ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

BACTERIAL PROFILE, ANTIBIOTIC RESISTANCE PATTERNS, AND ASSOCIATED FACTORS AMONG HEMATOLOGICAL MALIGNANT PATIENTS IN ERBIL CITY

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A B S T R A C T:

Background and Objectives: Cancer are one of the major global health problems**,** patients with hematological malignancies are highly susceptible to almost any type of bacteria. In this study, we aimed to determine the bacterial profile, antimicrobial resistance pattern, and associated factors among patients with hematological malignancies.

Method: A consecutive 70 hematological malignancies patients were enrolled from January to October, 2020; at Nanakaly hospital for blood disease and cancer in Erbil- Kurdistan region. Clinical data and Socio-demographic were collected by a structured questionnaire. Culture and antibiotic resistance were performed following standard microbiological procedures.

Result: The incidence of bacterial infection among examined cancer patients were 62.8 % (44/70). *E.coli* was among the predominant bacterial isolates (20%), followed by *Klebsiella pneumoniae* (11%), *Streptococcus parasnguinis*, and *Staphylococcus haemolyticus* (9%). These bacterial isolates were resistant to different antibiotics. Gram- negative bacteria were highly resistant to several antibiotics including, ciprofloxacin, gentamycin, sulfamethoxazole/trimethoprim, piperacillin, and cefepime, but they were sensitive to imipenem, amikacin and tigecycline. While gram-positive bacteria were highly resistant to tetracycline, ceftriaxone, levofloxacin, ampicillin, and erythromycin, but they were highly sensitive to linezolid, tigecycline, imipenem and vancomycin. The majority of resistance organism against fluoroquinolone were *E.coli* (72.7%) followed by *Klebsiella pneumoniae* (66.7%). Among gram-positive bacteria *Streptococcus parasnguinis* was highly resistance while sensitive organisms were *Staphylococcus aureus*, CoNS, *viridance streptococcus* and *Enterococcus faecalis.*

Conclusion: Among hematological malignant patients, the majority of patients were diagnosed as acute leukemia, gram-negative bacteria were more frequently isolates comparing with gram- positive bacteria. *E coli* was among predominant pathogen followed by *Klebsiella pneumoniae*, *Streptococcus parasnguinis* and *Staphylococcus haemolyticus*.

KEY WORDS: Bacterial profile, antibiotic resistance pattern, Hematological malignancy.
DOI: http://dx.doi.org/10.21271/ZJPAS.33.3.8
ZJPAS (2021), 33(3);70-84.

1. INTRODUCTION:

Cancer are one of the top global health and hygiene matters after cardiovascular diseases, major crises, and traumatic accidents worldwide. Cancer caused around 13% of all human deaths globally (Abdollahi *et al.,* 2016). More than half of all cancer cases and about 60% of deaths occur in developing countries (Qin *et al.,* 2007). Approximately 9 million people worldwide died by reason of complications from cancer, and the incidence is expected to double by 2030 (Ferlay *et al.,* 2015). There are many types of cancers classified in solid tumor and hematological tumor, the incidence and risk factors are in continuous change depending on the personal and environmental factor (Bray *et al.,* 2018).

Better care for cancer patients over the past several decades have significant improvement in patients survival (Fentie *et al.,* 2018a). Patients with cancer are susceptible to serious

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Article History:
Received: 29/12/2020
Accepted: 28/02/2021
Published: 20/06 /2021

complications, among them infections were responsible for substantial increment mortality and morbidity (Fentie *et al.,* 2018a). Patients with cancer who are undergoing chemotherapy are highly susceptible to almost any type of bacterial infection (Vento and Cainelli, 2003). Cancer patients obtaining infection of bacterial either through exogenously from the hospital environments or endogenously from normal flora near the operative sites (Nurain *et al.,* 2015).

The pattern of bacteria causing infection in patients with cancer have altered over the past decades(Kanamaru and Tatsumi, 2004). Gram-negative bacteria were detected as the common microorganism in1970. However, gram-positive bacteria became the predominant microorganism in1980 (Rasmy *et al.,* 2016). The incidence of gram-negative bacteria increased throughout the last two decades in an adult, whereas in pediatric patients, an increase in gram-positive bacteria was detected. In cancer patients, particularly during treatment with chemotherapy agents, most cells of the human body undergo undesirable changes which cause disruptions of bodies' defense system. Moreover, exposures to potentially pathogenic microorganisms increase as result of the frequent use of invasive procedures beside the empirical use of broad spectrum antibiotics (Meidani *et al.,* 2013).

The infection of patients with hematological malignancy may affect any organ most commonly affecting the respiratory tract, urinary tract, blood, and skin (Azoulay and Schlemmer, 2006) (Lagier *et al.,* 2016).

The susceptibility of microorganisms for antibiotic also changes with the period, with the emergence of multidrug-resistant organisms since the discovery of antimicrobial agents, microorganisms have developed resistance to them through mechanisms such as mutations and increased enzyme production (Anderson *et al.,* 2012). Resistance to commonly used antibiotics is an important problem worldwide (Graffunder *et al.,* 2005). Infection pathogens with multidrug-resistant (MDR) counting extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are most predominant among cancer patients (Biehl *et al.,* 2016). Enterobacteriaceae cause around 65%–80% of documented gram-negative infections in cancer patients (Saghir *et al.,* 2009). Patients profile, environmental factor and geographical distribution were mainly responsible for emerging resistant pattern among cancer patients (Versporten *et al.,* 2018) (Tsutsui and Suzuki, 2018). Therefore a periodic epidemiological data and molecular studies are necessary for knowing the pattern of microbial resistance which guides the clinician for better and effective use of empirical therapy and better infection (Lebea and Davies, 2017). The aim to this study was to determine the bacterial profile, antimicrobial resistance pattern, and associated risk factors among patients with hematological malignancy.

MATERIALS AND METHODS

Study Population and Sampling

This is a cross sectional prospective study done at the Nanakaly hospital for blood disease and cancer in Erbil city- Kurdistan Region. Seventy cancer patients (39 males and 31 females) were include in this study from - January 2020 to October 2020; patient were provided with informed consent. This study was achieved according to the ethical committing at Hawler Medical University. Cancer patients were selected after an interview through a structured questionnaire designed for such purpose, which consists of three parts including, demographic information: include (age, gender, occupation, marital status, level of education), patients statue and cancer types as well as types of treatment that patient receives. A total of 144 clinically related specimens were collected from 70 patients diagnosed with hematological malignancy, specimens were collected from different clinical site including; sputum, blood, urine, wound swab, throat swab and stool.

Blood sample processing and collection:

Blood samples (8–10 mL blood from a patient) for cultures were taken from each patient who developed a fever at the time of diagnosis. Blood samples were drawn from two different sites of peripheral vein aseptically (disinfecting with 70% alcohol and 2% tincture of iodine .which are used for blood cultures by experienced nurses prior to any antibiotic use) (Little *et al.,* 1999) (Calfee and Farr, 2002). Samples were immediately transferred into the Automated BacT/ALERT3D (bioMerieux, France) system, plus blood culture bottles (Doern *et al.,* 2014). These bottles were specifically designed to

provide rapid and sensitive detection of micro-organisms (bacteria and yeast), when only a small volume of blood was available. They contained a smaller volume of broth, thereby still providing an optimal blood to broth ratio when a limited volume of blood was collected. The BacT/ALERT® PF Plus blood culture (bioMerieux, France) system, could accommodate up to 4 mL of blood (Doern *et al.,* 2014). As such, it was appropriate for blood cultures from hematological malignancy patients, bottle were labeled with identification number, date, gender and age. Then it was taken into BacT/ALERT3D 60 remarkably complete by recording barcodes, all blood cultures have been observed for at least one week to appear either infectious or noninfectious samples of blood by their screen (Doern *et al.,* 2014).

Urine Sample Collection and Processing:

Midstream urine was collected with a sterile urine container from both symptomatic and asymptomatic urinary tract infection (UTI) cases. Standard wire loop (0.001/ mL) used for taking specimen for culture. Specimen were inoculated on MacConkey agar and 5% sheep blood agar. All sample were incubated at 37°C for 18–24 hours. Significant bacteriuria was defined as a colony count ≥105 CFU/mL urine (Fentie *et al.,* 2018b).

Wound /Throat swab Processing and Collection:

Wound and throat swab samples were collected aseptically based on the clinical manifestations of the cancer patients by using a sterile saline moistened cotton swab. The swabs were streaked on MacConkey agar, blood agar plates, and Mannitol salt agar. These plates were then aerobically incubated for 18–24 hours at 37°C (Fentie *et al.,* 2018b).

Sputum Collection and Processing

Sputum samples in the early morning were collected from each patient, the expectorated specimen was placed in a sterile petri dish .through the use of a sterile wire loop 0.001ml, specimens were cultured on blood agar medium incubated aerobically at 37°C for 48 hrs (Bartlett and Finegold, 1978).

Specimen cultivation

Different types of culture media including: MacConkey agar, Mannitol salt agar, blood agar and Eosin Methylene Blue (EMB) were used to obtain a pure isolates. The urine specimens were inoculated on the plates of (EMB) and MacConkey agar and then distributed on the surface of plate for incubation, to obtain a single colony. After incubation the pure isolated colonies were tested for colonial morphology and lactose fermentation. The wound and throat swabs were cultured on blood agar, MacConkey agar and Mannitol salt agar and incubated. After incubation the pure isolated colonies were tested for colonial morphology. All the media were incubated at 37°C for 18–24 hours. For further identification of culture pathogen other tests have been performed including, test describing morphological characteristics and biochemical characteristic of isolation pathogen (Elmanama *et al.,* 2013).

Identification Technique of the Isolated Bacteria

Sub-Culture of the Isolated Bacteria:

Sub-culture of single colony of isolated bacteria was achieved by inoculating single colony into the plate by quadrant method. The inoculated plates were incubated at 37 ˚C for 24 hrs. And then the growth spread over a wide area (Ge and Taylor, 1997). Isolation, identification and purification of isolated bacteria by traditional methods depend on cultural, morphology of bacteria, such as hemolysis phenomenon, and lactose fermentation ,identification of bacterial shape one according to the result from Gram stain method (Atlas, 2010).

Gram Staining:

Is the first step of bacterial identification, a smear of bacteria was deposited on a glass slide and carefully air-dried, then after stained for 1 min in Crystal Violet solution, 1 min in an iodine solution, washed for 10 sec. in ethanol, and finally, counterstained with safranin for 1 min. The glass slide examined under oil immersion under light microscope (Pandolfi and Pons, 2004).

Culture Media:

Nutrient Agar Medium

This medium was used for preservation of pure culture on slant. It also useful for detect of pyocyanin (water soluble bluish-green pigment) production by *Pseudomonas aeruginosa (Atlas, 2010).*

Blood Agar Medium

Blood agar is frequently used as a universal enrichment medium. Most human bacterial pathogens grow on blood agar. It is prepared by autoclaving blood agar base at 121 °C for 15 minutes, after cooling to 45-50 °C. 50 ml of sterile defibrinated human blood were added aseptically

to 1 liter of the medium, mixed thoroughly and poured into sterile Petri dishes (Atlas *et al.,* 1995).

MacConkey's Agar Medium

This medium is both Selective and differential agar used for isolation of Gram-negative enteric bacilli and differentiation of lactose fermenters from non-lactose fermenters (Forbes *et al.,* 2007).

Eosin Methylene Blue Agar (EMB)

This medium is both a selective and differential agar. It inhibits Gram-positive bacteria, so it is instrumental in isolating Gram-negative bacteria. The normal flora bacterium *Escherichia coli* is readily detected on EMB agar by the green sheen that the colonies develop (McKane and Judi, 1996).

Mannitol Salt Agar

It is an indicator as well as selective medium. It contains Mannitol, NaCl (7.5%) and phenol red in nutrient agar. *Staphylococcus aureus* strains form colonies surrounded by yellow zones due to fermentation of Mannitol. NaCl inhibits the growth of other bacteria (Pachauri *et al.,* 2013).

Biochemical Tests:

Simmon's Citrate Agar:

Slants of Simmons citrate medium were inoculated with the test bacteria by stabbing, then tubes were incubated at 37°C for 24-48 hours. After incubation period the tubes were checked for Color change, blue Color indicated positive and green Colour indicated negative test (Dheyab *et al.,* 2018).

Catalase Test (Slide Test):

Transfer a small amount of bacterial colony to a surface of clean, dry glass slide using a loop or sterile wooden stick. Place a drop of 3% Hydrogen peroxide (H_2O_2) on to the slide and mix. A positive result is the rapid evolution of oxygen (within 5-10 sec.) as evidenced by bubbling. A negative result is no bubbles or only a few scattered bubbles (Koneman *et al.,* 1997).

Oxidase Test:

Oxidase was detected by taking a filter paper soaked with the test reagent (tetramethyl-p-phenylenediamine dihydrochloride). Pick the colony to be tested with a wooden stick or loop and smear in the filter paper. Positive result observes inoculated area of paper for a color change to deep blue or purple within 10-30 sec. A negative result is no color change observed (Goldman and Green, 2015).

Coagulase Test:

This test used to detect coagulase, an enzyme produced by pathogenic *Staphylococci* (Vandepitte *et al.,* 2003).

Detection of Hemolysis on Blood Agar

All the isolates were tested for hemolysis after overnight incubation at 37 °C on blood agar. Hemolysis was recorded as alfa-hemolysis (α-hemolysis), beta-hemolysis (β-hemolysis) and Gama-hemolysis (γ-hemolysis) or (no hemolysis) *Staphylococcus aureus* ATCC 29213 used as positive control strain (Boerlin *et al.,* 2003).

Lactose Fermentation and Bile Salt Tolerance

It was done by streaking bacterial isolates on MacConkey agar (Deben Diagnostics Ltd, UK without crystal violet), then incubated at 37 ˚C for 24 hrs. The colonies that tolerate bile salt and ferment lactose appeared as pale pink to red (Irving *et al.,* 2004) .

VITEK-2 Compact System:

All the isolates were screened and identified through the VITEK-2 compact System (BioMérieux, Marcy L'Etoile, and France) at Nanakaly hospital Erbil - Kurdistan-Iraq, in accordance with the manufacturer's instructions. This is a phenotypic type of identification that depends on biochemical reactions to identify the isolates (Al-Hasan, 2013). Gram-Negative Card (GNC) is used for the automated identification of 135 taxa of the most significant non-fermenting and fermenting gram-negative bacilli. The GNC is based on established biochemical techniques and newly developed substrates measuring the source of carbon utilization, activities of enzymatic, and resistance. There are 48 biochemical exams and one negative control as well. While gram-positive Card (GPC) is used for the automated identification of 115 taxa of the most important non-spore-forming and primarily cocci. There are 43 biochemical tests measuring enzymatic activities, resistance and carbon source utilization. Final identification results were available in approximately eight hrs (Pincus, 2006).

Antimicrobial Susceptibility Testing (AST)

Susceptibility antimicrobial testing was performed for 18 different therapeutically relevant antibiotics by VITEK 2 compact System (AST - P592, AST - GN77 and AST- ST03) purchased from (BioMérieux, France). Minimum inhibitory concentration (MIC) was carried out in triplicate and the average MIC was calculated, as suggested by the Clinical and Laboratory Standards Institute

(CLSI). Separates resistant to three or more of antimicrobials classes were measured as multidrug-resistant isolates. The tested agents used five different of antimicrobials classes: the β-lactams (ampicillin 10 µg, amoxicillin/clavulanic acid 20 µg/10 µg , cefotaxime 30 µg, ceftazidime 30 µg, cefoxitin 30 µg, ceftriaxone 30 µg, cefepime 30 µg, cefazolin 30 µg, ampicillin/sulbactam 20 µg/10 µg, piperacillin/tazobactam 100 µg/10 µg, imipenem 10 µg, ertapenem 10 µg, and meropenem 10 µg), aminoglycosides (amikacin 30 µg, gentamicin 10 µg, and tobramycin 10 µg), FQs (ciprofloxacin 5 µg and levofloxacin 5 µg), antimetabolites (sulfonamides/trimethoprim 23.75 µg/1.25 µg), other antibiotic groups, Linezolid 30 µg and tetracycline 30 µg. The inhibition of zone was reported and measured as susceptible (S), sensitive (I), intermediate, (R), resistance according to the clinical and laboratory standard institute (CLSI) guideline (Patel *et al.*, 2015).

Statistical Analysis: Statistical Package for the Social Sciences (SPSS) and Microsoft Office Excel were used for data entry and analysis (Meidani *et al.*, 2013).

RESULTS

Socio-demographic status of cases enrolled in the study

This study was done on 70 cases (39 males and 31 females), male to female ratio was 1.25:1. The age mean was 41 years, ranging from (4 to 81) years. Nearly two-third of the cases resides in urban areas (62.9%) and one third (37.1%) were in the rural areas. The majority of cases were unemployed (75.7%), and (74.3%) of cases were married. Almost all of cases (94.3%) were inpatients, the educational level of the patients was nearly similar for illiterate, primary, secondary and high education (28.6%, 24.3%, 27.1% and 20% respectively), as shown in Table 1.

Table 1: Socio demographic status of cases enrolled in the study

Characteristics (n=70)		
Age group	**Frequency**	**Percent (%)**
<25	19	27.1
15-44	24	34.3
45-64	13	18.6
≥ 65	14	20.0
Gender		
Male	39	55.7
Female	31	44.3
Residency		
Urban	44	62.9
Rural	26	37.1
Employment		
Employed	17	24.3
Unemployed	53	75.7
Marital states		
Single	18	25.7
Married	52	74.3
Patient setting		
Inpatient	66	94.3
Outpatient	4	5.7

Education		
Illiterate	20	28.6
Primary	17	24.3
Secondary	19	27.1
High Education	14	20.0

Clinical parameter of the patients

Among examined patients 45(64%) of patients were febrile, and 63 (90%) out of 70 patients received chemotherapy. Most of the cases 50(71.4%) were non-smoking, a history of catheterization were positive in 28 (40 %) patients, as shown in Table 2.

Table 2: Clinical characteristics of the patients.

Clinical cases	**Frequency**	**Percent %**
Febrile		
Yes	45	64.3
No	25	35.7
Symptomatic		
Yes	32	45.7
No	38	54.3
Family history		
Yes	13	18.6
No	41	58.6
Not Sure	16	22.9
Started therapy		
Chemotherapy	63	90
Non chemotherapy	7	10
Smoking		
Yes	20	28.6
No	50	71.4
History of catheter use		
Yes	28	40
No	42	60

Distribution of Patients according to the types of hematological malignancies

Out of 70 cases of hematological malignancies 19 cases (27.1%) were diagnosed as acute lymphocytic leukemia (ALL), followed by acute myelocytic leukemia (AML) 17 (24.3%) and Non-

Hodgkin Lymphoma (NHL)12(17.1),chronic lymphocytic leukemia accounts for the minority with only one case 1 (1.4 %), as shown in Figure1.

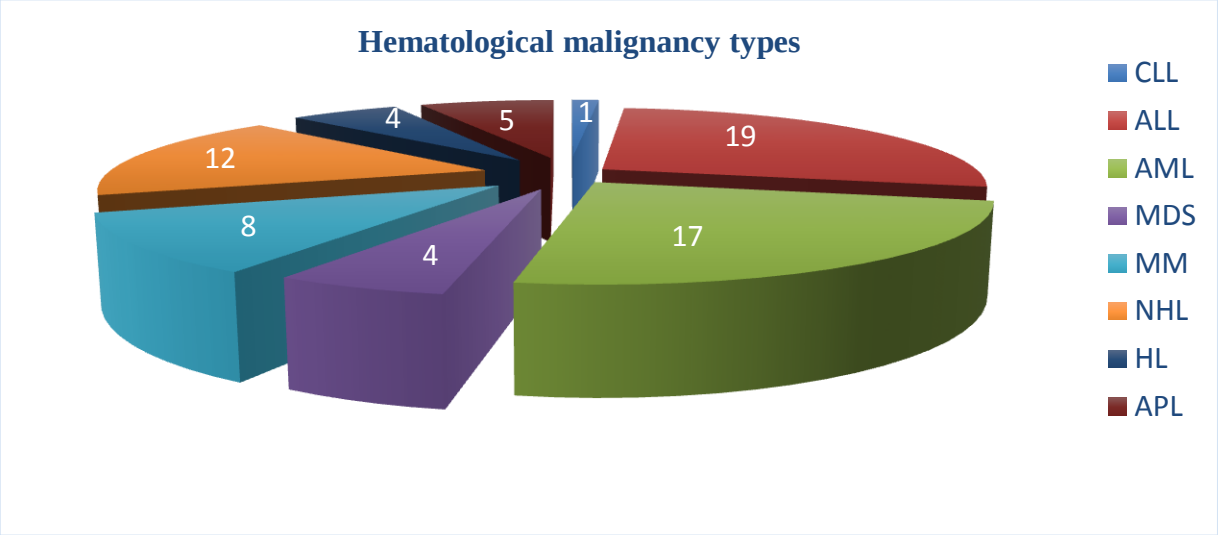

Figure 1: Distribution of types of hematological malignancies patients.

Bacterial profiles and site of isolation

Specimen culture was done for all 70 cases that are included in this study, bacterial pathogen was positive in 44 out of 70 patients, in some patient more than one specimen (different specimen) were send for culturing. Therefore growth had been detected in 56 out of 144 examined samples. Different type of specimens was taken from examined patients according to patients complain, among them bacterial growth could be easily detected from sputum samples which constituted 21(37.5%) of growths of all specimens followed by urine samples which constituted 17 (30.4%) of growths of all the specimens, blood samples came in the 3rd place which constituted 12(21.4%) followed by wound swab and throat swab, 3 (5.4%) of growths from all specimen samples. The predominant bacterial growth that had been isolated from the cultures of different specimens was *Escherichia coli* which accounts for 11(19.6%) of the isolates, followed by *Klebsiella pneumoniae spp pneumonia* and *Klebsiella pneumonia* which accounts for 6(10.7%) of the isolates for each of them. Fisher's Exact Test shows significant association between type of specimen and bacterial growth with a P value of <0.001. As shown in table 3 and 4.

Table 3: Result of culture according to specimen sites in patients with hematological malignancies

Culture	Blood	Urine	Sputum	Throat swab	Wound swab	Stool	Total
Growth	12 (21.4%)	17 (30.4%)	21 (37.5)	3 (5.4%)	3 (5.4%)	0 (0%)	56 (38.9%)
No growth	42 (47.7%)	30 (34.1%)	4 (4.5%)	1 (1.1%)	1 (1.1%)	10 (11.4%)	88 (61.1%)

Total	54 (37.5%)	47 (32.6%)	25 (17.4%)	4 (2.8%)	4 (2.8%)	10 (6.9%)	144 (100%)

Table 4: Distribution and predominate of bacterial isolates from different clinical specimens among hematological malignancies patients.

Isolated organism	Blood	Urine	Sputum	Throat swab	Wound swab	Total
Escherichia coli	3 (25%)	6 (35%)	0	1 (33.3%)	1(33.3%)	11(19.6%)
Klebsiella pneumoniae spp pneumonia	1 (8.3%)	2 (11.7%)	2 (9.5%)	0	1(33.3%)	6 (10.7%)
Klebsiella pneumoniae	0	1 (5.8%)	4 (19%)	1 (33.3%)	0	6 (10.7%)
Pseudomonas aeruginosa	0	0	1 (4.7%)	0	0	1 (1.7%)
Stenotrophomonas maltophilia	1 (8.3%)	0	0	0	0	1(1.7%)
Raoultella ornithinolytica	0	0	1 (4.7%)	0	0	1(1.7%)
Cedecea lapagei	1 (8.3%)	0	0	0	0	1(1.7%)
Sphingomonas paucimobilis	0	0	1 (4.7%)	0	0	1(1.7%)
Acinetobacter haemolyticus	2 (16.6%)	0	0	0	0	2 (3.57%)
Enterococcus faecalis	1 (8.3%)	2 (11.7%)	0	0	0	3(5.3%)
Streptococcus parasnguinis	0	0	4(19%)	1 (33.3%)	0	5 (8.9%)
Streptococcus viridans group except S. pneumoniae	0	0	1 (4.7%)	0	0	1(1.7%)
Staphylococcus aureus	0	1 (5.8%)	0	0	1(33.3%)	2(3.57%)
Staphylococcus haemolyticus	0	4 (23.5%)	1 (4.7%)	0	0	5(8.9%)
Staphylococcus saprophyticus	0	1 (5.8%)	0	0	0	1(1.7%)
Staphylococcus epidermidis	2 (16.6%)	0	0	0	0	2(4.0%)
Staphylococcus pseudintermedius	1 (8.3%)	0	0	0	0	1(1.7%)
Streptococcus pneumonia	0	0	2 (9.5%)	0	0	2(3.57%)
Streptococcus iniae	0	0	1 (4.7%)	0	0	1(1.7%)
Rothia mucilaginosa	0	0	1 (4.7%)	0	0	1(1.7%)
Streptococcus mitis/Streptococcus oralis	0	0	1 (4.7%)	0	0	1(1.7%)
Streptococcus viridans	0	0	1 (4.7%)	0	0	1(1.7%)
Total	**12(100%)**	**17(100%)**	**21(100%)**	**3(100%)**	**3(100%)**	**56(100%)**

Gram stain isolation according to different site of infection

Based on gram staining, gram-negative bacteria (GNB) were higher than the growth for gram- positive bacteria (GPB) [30 (53.6%) vs. 26

(46.4%)]. Gram-negative bacterial growth from samples taken from blood, throat and wound swabs were (66.7%), followed by urine culture (52.9%) and sputum cultures (42.9%). On the other hand gram-positive bacteria growth from samples taken from sputum accounted for (57.1%), followed by urine cultures 8(47.1%) while blood, throat swabs and wound swabs came in the 3rd stage which accounted for (33.3%) of each of them, Chi-square test shows no statistical significant association between the gram stain and specimen sites as shown in Table 5.

Table 5: Association between grams stain and culture specimen sites (Column percent).

Gram stain	Blood	Urine	Sputum	Throat swab	Wound swab	Total
Gram Negative	8 (66.7%)	9 (52.9%)	9 (42.9%)	2 (66.7%)	2 (66.7%)	30 (53.6%)
Gram Positive	4 (33.3%)	8 (47.1%)	12 (57.1%)	1 (33.3%)	1 (33.3%)	26 (46.4%)
Total	12 (100%)	17 (100%)	21 (100%)	3 (100%)	3 (100%)	56 (100%)

Prevalence of bacterial infections among hematological malignancy patients

The prevalence of infection was highest among patients with acute leukemia as ALL accounts for (16) cases, AML (8), APL (3), NHL (7). The least growth of bacteria was found among patient with MM witch counts for (3), followed by MDS (3), and HL (3). Among patients included in this study only one patient was diagnosed as chronic lymphocytic leukemia CLL. Fissures exact test shows no significant association between types of hematological malignancies and bacterial growth, as shown in Figure 2.

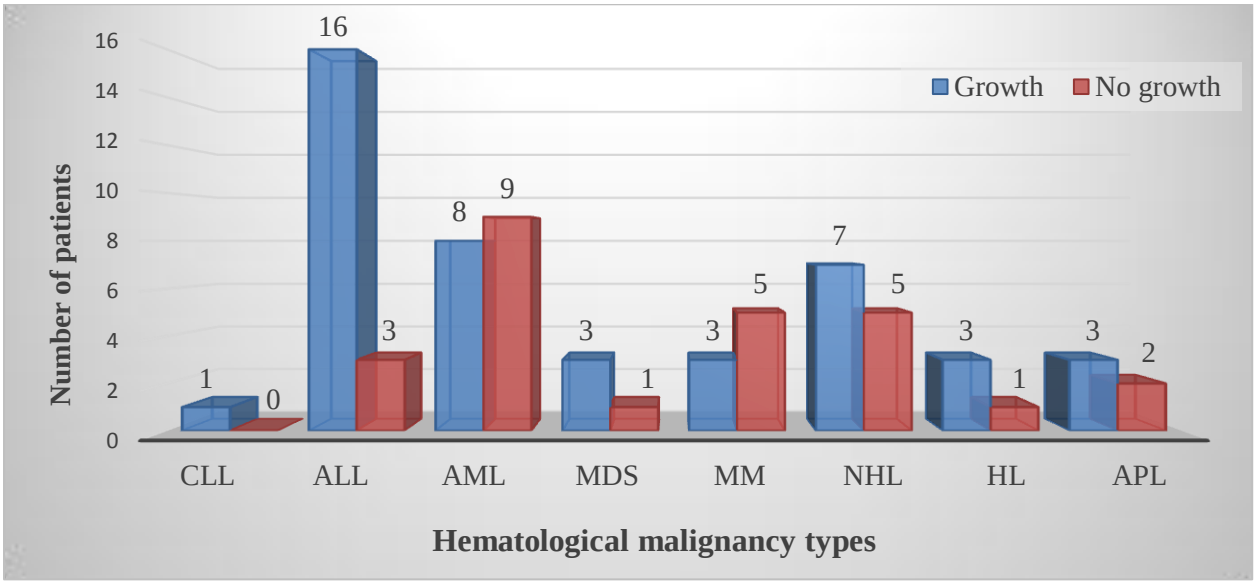

Figure 2: Distribution of bacterial infections among hematological malignancy patients.

Antibiotic susceptibility test (AST) to GNB and GPB isolates

Antibiotic sensitivity test and gram staining performed for all patients included in this study, showing that GNB were highly resistance to ciprofloxacin, gentamycin, sulfamethoxazole /trimethoprim, piperacillin and cefepime, but sensitive to imipenem, amikacin and tigecycline. While GPB highly resistance were to tetracycline, ceftriaxone, levofloxacin, ampicillin and erythromycin, but highly sensitive to linezolid, Tigecycline, Imipenem and vancomycin, as shown in Table 6.

Table 6: The percentage of susceptibility pattern of Gram-negative and Gram-positive bacteria to 18 various antibiotics using VITEK-2 compact system.

Isolated bacteria	**Gram-negative bacteria**			**Gram-positive bacteria**		
Antibiotic scientific name	MIC Interpretive Criteria (µg/mL)			MIC Interpretive Criteria (µg/mL)		
	R	S	I	R	S	I
Ciprofloxacin	60.0	10.0	10.0	0	9.7	3.2
Gentamycin	46.7	30.0	10.0	18.8	18.8	43.8
Tobramycin	30.0	26.7	3.3	25.0	25.0	6.3
Amikacin	10.0	46.7	0	x	6.3	x
Piperacillin	35.5	12.9	3.2	4.5	4.5	x
Amoxiclav/ clavulanic acid	25.8	12.9	12.9	4.5	9.1	x
Cefepime	32.3	16.1	6.5	x	x	x
Ampicillin	29.0	x	x	52.9	x	x
Imipenem	16.6	79.0	x	x	75.0	x
Erythromycin	29.4	x	x	42.3	11.5	7.7
vancomycin	17.4	4.4	x	3.3	63.3	x
Tetracyclines	33.3	4.2	4.2	72.0	12.0	4.0
Sulfamethoxazole /Trimethoprim	39.3	25.0	3.6	33.3	20.0	x
Nitrofurantion	6.7	16.7	x	x	38.7	3.2
ceftriaxone	25.8	12.9	3.2	58.8	5.88	x
Levofloxacin	26.7	3.3	10.0	53.8	6.5	6.5
linezolid	x	10.7	x	4.1	79.0	x
Tigecycline	3.6	39.3	x	x	75.0	x

S: Sensitive, R: resistant, I: Intermediate, X: Not performed.

DISCUSSION

Cancer is one of the major global health problems worldwide. Patients with hematological malignancies are extremely susceptible to nearly any kind of bacterial infection .The overall prevalence of bacterial infection among hematological malignant patients were 44 (62.9%) out of 70 cases, which differ with the result from study done in Iran, reported that the prevalence of infection among cancer was (24.6%) (Eslami Nejad *et al.,* 2010), and with the study done in Romania revealed that the frequency of infection were (14.92%) (Adipocytes, 2014). Our result close to previous study done in Iraq and Sudan showing the frequency of infection among cancer patients were (mean of 44.2%), and (48%) respectively (Almaziny, 2014, Nurain *et al.,* 2015). The difference in prevalence might be explained by the fact that patients profile, environmental and geographical factor play a major role in such group of patients (Grasgruber *et al.,* 2018).

The hematological malignancies (HMs) were slightly higher among male gender (39 males and 31 females) the male: female ratio in our study was 1.25:1. Our study was in agreement with other study done in Iran, that the incidence of cancer was higher in men than women with the ratio of (1.25). The maximum gender ratio was reported in Hamadan (1.45) and the minimum was reported in Yazd (1.15) (Mashhadi *et al.,* 2010). Other studies also showing male predominance among hematological malignant patient, such results lacks a clear explanation but occupation exposure , hormonal influence and migrate smoking might have a role, further studies are warranted both experimentally epidemiological for further explanation such association (Kim *et al.,* 2018). In our study majority of cases (71.4%) were non-smoker, however many studies show association of smoking with hematological malignancy(Brownson *et al.,* 1993), while others shows no association(Kasim *et al.,* 2005, Ugai *et al.,* 2017). Further studies are reasonable to further investigate such association.

Among homologically malignant patients included in this study, the prevalence of infections was more common among patients with acute leukemia (38.5%). This result was similar to those studies that have been done in India and in China showing similar infection prevalence among all patients (46.5%), (34.3%) respectively (Gupta *et al.,* 2019, Tang *et al.,* 2020). Gram-negative bacteria were higher than gram-positive bacteria. Several studies in recent years have noted a shift of prevalence from GPB to GNB (Gudiol *et al.,* 2013, Kokkayil *et al.,* 2018). A study from Italy, consistent with this study reported that Gram-negative bacteria were isolated as the most common cause in patients with hematological malignancies than Gram-positive bacteria. Several studies reported that, GPB was the main cause of bacterial infection as compared to GNB. In hematological neoplasia (Eslami Nejad *et al.,* 2010, Fentie *et al.,* 2018a). This finding incompatibility with this study.

The bacterial isolates detected in our study showing that Gram-negative bacteria were higher than gram-positive bacteria. This result is in accordance with other studies done in Italy, reporting that Gram-negative bacterial isolated were the most common type in patients with hematological malignancies than Gram-positive bacteria (Eslami Nejad *et al.,* 2010, Fentie *et al.,* 2018a). Several other studies in recent years have noted a shift of prevalence from GPB to GNB (Gudiol *et al.,* 2013, Kokkayil *et al.,* 2018). The predominant bacterial isolates from our study was *Escherichia coli* which constituted (19.6%) of the isolates, followed by *Klebsiella pneumoniae spp pneumonia* and *Klebsiella pneumonia* which constituted (10.7%) of the isolates for each of them, similar results were found in Tehran-Iran that illustrated as *Escherichia coli* was the most common microorganism isolated from the leukemia patient (Abdollahi *et al.,* 2016). Several other study at international level had similar result, showing that the bacterium *E. coli* was the most prevalent gram-negative isolated bacteria (Alcala-Guanzon and Tan-Torres, 1998, Ashour and El-Sharif, 2009). Furthermore, in this study *E. coli* was among predominant GNB isolated from patient with septicemia, which accounts for 8 of 12 isolates (66.7%). A study done in India showing a similar result (Mathur *et al.,* 2002); (Ghosh *et al.,* 2012).

A study from Germany illustrated that the most prevalent gram-positive bacteria in respiratory tract infections (RTIs) in cancer patients were *Streptococcus* and *Staphylococcus species* while *Klebsiella pneumonia* was the common isolated gram-negative bacteria from throat and sputum (Hoheisel *et al.,* 2003). In compatibility with this study our result showing

that 11[21(52.3%)] isolated GPB from RTIs were *Staphylococcus* and *Streptococcus species* whereas among GNB, *Klebsiella species* accounts about 4 [21(19%)] from sputum followed by 1[3(33.3%)] from throat swab.

In current study *E.coli* 6[17(35 %)] was the most common bacterial isolate among patients with UTI, followed by *K. pneumoniae* 3[17(17.6 %)]. While the predominant species among gram-positive isolates were, *Staphylococcus haemolyticus* 4[17(23.5 %)], followed by *Enterococcus faecalis* 2[17(11.7 %)]. This is in accordance with other studies showing that Gram- negative bacteria are highly associates with UTI patient (Kline and Lewis, 2017).*Escherichia Coli* is the most frequently isolated bacteria from the urine, blood, throat, and wound swab cultures in our study, since it is the most prevalent commensal inhabitant of the gastrointestinal tract, it is a common pathogen liked with community-associated as well as hospital-acquired infections (Drago *et al.,* 2010). Several other studies confirming similar results(Ashour and El-Sharif, 2009;Nurain *et al.*, 2015) (Chiu and Chang, 2009, Sharma *et al.*, 2011).

Regarding antimicrobial resistant pattern, our study showing that GNB were highly resistant to Ciprofloxacin, Gentamycin, Sulfamethoxazole /Trimethoprim, Piperacillin, and Cefepime, whereas they are highly sensitive to Imipenem, Amikacin and Tigecycline. While GPB showing highly resistant for Tetracyclines, ceftriaxone, Levofloxacin, Ampicillin and Erythromycin, but highly sensitive for linezolid, Tigecycline, Imipenem, and vancomycin.

Comparable with this result, several other studies reported that, GNB were highly resistant against cephalosporins, quinolones and penicillins (Marin *et al.,* 2014, Yao *et al.,* 2017). Another study demonstrated that antibiotics resistance among GPB were more common for tetracycline's, penicillins, erythromycin and quinolones (El Haddad *et al.,* 2018). Furthermore, in compatibility with our result, a retrospective study in Iraqi showed that the susceptibility of gram-positive organisms to antibiotics Imipenem was found to be the most effective, as for gram-negative organisms, demonstrated the highest sensitivity to Amikacin (Al-Zubaidy *et al.,* 2020). On the other hand, a study from Malaysia demonstrated that all isolated gram-negative bacteria were resistant for Ampicillin, cefazolin, ceftriaxone, piperacillin. Whereas all isolated gram-negative bacteria were extremely resistant to imipenem which disagree with our finding (Baskaran *et al.,* 2007).

Today development of MDR is become natural phenomenon, due to interestingly raise in the number of immunocompromised conditions, blind and improper use of broad spectrum of antibiotics as well as poor infection prevention, beside that patients profile, environmental and geographical factor were among important player determining the bacterial profile and resistance pattern (Weinstein, 2001); (Lebea and Davies, 2017, Weinstein, 2001).

CONCLUSION

Acute leukemia was the common hematological malignancies with slight male predominance. Gram negative bacteria isolates were higher than gram positive bacteria. *Escherichia coli* was the most frequently isolated bacteria. The majority of bacterial isolates were resistant to various antibiotics. Among GNB were highly resistant to Ciprofloxacin, Gentamycin, Sulfamethoxazole /Trimethoprim, Piperacillin, and Cefepime, Also highly sensitive to Imipenem, Amikacin and Tigecycline. While among GPB highly resistant was to Tetracyclines, ceftriaxone, Levofloxacin, Ampicillin and Erythromycin, Also highly sensitive to linezolid, Tigecycline, Imipenem, and vancomycin

ACKNOWLEDGMENTS

I would like to express my very great appreciation to the directorate of Nanakaly Hospital working in the laboratory, as well as to all those who have helped to make possible my undertaking of this research.

CONFLICTS OF INTEREST

There are no conflicts of interests to be declared.

REFERENCE

ABDOLLAHI, A., HAKIMI, F., DOOMANLOU, M. & AZADEGAN, A. 2016. Microbial and Antibiotic Susceptibility Profile among Clinical Samples of Patients with Acute Leukemia. *International Journal of Hematology-Oncology and Stem Cell Research,* 10**,** 61-69.

ADIPOCYTES, O. S. M. T. 2014. BASIC SCIENCES UPDATES. *The Medical-Surgical Journal,* 118.

AL-HASAN, A. R. 2013. Study of carbapenem resistance in Acinetobacter baumannii isolates from Kuwait.

AL-ZUBAIDY, A. S., JUMAAH, S. S. & RADHI, Q. R. 2020. Bacteriological Study of Febrile Neutropenia

in Patients with Hematological Malignancies in Baghdad Teaching Hospital. *IRAQI POSTGRADUATE MEDICAL JOURNAL*, 19.

ALCALA-GUANZON, M. & TAN-TORRES, T. 1998. Outcom of Bacteremia at the Philippine General Hospital. *Phil J Microbiol Infect Dis*, 27**,** 103-8.

ALMAZINY, M. A. 2014. Isolation, identification, and profile of antibiotic resistance of bacteria in childhood febrile neutropenia patients. *Eur J Exp Biol*, 4**,** 1-6.

ANDERSON, R., GROUNDWATER, P. W., TODD, A. & WORSLEY, A. 2012. *Antibacterial Agents: Chemistry, Mode of Action, Mechanisms of Resistance and Clinical Applications*, John Wiley & Sons.

ASHOUR, H. M. & EL-SHARIF, A. 2009. Species distribution and antimicrobial susceptibility of gram-negative aerobic bacteria in hospitalized cancer patients. *Journal of translational medicine*, 7**,** 14.

ATLAS, R. M. 2010. *Handbook of Microbiological Media*, CRC Press.

ATLAS, R. M., BROWN, A. E. & PARKS, L. C. 1995. *Laboratory manual of experimental microbiology*, Mosby.

AZOULAY, É. & SCHLEMMER, B. 2006. Diagnostic strategy in cancer patients with acute respiratory failure. *Intensive care medicine*, 32**,** 808-822.

BARTLETT, J. G. & FINEGOLD, S. M. 1978. Bacteriology of Expectorated Sputum with Quantitative Culture and Wash Technique Compared to Transtracheal Aspirates. *American Review of Respiratory Disease*, 117**,** 1019-1027.

BASKARAN, N. D., GAN, G. G., ADEEBA, K. & SAM, I. C. 2007. Bacteremia in patients with febrile neutropenia after chemotherapy at a university medical center in Malaysia. *International Journal of Infectious Diseases*, 11**,** 513-517.

BIEHL, L. M., SCHMIDT-HIEBER, M., LISS, B., CORNELY, O. A. & VEHRESCHILD, M. J. 2016. Colonization and infection with extended spectrum beta-lactamase producing Enterobacteriaceae in high-risk patients–review of the literature from a clinical perspective. *Critical reviews in microbiology*, 42**,** 1-16.

BOERLIN, P., KUHNERT, P., HÜSSY, D. & SCHAELLIBAUM, M. 2003. Methods for identification of Staphylococcus aureus isolates in cases of bovine mastitis. *Journal of clinical microbiology*, 41**,** 767-771.

BRAY, F., FERLAY, J., SOERJOMATARAM, I., SIEGEL, R. L., TORRE, L. A. & JEMAL, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68**,** 394-424.

BROWNSON, R. C., NOVOTNY, T. E. & PERRY, M. C. 1993. Cigarette smoking and adult leukemia: a meta-analysis. *Archives of internal medicine*, 153**,** 469-475.

CALFEE, D. P. & FARR, B. M. 2002. Comparison of four antiseptic preparations for skin in the prevention of contamination of percutaneously drawn blood cultures: a randomized trial. *Journal of clinical microbiology*, 40**,** 1660-1665.

CHIU, S.-K. & CHANG, F.-Y. 2009. Pyomyositis caused by extended-spectrum β-lactamase-producing Escherichia coli in a patient with acute myeloid leukemia. *International Journal of Infectious Diseases*, 13**,** e85-e87.

DHEYAB, A. S., ALJUMAILI, O. I. & HUSSEIN, N. M. 2018. Study of Virulence Factors in Urease-Positive Bacteria Isolated from Urinary Tract Infections Clinical Specimens. *Journal of PurE and aPPliEd Microbiology*, 12**,** 1465-1472.

DOERN, C. D., MIRRETT, S., HALSTEAD, D., ABID, J., OKADA, P. & RELLER, L. B. 2014. Controlled clinical comparison of new pediatric medium with adsorbent polymeric beads (PF Plus) versus charcoal-containing PF medium in the BacT/Alert blood culture system. *Journal of clinical microbiology*, 52**,** 1898-1900.

EL HADDAD, H., CHAFTARI, A.-M., HACHEM, R., CHAFTARI, P. & RAAD, I. I. 2018. Biomarkers of sepsis and bloodstream infections: the role of procalcitonin and proadrenomedullin with emphasis in patients with cancer. *Clinical Infectious Diseases*, 67**,** 971-977.

ELMANAMA, A. A., AL LAHAM, N. A. & TAYH, G. A. 2013. Antimicrobial susceptibility of bacterial isolates from burn units in Gaza. *Burns*, 39**,** 1612-1618.

ESLAMI NEJAD, Z., GHAFOURI, E., FARAHMANDI-NIA, Z., KALANTARI, B. & SAFFARI, F. 2010. Isolation, identification, and profile of antibiotic resistance of bacteria in patients with cancer. *Iranian Journal of Medical Sciences*, 35**,** 109-115.

FENTIE, A., WONDIMENEH, Y., BALCHA, A., AMSALU, A. & ADANKIE, B. 2018a. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. *Infection and Drug Resistance*, Volume 11**,** 2169-2178.

FENTIE, A., WONDIMENEH, Y., BALCHA, A., AMSALU, A. & ADANKIE, B. T. 2018b. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. *Infection and drug resistance*, 11**,** 2169.

FERLAY, J., SOERJOMATARAM, I., DIKSHIT, R., ESER, S., MATHERS, C., REBELO, M., PARKIN, D. M., FORMAN, D. & BRAY, F. 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer*, 136**,** E359-E386.

FORBES, B. A., SAHM, D. F. & WEISSFELD, A. S. 2007. *Diagnostic microbiology*, Mosby St Louis.

GE, Z. & TAYLOR, D. E. 1997. Methods in molecular medicine, Helicobacter pylori protocols.

GHOSH, I., RAINA, V., KUMAR, L., SHARMA, A., BAKHSHI, S., THULKAR, S. & KAPIL, A. 2012. Profile of infections and outcome in high-risk febrile neutropenia: experience from a tertiary care cancer center in India. *Medical Oncology*, 29**,** 1354-1360.

GOLDMAN, E. & GREEN, L. H. 2015. *Practical handbook of microbiology*, CRC press.

GRAFFUNDER, E. M., PRESTON, K. E., EVANS, A. M. & VENEZIA, R. A. 2005. Risk factors associated with extended-spectrum β-lactamase-producing organisms at a tertiary care hospital. *Journal of Antimicrobial Chemotherapy,* 56**,** 139-145.

GRASGRUBER, P., HRAZDIRA, E., SEBERA, M. & KALINA, T. 2018. Cancer incidence in Europe: an ecological analysis of nutritional and other environmental factors. *Frontiers in oncology,* 8**,** 151.

GUDIOL, C., BODRO, M., SIMONETTI, A., TUBAU, F., GONZÁLEZ-BARCA, E., CISNAL, M., DOMINGO-DOMENECH, E., JIMÉNEZ, L. & CARRATALÀ, J. 2013. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clinical Microbiology and Infection,* 19**,** 474-479.

GUPTA, N., PAWAR, R., BANERJEE, S., BRAHMA, S., RATH, A., SHEWALE, S., PARIHAR, M., SINGH, M., ARUN, S. R. & KRISHNAN, S. 2019. Spectrum and immunophenotypic profile of acute leukemia: a tertiary center flow cytometry experience. *Mediterranean Journal of Hematology and Infectious Diseases,* 11.

HOHEISEL, G., LANGE, S., WINKLER, J., RODLOFF, A. C., LIEBERT, U. G., NIEDERWIESER, D., SCHAUER, J. & ENGELMANN, L. 2003. Nosocomial pneumonias in haematological malignancies in the medical intensive care unit. *Pneumologie (Stuttgart, Germany),* 57**,** 73-77.

IRVING, W., BOSWELL, T. & ALA'ALDEEN, D. 2004. *BIOS Instant Notes in Medical Microbiology*, Taylor & Francis.

KANAMARU, A. & TATSUMI, Y. 2004. Microbiological data for patients with febrile neutropenia. *Clinical infectious diseases,* 39**,** S7-S10.

KASIM, K., LEVALLOIS, P., ABDOUS, B., AUGER, P. & JOHNSON, K. C. 2005. Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes & Control,* 16**,** 489-500.

KIM, H.-I., LIM, H. & MOON, A. 2018. Sex Differences in Cancer: Epidemiology, Genetics and Therapy. *Biomolecules & Therapeutics,* 26**,** 335-342.

KLINE, K. A. & LEWIS, A. L. 2017. Gram-positive uropathogens, polymicrobial urinary tract infection, and the emerging microbiota of the urinary tract. *Urinary Tract Infections: Molecular Pathogenesis and Clinical Management***,** 459-502.

KOKKAYIL, P., AGARWAL, R., MOHAPATRA, S., BAKSHI, S., DAS, B., SOOD, S., DHAWAN, B. & KAPIL, A. 2018. Bacterial profile and antibiogram of blood stream infections in febrile neutropenic patients with haematological malignancies. *The Journal of Infection in Developing Countries,* 12**,** 442-447.

KONEMAN, E. W., ALLEN, S. D., JANDA, W. M., SCHRECKENBERGER, P. C. & WINN, W. C. 1997. Diagnostic microbiology. *The nonfermentative gram-negative bacilli. Philedelphia: Lippincott-Raven Publishers***,** 253-320.

LAGIER, D., PLATON, L., CHOW-CHINE, L., SANNINI, A., BISBAL, M., BRUN, J. P., BLACHE, J. L., FAUCHER, M. & MOKART, D. 2016. Severity of Acute Respiratory Distress Syndrome in haematology patients: long-term impact and early predictive factors. *Anaesthesia,* 71**,** 1081-1090.

LEBEA, M. M. & DAVIES, V. 2017. Evaluation of culture-proven neonatal sepsis at a tertiary care hospital in Johannesburg, South Africa. *South African Journal of Child Health,* 11**,** 170-173.

LITTLE, J. R., MURRAY, P. R., TRAYNOR, P. S. & SPITZNAGEL, E. 1999. A randomized trial of povidone-iodine compared with iodine tincture for venipuncture site disinfection: effects on rates of blood culture contamination. *The American journal of medicine,* 107**,** 119-125.

MARIN, M., GUDIOL, C., ARDANUY, C., GARCIA-VIDAL, C., CALVO, M., ARNAN, M. & CARRATALÀ, J. 2014. Bloodstream infections in neutropenic patients with cancer: differences between patients with haematological malignancies and solid tumours. *Journal of Infection,* 69**,** 417-423.

MASHHADI, M. A., ZAKERI, Z. & ABDOLLAHINEJAD, M. J. 2010. Cancer incidence in South East of Iran: results of a population-based cancer registry.

MATHUR, P., CHAUDHRY, R., KUMAR, L., KAPIL, A. & DHAWAN, B. 2002. A study of bacteremia in febrile neutropenic patients at a tertiary-care hospital with special reference to anaerobes. *Medical Oncology,* 19**,** 267-272.

MCKANE, L. & JUDI, K. 1996. Microbiology Essentials and Applications, McGrow-Hill. *Inc. USA***,** 787-809.

MEIDANI, M., BAGHERI, A. & KHORVASH, F. 2013. A population-based study of bacterial spectrum in febrile neutropenic patients.

NURAIN, A. M., BILAL, N. E. & IBRAHIM, M. E. 2015. The frequency and antimicrobial resistance patterns of nosocomial pathogens recovered from cancer patients and hospital environments. *Asian Pacific Journal of Tropical Biomedicine,* 5**,** 1055-1059.

PACHAURI, S., VARSHNEY, P., DASH, S. K. & GUPTA, M. K. 2013. Involvement of fungal species in bovine mastitis in and around Mathura, India. *Vet World,* 6**,** 393-395.

PANDOLFI, D. & PONS, M.-N. L. 2004. Gram-staining characterisation of activated sludge filamentous bacteria by automated colour analysis. *Biotechnology Letters,* 26**,** 1841-1846.

PATEL, J. B., COCKERILL, F. R. & BRADFORD, P. A. 2015. Performance standards for antimicrobial susceptibility testing: twenty-fifth informational supplement.

PINCUS, D. H. 2006. Microbial identification using the bioMérieux Vitek® 2 system. *Encyclopedia of rapid microbiological methods,* 1**,** 1-32.

QIN, T., MI, Y., FENG, S., LI, D., WEI, J., YANG, D., HAN, M., WANG, J. & BIAN, S. 2007. Clinical study on fluoroquinolone prophylaxis in

neutropenia patients with acute leukemia. *Zhonghua yi xue za zhi,* 87**,** 1389-1393.

RASMY, A., AMAL, A., FOTIH, S. & SELWI, W. 2016. Febrile neutropenia in cancer patient: epidemiology, microbiology, pathophysiology and management. *J Cancer Prev Curr Res,* 5**,** 00165.

SAGHIR, S., FAIZ, M., SALEEM, M., YOUNUS, A. & AZIZ, H. 2009. Characterization and anti-microbial susceptibility of gram-negative bacteria isolated from bloodstream infections of cancer patients on chemotherapy in Pakistan. *Indian journal of medical microbiology,* 27**,** 341.

SHARMA, U., SCHWAN, W. R. & AGGER, W. A. 2011. Escherichia coli pyomyositis in an immunocompromised host. *WMJ: official publication of the State Medical Society of Wisconsin,* 110**,** 182.

TANG, Y., WU, X., CHENG, Q. & LI, X. 2020. Inappropriate initial antimicrobial therapy for hematological malignancies patients with Gram-negative bloodstream infections. *Infection,* 48**,** 109-116.

TSUTSUI, A. & SUZUKI, S. 2018. Japan nosocomial infections surveillance (JANIS): a model of sustainable national antimicrobial resistance surveillance based on hospital diagnostic microbiology laboratories. *BMC health services research,* 18**,** 799.

UGAI, T., MATSUO, K., SAWADA, N., IWASAKI, M., YAMAJI, T., SHIMAZU, T., SASAZUKI, S., INOUE, M., TSUGANE, S. & GROUP, J. P. H. C.-B. P. S. 2017. Smoking and subsequent risk of leukemia in Japan: the Japan public health center-based prospective study. *Journal of Epidemiology,* 27**,** 305-310.

VANDEPITTE, J., VERHAEGEN, J., ENGBAEK, K., ROHNER, P., PIOT, P., HEUCK, C. C. & HEUCK, C. C. 2003. *Basic laboratory procedures in clinical bacteriology*, World Health Organization.

VENTO, S. & CAINELLI, F. 2003. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment. *The lancet oncology,* 4**,** 595-604.

VERSPORTEN, A., ZARB, P., CANIAUX, I., GROS, M.-F., DRAPIER, N., MILLER, M., JARLIER, V., NATHWANI, D., GOOSSENS, H. & KORAQI, A. 2018. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *The Lancet Global Health,* 6**,** e619-e629.

WEINSTEIN, R. A. 2001. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerging infectious diseases,* 7**,** 188.

YAO, J.-F., LI, N. & JIANG, J. 2017. Clinical characteristics of bloodstream infections in pediatric acute leukemia: A single-center experience with 231 patients. *Chinese medical journal,* 130**,** 2076.