
Alkylating agents (busulfan, chlorambucil, cyclophosphamide) Antimetabolites (methotrexate, 6-mercaptopurine, 5-fluorocytosine) Antibiotics (chloramphenicol, penicillins, sulfonamides) Phenothiazines Tranquillizers (meprobamate) Antiepileptic drugs (carbamazepine) Antipsychotic drugs (clozapine) Certain diuretics Anti-inflammatory drugs Antithyroid drugs, etc.	**Hypersplenism**
	Autoimmune diseases
	Rheumatoid arthritis Felty's syndrome Systematic lupus erythematosus
	Drugs acting ashaptens
	Phenylbutazone Certain diuretics Phenothiazines Alpha-methyldopa
	Wegener's granulomatosis
	Peripheral pooling (transient neutropenia)
Vitamin B12 and folic acid deficiency	**Severe bacterial muscle infection** (acute endotoxemia)
Infections	
Tuberculosis Typhoid fever Brucellosis Tularemia Infectious mononucleosis Malaria Leishmaniasis Viral hepatitis AIDS	**Dialysis**
	Cardiopulmonary bypass
	Blood diseases
	Idiopathic Cyclic neutropenia Aplastic anaemia Myelodysplastic syndromes Chediak-Higashi syndrome Genetic syndromes
	Marrow infiltration and Myelofibrosis

Neutropenia is the decrease in peripheral blood platelets to <150X109/L. It results in haemorrhagic tendency, it manifests various abnormal conditions (Table 3 (Bo et al., 2020)) and its severity is often associated with the prognosis of blood diseases. The development of pancytopenia limits the number of possible clinical diagnoses. Research teams around the world have tried to record the cases of pancytopenia they have clinically managed, to get a realistic overview of the frequency of diseases manifested with pancytopenia (Antoniadou & Giamarellou, 2007). A comparative description of the results of such studies is presented in Table 4.

The causes of febrile neutropenia are identified in relatively low rates, in the order of 40%, and involve Gram(+) and Gram(-) bacteria. The former include *Staphylococcus aureus* and CNS, and the latter *Escherichia coli* and *Pseudomonas aeruginosa*. Furthermore, additional micro-organisms have been accused of infections in neutropenic patients. Specifically, fungi and viruses (such as herpes simplex, herpes zoster and cytomegavirus) are deemed responsible for opportunistic infections in neutropenic patients. Non-infectious causes may also be blamed, such as medications (bleomycin and aracytin), as well as reactions to blood products. The main foci of infection are the buccopharynx, upper respiratory tract, skin and soft tissue, and lesser ones are the paranasal sinuses and the urinary tract. An interesting element of these infections is their clinical expression. In general, the clinical presentation of the infection in an immunocompromised patient differs significantly from conventional symptomatology. So, in pneumonia the symptoms are generally mild, with coughing and expectoration encountered in about half of the cases. By the same token, purulent exudate is encountered in 1/5 of cases, while urinary tract infections have a milder clinical presentation, with dysuretic symptoms appearing in around 1/3 of cases. (Antoniadou & Giamarellou, 2007; De Pauw & Verweij, 2005)

The criteria for initiation of antimicrobial therapy are:

- **Neutropenia**

When the neutrophils are <500/cc or <1000/cc and there is a prospect of their number dropping <500/cc in the next 48 hours.

- **Fever**

A wave of fever higher than 38.3° C or, alternatively, fever higher than 38° C for at least one hour.

- **Presence of symptoms**

These are signs and symptoms beyond fever, such as coughing with expectoration in pneumonia, with accompanying presence of non-musical crackles during auscultation of the lung fields.

The physical examination in this group of patients must be as meticulous as possible, given that an infection may be mistaken as subclinical. The examination of the *buccopharynx, skin* and *soft tissues,* but also the *digestive tract* is extremely important. The examination of the buccopharynx may reveal mucositis, herpetic stomatitis or the smear associated with candida infections. Gingivitis and periodontitis are just as common in patients with leukaemia.

Perineal cellulitis may be detected in the skin and soft tissues, which is very common in patients with myelomonocytic leukaemia. Ecthymagangrenosum is also common, found in moist areas of the skin, such as the perineum, the femoro-inguinal space and the axilla. It is typical in bloodstream infections caused by *Pseudomonas aeruginosa* and *Aeromonas spp.*, but also in infections caused by *Fusarium* spp.

The most common gastrointestinal disorders include diarrhoea, which may be due to an underlying condition, e.g. leukaemia, but it may possibly be a manifestation of *Clostridium* infection, in the event of accompanying, long-term use of antimicrobials. Another typical sign of febrile neutropenia is typhlitis, caused by anaerobic bacteria, such *Clostridium septicum,* which develops very quickly. In this case, the symptoms are severe and may lead to acute abdomen. They include nausea, vomiting and colicky abdominal pain, and are quite severe. *Strongyloidesstercoralis* may also be considered as the cause of infectious diarrhoea, especially in patients who report recent travel to developing countries. (Klastersky, 2004; Viscoli et al., 2005)

Laboratory and imaging tests will confirm the infection and its infectious focus.

Diagnostic approach

The evaluation of a neutropenic patient includes taking down a detailed personal, family and social medical history and performing a physical examination. The personal medical history will provide information about the underlying condition, which, as a rule, involves a blood malignancy or solid organ neoplasm, possible chemotherapy and/or radiotherapy regimen, possible contact with a person with bacterial or viral infections, and a previous history of infections.

The physical examination includes meticulous assessment of the respiratory system mainly, as well as the skin and mucous membranes to detect a potential focus of inflammation. So, the oral cavity, pharynx, eyes, perineum and anus are examined in detail. It is of major importance to examine the entry points of central catheters, as they often act as a gateway to the blood circulation for bacteria, and also to perform haemodynamic monitoring and to observe the patient's level of consciousness. Taking preventive measures is just as important for these patients, including meticulous cleaning and hygiene of the skin and oral cavity with antiseptic solutions. Medical rectal manipulation is forbidden, while central catheters must be cared for using sterile gloves and in aseptic conditions in general. Nutrition is very important, by following a neutropenic diet, which must not include fresh fruit and vegetables, or conserved food, that have not been boiled or cooked well (Hellenic Society of Chemotherapy, 2015)

The paraclinical examinations include:

- Blood and biochemical tests.
- Inflammation marker tests (pCT and CRP).
- Collection of blood cultures, both from the central catheter and from a peripheral vein. Specifically, two blood cultures are collected before initiation of antimicrobial therapy, with a 15-minute interval in between. If the fever persists, the blood cultures must be repeated daily.
- Urine and bronchial secretion cultures or bronchoalveolar lavage.
- Sputum or pus cultures in case of increased clinical suspicion of infection. (In neutropenic patients, the sputum is not rejected if it does not contain pus cells.)
- Serologic testing for specific pathogens. Galactomannan measurement using the ELISA test (up to three times a week), combined with beta-d-glucan measurement, may lead to treatment initiation for *Aspergillus*.
- Imaging with chest X-ray, as a rule. It is necessary – though, as a rule, it is expected to come up negative in the beginning – in order to monitor the progress of the disease.
- The use of high-definition CT imaging is controversial. It is recommended if the fever persists after three to four days, despite the administration of antimicrobial therapy, as it may possibly reveal respiratory infection in half the cases of patients with a negative chest X-ray 9 (HSC, 2015).

Classification of patients in risk groups

Various prognostic scores have been used to classify patients as high or low risk. The main ones are MASCC, CISNE and *Talcott*, with the Multinational Association for Supportive Care in Cancer (MASCC) score being the one used more often.

With the *MASCC* score the decision for home care and treatment will depend on many factors, such as the ability to comprehend instructions, the presence of a caretaker and the possibility of immediate access to a hospital, beyond allocating a low score to a patient. The MASCC score is performed during the first visit and is assessed every 24 hours thereafter.

The way the MASCC score is calculated is outlined in the following table.

Characteristic	Score
Burden of illness: - No or mild symptoms - Moderate symptoms - Severe symptoms	 5 3 0
No hypotension (systolic BP > 90mmHg)	5
No COPD	4
Solid tumour or lymphoma with no history of fungal infection	4
No dehydration	3
Outpatient onset of fever	3
Outpatient onset of fever	2
Maximum score = 26, Score > 21 is an indication of relatively low risk	

Another prognostic index is the *Clinical index of stable febrile neutropenia* (CISNE). This index takes into account the possible presence of chronic diseases, such as chronic obstructive pulmonary disease and congestive heart failure, stress-induced hyperglycaemia, number of monocytes below 200/μL, presence of mucositis and the general clinical condition of the patient, based on established criteria.

Table 2.

Mucositis
Graft versus host disease (GVHD)
Myeloid reconstitution syndrome
Pre-engraftment syndrome
Drug fever
Tumor fever
Deep venous thrombosis (DVTs), thromboembolism
Stroke
Transfusion-related fevers
Fever secondary to G-CSF/ GM-CSF
Radiation-related fevers

Based on the ASCO/IDSA guidelines, both the Talcott and the MASCC score may classify certain patients as low risk, while they may not be so, as opposed to the CISNE score, which presents fewer false negative results compared to the other two indexes. As a general rule, sensitivity is considered more important that specificity when it comes to classifying patients as low or high risk. To this end, the CISNE score, which presents increased sensitivity, is considered more useful for the clinical evaluation of febrile neutropenia (Bo et al., 2020; Baluch, 2019)

Outpatient care for low-risk patients

A significant number of patients may receive *home care treatment.* The absence of gastrointestinal problems is considered important, so that oral antimicrobial therapy may be well tolerated. Daily clinical and laboratory evaluation is a must, while if the fever persists for more than three days, inpatient care is deemed necessary. The combination of amoxicillin/clavulanic acid and ciprofloxacin is the preferred option. Alternatively, clindamycin is preferable for patients allergic to penicillin. Moxifloxacin or levofloxacin (newer quinolones) may be administered as monotherapy (Klastersky at al., 2016)

The following table lists the criteria for excluding oral antimicrobial therapy at home.

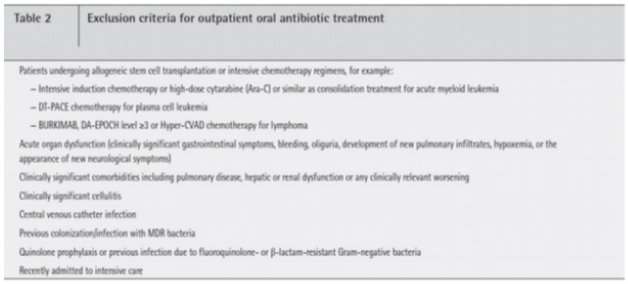

Table 2 Exclusion criteria for outpatient oral antibiotic treatment

Patients undergoing allogeneic stem cell transplantation or intensive chemotherapy regimens, for example:
- Intensive induction chemotherapy or high-dose cytarabine (Ara-C) or similar as consolidation treatment for acute myeloid leukemia
- DT-PACE chemotherapy for plasma cell leukemia
- BURKIMAB, DA-EPOCH level ≥3 or Hyper-CVAD chemotherapy for lymphoma

Acute organ dysfunction (clinically significant gastrointestinal symptoms, bleeding, oliguria, development of new pulmonary infiltrates, hypoxemia, or the appearance of new neurological symptoms)

Clinically significant comorbidities including pulmonary disease, hepatic or renal dysfunction or any clinically relevant worsening

Clinically significant cellulitis

Central venous catheter infection

Previous colonization/infection with MDR bacteria

Quinolone prophylaxis or previous infection due to fluoroquinolone- or β-lactam-resistant Gram-negative bacteria

Recently admitted to intensive care

Inpatient care for high-risk patients

Antimicrobial treatment includes third-generation cephalosporins, and specifically ceftazidime, which has antipseudomonal action, and cefepime from the fourth-generation cephalosporins, piperacillin / tazobactam, meropenem and imipenem, fluoroquinolones, monobactams and aminoglycosides, but also glycopeptides, such as vancomycin. The administration of piperacillin / tazobactam or cephalosporin with antipseudomonal action is preferred as escalation therapy. On the contrary, penems (imipenem or meropenem) are preferred as de-escalation therapy in gravely ill septic patients, patients with an increased risk of resistant pathogen carrier status, as well as in cases of proven epidemiological existence of increased resistance to commonly used antimicrobials, as is the case in ICUs. In addition, the combination of antipseudomonal beta-lactam and aminoglycoside or fluoroquinolone is recommended (Francesca et al., 2019). Antimicrobials may be used as monotherapy along with a broad-spectrum antibiotic, combined with antipseudomonal beta-lactam and aminoglycoside, but also with the addition of vancomycin in the aforementioned regimen, to manage the Gram(+) bacteria. It has not been documented whether the addition of aminoglycoside is superior to monotherapy; however, it is used for 3-5 days, mainly in Gram(+) blood steam infections, due to its bactericidal action. On the other hand, vancomycin, and antimicrobials acting against Gram(+) bacteria in general, are indicated for:

- Pneumonia.
- Soft tissue infection.
- Central catheter infection.
- Severe form of mucositis, especially if chemoprophylaxis or the initial therapy included quinolone or ceftazidime.
- MRSA colonisation, resistant streptococci and VRE. Positive blood culture for Gram(+) bacteria in general.
- Haemodynamic instability.

Monotherapy with third- or fourth-generation cephalosporins is recommended for high-risk febrile patients, without an evident focus, with short-duration neutropenia. The presence

of multiresistant Gram(-) bacteria, such as *Acinetobacter* spp., and mainly *Acinetobacterbaumannii,Pseudomonas* and*Stenotrophomonas,* led to the use of colistin, based on an antibiogram as a rule, although its usefulness in febrile neutropenia has not been adequately documented (Klastersky, 2004; Rolston, 2015)

Antimicrobial	Administration route	Dosage*
Cefepime	IV	2g/8hrs
Ceftazidime[a]	IV	2g/8hrs
Aztreonam	IV	2g/8hrs
Imipenem	IV	1g/8hrs
Meropenem (in 3-hour infusion)	IV	2g/8hrs
Doripenem (in 4-hour infusion)	IV	1g/8hrs
Moxifloxacin	IV/PO	400mg/24hrs
Levofloxacin	IV/PO	750mg/1hr or 500mg/12hrs
Ciprofloxacin	IV	400mg/1hr or 750mg or 1g/12hrs
Amikacin[b]	IV	15mg/kg/24hrs
Gentamicin[b]	IV	7 mg/kg/24hrs
Tobramycin[b]	IV	7 mg/kg/24hrs
Piperacillin / Tazobactam	IV	4.5 g/6hrs
Vancomycin[c]	IV	1g (15-20mg/kg)/12hrs
Teicoplanin[c]	IV	10mg/kg/24hrs
Linezolid	IV	600mg/12hrs
Daptomycin	IV	6-10mg/kg/24hrs
Colistin (methanesulphonate)	IV	Loading dose 9,000,000 followed by 4,500,000/12hrs
Tigecycline	IV	Loading dose 100mg followed by 50 mg/12hrs

*For normal renal function in adults.

[a] In cases of marginal sensitivity of the pathogen (evaluation based on MIC), a dose of 3 g/8hrs. may be administered.

[b] A loading dose precedes for tobramycin and gentamicin, with 3 mg/kg, and for amikacin with 10 mg/kg. The trough levels must be < 1 μg/ml for gentamicin and tobramycin and 4-5 pg/ml for amikacin.

[c]In established infection, a loading dose of 25-30 mg/kg is required, as well as monitoring of the trough levels of the drug (15-20 mg/L). Vancomycin is not used when the pathogen has an MIC > 1 mg/L.

[d]A loading dose precedes, with dose administration every 12 hours in the first 24 hours.

As a rule, antimicrobial therapy must be designed and applied based on the localised focus of the fever, as shown in the table below:

Table 1 Empirical antibiotic therapy according to clinical focus of infection

Entity	Antibiotic treatment
Mild oropharyngeal mucositis	- Cefepime
Moderate-severe oropharyngeal mucositis	- Piperacillin-tazobactam - Imipenem or meropenem
Neutropenic enterocolitis	- Piperacillin-tazobactam - Imipenem or meropenem * Consider treating *C. difficile* if high index of suspicion
Skin and soft tissue infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- - Vancomycin, daptomycin, or linezolid (if history of MRSA colonization/infection) * Consider adding clindamycin if severe necrotizing infection
Intravascular catheter infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- - Vancomycin or daptomycin
Pneumonia	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem +/- - Fluoroquinolones, aminoglycosides, colistin * Consider association with fluoroquinolones or macrolides if pneumonia is community-acquired and an atypical bacterial etiology is suspected. * In patients with MRSA colonization or an epidemiological situation of high endemicity, consider combination with linezolid or vancomycin. * In severely ill patients, those previously colonized/infected with MDR Gram-negative bacilli, or nosocomial cases, according to local epidemiology. * During the flu season, use empirical oseltamivir until PCR results are received. * Consider the possibility of alternative causes (*Pneumocystis jirovecii*, Cytomegalovirus) in risk patients with bilateral infiltrates.
Urinary tract infection	- Cefepime - Piperacillin-tazobactam - Imipenem or meropenem
Acute meningitis	- Cefepime or meropenem + - Ampicillin * In risk patients with suggestive clinical forms, or space-occupying lesions, consider alternative causes (*Cryptococcus, Listeria, Nocardia*, filamentous fungi, toxoplasmosis, and *Mycobacterium tuberculosis*)
Meningoencephalitis	Use same treatment as acute meningitis, with adding of Acyclovir

MRSA: methicillin-resistant *Staphylococcus aureus*

Febrile Neutropenia in Immunocompromised Patients Part 2

Resolution of fever

Re-assessment of the antimicrobial therapy is recommended within three days from initiation of said therapy. Upon indication of apyrexia, the initial antimicrobial therapy is continued, until the number of neutrophils reaches 500/cc. The treatment duration is adjusted depending on the focus of the infection and the corresponding pathogen. In all events, it is best to avoid de-escalation of the antimicrobial therapy to a narrow-spectrum antibiotic due to the risk of superinfection. In the case of central catheter blood stream infection, lock therapy, meaning the locking of the catheter lumens, is considered effective.

Persistent fever

Upon indication of persistent fever beyond three days, and provided the patient remains clinically stable, modification of the antimicrobial therapy is not recommended, but re-evaluation and investigation of the infection for atypical pathogens, fungi, *Pneumocystis jirovecii, Listeria* or *Nocardia*. In addition, the possibility of non-infectious aetiology of the fever – e.g. due to transfusions, pharmaceutical treatment, phlebitis or graft versus host disease (GvHD) – must be investigated. In these cases, a chest and paranasal sinus CT is recommended for diagnosis of possible (systemic) fungal infection. Empirically,

antifungal therapy is added after at least five days of apyrexia. The possibility of chronic systemic candidiasis becomes strong in the event of persistent fever and resolution of neutropenia, in which case, the discontinuation of antimicrobial therapy is recommended.

Upon indication of negative imaging and other laboratory tests, measurement of beta-d-glucan and galactomannan is recommended.

All of the above are depicted in the following figure.

<table>
<tr><td colspan="4">Re-assessment after 3-5 days</td></tr>
<tr><td colspan="2">Afebrile patient (oral temperature ≤37.8ºC)</td><td colspan="2">Persistent fever without evident focus of infection (FUO)</td></tr>
<tr><td>No cause identified for the fever</td><td>Documentation of infection</td><td rowspan="2">If patient is stable, continue treatment</td><td rowspan="2">Re-assessment and chest and paranasal sinus CT, upper abdominal U/S, serological markers for systemic fungal infections</td></tr>
<tr><td>Continuation of initial antibiotic therapy, discontinuation of aminoglycoside or colistin or tigecycline</td><td>Treatment modification if necessary</td></tr>
<tr><td></td><td></td><td>Stable clinical condition</td><td>Deteriorating clinical condition</td></tr>
<tr><td></td><td></td><td>Continuation of initial treatment. Discontinuation of vancomycin or therapy for multiresistant Gram(-) if administered initially</td><td>Change of antibiotics. Addition of vancomycin upon indication or treatment for carbapenem-resistant bacteria</td></tr>
<tr><td>Empirical antifungal therapy. Continuation of antimicrobials</td><td></td><td>Persistent FUO after 5th day while increase in neutrophils not expected</td><td>Re-assessment for fungal, viral or mycobacterial infections</td></tr>
<tr><td>Response</td><td>Persistent FUO</td><td>Re-assessment</td><td></td></tr>
<tr><td colspan="2">Continuation of antifungals for ≥2 and until the neutrophils increase</td><td></td><td></td></tr>
</table>

Treatment duration

Upon apyrexia after three to five days, discontinuation of the antimicrobial therapy is recommended, provided the neutrophils are more than 500/cc.

If the fever persists, the antimicrobials may be discontinued for four to five days, provided the neutrophils have increased to more than 500/cc. In all events, clinical and laboratory evaluation is recommended after the end of antimicrobial therapy, to avoid the risk of resurgence of the infection or the risk of superinfection (Freifeld et al., 2011)

Prophylactic antimicrobial therapy is not recommended, apart from the case of patients with allogeneic haematopoietic stem cell transplantation, chronic intake of corticosteroids and leukaemia or lymphoma, who have an increased risk of developing pulmonary infection from *Pneumocystis jirovecii,* for whom the administration of trimethoprim/sulfamethoxazole is recommended. Especially for transplant patients, prophylaxis is recommended after bone marrow regeneration. Newest findings recommend the use of prophylactic therapy with fluoroquinolone in high-risk patients with fewer than 100/cc neutrophils and neutropenia duration expected to exceed one week. The use of growth factors is important for the prevention of infections. They are recommended for expected long-term fever (> 1 week) and in significant-risk fever (>20%). However, the decrease in mortality from their use has not been documented (Lyman & Kleiner, 2011; Tzeletas et al., 2019)

Fungal infections

Suspicion of fungal infection sets in after the second, and usually the third, week of treatment, and provided the patient has received antimicrobial therapy without the fever receding. The risk of fungal infection is also high in patients who have undergone allogeneic haematopoietic stem cell transplantation or took corticosteroids for a long period of time, many times, even for months or years. The main pathogens for fungal infections are the *Candida* and *Aspergillus* species, especially after the third week of neutropenia. Other pathogenic fungi include: *Mucor, Acremonium, Trichosporon,* etc. Antifungal therapy includes amphotericin B and its lipid formulations, which are preferable due to their low toxicity, echinocandin and voriconazole, especially upon suspicion of aspergillosis. The administration of voriconazole is best be avoided in patients with renal failure (creatinine clearance < 50 ml/min). Treatment may be discontinued after two weeks, provided the patient is afebrile and the neutrophils are over 500/cc.

The treatments of choice based on the corresponding fungus are listed in the table below.

Fungal infection (possible or documented)	Proposed treatment	Alternative treatment
Candida sp. infection Before identification Candida albicans, tropicalis	Echinocandin[a] Fluconazole	Lipid formulation of amphotericin B[b] Lipid formulation of amphotericin B[b] Echinocandin, Voriconazole
Candida glabrata	Echinocandin	Lipid formulation of amphotericin B[b]
Candida krusei	Echinocandin	Lipid formulation of amphotericin B[b] Voriconazole
Candida parapsilosis	Fluconazole	Lipid formulation of amphotericin B[b] Voriconazole
Aspergillosis (*Aspergillus sp.*)	Voriconazole	Lipid formulation of amphotericin B[b] Echinocandin[a], Itraconazole, Posaconazole
Fusariosis (Fusarium sp.)	Voriconazole	Lipid formulation of amphotericin B[b]
Zygomycosis / Mucormycosis (*Zygomycetes sp.* / *Mucorales sp.*)	Lipid formulation of amphotericin B[b]	Posaconazole
Phaeohyphomycosis Scedosporiumprolificans, Alternaria, Bipolaris, CurvulariaExophiala etc.	Itraconazole + surgical resection	Voriconazole Posaconazole
Scedodporlumapiospermum	Voriconazole	Itraconazole
Disease from Penicillium sp.	Lipid amphotericin B[b]	Itraconazole
Sporotrichosis Cutaneous Disseminated, meningeal	Itraconazole Lipid formulation of amphotericin B[b]	Fluconazole Fluconazole
Cryptococcosis	Lipid formulation of amphotericin Bb + fluorocytosine (2 wks.) Followed by fluconazole	Fluconazole + fluorocytosine (2 wks.) Followed by fluconazole
Empirical treatment of febrile neutropenia	Lipid formulation of amphotericin Bb Echinocandin	Voriconazole

[a]*Echinocandin: Caspofungin or micafungin.*
[b]*Liposomal amphotericin B (Ambisome), lipid complex of amphotericin B (Abelcet).*

Table 4: Treatment of choice and alternative treatment for the most common fungal infections.

Prophylactic antifungal therapy is recommended in patients who have undergone allogeneic transplantation, in which case fluconazole, micafungin and voriconazole are used, whereas posaconazole is recommended for the prevention of infiltrating aspergillosis in patients with acute myelogenous leukaemia undergoing intensive chemotherapy and patients who have undergone allogeneic transplantation. Use of special high efficiency particulate air (HEPA) filters within the rooms of neutropenic patients may prove an essential measure for the prevention of hyphomycetes. Besides, it is best combined with a positive pressure environment (HSC, 2015; Pappas et al., 2015; Cornery et al., 2007)

Viral infections

Herpetic infections develop in neutropenic patients with increased morbidity, especially the ones who have undergone allogeneic haematopoietic stem cell transplantation, in the first month post-transplantation. Therefore, the incidence of herpes type 1 and 2, varicella-zoster virus (VZV) and CMV infections increases. The infections they cause include pleuritis, encephalitis, colitis and retinitis. In addition, infections may also be caused by the respiratory syncytial virus (RSV). In these cases, the medications administered are acyclovir and ganciclovir (for cytomegavirus infection), ribavirin (for RSV infection), and oseltamivir and zanamivir (for the influenza virus). Empirical antiviral therapy without indications is not recommended. Prophylaxis with acyclovir is recommended when taking fludarabine in patients with chronic intake of corticosteroids or allogeneic transplantation (HSC, 2015; Cornery et al., 2007)

Conclusions

Febrile neutropenia is an emergency condition demonstrating high mortality if not treated early with proper antimicrobial therapy. Ongoing clinical and laboratory evaluation of patients during hospitalisation is the cornerstone for its

proper management and cure. It is very important to note that the infection-related clinical signs are greatly modified in neutropenic patients. Moreover, infections caused by atypical bacteria are frequent, as are infections by viruses and fungi or protozoa, such as *Pneumocystis jirovecii*. The role of the clinical physician is extremely important for its proper diagnosis and documentation, and for the administration of suitable treatment for the right period of time, and its possible modification if necessary.

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