Outcome Predictors of Multi-drug Resistant Gram Negative Bacteremia in Children with Hematological Malignancies

Amr Abdalla, M.D[1,2], Mai Ahmed Mohamed, M.Sc[1,2], Samah Mohamed Radwan, M.D [3]

[1]Department of Pediatric Oncology, National Cancer Institute (NCI), Cairo University, Egypt
[2]Department of Pediatric Oncology, Children Cancer Hospital Egypt (CCHE-57357), Cairo, Egypt
[3]Department of Clinical Pathology, National Cancer Institute (NCI), Cairo University, Egypt
amr.abdalla@nci.cu.edu.eg, maiiyoussef2010@gmail.com, dr_samah_nci@yahoo.com

Abstract: Background: Antibiotic resistant bacteria are able to survive and even multiply in the presence of an antibiotic. They are associated with increased morbidity and mortality in cancer patients. The aim of this study is to identify the outcome and its predictors in febrile neutropenic pediatric patients with multi-drug resistant (MDR) gram negative bacteremias. This is a retrospective descriptive study that included 72 episodes of MDR gram negative bacteremias in 65 patients with hematological malignancies at the Pediatric Oncology Department, National Cancer Institute, Cairo University from January to December 2014. **Results:** This study included 35 patients with acute myeloid leukemia (AML), 21 with acute lymphoblastic leukemia (ALL), 14 with lymphomas and 2 with Langerhans's cell histiocytosis (LCH). *Klebsiella* species was the most frequently isolated organism (38.9%). Piperacillin / tazobactam was the first line treatment used in 62 episodes (86.1%). Carbapenems were used as a first line treatment in 10 episodes (13.9%), and as a second line in 58/62 episodes (93.5%). Indication of treatment modification was based on culture and sensitivity result, vital instability and clinical focus of infection in 56.9%, 27.7% and 15.4% of episodes, respectively. Eleven percent of patients had history of previous cultures with MDR Gram-negative bacteria (GNB) within the past 3months. **Conclusion:** Mortality predictors were AML as an underlying diagnosis, active disease, vital instability, ICU admission, TLC <500/cc, platelet count <20,000/cc, impaired liver function tests, impaired renal function tests, impaired electrolytes, coagulopathies, treatment modification due to vital instability and history of previous culture with MDR-GNB.

[Amr Abdalla, Mai Ahmed Mohamed, Samah Mohamed Radwan**. Outcome Predictors of Multi-drug Resistant Gram Negative Bacteremia in Children with Hematological Malignancies.** *Cancer Biology* 2019;9(3):66-77]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net. 9. doi:10.7537/marscbj090319.09.

Keywords: multidrug resistance, gram negative bacteremias, febrile neutropenia, infection

1. Introduction

Multidrug resistant (MDR) Gram-negative bacteria (GNB) have emerged as important pathogens and a serious challenge in the management of neutropenic patients worldwide. The great majority of infections are caused by the *Enterobacteriaceae* (especially *Escherichia coli* and *Klebsiellaspp*), *Pseudomonas aeruginosa*, less frequently *Acinetobacter spp.* and *Stenotrophomonas maltophilia*.[1]

Despite the widespread use and availability of powerful antibiotics, bacteremia/sepsis remains the most important independent prognostic marker for mortality in children with cancer who have febrile neutropenia (F & N). A diagnosis of sepsis or bacteremia conferred a 10-fold increase in the risk of death.[2]

Patients with hematological malignancies have a predisposition towards severe, life- threatening infections that result in prolonged hospitalization and higher mortality rates.[3,4]

The majority of cancer patients harbor high risk for infections that are mostly assumed to be caused by immunosuppressive therapies.[5]

Because of the high mortality rates due to infections, commencing appropriate empirical antimicrobial therapy is crucial. The causative pathogens are usually equivocal; therefore, it is important to know the local epidemiological data before starting adequate empirical antimicrobial therapy.[6]

The epidemiological characteristics of causative isolates of bloodstream infections (BSIs) in cancer patients have changed recently, with a shift toward Gram-negative infections. A broader-spectrum empiric antibiotic regimen is usually recommended in patients with a history of prior BSI caused by an MDR-GNB, in those colonized by an MDR-GNB, and if MDR-GNBs are frequently isolated in the initial blood cultures. In any situation, de-escalation to standard empiric regimen is advised if infection with MDR-GNB is not documented.[1]

Delayed initiation of appropriate antimicrobial therapy and the emergence of infections with MDR-GNB, known to be associated with higher morbidity and mortality than non-MDR pathogens.[7-9]

The aim of this study is to identify the epidemiology, risk factors and to assess the outcome

of MDR gram negative bacteremia in pediatric patients with hematological malignancies at National Cancer Institute, Cairo University.

2. Methods

Study Design

This retrospective study was conducted at the Pediatric Oncology Department, National Cancer Institute, Cairo University to investigate the outcome of MDR gram negative bacteremias in febrile neutropenic patients below 18 years of age at diagnosis with hematological malignancies from 1st of January 2014 to 31st of December 2014.

Blood cultures were repeated throughout each infection episode initially and every 48 hours to isolate the causative pathogen (s) and to document the eradication of the isolated pathogen (s). A new episode was defined as positive blood culture after a new cycle of chemotherapy.

MDR-GNB was defined as resistance to at least one agent in at least three antimicrobial classes of the following five classes[10]: cephalosporins (cefepime, ceftazidime), β- lactam/ β - lactamase inhibitor combination (piperacillin, piperacillin/tazobactam), carbapenems (imipenem, meropenem, doripenem), fluoroquinolones (ciprofloxacin or levofloxacin) and aminoglycosides (gentamicin, tobramycin or amikacin).

There were 3 types of MDR gram negative organisms analyzed in our study; (a) fermenters which included *E-coli*, *Enterobacter* and *Citrobacter*, (b) non –fermenters which included *Acinetobacter* and *Pseudomonas*, and (c) *Klebsiella* species.

Patients started their empirical treatment either with piperacillin/tazobactam or meropenem (with or without amikacin). Initial antimicrobial treatment was considered inappropriate if the treatment regimen did not include at least one antibiotic active against the microorganism in vitro. Empirical therapy was modified either empirically according to general condition (vital signs and clinically documented infection) or according to result of blood culture and sensitivity by shifting from antimicrobial agent to another agent (like meropenem) or by adding polymyxin E and/or tigecycline.

Seventy two episodes of MDR gram negative bacteremias were recorded in 65 patients with hematological malignancies. Collected data during each episode included age, sex, underlying hematological malignancy, disease status, vital status, admission to intensive care unit (ICU), focus of infection, total leucocytic count (TLC), platelet count, hemoglobin count, liver function tests, renal function tests, serum electrolytes, coagulation profile, type of organism, number of organisms per episode, first line of antibiotics used, modification of treatment and history of previous cultures with MDR organisms within the last 3 months. Toxicity criteria were recorded according to Common Terminology Criteria for Adverse Events (CTCAE)[11] as emphasized in (Appendix1).

End Points and Statistical Methods

Outcome was assessed during and at completion of each episode. Outcome was categorized as (favorable) if all of the following criteria were found: patient became a febrile (< 38˚c) for at least 3 consecutive days, clearance of signs and symptoms of infection and eradication of isolated infectious microorganism or (unfavorable) if the episode ended up with death.

Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann- Whitney test (non-parametric t-test). All tests were two-tailed. A p-value < 0.05 was considered significant.

3. Results

Patients Characteristics

This study included 65 patients with hematological malignancies who developed 72 episodes of bacteremia with MDR gram negative organisms (GNOs). All parameters were assessed as regards to number of episodes rather than number of patients. The median age at diagnosis was 7 years (range from 1 to 18 years) and male to female ratio was 1.48:1.

The majority of episodes (48.6%) occurred in patients diagnosed with acute myeloid leukemia (AML). Patients' characteristics and laboratory findings were summarized in tables (1) and (2), respectively.

Total number of collected blood cultures was 118 in 72 episodes. In 61/72 episodes, single MDR-gram negative organism was isolated, while in 11 episodes more than one organism was isolated. Frequency of isolated organisms and their susceptibility to different antimicrobial agents are illustrated in tables (3, 4) and figure (1).

Piperacillin / tazobactam was the first line agent used in 62/72 episodes (86.1%). It was used as a single agent in 27 episodes, while was used in combination with amikacin in the remaining 35 episodes. Out of the whole 62 episodes (where piperacillin / tazobactam was used as a first line), there was a culture history of MDR-GNB (within 3 months before the episode) in only 5 episodes. Mortality due to sepsis occurred in 4 / 5 episodes. Carbapenems were used as the first line

agent in 10/72 episodes (13.9%). Meropenem was used as a single agent in 5 episodes, in combination with amikacin in 3 episodes and in combination with amikacin and colistin in 2 episodes. Out of those whole 10 episodes (where carbapenems were used as a first line), there was a culture history of MDR-GNB (within 3 months before the episode) in 3 episodes. All of the 3 episodes passed uneventful with favorable outcome.

Carbapenems were used as a second line agent in 58 out of the 62 episodes where piperacillin / tazobactam was used as the first line (93.5%). Out of the whole 72 episodes, colistin was added in 28 episodes (38.9%) while tigecycline was added in 19 episodes (26.4%). In total, 65 out of the whole 72 episodes (90%) had treatment modifications (either by switching to carbapenems as a 2nd line or by adding another anti-gram negative agents); 37 episodes were based on results of culture & sensitivity, 18 episodes were based on vital instability, while 10 episodes were based on clinical focus of infection. The median duration of treatment modifications was 10 days (ranging from 1 to 33 days).

Mortality and its Relation to Different Variables

The mortality rate for the whole episodes was 56.9%. Univariate analysis revealed statistically higher mortality rate among patients with AML (P=0.045), in relapse (P=0.007), vital instability (P<0.001), ICU admission (P<0.001), TLC <500/cc (P=0.003), platelet count less than 20,000/cc (P=0.004), impaired electrolytes (P=0.003), impaired liver function tests (P=0.014), impaired renal function tests (P=0.001), coagulopathy (P=0.001), history of previous culture of MDR-GNB who started their treatment with piperacillin/tazobactam (P=0.041), and treatment modification based on vital instability (P=0.004). Other risk factors didn't show statistical impact on mortality (Table 5).

Table (1): Characteristics of the whole cohort of patients

Characteristic	N (%)
Total number of episodes	72
Sex	
Male	43(59.7)
Female	29(40.3)
Age at diagnosis	
< 5years	25(34.7)
≥ 5years	47(65.3)
Median age (years)	7
Range (min –max)	1 – 18
Diagnosis of the studied episodes	
AML	35(48.6)
ALL	21(29.2)
Lymphomas	14(19.4)
LCH	2 (2.8)
Disease status of the studied episodes	
Complete remission (CR) CR1	37 (51.4)
CR2	31(43)
Still having disease	6(8.4)
Not evaluated for disease status	2(2.8)
	33 (45.8)
Vital stability	
Stable	27(37.5)
Unstable	45(62.5)
Focus of infection	
Pneumonia	34(47.2)
Soft tissue infection	22(30.6)
Typhlitis /colitis	14(19.4)
Absent	2 (2.8)
ICU admission	
Yes	54(75)
No	18(25)

AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, LCH; Langerhan cell histiocytosis, CR; complete remission

Table (2): Laboratory findings among the whole episodes

Characteristic	N (%)
Total number of episodes	72
TLC	
<500/cc	63 (87.5)
≥500 /cc	9 (12.5)
Median (/cc)	100
Range (/cc)	10 – 5,600
Hemoglobin	
<7g/dL	23(31.9)
≥7g/dL	49(68.1)
Median (g/dL)	7
Range (g/dL)	5 – 11
Platelets	
<20,000/cc	54(75)
≥20,000 /cc	18(25)
Median (/cc)	12,000
Range (/cc)	2,000 – 616,000
Liver function tests	
Impaired	42(58.3)
Notimpaired	30(41.7)
Renal function tests	
Impaired	12(16.7)
Notimpaired	60(83.3)
Electrolytes	
Impaired	33(45.8)
Notimpaired	39(54.2)
Coagulation profile	
Impaired	29(40.3)
Notimpaired	43(59.7)

TLC; Total leucocytic count

Table (3): Frequency of isolated organisms in 118 blood cultures

Organism	N (%)
Klebsiella species	46 (38.9)
Fermenters	
E-coli	37 (31.3)
Enterobacter species	6 (5)
Citrobacterfreudii	1 (0.84)
Non-fermenters *Pseudomonas* species	14 (11.4)
Acinetobacter species	14 (11.4)
Total	**118 (100)**

Table (4): Susceptibility of organisms to antimicrobial agents

Antimicrobial	Sensitive N (%)	Resistant N (%)
Meropenem	8 (6.8%)	110 (93.2%)
Ciprofloxacin	8 (6.8%)	110 (93.2%)
Levofloxacin	10 (8.5%)	108 (91.5%)
Imipinemcilastatin	13 (11.1%)	105 (88.9%)
Gentamycin	17 (14.5%)	101 (85.5%)
Amikacin	31 (26.3%)	87 (73.7%)
Colistin	45 (38.1%)	73 (61.9%)
Tigecycline	53 (45%)	65 (55%)

Table (5): Mortality and its relation to different variables

Variable	Number	Mortality (%)	P-value
Sex			
Male	43	55.8	0.814
Female	29	58.6	
Age (years)			
<5	25	48	0.246
≥5	47	61.7	
Diagnosis			
AML	35	71.4	
ALL	21	47.6	0.045
Lymphomas & LCH	16	37.5	
Disease status			
Induction therapy	29	65.5	
CR	30	36.7	0.007
Relapse	13	84.6	
Vital signs			
Stable	27	14.8	<0.001
Unstable	45	82.2	
Admission to ICU			
Yes	54	75.9	<0.001
No	18	0	
Pneumonia			
Yes	34	58.8	0.761
No	38	55.3	
Typhlitis / Colitis			
Yes	14	64.3	0.537
No	58	55.2	
Soft tissue infection			
Yes	22	50	0.43
No	50	60	
TLC			
<500 /cc	63	63.5	0.003
≥500 / cc	9	11.1	
Hemoglobin			
<7g/dL	23	65.2	0.331
≥7g/dL	49	53.1	
Platelet count			
<20,000 /cc	54	66.7	0.004
≥20,000 / cc	18	27.8	
Electrolytes			
Normal	39	41	0.003
Impaired	33	75.8	
Liver function tests			
Normal	30	40	0.014
Impaired	42	69	
Renal function tests			
Normal	60	48.3	0.001
Impaired	12	100	
Coagulation profile			
Normal	43	34.9	0.001
Impaired	29	89.7	
Type of organism			
Fermenter	21	52.4	0.559

Variable	Number	Mortality (%)	P-value
Non-fermenter	16	68.8	
Klebsiella species	24	54.2	
Number of organisms per episode			
Single	61	57.4	0.861
Two or more	11	54.5	
First line antimicrobial			
Piperacillin /Tazobactam	62	59.7	0.244
Carbapenems	10	40	
Antimicrobial modification			
Vital instability	18	88.9	
Clinical focus of infection	10	70	0.004
Results of blood cultures	37	43	
Modification by switching to carbapenems			
Yes	58	63.8	0.017
No	14	28.6	
Modification by adding colistin			
Yes	28	53.6	0.645
No	44	59.1	
Modification by adding tigecycline			
Yes	19	47.4	0.326
No	53	60.4	
Previous culture with MDR organism			
1st line: Piperacillin /Tazobactam	5	80	0.041
1st line: Carbapenems	3	0	

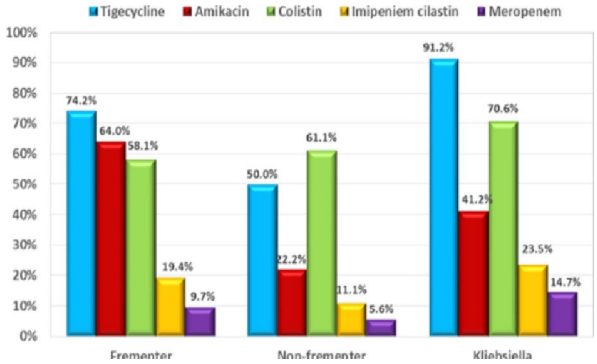

Figure (1): Susceptibility pattern of different organisms to antimicrobials

4. Discussion

Despite significant improvement in antimicrobial treatment, antibiotic resistance represents an emergency condition, particularly in immune compromised patients. Also, infections due to MDR-GNB are leading causes of death.[12]Therefore, we attempted to investigate the outcome (and its predictors) of MDR gram-negative bacteremia in children with hematologic malignancies who presented to our department.

During the study period, 65 patients with hematological malignancies developed 72 episodes of bacteremia with isolation of MDR-GNOs. Numbers are different from other Egyptian studies at National Cancer Institute, Cairo University; *El-Mahallawy et al,* who studied 239 febrile neutropenic episodes in 193 patients, of those 33 episodes had MDR-GNB[2], and *El- Mahallawy et al,* who studied 232 febrile neutropenic episodes in 192 patients, of those 119 episodes had MDR-GNB.[13]

In the current study, age of the patients ranged from 1 year to 18 years with a median age of 7 years. This is similar to what was reported by *El-Mahallawy et al,* whereas age ranged from 1.5 month to 18 years with a median age of 6.8 years[13], and *Costa et al,* whereas age ranged from 2 months to 18 years with a median age of 7 years.[14]

In the current study, AML was the most common hematological malignancy. This also correlates with *El- Mahallawy et al,*[2] and *Gedik et al,*[15] who reported AML as the most common hematological malignancy in their cohorts of patients with MDR-GNB; 50% and 37%, respectively. However, ALL was the dominant diagnosis among the cohort of 2 other studies; *El-Mahallawy et al,* (37.5%)[13] and *Haeusler et al,* (54.8%).[16] In our study, the mortality rate was significantly higher among patients with AML as compared to other diagnoses (P=0.045), which is expected due to the higher intensity of chemotherapy they received.

In our study, almost half of the patients weren't

in CR. This high percentage contributes to the occurrence of MDR gram negative bacteremia. That was also demonstrated by *Costa et al,* who reported 85.1% of their patients were still having disease and 14.9% were in CR.[14]Our study showed significant higher mortality rate among patients who were in relapse (P=0.007).

Infections with MDR-GNB are associated with ICU admission along with higher mortality in patients with hematological disorders.[17]Inthe current study, vital instability was documented in 62.5% of episodes, while ICU admission was encountered in 75%. Mortality was higher among such group of patients as compared to those who were vitally stable or were not admitted to ICU with significant P-value < 0.001. This is similar to what was reported by *Gudiol et al,*[17] who reported that ICU admission was higher in MDR-GNB arm than non-MDR-GNB arm with significant P-value = 0.023 and *Freire et al,*[18] who reported that the need for ICU admission was associated with poor outcomes with significant P-value = 0.001. In contrast to *Haeusler et al,*[16]who reported 17.5% of patients in antibiotic resistant (AR)-GN arm were admitted to ICU with non-significant P-value = 0.63 as compared to non-ARGN arm.

Patients who are receiving chemotherapy are at increased risk for contracting infections as their white blood cell count is declining. For those patients, infections can become serious, and prompt antibiotics are crucial for prevention of severe complications and death. Thus, it is evident that neutropenia is still a major determinant indicator of mortality risk in febrile neutropenic patients.[13]In our study, mortality was higher in patients whom their TLC was <500/cc (P=0.003), and whom their platelet count was <20,000/cc (P=0.004). This supports the fact that increasing the intensity of chemotherapy is associated with more myelosupperssion, and hence more infection related morbidities and mortalities.

Mortality is significantly higher in patients with sepsis and multiple organ dysfunction.[19]In the current study, impaired liver functions was observed in 58.3% of patients, impaired renal functions in 16.7%, electrolytes disturbance in 45.8% and coagulopathies in 40.3% of patients. Mortality was significantly higher in these patients with P-value of 0.014, 0.001, 0.003 and 0.001, respectively.

In patients known to have malignancies, *Klebsiellapneumoniae* is an important agent of infection. The mortality risk is 18–30%, and is even higher in the set up of having multidrug- resistant strains.[18]The mortality rate approaches 35.8–83.3% in hematology patients infected with MDR *Pseudomonas aeruginosa*.[20,21]In our cohort, the mortality rate among patients infected with *Klebsiella* species, fermenters (*E-coli, Enterobacter* species and *Citrobacterfreudii*), and non-fermenters (*Pseudomonas* species and *Acinetobacter* species) is 54.2%, 52.4% and 68.8%, respectively with non-significant P-value. The higher mortality rate in our patients is attributed to the lack of appropriate supportive care in our center.

In the current study, high frequency of resistance was observed in all isolates. Susceptibilities to tigecycline, colistin, amikacin, gentamycin, imipinemcilastatin, levofloxacin, meropenem and ciprofloxacin were 46%, 38.1%, 26.3%, 14.5%, 11.1%, 8.5%, 6.8% and 6.8%, respectively. *Freire et al,*[18] who studied infection with *Klebsiellapnueomoniae* carbapenemase (KPC) producing *Klebsiellapneumoniae*in cancer patients, reported a high frequency of resistance observed in all of the carbapenems tested, with the levels of susceptibility being highest for tigecycline and amikacin. Between 2010 and 2013, there was an overall decrease in susceptibility to meropenem from 37 to 0 % and to imipenemcilastatin from 37 to 4%.

An important determining factor that dictates the outcome of patients with infections is the appropriate empirical antibiotic therapy within the first 2 days of the initial presentation and within the first 24 hours of a positive blood culture.[22]Inour study, the mortality rate did not differ among patients who started their first line therapy with piperacillin/tazobactam or carbapenems. However, significant difference was observed when comparing mortality rate among a subset of both groups who had culture history of MDR-GNB 3 months before the onset of their studied episodes; 80% for those who started their first line therapy with piperacillin/tazobactam versus 0% for those who started their first line therapy with carbapenems (P=0.041).

Although inadequate empirical antibiotic therapy has been related with mortality in gram- negative bacteremia,[23,24]we were not able to find statistical difference, may be due to low number of patients who initially started carbapenems (only 10 patients). Also, we did not compare the outcome of patients with multidrug resistant organisms (MDROs) versus those with non-MDROs.

Mortality rates for patients whom treatment was modified based on vital instability, clinical focus of infection and result of culture and sensitivity were 88.9%, 70% and 43.2%, respectively (P=0.004).

Conclusion

In summary, mortality predictors were AML, active disease, vital instability, ICU admission, TLC <500/cc, platelet count <20,000/cc, impaired liver function tests, impaired renal function tests, impaired electrolytes, coagulopathies, treatment modification due to vital instability and history of previous culture with MDR-GNB.

Declarations:

Ethics Approval and Consent to Participate: not applicable.

Consent for Publication: not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding: not applicable.

Acknowledgements: not applicable.

Competing interests:

The authors declare that they have no competing interests.

List of abbreviations

Abbreviation	Full term
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AR	Antibiotic resistant
AR-GN	Antibiotic resistant Gram-negative
BSIs	Blood-stream infections
CR	Complete remission
CTCAE	Common Terminology Criteria for Adverse Events
F & N	Febrile neutropenia
GNB	Gram-negative bacteria
ICU	Intensive care unit
KPC	*Klebsiellapnueomoniae* carbapenemase
LCH	Langerhans's cell histiocytosis
MDR	Multi-drug resistant
MDR-GNB	Multi-drug resistant Gram-negative bacteria
MDR-GNOs	Multidrug resistant gram negative organisms
MDROs	Multidrug resistant organisms
TLC	Total leucocytic count

References

1. Nouér SA, Nucci M, Anaissie E. Tackling antibiotic resistance in febrile neutropenia: current challenges with and recommendations for managing infections with resistant Gram-negative organisms. Expert Rev Hematol 2015;8(5):647–58.
2. El-Mahallawy HA, El-Wakil M, Moneer MM, Shalaby L. Antibiotic resistance is associated with longer bacteremic episodes and worse outcome in febrile neutropenic children with cancer. Pediatr Blood Cancer 2011;57(2):283–8.
3. Passerini R, Ghezzi TL, Sandri MT, Radice D, Biffi R. Ten- year surveillance of nosocomial bloodstream infections; trends of aetiology and antimicrobial resistance in a comprehensive cancer centre. E cancer medical science 2011;5:191.
4. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24, 179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39(3):309–17.
5. Chen CY, Tsay W, Tang JL, Tien HF, Chen YC, Chang SC, Hsueh PR. Epidemiology of bloodstream infections in patients with haematological malignancies with and without neutropenia. Epidemiol Infect. 2010; 138(7):1044–51.
6. Mohsen Meidani, Ahmad Bagheri, Farzin Khorvash. A Population Based Study of Bacterial Spectrum in Febrile Neutropenic Patients. Jundishapur J Microbiol2013;6:150–6.
7. 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.
8. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by Klebsiellapneumoniae carbapenemase-producing K. pneumoniae: importance of combination therapy. Clin Infect Dis

2012;55(7):943– 50.
9. Montassier E, Batard E, Gastinne T, Potel G, de La Cochetière MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis 2013;32(7):841–50.
10. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol. 2013;34(1):1–14.
11. CTCAE: Common Terminology Criteria for Adverse Events. Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). U. S. department of health and human services. National Institutes of Health. National Cancer Institute.
12. Bassetti M, Righi E. Multidrug-resistant bacteria: what is the threat? Hematology Am Soc Hematol Educ Program. 2013;2013:428–32.
13. El-Mahallawy HA, Hassan SS, El-Wakil M, Moneer MM, Shalaby L. Increasing Antimicrobial Resistance Monitored in Surveillance Analysis of Blood Stream Infections in Febrile Neutropenic Pediatric Oncology Patients. Asian Pac J Cancer Prev. 2015;16(14):5691–5.
14. Costa Pde O, Atta EH, Silva AR. Infection with multidrug-resistant gram-negative bacteria in a pediatric oncology intensive care unit: risk factors and outcomes. J Pediatr (Rio J). 2015;91(5):435–41.
15. Gedik H, Şimşek F, Yıldırmak T, Kantürk A, Aydın D, Demirel N, et al. Which Multidrug-Resitant Bacteria are Emerging in Patients with Hematological Malignancies?: One-Year Report. Indian J Hematol Blood Transfus. 2015;31(1):51–6.
16. Haeusler GM, Mechinaud F, Daley AJ, Starr M, Shann F, Connell TG, et al. Antibiotic- resistant Gram-negative bacteremia in pediatric oncology patients--risk factors and outcomes. Pediatr Infect Dis J. 2013;32(7):723–6.
17. Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R, et al. Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother.2010;65(2):333–41.
18. Freire MP, Pierrotti LC, Filho HH, Ibrahim KY, Magri AS, Bonazzi PR, et al. Infection with Klebsiellapneumoniae carbapenemase (KPC)-producing Klebsiellapneumoniae in cancer patients. Eur J Clin Microbiol Infect Dis. 2015;34(2):277–86.
19. Tantaleán JA, León RJ, Santos AA, Sánchez E. Multiple organ dysfunction syndrome in children. Pediatr Crit Care Med.2003;4(2):181–5.
20. Cattaneo C, Casari S, Bracchi F, Signorini L, Ravizzola G, Borlenghi E, et al. Recent increase inenterococci, viridansstreptococci, Pseudomonasspp. And multiresistant strains among haematological patients, with a negative impact on outcome. Results of a 3-year surveillance study at a single institution. Scand J Infect Dis. 2010;42(5):324–32.
21. Cattaneo C, Antoniazzi F, Casari S, Ravizzola G, Gelmi M, Pagani C, et al. P. aeruginosa bloodstream infections among hematological patients: an old or new question? Ann Hematol.2012;91(8):1299–304.
22. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, et al. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother. 2011;66(3):657–63.
23. Ortega M, Marco F, Soriano A, Almela M, Martínez JA, Muñoz A, Mensa J. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother.2009;63(3):568–74.
24. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, et al. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. J Infect. 2009;58(4):299–307.

Appendix (1): Common Terminology Criteria for Adverse Events; Version 4.0

Criteria	Definition
Neutropenia	Neutrophil count decreased; **Grade1**: <LLN - 1.5 × 10^9/L; **Grade 2**: <1.5 - 1.0 × 10^9/L **Grade 3**: <1.0 - 0.5 × 10^9/L **Grade 4**: <0.5 × 10^9/L
Fever	A disorder characterized by elevation of the body's temperature above the upper limit of normal; – Grade 1: 38.0 - 39.0 degrees C – Grade 2: >39.0 - 40.0 degrees C – Grade 3: >40.0 degrees C for ≤24 hrs – Grade 4: >40.0 degrees C for >24 hrs – Grade 5: death
Febrile neutropenia	Absolute neutrophilic count (ANC) <1000/mm^3 with a single temperature of >38.3 degrees C or a sustained temperature of ≥38 degrees C for more than one hour
Bacteremia	The isolation of bacterial pathogen from the blood without fever
Clinically documented infections (CDI)	Considered when there was a focus of infection on physical examination, without microbiological documentation included: ● *Mucositis oral;* a disorder characterized by inflammation of the oral mucosa ● *Anal mucositis;* a disorder characterized by inflammation of the mucous membrane of theanus ● *Enterocolitis;* a disorder characterized by inflammation of the small and large intestines ● Colitis; a disorder characterized by inflammation of the colon ● *Typhlitis;* a disorder characterized by inflammation of the cecum ● *Abdominal infection;* a disorder characterized by an infectious process involving the abdominal cavity ● *Soft tissue infection;* a disorder characterized by an infectious process involving soft tissues ● *Pneumonia*
Anemia	A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood; – Grade 1: Hemoglobin (Hgb) < 10.0 g/dL Grade 2: Hgb<8.0 - 10.0g/dL – Grade 3: Hgb< 4.9 - 8.0 g/dL (transfusion indicated) – Grade 4: Life-threatening consequences (urgent intervention indicated)
	– Grade 5: death
Thrombocytopenia	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen; Grade1: <LLN -75.0 × 10^9 /L Grade2: <75.0- 50.0 × 10^9/L Grade3: <50.0- 25.0 × 10^9/L Grade4: <25.0 × 10^9/L
Impaired liver functions	Considered when there was increase of either; ● *Alanine aminotransferase* or *Aspartate aminotransferase* above upper limit; – Grade 1: 3.0 ×ULN

	Grade 2: >3.0 - 5.0 ×ULN Grade 3: >5.0 - 20.0 ×ULN – Grade 4: >20.0 × ULN, or ● *Blood bilirubinincreased;* – Grade 1: >ULN - 1.5 × ULN Grade2: >1.5 - 3.0 ×ULN Grade 3: >3.0 - 10.0 ×ULN – Grade 4: >10.0 ×ULN
Impaired renal functions	Considered when there was creatinine increased; Grade 1: >1 - 1.5 ×ULN Grade 2: >1.5 - 3.0 ×ULN Grade3: >3.0 - 6.0 ×ULN – Grade 4: >6.0 ×ULN
Electrolytes disturbance	Imbalance of certain ionized salts (i.e., bicarbonate, calcium, chloride, magnesium, phosphate, potassium, and sodium) in the blood. Were considered when there was: ● *Hypokalemia* – Grade 1: <LLN - 3.0 mmol/L – Grade 2: <LLN - 3.0 mmol/L; symptomatic; intervention indicated; – Grade 3: <3.0 - 2.5 mmol/L; hospitalization indicated – Grade 4: <2.5 mmol/L; life-threatening consequences – Grade 5: death ● *Hypomagnesaemia* – Grade 1: <LLN - 1.2mg/dL Grade 2: <1.2 - 0.9mg/dL Grade 3: <0.9 - 0.7mg/dL – Grade 4: <0.7 mg/dL – Grade 5: death
Coagulopathy **Vital instability**	● *Hypophosphatemia* – Grade 1: <LLN - 2.5mg/dL Grade 2: <2.5 - 2.0mg/dL Grade 3: <2.0 - 1.0mg/dL – Grade 4: <1.0 mg/dL – Grade 5: death Considered when there was *INR increased;* a finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood; Grade 1: >1 - 1.5 ×ULN Grade2: >1.5 - 2.5 ×ULN – Grade3: >2.5 ×ULN Considered when there was ● *Hypotension;* a disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment; – Grade 1: asymptomatic, intervention not indicated – Grade 2: non-urgent medical intervention indicated – Grade 3: medical intervention or hospitalization indicated – Grade 4: life threatening and urgent intervention indicated – Grade 5: death, or ● *Tachycardia;* a disorder characterized by a dysrhythmia with a heart

	rate greater than 100 beats per minute that originates in the sinusnode and not proportionate to fever
Sepsis	A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock
	A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end- diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema;
Left ventricular systolic dysfunction	– Grade 3: Symptomatic due to drop in ejection fraction responsive to intervention
	– Grade 4: Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated
	– Grade 5: death

8/3/2019