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Management of Febrile Neutropenia in Children with Cancer

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Abstract

Febrile neutropenia (FN) is the most common complication of childhood cancer treatment with mortality rates of untreated patients up to 21%.

The recognition and management of FN is fundamental to preserve the children health status and avoid life-threatening complications. Physical and laboratory assessments should be performed in every patient with FN to identify any potential site of infection to be promptly treated. Hence, an empiric antimicrobial therapy remains the gold standard for the management of these patients. Antimicrobial treatment should be based on local epidemiological data and antibiotic susceptibility; a combination of a fourth-generation antipseudomonal cephalosporin with an aminoglycoside is generally adopted. Empirical administration of glycopeptides, in absence of documented Gram-positive bacterial infection is not recommended for routine use. Despite the progress in the management of febrile neutropenia and its relatively low mortality, the emergence of resistant pathogens is increasing, and the development of new effective antimicrobials are needed. Established criteria for a risk adapted approach is still lacking and no definitive data supporting the duration of empiric treatment are present. De-escalation strategies should be implemented to reduce both antibiotic exposure and resistance as well as hospital stay.

Keywords: Children, Febrile Neutropenia, Cancer

Introduction

Cancer treatments and cancer can cause potential side effects. Fever with neutropenia is a common clinical problem in patients receiving cancer treatment. Likewise, infections remain an important cause of morbidity and mortality for these patients (1-4).

Antineoplastic drugs have cytotoxic effects on the bone marrow cells, leading to disruption in immunological protection. Neutropenia is the most prominent chemotherapy-induced immune defect and can cause increased patients' susceptibility to bacterial, fungal, viral, or protozoan infections (5). Fever during neutropenia may be the only sign of an infectious episode. Because of the risk of a complicated clinical course due to pathogens causing severe and life-threatening bacterial infections in paediatric cancer patients, timely inpatient treatment with broad-spectrum antibiotics is the standard of care. Despite this consensus, previous surveys performed in paediatric cancer centres from different countries revealed a high level of heterogeneity in many key topics of clinical management (6).

This paper aims to provide a therapeutic protocol for the prompt management of febrile neutropenia in children with cancer.

Definition: At present, there is no international uniformly agreed definition of febrile neutropenia.

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According to recent data, febrile neutropenia is referred to as a temperature once > 38.5°C or > 38°C with repeated measurement after one hour with an absolute neutrophil count of less than 500/microl.

When the neutrophil count decreases to <1000/microl, the susceptibility to the infections increases, and patients with a neutrophil count of <500/microl are considered at higher risk for bacterial and fungal infections. The duration and the severity of neutropenia are directly related to the risk of severe infection. With a neutrophil count between 1000 and 500/microl, the risk is about 15%, between 500 and 100 of 20-35%, with counts <100 up to 50% (7). Moreover, disease-related myelosuppression, abnormalities of phagocytic function, damage to the natural barriers (skin and mucosae), surgery, and use of a central venous catheter may further increase the risk of infection in neutropenic children (8,9).

Aetiology: The main source of pathogens in patients with febrile neutropenia is the host's endogenous flora (10). In many cases, endogenous flora is changed by long-lasting antibiotic treatments and by chemotherapy itself. However, many other exogenous microorganisms can be acquired. Approximately 50% of pathogens can grow during hospitalization. They can be acquired from contaminated air or water, from contact with other patients, personnel, or equipment.

Gram-positive bacteria, as Staphylococcus, Streptococcus, Enterococcus faecalis, Bacillus species, and other bacteria, now account for about 60-70% of all microbiologically documented infections. Some gram-positive organisms may be methicillin-resistant (S. aureus, Viridans streptococci, and Pneumococci) and can be responsible for fulminating infections if not promptly treated (11,12). Moreover, S. aureus and coagulase-negative staphylococci are the most common causes of catheter-associated infections (13,14). As for gram-negative bacteria, P. aeruginosa, E. coli, and Klebsiella species represent significant causes of infection and must be treated with selected antibiotics (15,16). Anaerobic bacteraemia occurs in less than 5% of patients with febrile neutropenia (17). Patients with cancer who have neutropenic colitis, intrabdominal infections, perirectal abscesses, or periodontal disease are at risk for anaerobic bacteraemia, frequently in the context of a polymicrobial infection.

An emerging challenge is the increasing rate of multidrug-resistant gram-negative bacteria related to the antibiotic selection pressure and induction of beta-lactamases after the use of beta-lactams, including the carbapenems (18,19). Similarly, the incidence of resistance of the common gram-positive cocci to beta-lactams is increasing in neutropenic patients (20). The emergence of antibiotic-resistant gram-positive pathogens led to the extensive use of vancomycin as part of the initial empirical treatment of febrile neutropenia. On the other hand, a decreased susceptibility to vancomycin for some gram-positive bacteria has been registered.

Fungal infections (Candida and Aspergillus species) are rare at the beginning of the febrile state, but they may occur during long-lasting antibiotic therapy, protracted neutropenia, or during the resolution of the neutropenia itself (21). Candida species can also cause catheter-related infections. Candida albicans followed by C. glabrata, C. tropicalis, and C. parapsilosis is among the more frequent candidemia (22,23).

Assessment of patients with febrile neutropenia

Physical examination: Physical examination is the first initial medical approach to evaluate any possible site of infection. Physicians should perform a careful physical examination, including the skin, skin folds, genitalia, anal area, oropharynx, mouth, and ears. Signs of infection in one or more of these sites might lead to more selective and more efficacious empirical therapy. Besides, intravenous central line sites should be inspected carefully for signs of inflammation and any exudates from the catheter site should be

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stained and cultured. Vital signs (temperature, respiratory rate, blood pressure, and heart rate) should be registered (24-28).

Laboratory evaluation: Before the beginning of antibiotic treatment, blood samples should be obtained from the central venous catheter (CVC) and the peripheral vein for bacterial and fungal cultures (29). Routine blood tests should include full blood count, renal and liver function tests; markers of inflammation such as c-reactive protein (CRP), and procalcitonin. A blood gas for venous lactate should be considered if the patient is unwell to assess for sepsis (30).

Empirical imaging for the asymptomatic patient is usually not indicated, however, the following modalities can be considered: chest X-ray (CXR) if there are respiratory signs or symptoms or considered if the focus of infection is unclear [31,32]. CXR may not show abnormalities if the patient is profoundly neutropenic and should be interpreted with caution. If no pathological changes are detected on CXR despite respiratory symptoms then a chest computed tomography (CT) should be considered. Abdominal ultrasound can be considered if fever is persistent (at least 72 hours) to assess a fungal involvement of the kidneys and/or liver.

If a catheter entry site is inflamed or draining, the fluid exuded should be sent for staining and culture. Swabs of any inflamed or discharging skin or mucous membrane sites, especially purulent discharge, should be regularly considered for culture.

Empiric antibiotic therapy: Empiric antibiotic treatment of febrile neutropenia should be started as soon as possible. The clinical deterioration in patients with febrile neutropenia can be rapid and potentially life-threatening. The infecting agent is confirmed microbiologically in only one-third of neutropenic patients so the scheme of empiric therapy should be based on local epidemiological data about the most probable isolated pathogen and its antibiotic susceptibility (33).

Treatment should be started within 6 hours from the temperature spike and include a fourth-generation antipseudomonal cephalosporin (i.e. Cefepime 100 mg/kg/day) and an aminoglycoside (i.e. Amikacin 15 mg/kg/day). Recent data suggest that using the same dosage of aminoglycoside in a single daily dose instead of two or three daily administrations is more effective and less toxic (34-37). Because of aminoglycosides nephrotoxicity, drug plasma concentration should be monitored in patients with impaired renal function, and dosage should be adjusted until the optimal therapeutic concentration is achieved (16). When the drug is administrated as a single dose, its blood level has to be detected 8 hours after the end of infusion and should be maintained below 15 mg/l (38).

Several studies, in adults, have shown no striking differences between monotherapy, especially with carbapenem antibiotics, and multidrug combinations for empiric treatment of uncomplicated episodes of fever in neutropenic patients (39,40).

The advantage of combination therapy is due to the potential synergistic effects against some Gram-negative bacilli and the minimal emergence of drug-resistant strains during treatment (41-43).

In presence of mucous membrane lesions due to herpes simplex virus, an antiviral drug (Acyclovir) should be considered.

Addition of glycopeptides to the empiric regimen: Based on the emergence of vancomycin-resistant organisms, administration of Vancomycin or Teicoplanin in the initial empirical regimen should be limited to specific indications, such as 1) clinical suspicion (catheter-related infection, skin abscesses, acne, etc) of Gram-positive bacteria infection; 2) microbiological documentation of Gram-positive bacteria infection, resistant to the initial antibiotic regimen; 3) institution where Gram-positive organisms are common causes of serious infections.

CVC removal should be considered in patients with persistent bacteraemia despite 48

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hours of appropriate intravenous antibiotic therapy (44-47).

Duration of treatment: Following an afebrile status within 48 hours since the beginning of the antibiotic treatment, the empiric therapy can be continued until the neutrophil count rises to > 500/microl.

If fever persists, cultures from additional blood samples and specimens of specific sites of infection should be repeated. It would be reasonable not to change the initial regimen for the first 3 days, even if the patient remains febrile but clinically stable (16).

In that circumstances, a glycopeptide, such as Vancomycin, 40 mg/kg/day in four doses, should be added to the empiric treatment. In case of infusion in a peripheral line, or when a reduced fluid intake is needed, Teicoplanin has to be preferred to Vancomycin.

Antibiotic therapy should be continued after defervescence is obtained (for more than 48 hours) and neutropenia is resolving (neutrophil count >500/microl).

The criteria retained in several studies for the early suspension of the antibiotic therapy are apyrexia for at least 24 hours, a satisfactory clinical status, the absence of positive blood cultures, and haematological signs showing the end of aplasia in patients in remission of their disease (16).

Antifungal treatment: A persisting fever after 5 days of empirical antibiotic therapy can be due to a non-bacterial aetiology. Diagnostic reassessment should be directed at fungal infections (especially chronic systemic candidiasis, aspergillosis, histoplasmosis, and trichosporonosis). The proportion of documented fungal infection increases up to 30% in febrile patients with cancer as neutropenia persists, so that a delayed administration of antifungal therapy may be detrimental (48).

The introduction of empirical antifungal therapy (i.e. liposomal Amphotericin B 1-3 mg/kg/day). is recommended from the fifth day of persistent fever. Recently, Fluconazole has been suggested in patients with low risk of mould pathogens infection (such as Aspergillus species), but should not be used in patients on previous fluconazole prophylaxis (49).

Voriconazole, a second-generation triazole, has been investigated as a possible alternative to the liposomal Amphotericin B. A randomized multicentre trial compared the efficacy of the two compounds, showing no statistically significant differences in terms of defervescence for 48 h before the recovery of the neutrophil count, breakthrough fungal infections, fungemia-related deaths, the response of baseline infection, and discontinuation of the study drug because of adverse events. Nevertheless, the study has shown that the incidence of major adverse events, including nephrotoxicity and hepatotoxicity, was less frequent with Voriconazole (50).

Another randomized trial compared liposomal Amphotericin B vs. Caspofungin (the first licensed agent of the echinocandin class) and no significant differences in the efficacy of the two drugs were shown, whereas nephrotoxicity, infusional reactions, and drug-related adverse events were less frequent in the Caspofungin group (51).

If a documented infection is detected, the regimen should be modified according to the antibiogram, but it should still provide broad-spectrum coverage for the potential presence of co-pathogens and for preventing bacterial superinfection.

Intravascular catheter-related infections: Management of catheter-related infection varies according to the type of catheter involved. CVC removal should be considered in patients with persistent bacteraemia despite 48 hours of appropriate antibiotic therapy o when clinical signs of unexplained sepsis.

For the management of bacteraemia and fungemia from an implantable device, such as a

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port-a-cath, it is important to ascertain a true catheter-related bloodstream infection, rather than skin contamination, catheter colonization, or infection from another source. The decision to remove the catheter should be based on the severity of the patient's illness, documentation that the vascular-access device is infected, assessment of the specific pathogen involved, and presence of complications (52).

Recommendations for patients at the end of aplasia: If the fever is still persistent at the end of aplasia, blood, sputum, and urine samples should be collected for microscopy and culture, and deep infection (abdominal abscesses, sinusitis, fungal pulmonary site,..) should be investigated (16,53-58).

When the neutrophil count rises to > 500/ microl and the patient is apyretic for at least 48 hours, antibiotic treatment can be stopped (16,53-58).

Options for initial empiric therapy in low-risk febrile neutropenic patients: Currently, it has been evaluated the possibility of treating febrile neutropenic patients at home or as outpatient patients. Many studies demonstrated that in some cases with good logistics (patients living near the hospital and with the availability of home care) the admission to the hospital just for the administration of antibiotics can be avoided (49).

Patients with recovering monocyte count are generally considered to be better candidates for outpatient treatment than patients with decreasing counts or no indication of marrow recovery. Children presenting with an initial absolute monocyte count >100/microl, without any comorbidity, and with normal chest X-ray findings are at low risk for significant bacterial infections.

A collaborative, prospective, multicentre study on the paediatric population pointed out five clinical and laboratory variables at the onset of febrile neutropenia that could identify children at high risk for invasive bacterial infection (IBI): 1) serum C-reactive protein (CRP) levels of 90 mg/L or greater; 2) hypotension; 3) relapse of leukaemia as cancer type; 4) platelet count of 50,000/μL or less; 5) recent (d" 7 days) chemotherapy. An IBI occurred in 2%, 17%, 48%, 75%, and 100% of episodes presenting with none, one, two, three, four, or more risk factors, respectively (59).

The current evidence is that children at low risk for IBI can be treated as outpatients with a comparable outcome to children treated in the hospital (60).

As an alternative to initial outpatient therapy, early discharge with continued outpatient oral therapy may be considered after a brief inpatient admission during which intravenous therapy is initiated, if a severe infection is excluded and the status of initial culture specimens is ascertained.

Conclusions

Evidence in adult patients with fever and neutropenia allows drawing clear guidelines, while data collected in the paediatric population does not provide the same confidence level.

To date, the prompt institution of empiric broad-spectrum antibiotics at the onset of fever is the gold standard for the treatment of febrile neutropenic children undergoing chemotherapy. With this approach, morbidity and mortality have been significantly reduced even if they have not been eliminated. Current clinical guidelines for febrile neutropenia management indicate that all children with febrile neutropenia should be managed with appropriate antibacterial therapy until the resolution of febrile neutropenia.

Despite the progress in the management of febrile neutropenia and its relatively low mortality, the emergence of resistant pathogens requires the development of new effective antimicrobials. Moreover, treatment with either an oral antibacterial regimen as initial therapy or early discontinuation of antibacterial therapy in an outpatient setting should remain investigational at present. A prerequisite before recommending implementation of an outpatient management program in different

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settings is to have an experienced medical team that can assure close follow-up of patients and a rapid response for patients who show clinical deterioration.

Conflict of interest

Authors have no conflict of interest.

References

1. Viscoli, C. and Castagnola, E. (1998). Planned progressive antimicrobical therapy in neutropenic patients. Br J Haematol. 102:879-888
2. Ruggiero, A., Ferrara, P., Attinà, G., Rizzo, D. and Riccardi, R. (2017). Renal toxicity and chemotherapy in children with cancer. Br J Clin Pharmacol. 83(12):2605-2614
3. Ruggiero, A., Triarico, S., Trombatore, G., et al. (2013). Incidence, clinical features and management of hypersensitivity reactions to chemotherapeutic drugs in children with cancer. Eur J Clin Pharmacol. 69(10):1739-1746
4. Triarico, S., Rinninella, E., Cintoni, M., et al. (2019). Impact of malnutrition on survival and infections among pediatric patients with cancer: a retrospective study. Eur Rev Med Pharmacol Sci. 23(3):1165-1175
5. Crawford, J., Dale, D.C. and Lyman, G.H. (2004).Chemotherapy-induced neutropenia. Cancer.100:228-237
6. Davis, K. and Wilson, S. (2020). Febrile neutropenia in paediatric oncology. Paediatr Child Health (Oxford). 30(3):93-97
7. Meena, J.P. and Gupta, A.K. (2021). Shorter Duration of Antibiotics in Low-Risk Febrile Neutropenia in Children with Malignancy. Indian J Pediatr. Jan 7. doi: 10.1007/s12098-020-03654-9
8. Lieske, G.J. and Burgess, A.W. (1992). Granulocyte Colony-stimulating Factor and Granulocyte-Macrophage Colony-stimulating Factor. N Engl J Med. 327:28-35
9. Barton, C.D., Waugh, L.K., Nielsen, M.J. and Paulus, S. (2015). Febrile neutropenia in children treated for malignancy. J Infect. 71 Suppl 1:S27-35
10. Murono, K., Hirano, Y., Hoyano, S., Ito, K. and Fujieda, K. (2003).Molecular comparison of bacterial isolates from blood with stainscolonizing pharynx and intestine in immunocompromised patients with sepsis. J Med Microbiol.52:527-530
11. Bochud, P.Y., Calandra, T. andFrancioli, P. (1994).Bacteremia due to viridans streptococci in neutropenic patients: a review. Am J Med. 97:256-264.
12. Pizzo, P.A., Ladish, S. and Robichaud, K. (1980).Treatment of gram-positive septicaemia in cancer patients. Cancer. 45:206-207.
13. Douard, M.C., Arlet, G., Longuet, P., et al. (1999).Diagnosis of venous access port–related infections. Clin Infect Dis. 29:1197–202.
14. Benezra, D., Kiehn, T.E., Gold, J.W., et al.(1988).Prospective study of infections in indwelling central venous catheters using quantitative blood cultures. Am J Med. 85:495-8.
15. Rolston, K.V.I. and Tarrand, J.J.(1999). Pseudomonas aeruginosa—still a frequent pathogen in patients with cancer: 11-year experience at a comprehensive cancer center. Clin Infect Dis. 29:463–4.
16. Hughes, W.T., Armstrong, D., Bodey, G.P, Bow, E.J., Brown, A.E., Calandra, T., Feld, R., Pizzo, P.A., Rolston, V.I., Shenep, J.L. and Young, L. (2002). Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. Clin Infect Dis. 34:730–51
17. Fainstein, V., Elting, L.S. and Bodey, G.P. (1989).Bacteremia caused by non-sporulating anaerobes in cancer patients. A

Vol. 15 (2) 115-123, April 2021, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2021.2.13

12-year experience. Medicine (Baltimore). 68:151–162.

18. Gomez, L., Garau, J., Estrada, C., et al. (2003).Ciprofloxacin prophylaxis in patients with acute leukemia and granulocytopenia in an area with a high prevalence of ciprofloxacin-resistant Escherichia coli. Cancer. 97:419–424.

19. Minami, S., Akama, M., Arkai, H., et al.(1996).Imipenem and cephem resistant Pseudomonas aeruginosa carrying plasmids coding for class-B beta-lactamase. J Antimicrob Chemother. 37:433–444.

20. Rolston, K.V.I., Raad, I., Whimbey, E. and Bodey, G.P. (1997).The changing spectrum of bacterial infections in febrile neutropenic patients. In: Klastersky ,J.A., editor. Febrile neutropenia. Berlin: Springer-Verlag, 53–56.

21. Lessiones, J.A., Lee, J.W., Navarro, E.E, et al. (1992). Vascular catheterassociated fungemia in patients with cancer: analysis of 155 episodes. Clin Infect Dis. 14:875–883.

22. Edmond, M.B., Wallace, S.E., McClish, D.K., Pfaller, M.A., Jones, R.N., Wenzel, R.P. (1999).Nosocomial bloodstream infections in the United States hospitals: a three-year analysis. Clin Infect Dis. 29:239–244.

23. Kontoyiannis, D.P. and Bodey, G.P. (2002).Invasive aspergillosis in 2002: an update. Eur J Clin Microbiol Infect Dis. 21:161–172.

24. Pherwani, N., Ghayad, J.M., Holle, L.M. and Karpiuk, E.L. (2015). Outpatient management of febrile neutropenia associated with cancer chemotherapy: risk stratification and treatment review. Am J Health Syst Pharm. 72(8):619-31.

25. Scheler, M., Lehrnbecher, T., Groll, A.H., et al. (2020). Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. Infection. 48: 607–618

26. Falsini, B., Ziccardi, L., Lazzareschi, I., et al. (2008). Longitudinal assessment of childhood optic gliomas: relationship between flicker visual evoked potentials and magnetic resonance imaging findings. J Neurooncol. 88: 87-96

27. Falsini, B., Chiaretti, A., Barone, G., et al. (2011).Topical nerve growth factor as a visual rescue strategy in pediatric optic gliomas: a pilot study including electrophysiology. Neurorehabil Neural Repair. 25: 512-520

28. Iuvone, L., Peruzzi, L., Colosimo, C., et al. (2011). Pretreatment neuropsychological deficits in children with brain tumors. NeuroOncol. 13(5):517-524

29. Rolston, K.V.I. (1999). New trends in patient management: risk-based therapy for febrile patients with neutropenia. Clin Infect Dis.29:515–21

30. Allen, U., Smith, C.R. and Prober, C.G. (1986). The value of skin biopsies in febrile, neutropenic, immunocompromised children. Am J Dis Child. 140:459–461

31. Korones, D.N. (2004). Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer? Pediatr Blood Cancer. 43(7):715-717

32. Renoult, E., Buteau, C., Turgeon, N., Moghrabi, A., Duval, M. and Tapiero, B. (2004). Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer ? Pediatr Blood Cancer. 43(3):224-228

33. Bodey, G.P., Rodriguez, V., Chang, H.Y. and Narboni, G. (1978). Fever and infection in leukemic patients. A study of 494 consecutive patients. Cancer. 41:1610-1622

Vol. 15 (2) 115-123, April 2021, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2021.2.13

34. Cometta, A., Calandra, T., Gaya, H., et al. (1996). Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother .40:1108-1115

35. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. (1993). Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infections in patients with cancer and granulocytopenia. Ann Intern Med. 119:584-593

36. Cometta, A., Zinner, G., de Bock, R., et al. (1996). Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother. 39:445-452

37. Viscoli, C., Dudley, M., Ferrea, G., et al. (1991). Serum concentrations and safety of single daily dosing of amikacin in children undergoing bone marrow transplantation. J. Antimicrob Chemother. 27(Suppl. C):113-120

38. Viscoli, C., Castagnola, E., Caniggia, M., et al. (1998). Italian guidelines for the management of infectious complications in pediatric oncology: empirical antimicrobial therapy of febrile neutropenia. Oncology. 55(5):489-500

39. Rubinstein, E., Lode, H. and Grassi, C. (1995). Ceftazidime monotherapy vs. ceftriaxone/tobramycin for serious hospital-acquired Gram-negative infections. Antibiotic Study Group. Clin Infect Dis. 20:1217-28

40. Viscoli, C., Cometta, A., Kern, W.V., Bock, R., Paesmans, M., Crokaert, F., Glauser, M.P., Calandra, T.(2006). International Antimicrobial Therapy Group of the European Organization for Research and Treatment of Cancer. Piperacillin-tazobactam monotherapy in high-risk febrile and neutropenic cancer patients. Clin Microbiol Infect. 12(3):212-6

41. Klastersky, J., Vamecq, G., Cappel, R., Swings, G. and Vandenborre, L. (1972). Effects of the combination of gentamicin and carbenicillin on the bactericidal activity of serum. J Infect Dis. 125:183-6

42. Sepkowitz, K.A., Brown, A.E. and Armstrong, D. (1994). Empirical therapy for febrile neutropenic patients: persistence of susceptibility of Gram-negative bacilli to Aminoglycoside antibiotics. Clin Infect Dis.19:810-1

43. Brown, A.E., Kiehn, T.E. and Armstrong, D. (1995). Bacterial resistance in the patient with neoplastic disease. Infect Dis Clin Pract. 4:136-44

44. European Organization for Research and Treatment of Cancer (EORTC). International Antimicrobial Therapy Cooperative Group, National Cancer Institute of Canada-Clinical Trials Group. (1991). Vancomycin added to empirical combination antibiotic therapy or fever in granulocytopenic cancer patients. J Infect Dis. 163:951-958

45. Sipsas, N.V., Bodey, G.P. and Kontoyiannis, D.P. (2005). Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. Cancer. 103(6):1103-13.

46. Elting, L.S., Bodey, G.P. and Keefe, B.H. (1992). Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis. 14:1201-7

47. Raad, I.I., Escalante, C., Hachem, Ry., et al. (2003). Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized

Vol. 15 (2) 115-123, April 2021, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2021.2.13

study comparing imipenem and cefepime. Cancer. 98:1039-1047

48. De Pauw, B.E., Deresinski, S.C., Feld, R., Lane-Altman, E.F. and Donnelly, J.P. (1994). Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. Ann Intern Med. 120:834-844

49. Viscoli, C., Castagnola, E.,Van Lint, M.T., et al. (1996). Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. Eur J Cancer. 32A:814-820

50. Walsh, T.J., Pappas, P., Winston, D.J., et al. (2002). Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med. 346:225-34

51. Walsh, T.J., Teppler, H., Donowitz, G.R., et al.(2004). Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med. 351(14):1391-402

52. Mermel, L.A., Farr, B.M., Sherertz, R.J., et al. (2001). Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 32:1249-1271

53. Timeus, F., Crescenzio, N., Longoni, D., et al. (2014). Paroxysmal nocturnal hemoglobinuria clones in children with acquired aplastic anemia: a multicentre study. PLoS One. 9(7):e101948

54. Ruggiero, A,, Cefalo, M.G., Coccia, P., Mastrangelo, S., Maurizi, P. and Riccardi, R. (2012). The role of diet on the clinical pharmacology of oral antineoplastic agents. Eur J Clin Pharmacol. 68(2):115-122

55. Ruggiero, A., Rizzo, D., Trombatore, G., Maurizi, P. and Riccardi, R. (2016). The ability of mannitol to decrease cisplatin-induced nephrotoxicity in children: real or not?. Cancer Chemother Pharmacol. 77(1):19-26

56. Wang, X.J. and Chan, A. (2017). Optimizing Symptoms and Management of Febrile Neutropenia among Cancer Patients: Current Status and Future Directions. Curr Oncol Rep. 19(3):20

57. Maurizi, P., Russo, I., Rizzo, D., et al.(2014). Safe lumbar puncture under analgo-sedation in children with acute lymphoblastic leukemia. Int J Clin Oncol. 19(1):173-7.

58. Triarico, S., Maurizi, P., Mastrangelo, S., et al. (2019). Improving the Brain Delivery of Chemotherapeutic Drugs in Childhood Brain Tumors. Cancers (Basel). 11(6):824.

59. Santolaya, M.E., Alvarez, A.M., Becker, A., et al. (2001). Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia and fever. J Clin Oncol. 19:3415-3421

60. Santolaya, M.E., Alvarez, A.M., Becker, A., et al. (2004). Early hospital discharge followed by outpatient management versus continued hospitalization of children with Cancer, fever, and neutropenia at low risk for invasive bacterial infection. J Clin Oncol. 22:3784-9