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Original Article

Clinical and microbiological profile of infections during induction phase of acute myeloid leukemia

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Abstract

Background: The primary objective of this study is to describe clinical and microbiological profile of infections during induction phase of acute myeloid leukemia (AML).

Patients and methods: We reviewed the case records of 50 hospitalized patients with AML undergoing standard dose induction chemotherapy from January to December 2015.

Results: Out of 50 cases, 34 were males 16 females with median age of 30 years. Most common presenting symptoms were fever followed by bleeding diathesis. The clinical sites of infections were gastrointestinal tract including oral cavity (48%), respiratory tract (4%), skin/soft tissue (4%) and genitourinary tract (4%). Clinically (58%) or microbiologically (30%) documented infections were 88%, while 12% had fever without identifiable source. Overall, in 21 episodes microorganisms were isolated. Common sites of isolates were blood stream (11), stool (8), sputum (1) and urine (1). Gram negative infections accounted for 81% of total isolates; Escherichia coli (E. coli) being the commonest. Gram positive microorganisms were isolated in 19% of which methicillin resistant staphylococcus aureus (MRSA) was the most common. Gram negative bacterial infections were associated with higher mortality.

Conclusion: Gastrointestinal tract is the most common clinical site of infection. Blood stream infection is the most common site for positive bacterial isolates. Gram–negative bacilli were the predominant cause of infections with E. coli being the most common pathogen isolated. Empiric antibiotic treatment for febrile neutropenia should be tailored to the locally prevalent pathogens and their susceptibility patterns

Keywords: AML, induction chemotherapy, blood stream infection, Escherichia coli, E. Coli

Introduction

Infectious complications are frequent cause of morbidity and mortality in patients of AML undergoing induction chemotherapy. Induction phase of AML is categorized as high risk for infectious complications as per guidelines of Infectious Diseases Society of America. [(1)] Administration of induction chemotherapy results in profound neutropenia, lymphocytopenia and severe mucositis. The risk of infection in neutropenic patient is determined by the severity and duration of neutropenia, hemorrhagic diathesis of skin/mucosal tissue and use of central venous line. [(2)] High index of suspicion, early use of empirical antibiotics along with supportive care are the key interventions to reduce the induction related mortality. Empirical antibiotics should be based on the possible clinical site of infection and subsequently modified according to the microbial culture and susceptibility report as soon as possible. The primary objective of the study is to report the profile of infections during induction phase of AML which helps us guide first line empirical antibiotics during febrile episode. While there are numerous studies from the Western countries with respect to type of infectious agent, choice of empiric antibiotics and outcome of AML induction, clinical data from India is few. Hence, it is worthwhile to evaluate the clinical profile, pathogenic organisms, pattern of antibiotic resistance and the outcome of induction treatment in AML.

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Patients and methods

In this retrospective study, 50 patients with newly diagnosed AML (age>14 years) admitted and treated with induction chemotherapy during one calendar year at a single center were included. Case records of patients who completed induction chemotherapy were reviewed for the diagnosis, clinical presentation and type of chemotherapy received. Use of antibiotics, use of granulocyte colony stimulating factor (G–CSF), clinical and/or radiological sites of infection, culture positivity, microorganisms isolated, antibiotic susceptibility pattern, duration of neutropenia, duration of hospitalization and outcome of induction were recorded for all patients. Patients with acute promyelocytic leukemia, secondary AML and isolated granulocytic sarcoma were excluded. All patients were given standard dose induction chemotherapy consisting of "7+3" i.e. Cytarabine and Daunorubicin. [3,4,5] None of the patients received G–CSF. All except 1 patient had central venous line during the induction phase. Patients were included till the end of induction phase maximum up to 30 days or till recovery of absolute neutrophil count (ANC) more than 1500. All febrile patients were evaluated for relevant history, physical examination, complete hemogram, liver function tests, renal function tests, serum electrolytes and chest X–ray (CXR). Computed tomography (CT) scan of paranasal sinuses (PNS) was done if patient had PNS tenderness or if fungal infection of the PNS was suspected. CT scan of thorax was done whenever CXR suggestive of fungal mass/infiltrate or clinical suspicion of fungal infection. Microbiological culture of blood (two sets of blood culture, 10 ml each, one from central and another from peripheral line) was conducted routinely for all febrile episodes. Moreover, cultures were sent from throat, urine, central line, and any other suspicious clinical sites whenever indicated. Bacterial pathogens in samples yielding culture positivity were identified and their antibiogram was recorded.

Febrile neutropenia (FN) is defined as the occurrence of a single oral temperature of 38.3° C (101°F) or a temperature of greater than 38.0° C (100.4° F) sustained for more than 1 hour in a patient with neutropenia along with ANC≤1000/µl with predicted rapid decline during next 48 h [6]. An infectious episode was defined as a fever of unknown origin (FUO), clinically documented infection (CDI) and microbiologically documented infection (MDI) according to the presence of local inflammation evocative for infection and to the microbial documentation. 1) FUO: Isolated fever, no local inflammation evocative for clinical infection, and no microbial documentation of the episode. 2) CDI: fever associated with a local inflammation such as pneumonia, skin infection or cellulitis; whose microbiological pathogenesis cannot be proven or which cannot be examined. 3) MDI: defined as infectious organisms detected in blood cultures even without localized inflammation or localized microbiologically documented infection with or without positive blood cultures. [7] First–line empirical antibiotic with piperacillin/tazobactum or cefoperazone/sulbactum was started in clinically stable patients [7,8] while in clinically unstable patients carbapenum was started at the outset. Piperacillin/tazobactum was chosen based on the previous antibiotic resistance pattern in the institute and later on it was changed to cefoperazone/sulbactum. Treatment was unchanged for first 72 hours in afebrile patient with no hemodynamic compromise however, in case of non–responding fever, carbapenem group of antibiotics were started. Vancomycin was added initially if severe mucositis or suspected central line infection at insertion site. Vancomycin was administered subsequently to those, who had persistent fever, hypotension, and pneumonia or if patient was hemodynamically unstable. Once microbiological culture report was available, antibiotics were modified accordingly. However, in culture negative patients, same antibiotics were continued. Prophylactic fluconazole was given to all patients. Amphotericin B was initiated empirically if patient experienced pleuritic chest pain, fungal balls in CXR or fever persisted for more than 5 days despite antibiotics. In culture negative and stable patients; antibiotics were continued for 5–7 days or until recovery of ANC to more than 1000/ µl. Institutional review committee approval was taken for the publication of these data.

Results

A total of 50 patients with diagnosis of AML undergoing induction chemotherapy were observed during the study period (34 males and 16 females). The median age was 30 (range, 18–63) years. All except 1 patient had central venous line. Five patients were infected before starting induction chemotherapy. Fever was recorded during all episodes. The ANC was<500/µl prior to chemotherapy and further dropped down to <100 during nadir phase of induction chemotherapy. The mean duration of neutropenia was 7 (range, 7–15) days. The mean duration of fever was 2.95 (range, 0.4–13) days. The mean duration of hospitalizations was 20 days. There were 50 neutropenic episodes recorded during the induction phase. In 21 (42%) episodes no cause of fever could be established labeled as FUO, 29 (58%) episodes had CDI; while 21 (42%) episodes had MDI. Among CDI, common clinical symptomatology was diarrhea, pneumonia, dental abscess and cellulitis. Most common clinical sites of infection (29/50) in decreasing order of frequency were gastrointestinal tract (diarrhea, typhlitis, perirectal abscess, and enterocolitis) 24 (81.75%), respiratory tract

Types of pathogens isolated	Overall	Blood	Stool	Sputum	Urine
E. coli	14	6	8	-	-
MRSA	03	3	-	-	-
Acinetobacter baumannii	02	1	-	1	-
Pseudomonas aeruginosa	01	-	-	-	1
Streptococcus pneumoniae	01	1	-	-	-
Total	21	11	8	1	1

Table 1. Types of pathogens isolated in microbial culture of various sites

MRSA: Methicillin resistant staphylococcus aureus, E. coli: Escherichia coli

(pneumonia and sinus) in 2 (6.89%), skin/soft tissue infection (mucositis and cellulitis) in 2 (6.89%) and urinary tract infection in 1 (3.44%). Clinically suspected fungal pneumonia was observed in 4 patients.

Overall, 42% (21/50) episodes were culture positive while 58% (28/50) were culture negative. Among 21 positive isolates, 81% (17/21) were gram–negative and 19% (4/21) were gram positive. Among gram–negative isolates, E. coli and Acinetobacter baumannii were leading while in gram positive MRSA followed by Streptococcus pneumonia were common. Types of pathogens isolated in the culture across various sites are shown in Table 1.

Common sites of culture positivity (out of 21) were blood (11), stool (8), sputum (1) and urine (1). E. coli was the most common isolates constituting 66.6% of all isolates, followed by MRSA (14.28%), Acinetobacter baumannii (9.52%), Pseudomonas aeruginosa (4.76%) and Streptococcus pneumonia (4.76%). The main finding of the study is that bloodstream isolates were predominantly represented by E. coli constituting 54.54% of total isolates.

Antibiotic usage: Average number of antibiotics used in a patient were 3 (range, 1–5). First line empirical antibiotics used were cefoperazone/sulbactum in 3, piperacillin/tazobactum in 5 while 42 patients received carbapenem group subsequently in addition to piperacillin/tazobactum. Ceftazidime and cefexime was not used as the institutional antibiotic susceptibility pattern goes against the use of these drugs. Gram positive antibiotic coverage was required in majority. Among gram positive antibiotics, vancomycin, linezolid and teicoplanin were used in 46%, 38% and 10% respectively. Teicoplanin was preferred in patient with renal dysfunction. Treatment was unchanged for patients who were afebrile. However, due to persistent fever spikes, 42 patients were shifted to second line empirical treatment with carbapenem group. Antibiotics resistance pattern observed during this period is shown in Figure 1.

It was observed that the majority of the gram negative bacilli (GNB) were resistant to the piperacillin/tazobactum and clinically patients were not responding and so the subsequent empirical antibiotic was changed to the cefoperazone/sulbactum. Colistin was used in 7 and tigecycline in 3 patients based on either culture susceptibility data or as a last resort for those who had not responded to average of five antibiotics. This is an alarming sign that carbapenum resistance is also emerging. None of the patients had proven fungal infection; 4 (7%) patients had probable fungal pneumonia on clinical and/or radiological ground. There was one case with persistence

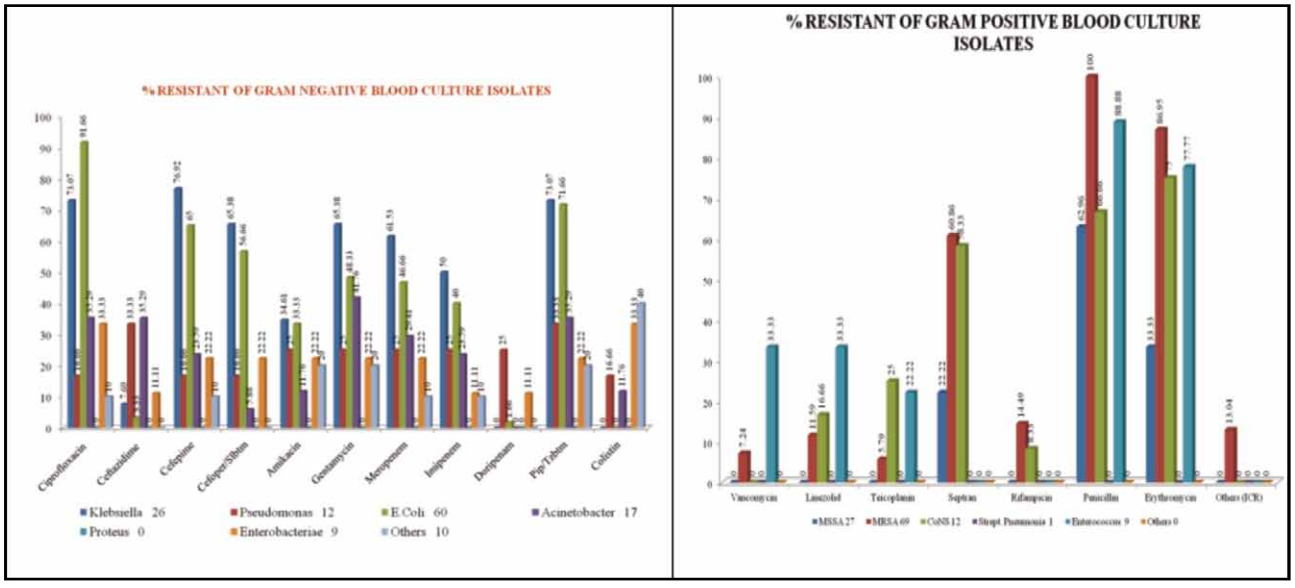


Figure 1. Antibiotic resistance pattern

fever despite antibiotics and CXR revealed multiple fungal balls. Nonetheless, empirical Amphotericin B was used in majority (thirty) with persistent fever despite five days of antibiotics and culture report failed to identify any microorganisms at that point of time.

Outcome of infection: Out of 50 patients, 36 (72%) were discharged, 7 (14%) died and 7 (14%) had left the hospital against medical advice. Among 7 patients who died during induction, 6 (85.7%) died because of septicemia secondary to neutropenic enterocolitis, 1 due to pneumonia while 1 secondary to intracranial bleed. In 3 patients, E coli was isolated either from blood or stool.

Discussion

In present study, among total isolates 81% (17/21) were GNB while 19% (4/21) were gram positive. A recent study (2015) by Lakshmaiah KC et al [8] reported GNB (63.64%) as predominant isolate followed by GPC (36.36%). Various studies from India during 1990s, [9,10,11,12] recent study in 2013 [13] and the present one still find GNB as the predominant cause of infection in hematological malignancies. This is in contrast to a rising incidence of gram positive bacteremia in FN patients reported over the past 30 years especially from the Western countries. This has been attributed to the increasing use of central venous lines, fluoroquinolone prophylaxis, aggressive chemotherapy regimens and H2 receptor blockers[14,15,32,33] In present study, only 3 isolates with MRSA were identified, despite majority had central venous line and none of them received fluoroquinolone prophylaxis.

Common microorganisms were E. coli (66.6%), MRSA (14.28%), Acinetobacter baumannii (9.5%), Pseudomonas aeruginosa (4.76%) and Streptococcus pneumonia (4.76%). In a series from the same institute in 2013[13] reported the most common organisms being E. coli (43%), Staphylococcus aureus (22%), Pseudomonas aeruginosa (17.4%) and Klebsiella pneumoniae (17.4%). Among gram negative isolates, E. coli (66.6%) was the predominant bacterial isolate; supported by many Indian as well as International studies. These finding has been supported by the studies reported from Pakistan, Turkey and Brazil[16,17,18] The Turkish [18] showed E. coli being the most frequent GNB, constituting 58.4% of microorganisms. Many other international studies also reported E. coli as the most frequently isolated GNB.[19,20,21] There was GNB predominance reported in an Iranian study [22] of neutropenic patients; 67% of GNB with predominant E. coli.

Rate of culture positivity is variable across the study. In present study, 42% (21/50) isolates were culture positive, showing a better yield than documented in the literature. In a study by Lakshmaiah et al, [8] bacterial culture yielded pathogens in 29.62% of the FN episodes in haematological malignancies. Blood stream infection is the major primary site of infection reported in 58% which has been documented in many studies cited before[13,16,19] A study from Eastern India documented incidence of positive blood culture in 29.1% of FN patients with hematological malignancies.[23] In another study, [24] MDI comprised 30% episodes and bacteremia 26% episodes. Various other studies have reported culture positivity rate of 34.2%, 31% and 21.3% respectively in a mixed population of solid tumor and hematological malignancies. [25,26,27]

Frequency of infectious complications during induction phase of AML is directly related to the depth and duration of neutropenia. Bodey [28] in 1966 first defined the quantitative relationships between circulating leucocytes and infection in patients with acute leukemia. The incidence of severe infection, the number of days spent on antibiotics and the number of days of fever inversely proportionate to depth and duration of neutropenia. In present study, the median duration of neutropenia was 11 days while the median days of hospitalization was 14. It has been reported as 8.5 days from India [13] and 9 days in Brazil. [17] Taj et al [16] reported median duration of neutropenia and hospitalization was 6 and 7 days respectively. Fever was reported in almost all patients exhibiting the importance of this vital clinical sign which is still in accordance with Brazilian and Indian studies.[13,17] Klastersky J [29] reported that fever is the commonest finding in patients with hematologic malignancies, occurring in over 80% of the patients during or after chemotherapy.

Most common clinical sites of infection were gastrointestinal tract (81.75%), respiratory tract (6.89%), skin/ soft tissue (6.89%) and genitourinary tract (3.44%). This may reflect advent of clinical and laboratory methods to document infections. In a study of 375 patients by Meidani et al [30] 77.3% and 22.7% of them were classified as FUO and sepsis respectively. Only 2.6% of patients had positive blood culture. [30] In present study, none of the patients had proven fungal infection nonetheless 4(7%) patients had probable fungal pneumonia. Microbiological confirmation of fungal species presents major clinical challenge. The proportion of fungal infections would be higher if more invasive diagnostic methods were used to identify the fungus, but such diagnostic methods may be not easy to conduct in leukemia patients with preexisting neutropenia and thrombocytopenia.

Life–threatening infection is observed in 48–60% of patients with FN. [31] The mortality has been variably reported as 5–39% in the various studies. [13,17,32] The mortality rate of 14% in present study is comparable with other published data. [24,31] Prolonged and profound

neutropenia, sepsis, hypotension, pneumonia and hypokalemia were associated with high mortality. The present study has its own limitations like small sample size, retrospective in nature and observed in small cohort of AML patients during induction phase of treatment.

Conclusion

Patients with AML receiving induction chemotherapy are at increased risk of infectious complications. Gastrointestinal tract is the most common clinical site while blood stream is the common site of positive bacterial isolate. E. coli was the most common pathogens isolated. Empiric antibiotic treatment for high risk FN should be tailored to the locally prevalent pathogens and their susceptibility patterns. These observations helped selecting empirical antibiotic treatment in high risk FN.

References

1. Freifeld AG, Bow EJ, Sepkowitz KA et al. infectious diseases society of America (IDSA) guidelines. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the IDSA. Clin Infect Dis 2010;5(4): e56–e93.
2. Young L. Management of infections in leukemia and lymphoma. In: Rubin R, Young L (Eds). Clinical approach to infection in the compromised host, 4th edn. p.497–522
3. Yates J, Glidewell O, Wiernik P, Cooper MR, Steinberg D, Dosik H, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: CALGB study. Blood 1982; 60:454–62.
4. Hervé Dombret and Claude Gardin. An update of current treatments for adult acute myeloid leukemia Blood 2016; 127:53–61.
5. Roboz GJ. Novel approaches to the treatment of acute myeloid leukemia. Hematology Am Soc Hematol Educ Program 201; 2011:43–50.
6. Neutropenic Fever Empiric Therapy: Empiric Therapy Regimens http://emedicine.medscape.com/article/2012185–overview (Accessed on July 2016).
7. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. Clin Infect Dis 1997; 25:551–73.
8. Lakshmaiah KC, Malabagi AS, Govind Babu, Shetty R, Sinha M, Jayashree RS. Febrile neutropenia in hematological malignancies: clinical and microbiological profile and outcome in high risk patients. J Lab Physicians 2015;7(2):116–20.
9. Srivastava VM, Krishnaswami H, Srivastava A, Dennison D, Chandy M. Infections in haematological malignancies: An autopsy study of 72 cases. Trans R Soc Trop Med Hyg 1996; 90:406–8.
10. Madiajagane R. A retrospective study of infections in neutropenic patients. J Indian Med Assoc 1998; 96:239–40.
11. Kumar L, Kochupillai V, Bhujwala RA. Infections in acute myeloid leukemia. Study of 184 febrile episodes. J Assoc Physicians India 1992; 40:18–20.
12. Das PK, Chhotaray MK, Rath RN, Kar S, Das B, Parida B. Infection in haematological malignancies. J Indian Med Assoc 1994; 92:328–30.
13. Karanwal AB, Parikh BJ, Goswami P, Panchal HP, Parekh BB, Patel KB. Review of clinical profile and bacterial spectrum and sensitivity patterns of pathogens in febrile neutropenic patients in hematological malignancies: a retrospective analysis from a single center. Indian J Med Paediatr Oncol 2013;34(2):85–88.
14. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: A three–year analysis. Clin Infect Dis 1999; 29:239–44.
15. Rubio M, Palau L, Vivas JR, Del Potro E, Diaz–Mediavilla J, Alvarez A, et al. Predominance of gram–positive microorganisms as a cause of septicemia in patients with hematological malignancies. Infect Control Hosp Epidemiol 1994;15(2):101–4.
16. Taj M, Farzana T, Shah T, Maqsood S, Ahmed SS, Shamsi TS. Clinical and microbiological profile of pathogens in febrile neutropenia in hematological malignancies: a single center prospective analysis. Journal of Oncology 2015; 2015:596–604.
17. Lima SS, Franca MS, Martinho GH, Jesus LA, Romanelli RMC, Clemente WT. Neutropenic patients and their infectious complications at university hospital. Revista Brasileira de Hematologia e Hemoterapia 2013;35(1):18–22.
18. Sacar S, Hacioglu SK, Keskin, Turgut H. Evaluation of febrile neutropenic attacks in a tertiary care medical center in Turkey. J Infec Dev Countr 2008;2(5):359–63.
19. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003;36(9):1103–10.
20. Kirby JT, Fritsche TR, Jones RN. Influence of patient age on the frequency of occurrence and antimicrobial resistance patterns of isolates from hematology/oncology patients: report from the chemotherapy alliance for neutropenic and the control of emerging resistance program (North America). Diagn Microbiol Infect Dis 2006; 56:75–82.

21. Chen CY, Tsay W, Tang JL, Tien HF, Chen YC, Chang SC, et al. Epidemiology of bloodstream infections in patients with haematological malignancies with and without neutropenia. Epidemiol Infect 2009;138(7):1044–51.

22. Yadegarynia D, Fatemi A, Mahdizadeh M, Movahhed RK, Alizadeh MA. Current spectrum of bacterial infections with nosocomial fever and neutropenia. Caspian J Intern Med 2013;4(3):698–701.

23. Mandal PK, Maji SK, Dolai TK, De R, Dutta S, Saha S, Bhattacharyya M. Micro–organisms associated with febrile neutropenia in patients with haematological malignancies in a tertiary care hospital in Eastern India. Indian J Hematol Blood Transfus 2015;31(1):46–50.

24. Ghosh I, Raina V, Kumar L, Sharma A, Bakhshi S, Thulkar S, Kapil A. Profile of infections and outcome in high–risk febrile neutropenia: experience from a tertiary care cancer center in India. Medical Oncology 2012;29(2):1354–7.

25. Jacob LA, Lakshmaiah KC, Govind Babu K, Suresh TM, Lokanatha D, Sinha M, et al. Clinical and microbiological profile of febrile neutropenia in solid tumors and hematological malignancies at a tertiary cancer care center in South India. Indian J Cancer 2014; 51:464–8.

26. Al–Ahwal MS, Al–Sayws F, Johar I. Febrile neutropenia comparison between solid tumours and hematological malignancies. PAN Arab Med 2005; 2:4–7.

27. Zahid KF, Hafeez H, Afzal A. Bacterial spectrum and susceptibility patterns of pathogens in adult febrile neutropenic patients: A comparison between two time periods. J Ayub Med Coll Abbottabad 2009; 21:146–9.

28. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leucocytes and infection in patients with acute leukemia. Ann Intern Med 1966; 64:328–40.

29. Klastersky J. Management of fever in neutropenic patients with different risks of complications. Clin Infect Dis 2004;39(Suppl 1): S32–7.

30. Meidani M, Rostami M, Moulaee S. Blood culture in neutropenic patients with fever. Int J Prev Med 2012; 3:141–2.

31. Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone–resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother 2008;61(3):721–8.

32. Govind Babu K, Lokanatha D, Lakshmaiah KC, Suresh Babu MC, Jacob LA, Gita R Bhat, et al. Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. Indian J Med Paediatr Oncol 2016;37(3):174–82.

33. Giamarellou H, Antoniadou A. Infectious complications of febrile leukopenia. Infect Dis Clin North Am 2001; 15:457–82.