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Mini Review

Febrile Neutropenia in Immunocompromised Patients: Part II

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Abstract

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). As a rule, antimicrobial therapy in febrile neutropenia must be designed and applied based on the localised focus of the fever. Part II of the article involves the re evaluation of treatment and also special infections due to fungus or viruses.

Keywords: Febrile Neutropenia; Virus; Fever

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 table 1.

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 [1-11].

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

Table 1: Guidelines for diagnosis and treatment of febrile neutropenia.

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 [12,13].

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 2 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, Curvularia Exophiala* etc.	Itraconazole + surgical resection	Voriconazole Posaconazole
Scedodporlum apiospermum	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 B[b] + fluorocytosine (2 wks.) Followed by fluconazole	Fluconazole + fluorocytosine (2 wks.) Followed by fluconazole
Empirical treatment of febrile neutropenia	Lipid formulation of amphotericin B[b] Echinocandin	Voriconazole
[a]*Echinocandin: Caspofungin or micafungin.* [b] *Liposomal amphotericin B* (Ambisome), lipid complex of amphotericin B *(Abelcet).*		

Table 2: 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 [6,14,15].

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 cytomega virus 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 [6,15].

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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