

## Bacteriological Diagnosis of Febrile Neutropenia in Oncology Teaching Hospital

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### ABSTRACT:

#### BACK GROUND:

Fever may be the only indication of a severe infection, it occurs in about (10 -50%) of patients with solid malignancy during chemotherapy-induced neutropenia.

#### OBJECTIVE:

To determine the common pathogens causing febrile neutropenia and their susceptibility to antibiotics in patients with solid malignancies in oncology teaching hospital.

#### PATIENTS AND METHODS:

50 patients with solid malignancy were enrolled in this cross sectional study. Blood culture and sensitivity test were investigated for them. Other sample cultures were investigated according to system involvement.

#### RESULTS:

Blood culture was positive in 18% of patients. Gram negative bacteria were predominant (81.81%). Among which E.coli being the most common (33.33%). E.coli was the isolate in the only 2 (4%) positive Urine culture.

The most frequently effective antibiotic for Gram negative infections was Amikacin followed by Imipenem compared to Ciprofloxacin, Tetracycline and Aztreonam for Gram positive ones.

#### CONCLUSION:

Gram negative bacteria were the most bacteria isolated in the studied patients.

**KEYWORDS:** neutropenia, oncology, fever

### 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<sup>(1)</sup>

When absolute neutrophil count falls below  $0.5 \times 10^9/L$ , the patient is likely to have recurrent infection and when it falls to less than  $0.2 \times 10^9/L$  the risk becomes very serious.<sup>(2)</sup>

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 antibiotic-resistant organisms. These would include methicillin-resistant *Staphylococcus aureus* (MRSA) or Vancomycin-resistant *Enterococcus* (VRE)<sup>(3,4)</sup>.

Neutropenia that develops in response to chemotherapy typically becomes evident in seven to fourteen days after treatment<sup>(3,4)</sup>.

Febrile neutropenia is defined as a single oral temperature measurement of  $\geq 38.3^\circ C$  ( $101^\circ F$ ) or

a temperature of  $\geq 38.0^\circ C$  ( $100.4^\circ F$ ) sustained over a 1-hour period with absolute neutrophil count (ANC) of  $\leq 500$  cells/mm<sup>3</sup> or ANC that is expected to decrease to  $\leq 500$  cells/mm<sup>3</sup> during the next 48 hour.<sup>(5,6,7,8,9,10)</sup>

Clinically documented infections occur in only 20%–30% of febrile episodes. Common sites of infection 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  $\leq 100$  neutrophils/mm<sup>3</sup>).<sup>(11,12,13)</sup>

Substantial fluctuation in the epidemiologic spectrum of Blood stream isolates obtained from febrile neutropenic patients has occurred over the past 40 years. In 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<sup>(14,15,16)</sup>

Currently, coagulase-negative staphylococci are the most common blood isolates in most centers while Enterobacteriaceae (example, *Enterobacter* species, *Escherichia coli* and *Klebsiella* species) and non-fermenting gram-negative rods (example: *Pseudomonas aeruginosa*) are isolated less often<sup>(17)</sup>

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Signs and symptoms of infection in neutropenic patients can be minimal particularly in those receiving corticosteroids. Vigilance is required in any patient at risk of febrile neutropenia who presents unwell, hypotensive, with a low grade temperature or afebrile, as they may be developing Gram-negative septicemia, requiring prompt treatment<sup>(11)</sup>

Urgent full blood counts, to ascertain the neutrophil level along with other investigations are crucial in guiding early management.

Patient evaluation should include a complete history and physical examination, with particular attention directed to the oropharynx, sites of catheters, the perineum/perirectal area, nail beds, nares, and external auditory canals. Laboratory evaluation should include a complete blood cell count with differential leukocyte count, basic chemistries, liver function tests and cultures from all potential sites, along with at least two sets of blood cultures from peripheral veins or one set each from a peripheral vein and a central venous catheter. Chest radiographs are not mandatory but should be obtained when clinical evidence of a respiratory infection is present. Computed tomography scan of the chest is recommended to detect signs of fungal infection in high-risk patients with unexplained fever who have not responded to 3 to 5 days of antibacterial therapy<sup>(18,19,20)</sup>.

Monotherapy with an antipseudomonal  $\beta$ -lactam agent, such as Cefepim, Carbapenem (Meropenem or Imipenem), or Piperacillin-tazobactam is recommended. Other antimicrobials (Aminoglycosides, Fluoroquinolones, and/or Vancomycin) may be added to the initial regimen for management of complications (eg, hypotension and pneumonia) or if antimicrobial resistance is suspected or proven. Vancomycin is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. This agent should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.<sup>(17,21,22,23)</sup>

In Low-risk patients, Ciprofloxacin plus Amoxicillin-Clavulanate in combination is recommended for oral empirical treatment<sup>(17,24,25)</sup>

Initial infections early in the course of fever and neutropenia are primarily bacterial, whereas antibiotic-resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections<sup>(26,27,28)</sup> Herpes simplex virus (HSV), respiratory syncytial virus (RSV), parainfluenza,

and influenza A and B are also occasionally initial pathogens.<sup>(28)</sup>

Infections due to *Candida* species may occur later in the course neutropenia, particularly because of gastrointestinal (GI) mucositis<sup>(27,29,30)</sup>

### PATIENTS AND METHOD:

Between April 1<sup>st</sup> 2015 and may 31<sup>st</sup> 2016, fifty adult Iraqi patients admitted in oncology teaching hospital with solid malignancy were enrolled in this cross sectional study.

### Eligibility criteria:

All in-patients with underlying solid malignancy and absolute neutrophil count  $\leq 0.5 \times 10^9/L$  plus either: Body temperature  $\geq 38.3^\circ C$  For a single episode or Body temperature of  $\geq 38^\circ C$  sustained over one hour. Verbal consent were obtained from patients considered eligible

All patients were investigated by Complete blood count with WBC differential, and blood culture and sensitivity for two 5c.c. blood samples obtained from two different peripheral blood vessels.

Other specimen for culture and sensitivity such as sputum, urine and stool were also obtained when guided by patient symptoms.

Statistical analysis was performed by using SPSS version 22 and micro soft Excel 2013. Chi square test, fisher exact test and student T-test were used at a level of significance P value less than 0.05.

### RESULTS:

Patients age range was (15-76) years, with a mean of  $(51.1 \pm 14.13)$  years, 18 (36%) patients were males and 32 (64%) were females (table 1). Nineteen patients (38%) had breast carcinoma, Nine (18%) with bronchogenic carcinoma other malignancies were less frequent (table 2)

Blood culture in nine (18%) patients were positive, the commonest isolated bacteria was *E.coli* (33.33%) other types of bacteria were less common (table 3)

Among eight (16%) patients investigated by urine culture the result was positive in two (25%) (*E. coli* in both) (tab 4)

No positive culture was obtained among sputum samples obtained from 15 (30%) patients and stool culture obtained from single (2%) patient.

Regardless the source of the specimen obtained, the overall results showed that gram negative bacteria were predominant (81.81%) (table 5)

The most frequently effective antibiotic was amikacin followed by imipenem for gram negative infection, and Ciprofloxacin, Tetracycline and Aztreonam followed by Chloramphenicol for gram positive organism (table 6) and (7).

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**Table 1: Demographic characteristics of patients.**

Factor	Number	Percentage
Age		
< 30years	5	10%
31– 50 years	16	32%
51-70 years	26	52%
>70	3	6%
Total	50	100%
Gender		
Male	18	36%
Female	32	64%

**Table 2: The primary malignancy in patients.**

Primary disease	Number	Percent
Breast carcinoma	19	38%
Bronchogenic carcinoma	9	18%
Ovarian carcinoma	8	16%
Gastric carcinoma	5	10%
Nasopharyngeal carcinoma	3	6%
Pancreatic carcinoma	2	4%
Angiosarcoma	1	2%
Osteosarcoma	1	2%
Testicular non seminoma	1	2%
Metastatic carcinoma of unknown primary	1	2%
Total	50	100%

**Table 3: Type of bacteria in blood culture of patients.**

Type of bacteria	Number percent	
Acinetobacter Baumannii	1	11.11%
E.coli	3	33.33 %
Klebsiella pneumonia	2	22.22%
Pseudomonas aeruginosa	1	11.11%
Staphylococcus aureus	2	22.22%
Staphylococcus species	0	0%
Streptococcus pneumonia	0	0%
Total	9	100%

**Table 4:Urine culture result in studied patients.**

Results	number	percent
Positive	2	(4%)
egative	6	(12%)
Not sent	42	(84%)
Total	50	(100%)

**Table 5:Results of gram stain of bacterial isolates in positive cultures.**

Type of specimen	Gram positive bacteria		Gram negative bacteria	
	No.	%	No.	%
Blood culture	2	18.8	7	63.63
Urine culture	0	0	2	18.8
Sputum culture	0	0	0	0
Total	2	18.8	9	81.81

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**Table 6: Antibiotic sensitivity in positive cultures .**

Antibiotic sensitivity	Acinetobacter Baumannii	E.coli	Klebsiella pneumonia	Pseudomonas aeruginosa	Staphylococcus aureus
Amikacin		3	2	1	
Ciprofloxacin		2		1	2
Piperacillin/Tazobactam		2			
Imipenem	1	2		1	
Chloramphenicol		1	1		1
Gentamycin				1	
Aztreonam					2
Tetracycline					2
Piperacillin			2		

**Table 7: Antibiotic resistance in positive cultures.**

Antibiotic sensitivity	Acinetobacter Baumannii	E.coli	Klebsiella pneumonia	Pseudomonas aeruginosa	Staphylococcus Aureus
Amikacin					2
Imipenem	1				
Gentamycin					1
Aztreonam	1	2			
Tetracycline		1		1	
Ampicillin	1	3	1	1	2
Piperacillin	1	2			
Ceftriaxone	1	2	1	1	2
Ceftazidime	1	3	1	1	1
Vancomycin					1
Cefepime			1		
Cefixime	1		1	1	1
Ticarcillin	1		1		

### DISCUSSION:

This cross sectional study included 50 febrile neutropenic episodes in patients with solid malignancy following chemotherapy; positive blood culture was obtained in 9 (18%), this is comparable to Hughes WT et al<sup>(6)</sup> who reported an incidence of positive blood culture in 20%, but higher than Abhayakumar SM et al<sup>(31)</sup> whose study in India showed positive blood culture in 12% .

Urine and sputum culture results were positive in 2 (4%) and 0(0%) in our study compared to 2%, and 9.7 respectively found by SM Abhayakumar et al<sup>(31)</sup>. and overall culture positivity results in our study were obtained in 22% which is comparable to 25% reported by Abhayakumar SM et al<sup>(31)</sup>

Relative incidence of gram positive and gram negative bacteria in all positive culture were 18.18% and 81.81% respectfully in our study comparable to (36.7% and 63.3%) reported by Safdar A et al<sup>(32)</sup>

E.coli was the most common gram negative bacteria and staphylococcus aureus was the most common gram positive bacteria identified in blood culture, E coli was the only type of bacteria identified in urine culture , these results are

similar to results reported by Abhayakumar and SM et al Taj, M., Farzana, T<sup>(31,33)</sup>

Sensitivity tests showed Amikacin as the most effective antibiotic, followed by Imipenem while Ghosh I et al<sup>(34)</sup> found Imipenem and Meropenem as most effective, followed by Amikacin.

For gram-positive organisms (Staphylococcus aureus), the effective antibiotics were Ciprofloxacin, Tetracycline and Aztreonam followed by Chloramphenicol, this is different from Ghosh I et al who found that Staphylococcus aureus was highly sensitive to Linezolid, Teicoplanin and Vancomycin and less sensitive to Ciprofloxacin<sup>(34)</sup>.

### CONCLUSION:

1. Gram negative bacteria (especially E. coli) were the most common bacterial pathogens identified in patients with solid malignancy and febrile neutropnia

2. The most frequently effective antibiotics were Amikacin, followed by Imipenem for gram-negative organisms and ciprofloxacin, tetracycline and Aztreonam followed by Chloramphenicol for gram-positive organism.

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### Acknowledgement

The authors are sincerely grateful to department of bacteriology at teaching laboratories, Medical City, for their supportive efforts in performing bacteriological investigations required for this study

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