Bacteriological Study of Febrile Neutropenia in Patients with Hematological Malignancies in Baghdad Teaching Hospital

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ABSTRACT: BACKGROUND:

Fever occurs in about 80% of patients with hematologic malignancy during chemotherapy-induced neutropenia. Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection.

OBJECTIVE:

To determine the common types of bacterial pathogens causing febrile neutropenia and their susceptibility to antibiotics in patients with hematological malignancies in Baghdad Teaching Hospital.

PATIENTS AND METHODS:

50 patients with hematological malignancies and febrile neutropenia were enrolled in this cross sectional study. All patients were sent for CBC, GUE, blood culture and sensitivity test. Other sample cultures were sent on indication

RESULTS:

AML (42%) was the most common malignancy .Blood culture was positive in (24%).

The most common bacteria isolated by blood culture was Staphylococcal aureus (41.67%), gram positive bacteria were predominant in hematological malignancy (62.5%), positive sputum culture was obtained in 4(8%) of patients.

The most frequently effective antibiotic was Imipenem for gram positive infections, and Amikacin, Imipenem and Piperacillin/Tazobactum for Gram negative infections.

CONCLUSION:

Gram positive bacteria were the most common bacteria with Staphylococcal aureus as the most common bacterial pathogen isolates in blood culture and streptococcal pneumonia in sputum culture, Imipenem was most commonly effective antibiotic.

KEYWORDS: Neutropenia, Fever, Bacteria

INTRODUCTION:

Neutrophils make up the majority of circulating white blood cells and serve as the primary defense against infections by destroying bacteria, bacterial fragments and immunoglobulin-bound viruses in the blood⁽¹⁾

When absolute neutrophil count falls below 0.5×10^{9} /l., the patient is likely to have recurrent infections. ⁽²⁾, and without prompt medical attention, the condition may become life-threatening (neutropenic sepsis). ⁽³⁾

The most common bacterial infection is caused by Gram-positive bacteria that_may contribute to 60-70% of bacterial infections. There are serious concerns regarding antibioticresistant organisms. These include methicillinresistant Staphylococcus aureus (<u>MRSA</u>) or Vancomycin-resistant Enterococcus (VRE).⁽⁴⁾

Neutropenia that develops in response to chemotherapy typically becomes evident in seven to fourteen days after treatment. Signs of infection in patients can be subtle. Fever is a common early observation. Sometimes hypothermia can be seen in neutropenic sepsis.⁽⁴⁾ Febrile neutropenia is defined as a single oral temperature measurement of \geq 38.3°C or a temperature \geq 38.0°C sustained over 1-hour with ANC of \leq 500 cells/mm3 or ANC that is expected to be \leq 500 cells/mm³ during the next 48 hours.⁽⁵⁾

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80% of patients with hematologic malignancies will develop fever during chemotherapy induced neutropenia.⁽⁶⁾

Clinically documented infections occur in only 20%–30% of febrile episodes. Common sites of tissue-based infections include the intestinal tract, lung and skin. Bacteremia occurs in 10–25% of all patients, with most episodes occurring in the setting of prolonged or profound neutropenia (ANC \leq 100 cell/mm³). ⁽⁷⁾

Substantial fluctuation in the epidemiologic spectrum of blood stream isolates obtained from febrile neutropenic patients has occurred over the past 40 years. In the 1960s and 1970s, gram negative pathogens were predominant. Then, during the 1980s and 1990s, gram-positive organisms became more common because of increased use of indwelling plastic venous catheters.⁽⁸⁾

Currently, coagulase-negative staphylococci are the most common blood isolates in most centers while Enterobacteriaceae and non-fermenting gram-negative rods are isolated less common.⁽⁹⁾ Drug-resistant gram-negative bacteria species are causing an increasing number of infections in febrile neutropenic patients. In some centers, this has led to an epidemiologic trend towards a predominance of gram-negative pathogens in the neutropenic population.^{(10).}

In addition, resistant gram-positive pathogens, such as MRSA and VRE have become more common and are the most prevalent resistant isolates in some centers, accounting for 20% and 50% of episodes, respectively.⁽¹¹⁾

PATIENTS AND METHODS:

Between April 1st 2015 and May 31st 2016, fifty adult patients were recruited from hematology unit at Baghdad Teaching Hospital, and enrolled in this cross sectional study.

All patients with hematological malignancy and absolute neutrophil count $\leq 0.5 \times 10^{-9}/L$,

plus either: Body temperature $\ge 38.3^{\circ}$ C for a single episode or body temperature of $\ge 38.0^{\circ}$ C sustained over one hour were included. Other causes of fever such as blood and blood product transfusion reactions were excluded.

All patients were investigated by Complete blood count with WBC differential, and GUE. In addition to two sets of 5 ml samples of venous blood and other specimen, such as sputum, urine or stool cultures (when appropriate) were sent for culture and sensitivity. Blood samples were incubated and transported by Brain-Blood infusion bottles and the media used for blood cultures were macconkey agar, chocolate agar and blood agar.

Statistical analysis were performed using SPSS version 22 and Microsoft Excel 2013. Chi square test were used at a level of significance P value < 0.05.

RESULTS:

Patients age range was (16-69), with a mean of (40 ± 14.95) years, 38 (76%) of them were males (tab.1).

Twenty one patients (42%) had AML; and eight (16%) had ALL (tab.2).

Positive blood cultures were obtained in 12 (24%) patients. The commonest isolate was staphylococcus aureus (41.67%) (Tab. 3), and amongst the 18 patients (36%) whose sputum culture was requested; positive results were obtained in only 4 patients (22.2%) with isolates of Streptococcal Pneumonia in two patients (50%), Streptococcal Viridans in one patient Morganella Morgagnii. In the (25%), and remaining patients (Tab. 4), while stool culture was requested for three patients and urine culture for seven all were found negative for pathological bacteria and the overall results showed that gram positive bacteria were predominant (62.5%), and showed variable sensitivity to antibiotics (tab.5-9).

Table (1): Demographic characteristics of the patients

uble (1). Demographic characteristics of the patient						
Factor	Number	Percentage				
Age						
< 30years	15	30%				
30- 50 years	24	48%				
51-70 years	11	22%				
Total	50	100%				
Gender						
Male	38	76%				
Female	12	24%				

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Primary disease	Number	Percent				
Acute myeloid leukemia	21	42%				
Acute lymphocytic leukemia	8	16%				
Non Hodgkin lymphoma	12	24%				
Hodgkin lymphoma	6	12%				
Multiple myeloma	2	4%				
Chronic myeloid leukemia (Blast crisis phase)	1	2%				
Total	50	100%				

Table (2): Underlying disease in studied patients

Table (3): Bacteria isolated in blood culture of the studied patients

Pastaria Isolatad	Patients (total 12 patients)			
Bacteria isolateu	No.	Percent		
Acinetobacter baumannii	0	0%		
E.coli	2	16.67%		
Klebsiella pneumonia	1	8.33%		
Pseudomonas aeruginosa	2	16.67%		
Staphylococcus aureus	5	41.67%		
Staphylococcus species	1	8.33%		
Streptococcus pneumonia	1	8.33%		
Total	12	100%		

Table (4): Bacteria isolated in sputum culture

Bcteria isolated	Number (total 4)	percent
Morganella morganii	1	25%
Streptococcal pneumonia	2	50%
Streptococcal viridans	1	25%
Total	4	100%

Table (5): Gram stain of bacterial isolates

Specimen	Gram j bact	am positive Gram nega bacteria bacteria		negative teria	Total	
	No	(%)	No.	(%)		
Blood culture	7	43.75	5	31.25	12	
Sputum culture	3	18.75	1	16.25	4	
Total	10	62.5	6	37.5	16	

 Table (6): Sensitivity to antibiotic in different isolates in blood

 (K.P: Klebsiella pneumonae, Ps. A: Pseudomonus Aerogenosa, S.A.: Staphylococcus Aureus, S.P.:

 Streptococcus pneumonae. S.Sp: Staphylococal species)

Antibiotic	S. P	E. coli	K.P.	Ps. A.	S.A	S. Sp
Amikacin		2		2		
Piperacillin/Tazobactam		2		2		
Imipenem		2		2	4	1
Chloramphenicol	1				2	1
Gentamycin		1		2		
Tetracycline					4	
Piperacillin	1					
Linezolid	1				3	
Tobramycin					4	
Clindamycin	1				4	
Vancomycin	1					1

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Antibiotic	S.P.	S. V.	M.M.
Vancomycin	1	1	
Amikacin			1
Piperacillin	2		1
Chloramphenicol	2		1
Gentamycin			1
Imipenem	2	1	1
Azithromycin	2		
Linezolid	1		

 Table (7): Antibiotic sensitivity in isolates from sputum culture (S.P: Streptococcus Pneumonae, S.V.:

 Streptococcus Viridans, M.M.: Morganella morganii)

Table (8): Antibiotic resistance in different isolate in blood (K.P: Klebsiella pneumonae, Ps. A: Pseudomonus Aerogenosa, S.A.: Staphylococcus Aureus, S.P. : Streptococcus pneumonae. S.Sp: Staphylococal species)

Antibiotic	S.P	E.coli	K.P.	Ps. A.	S.A	S.Sp.
Amikacin			1		4	
Ciprofloxacin		2		2	3	
Piperacillin/Tazobactam					3	
Imipenem			1			
Aztreonam			1	2		
Tetracycline	1		1	1		1
Oxacillin			1			
Ampicillin	1		1	2	4	
Piperacillin			1		3	
Linezolid			1			
Tobramycin			1			
Ceftriaxone		2	1			
Ceftazidime		2	1			
Levofloxacin		1		1	3	
Oxacillin					2	1
Amoxicillin					2	1
Erythromycin	1					1
Cefixime		2	1			
Ticarcillin			1	1	2	

 Table (9): Antibiotic resistance in isolate from positive tum

 (S.P: Streptococcus Pneumonae, S.V.: Streptococcus Viridans, M.M.: Morganella morganii)

Antibiotic	S.P.	S.V.	M.M.
Amikacin		1	
Ciprofloxacin	2	1	
Levofloxacin	1		
Gentamycin		1	
Ceftriaxone	2	1	
Ceftazidime		1	1
Tetracycline	2		1
Ampicillin	1		1

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DISCUSSION:

In this cross-sectional study which included 50 patients with hematological malignancy, positive blood cultures result were obtained in 12(24%) patients compared to Kuntegowdanahalli CL et al ⁽¹²⁾ who found in their study on a comparable population in south India a lower incidence of positive blood culture reaching 19.44%, and Esa et al ⁽¹³⁾ who Found slightly higher rate of 28%

Regarding urine culture, our study found no positive culture; a finding similar to that of Kuntegowdanahalli CL et al ⁽¹²⁾

Among the 18 samples of sputum sent for culture, positive results were obtained in (22.2%) which constitute 8% of total patients, close to results obtained by Kuntegowdanahalli CL et al $^{(12)}$ who found positive sputum culture in 7.41%. In our study gram positive bacteria were the predominant pathogens forming 62.5%, while gram negative bacteria was identified in only 37.5%. this is comparable to the result reported by Sharma A et al ⁽¹⁴⁾ who found that gram positive microorganism were the predominant bacteria, but not to the results reported by Lakshmaih K.C et al (15) who found Gram-negative (63.64%) as the predominant type, despite the fact that both studies were carried on neutropenic fever in patient with hematological malignancy. Similarly Nashwan AI et al (16) whose study was conducted at medical ward of Baghdad Teaching Hospital on a comparable population found that 75% of the isolated bacteria were gram negative; a discrepancy that may suggest a changing pattern of pathogens.

Staphylococcus aureus was the most common bacteria obtained from blood cultures in our patient cohort followed by E coli and pseudomonas aeruginosa, these results are comparable to those reported by Blahová J et al ⁽¹⁷⁾, who found that the most common type of bacteria identified was staphylococcus aureus followed by E.coli.

Regarding the susceptibility of gram-positive organisms to antibiotics, in our study, Imipenem was found to be the most effective followed by Tetracycline, Tobramycin and Clindamycin, this result was different from that found in a study conducted by Kuntegwdanahalli CL et $al^{(12)}$ that

were highly sensitive to Amikacin, Linezolid, Vancomycin, Teicoplanin, and Levofloxacin, as well as a study conducted by Taj M et $al^{(15)}$ who reported that Gram positive isolates were 100% sensitive to vancomycin.

As for gram-negative organisms, our study showed highest sensitivity to Amikacin, Imipenem and Piperacillin/Tazobactum ; a finding similar to that of Kuntegwdanahalli CL et al ⁽¹²⁾ that found gram negative bacteria highly sensitive to Imipenem, Piperacillin/ Tazobactum and moderate sensitivity to Amikacin.

CONCLUSIONS:

- 1. Gram positive bacteria were the most common bacteria in patients with hematological malignancy complicated by febrile neutropenia. staphylococcal aureus being the most common type.
- **2.** Streptococcal Pneumonia was the most common bacterial pathogen isolates in sputum culture in patients complaining of productive cough.
- **3.** The most frequently effective antibiotics in Gram-positive organisms were Imipenem followed by Tetracycline while the most effective antibiotics in gram-negative organisms were Amikacin, Imipenem and Piperacillin/Tazobactum.
- **4.** Compared to other studies, there is a major difference among different centers indicating a continuous change in the pattern of infective organism, and necessitating periodic updating of this pattern is required for every center.
- **5.** Imipenem, Amikacin, Clindamycin or Piperacillin/Tazobactum may be used as empiric therapy in febrile neutropenia in hematological malignancy until culture and sensitivity results become available.

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