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Distribution of Multi Drug Resistance of Gram-Positive Bacteria among Cancer Patient in Erbil Governorate/Iraq

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Abstract

Background: The evolution of cancer therapy and the changing epidemiology of major Gram-positive pathogens mean that ongoing efforts are needed to understand and mitigate the impact of these bacteria in patients with malignancy. The development of novel antibacterial, optimization of treatment approaches are all active areas of investigation in the goal of improving the survival of the cancer patient through amelioration of the disease burden of gram-positive bacteria.

Objectives: Our study aimed to carry out a retrospective study on Gram positive bacteria isolated from cancer patients in Erbil city and analyze its epidemiology, antibiotics susceptibility patterns.

Materials and methods: A total of 720 samples were collected from five different sources (urine, blood,throat swab, wound and sputum) from patient attending Nanakali Hospital and from both male and female from January 2018 to December 2018. Only 193 cases had been identified as Gram-positive bacteria identified by using microscopical, morphological, biochemical tests with ntibiotics susceptibility testing were performed by using Vitek2 compact system against 8 antibiotics: Amoxicillin, Cefotetan, Levofloxacin, Imipenem, Meropenem, Tetracycline, Ticarcillin-clavulanic acid and Vancomycin.

Results: From 720 samples collected only 193(26.8%) cases had been identified as Gram-positive bacteria. Results showed that *Staphylococcus epidermidis*. isolates are the most frequent encountered 52(7.2%), *Staphylococcus saprophyticus* isolates were 37(5%), *Staphylococcus aureus* 13(1.8%), *Staphylococcus homins* 9(1.25%), *Staphylococcus hemolyticus* 7(0.97%) followed by *Streptococcus pyogenes* isolates were 47(6.5%), *Streptococcus viridance* 2(0.3%), *Enterococcus spp*. were 26(3.6%) respectively. The number of isolated *Staphylococcus epidermidis* was high in female 35(18%) compared with 17(8.8%) in male. Other species showed lower number as male for *Staphylococcus saprophyticus* was 27(14%) in female and 10(5%)in male for *Staphylococcus aureus* in female is 8(4%) and male 5(2.6%) for *Staphylococcus homins* 7(3.6%) in female, *Staphylococcus haemolyticus* 4(2%) in female and 3(1.6%) in male, while for *Streptococcus pyogenes* was higher in males than females 29(15%) in male 18(9%) in female, *Streptococcus viridance* only found in females 2(1%) but for *Enterococcus spp*. was 22(12.4%) in female and 4(2%) in male, Gram positive bacteria isolates from cancer patients showed high resistance (60%) to Tetracycline, Levofloxacin (56%), (44.5%) to Vancomycin respectively. On the other hand, Gram positive bacteria isolates from cancer patients showed high susceptibility (63.7%) to Imipenem, Meropenem (62.3%) and Amoxicillin (28.5%) respectively.

Conclusion: These finding offer a reliable measure of prevalence of multidrug resistance Gram-positive bacteria in cancer patients in our region and provides a baseline for future studies which will enable the monitoring of trends overtime.

Keywords: Cancer; Gram-positive bacteria; Different clinical samples; Antibiotics resistant.

Introduction

Cancer is the second leading cause of death in the world after cardiovascular diseases. Half of men and one third of women in the United States will develop cancer during their lifetimes. Today, millions of cancer people extend their life due to early identification and treatment. Cancer is not a new disease and has afflicted people throughout the world. The word cancer came from a Greek words karkinos to describe carcinoma tumors by a physician Hippocrates (460-370 B.C) [1]. Throughout the 1960s and 1970s, gram-negative organisms were most frequently isolated from neutropenic cancer patients with cancer who had BSI. However, during the past 20 years, gram-positive organisms have become increasingly common. Coagulase-negative *Staphylococci*, viridians group *Streptococci, Staphylococcus aureus* [2]. Due to defects in their immunity cancer patients particularly those with profound and prolonged neutropenia are prone to serious infections with substantial morbidity and mortality [3]. Most infections in cancer patients are nosocomial in nature as a result of their prolonged and frequent contact with hospital environment [4]. In many institutions in developed countries, more Gram-positive bacteria, mainly *Staphylococci*, than Gram negative bacteria are isolated from cancer patients [5]. Over the past decade, the nature of bacteremia- in febrile, neutropenic patients with cancer has changed, with a reduction in Gram-negative infections and shift toward gram positive microbial predominance. Gram-positive bacteria account for at least half of all microbiologically documented infections in cancer patient, immunosuppression induced by the underlying cancer or its attendant therapy, such as neutropenia, and the breakdown in mucosal barriers, such as occurs following long-term vascular catheter placement or during graft vs host disease, synergize to make cancer patients particularly susceptible to gram-positive infections [6]. Cancer patients are at an increased risk of the Blood Stream Infections (BSI) due to their immune-compromised status, repeated hospitalizations, and various procedures. *Staphylococci*, particularly coagulase negative *Staphylococci* (Cons) are noteworthy pathogens in such cases, and the emergence of multi-drug resistance in *Staphylococci* is a cause of concern. *Staphylococcus aureus* infection incidence may be increasing, at least in some regions [7], probably due to higher number of invasive procedure and at-risk situation. Due to surgery, long term stay intravenous catheter repeated radiotherapy and chemotherapy cancer patient that suffer from inhibited bone marrow function, neutropenia and mucosal barrier damage can be easily infected with gram- positive bacteria [8], emerging resistance in gram-positive organism, especially Methicillin Resistance *S. Aureus* (MRSA) and vancomycin resistance Enterococcus faecium is also worrying. However, more new antimicrobial agents active against these organisms are becoming available, such as daptomycin and linezolid. Such infections are often caused by resistant organisms, such as MRSA and vancomycin-resistant enterococci due to healthcare- associated exposure and selection from antimicrobial Prophylaxis. Although a number of gram-positive organisms have been reported to cause disease in patients with malignancy, this article will focus on *S. Aureus, Streptococci, and Enterococci* [9]. Risk factors for antimicrobial resistance may vary depending on the type of organism and type of population studied. Risk factors for antimicrobial resistance for different MDR organisms identified in cancer and HSCT patients. In general, Catheter-Related SAB (CRSAB) in the general population has generally been considered transient with a removable focus of infection and a low incidence of complications. Predictors of complications in CRSAB include symptoms duration, hemodialysis dependence, presence of a long-term intravascular catheter or a no catheter device, and infection with methicillin-resistant *S. aurous* [10]. Multiple factors have led to this shift, including the increased use of indwelling catheters, the use of antimicrobial chemoprophylaxis, and the different types of chemotherapy drugs now available. Currently *S. aureus* is second only to coagulase-negative *Staphylococcus* as the most common cause of Gram-positive blood stream infections in patients with cancer [11] with the catheter being the most commonly identified source of bacteremia., chemoprophylaxis, and the different types of chemotherapy drugs now available. Currently *S. aureus* is second only to coagulase-negative *Staphylococcus* as the most common cause of Gram-positive blood stream infections in patients with cancer, with the catheter being the most commonly identified source of bacteremia [12]. The emergence of resistance to antimicrobial agents commonly used for the treatment of bacterial infections has become a significant problem worldwide, including onco hematological and HSCT patients. Prompt administration of appropriate empirical antibiotic therapy in neutropenic febrile cancer patients is the standard of care. However, choosing the right empirical antibiotic therapy in this era of growing antimicrobial resistance is a clinical challenge. In a recent prospective Spanish series of cancer patients, a dramatic increase in ampicillin-resistant, vancomycin-susceptible. *Faecium* BSI was documented [13]. In immunosuppressed patients with cancer and in HSCT recipients, administration of appropriate initial empirical antibiotic therapy is essential, especially during febrile neutropenic episodes. In fact, patient outcome may depend on it. The emergence of infections with MDR pathogens coupled with the lack of new antibiotics to combat these infections has reinforced the need to prolong the useful life of currently available antimicrobials by reducing their inappropriate use, the use of chemotherapy, either alone or in combination with radiotherapy, and/or surgery are common procedures used for the treatment of cancer, with increasing disease-free and overall survival in most neoplasia during the last two decades [14]. However, these therapeutic modalities may lead to healthcare-associated infections, increasing morbidity, mortality, and health-related costs [15]. Invasive methicillin susceptible *S. aureus* (MSSA) infection should be treated with anti-staphylococcal beta lactam such as cefazolin or nafcillin. In mached case control study in which approximately 40% of patients had cancer, treatment of MSSA bacteremia with vancomycin, as opposed to beta lactam, was associated with higher mortality [16]. Vancomycin remain the mainstay of treatment for MRSA, however high vancomycin failure rates among patient with cancer and MRSA blood stream infection have been reported [17].

Sample collection

A total of (720) samples were collected from seven sources (urine, stool, blood, abscess and wound swab, throat and tonsil swab, and sputum) from hospitalized patient with cancer (Acute myeloid leukemia, Chronic myeloid leukemia, Acute lymphocytic leukemia, Chronic lymphocytic leukemia) in Nanakali hospital in Erbil city during January 2018 - December of 2018. From male and female patients with the age of 10-79 years. For isolation of microorganisms, the specimen was directly inoculated on culture media; Blood culture and macConkey agar plates were incubated aerobically at 37℃ for (24-48) hours. Pure colonies of isolated microorganisms were identified using morphological, biochemical tests, Species identification and antibiograms for pathogens were performed using Vitek2 system [18].

Vitek2 compact system

The newly redesigned colorimetric Vitek2 compact system, with updated Advanced Expert System (AES) (bioMerieux, Marcy l'Etoile, France) was evaluated for its accuracy and rapidity to identify clinical isolates and to detect several antimicrobial resistances [19].

Principles of the Vitek2 is an automated microbiology system utilizing growth-based technology. This system accommodates the colorimetric reagent cards that are incubated and interpreted automatically. Overall, the Vitek2 gave 95.8% of compatibility with the reference API strips (bioMerieux) in the Identifications (ID) s of the Gram-Positive Cocci (GPC), Gram-Negative Rods (GNR), and yeasts. The accuracy was finally estimated to 98.3% through additional confirmatory tests. Also, >90% of identifications of GPC and GNR were obtained within 7 hours of incubation. The most resistant isolates were identified within 12 hours of incubation. In conclusion, the new colorimetric Vitek2. Identified within 12 hours of incubation. In conclusion, the new colorimetric Vitek 2 compact system with AES greatly improved is accuracy in species identification and detection of antimicrobial resistances, and it will be highly acceptable to clinical microbiology laboratory function [20]. The Vitek2 has everything health care laboratories need for fast, accurate microbial identification, and antibiotic susceptibility testing.

Vitek2 compact: Uses

Microbial identification bacteria and yeast identification. Antibiotic Susceptibility Testing (AST) and resistance mechanism detection. Epidemiologic trending and reporting [18]. Vitek2 systems use advanced colorimetry, an identification technology that enables identification of routine clinical isolates. Advanced colorimetry provides:

* High discrimination between species.

* Low rate of multiple choice and misidentified species.

* Minimal number of off- line tests.

Antimicrobial susceptibility test by Vitek2 compact system

The system includes an AES that analyzes Minimum Inhibitory Concentration (MIC) patterns and detects phenotypes for most organisms tested. This helps optimize laboratory efficiency for lean laboratory management. Rapid results allow clinicians to discontinue empiric therapy and prescribe targeted therapy, resulting in improved patient outcomes and enhanced antibiotic stewardship [21] with its ability to provide accurate "fingerprint" recognition of bacterial resistance mechanisms and phenotypes, the AES is a critical component of Vitek2 technology. The Vitek2 card contains 64 microwells. Each well contains identification substrates or antimicrobial. Vitek2 offers a comprehensive menu for the identification and antibiotic susceptibility testing of organisms [22]. The Vitek2 test card is sealed, which minimizes aerosols, spills, and personal contamination. Disposable waste is reduced by more than 80% over micro titer methods.

Statistical analysis

Data entry and statistical analysis were performed using SPSS v.23 software. Comparisons were made using Pearson Chi-square. A p-value of <0.05 was considered indicative of a statistically significant difference and p-value<0.01 was considered indicative of a highly statistically significant difference.

Ethical consideration

The bacterial strains used in this research were extracted from clinical routine specimens, and patients were given verbal consent. This study has been accepted by the College of Health Sciences/Hawler Medical University Scientific and Research Ethics Committee

Results

Incidence of gram-positive bacteria isolate in cancer patients

Out of 720 samples collected 193(27.4%) cases had been identified as Gram positive bacteria as in Table 1. Results showed that *Staphylococcus epidermidis* isolates are the most frequent encountered 52(7.2%), *Staphylococcus saprophyticus* isolates were 37(5%), *Staphylococcus aureus* 13(1.8%), *Staphylococcus homins* 9(1.25%), *Staphylococcus haemolyticus* 7(0.97%) followed by *Streptococcus pyogenes* isolates were 47(6.5%), *Streptococcus viridance* 2(0.3%), *Enterococcus spp* were 26(3.6%) respectively. Statistical analysis showed that highly significant (p<0.01) correlation between different species isolated from in cancer patients.

Table 1: Incidence of gram positive isolates in cancer patients.

Isolated pathogen	No +ve	% +ve	No. –ve	% -ve	Total P value
Staphylococcus Epidermidis	52	7.2%	668	92.8%	720
Staphylococcus Saprophyticus	37	5%	683	94.9%	720
Staphylococcus Aureus	13	1.8%	707	98.2%	720
Staphylococcus Homins	9	1.25%	711	98.75%	720
Staphylococcus haemolyticus	7	0.97%	713	99%	720
Streptococcus Pyogenes	47	6.5%	673	93.5%	720
Streptococcus Viridance	2	0.3%	718	99.7%	720
Enterococcus spp.	26	3.6%	694	96.4%	720
Total	193	26.6%	527	73.4%	720

Frequency of gram-positive isolates in cancer patient isolated from different clinical samples

193 samples among 720 collected samples were positive. Urine was the major source of bacterial isolates collected comprising 445/720 among them were 112 are positive, for *Staphylococcus epidermidis* 38(8.5%), and *Staphylococcus saprophyticus* is about 36(8.1%), *Staphylococcus aureus* 5(1.1%), *Staphylococcus haemolyticus* 6(1.35%), *Staphylococcus homins* 1(0.22%), *Streptococcus pyogenes* 1(0.22%) and *Enterococcus spp* 25(5.6%) were positive. For blood 145/720 among them 18 are positive, includes *Staphylococcus epidermids* 9(6.2%), *Staphylococcus Aureus* 1(0.7%), *Staphylococcus Homins* 7(4.8%), *Enterococcus spp* 1(0.7%). While for sputum 100/720 isolated among them 53 are positive, for *Staphylococcus epidermids* were 4(4%) and *Staphylococcus aureus* 2(2%), *Staphylococcus haemolyticus* 1(1%), *Staphylococcus saprophyticus* is about 1(1%), Streptococcus *pyogenes* 44(44%), *Streptococcus* viridance 1(1%). In addition, throat swab samples were 10/720 among them 4 are positive, for *Staphylococcus epidermidis* 1(10%), and *Streptococcus pyogenes* 2(20%), *Streptococcus* viridance 1(10%), and for wound 20/720 among them 5 are positive include *Staphylococcus aureus* 5(25%), as in (Table 2).

Table 2: Frequency of gram-positive isolates in cancer patient isolated from different clinical samples.

Isolated bacteria N(%)		Urine	Blood	Sputum	Throat swab	Wound	Total
Staphylococcus epidermidis	Infected	38 8.5%	9 6.2%	4 4%	/ /	/ /	52 7.2%
	Uninfected	407 91.5%	136 93.8%	96 96%	10 100%	20 100%	668 92.8%
Staphylococcus saprophyticus	Infected	36 8.1%	/ /	1 1%	/ /	/ /	37 5.14%
	Uninfected	409 91.9%	145 100%	99 99%	10 100%	20 100%	683 95%
Staphylococcus aureus	Infected	5 1.1%	1 0.7%	2 2%	/ /	5 25%	13 2%
	Uninfected	440 98.9%	144 99.3%	98 98%	10 100%	15 75%	707 98.2%
Staphylococcus homins	Infected	1 0.22%	7 4.8%	/ /	1 10%	/ /	9 1.25%
	Uninfected	444 99.78	138 95.2%	100 100%	9 90%	20 100%	711 98.75%
Staphylococcus N haemolyticus	Infected	6 1.35%	/ /	1 1%	/ /	/ /	7 1%
	Uninfected	439 98.7%	145 100%	99 99%	10 100%	20 100%	713 99%
Streptococcus N pyogenes	Infected	1 0.22%	/ /	44 44%	2 20%	/ /	47 6.5%
	Uninfected	444 99.78%	145 100%	56 56%	8 80%	20 100%	673 93.5%
Streptococcus N viridance	Infected	/ /	/ /	1 1%	1 10%	/ /	2 0.3%
	Uninfected	445 100%	145 100%	99 99%	9 90%	20 100%	718 99.7%
Enterococcus spp	Infected	25 5.6%	1 0.7%	/ /	/ /	/ /	26 3.6%
	Uninfected	420 94.4%	144 99.3%	100 100%	10 100%	20 100%	694 96.4%

Distribution of gram-positive bacteria isolate according to gender in patients with cancer

The number of isolated *Staphylococcus epidermidis* was high in female 35(18%) compared with 17(8.8%) in male and for *Staphylococcus saprophyticus* was 27(14%) in female and 10(5.2%) in male, for *Staphylococcus aureus* was 8(4%) in female and 5(2.6%) in male, for *Staphylococcus homins* 7(3.6%) in female and 2(1%) in male, *Staphylococcus haemolyticus* 4(2%) in female and 3(1.6%) in male, while for *Streptococcus pyogenes* was higher in males than females 29(15%) in male 18 (9%) in female, *Streptococcus viridance* in females 2(1%) and in male 0 but for *Enterococcus spp* was 24(12.4%) in female and 4(2.1%) in male as in (Table 3). Statistical analysis showed that highly significant ($p<0.01$) correlation between different species and Gender from in cancer patients.

Antibiotic susceptibility patterns for gram-positive bacteria in patients with cancer

All of 193 isolates of gram-positive bacteria were screened for their resistance to eight antibiotics, widely used antibiotics, the results were interpreted according to standard value by clinical and laboratory standard of antimicrobial sensitivity testing. It is obvious that gram positive bacteria isolates showed high resis-

Table 3: Distribution of gram-positive bacteria isolates according to gender in patients with cancer.

Isolated pathogen	Female		Male		Total		P value
	NO	%	NO	%	NO	%	
Staphylococcus epidermidis	35	18%	17	8.8%	52	27%	
Staphylococcus saprophyticus	27	14%	10	5%	37	19.1%	
Staphylococcus aureus	8	4%	5	2.6%	13	6.7%	
Staphylococcus homins	7	3.6%	2	1%	9	4.7%	
Staphylococcus haemolyticus	4	2%	3	1.6%	7	3.6%	
Streptococcus pyogenes	18	9%	29	15%	47	24.4%	
Streptococcus viridance	2	1%	/	/	2	1%	
Enterococcus spp	22	12.4%	4	2%	26	13.5%	
Total	123	64%	70	36%	193	100%	0.000005

tance (60%) to Tetracycline, (56%) to Levofloxacin, On the other hand, the lowest resistance were (22.3%) to Imipenem, (22.7%) to Meropenem, and (30%) to Cefotetan as in (Table 4). Statistical analysis showed that highly significant ($p<0.01$) correlation between Gram positive bacteria and different types of Antibiotics.

Table 4: Antibiotic susceptibility patterns for gram positive bacteria in patients with cancer.

Antibiotics	Resistance		Intermediate		Susceptible		P-value
	No.	%	No.	%	No.	%	
Amoxicillin	95	49.2%	43	22.3%	55	28.5%	
Cefotetan	58	30%	30	15.5%	105	54.5%	
Levofloxacin	108	56%	25	13%	60	31%	
Imipenem	43	22.3%	27	14%	123	63.7%	
Meropenem	44	22.7%	29	15%	126	62.3%	
Tetracycline	15	60%	27	14%	51	26%	
Ticarcillin-clavulanic acid	73	37.8%	26	13.5%	94	48.7%	
Vancomycin	86	44.5%	25	13%	82	42.5%	0.00002

Resistance rate of *Staphylococcus spp, Streptococcus spp and Enterococcus spp* isolates from cancer patient

Our result in (Tables 3-5) showed that *Staphylococcus epidermidis*. resistance to Levofloxacin followed by Tetracycline and Amoxicillin and ticarcillin-clavulanic acid revealed the highest percentage of resistance which were (67.3%, 57.6%, 57.6%, 40.3) respectively. For *Staphylococcus saprophyticus* showed resistance to Tetracycline followed by Levofloxacin and Amoxicillin revealed the highest percentage of resistance which were (83.7%, 54%, 48.6%) respectively. For *Staphylococcus aureus* spp. showed resistance to Levofloxacin followed by Amoxicillin and Ticarcillin-clavulanic acid revealed the highest percentage of resistance which were (84.6%, 77%, 69.2%) respectively. For *Staphylococcus homins* showed resistance to Tetracycline followed by Vancomycin and Imipenem revealed the highest percentage of resistance which were (100%, 88.8%, 66.6%) respectively. For *Staphylococcus hemolyticus.* Showed resistance to Cefotetan followed by Tetracycline and Vancomycin revealed the highest percentage of resistance which were (100%, 100%, 71.4%) respectively. Also, *Streptococcus pyogenes* showed resistance to Levofloxacin followed by Vancomycin and Tetracycline revealed the highest percentage of resistance which were (64%, 44.6%, 42.5%) respectively. But *Streptococcus viridance* showed resistance to Levofloxacin followed by Imipenem and ticarcillin-clavulanic acid and Cefotetan and Meropenem revealed the highest percentage of resistance which were (100%, 100%, 50%, 50%) respectively. Enterococci showed resistance to Amoxicillin followed by Vancomycin and Levofloxacin revealed the highest percentage of resistance which were (77%, 50%, 46%) respectively as in (Table 5).

Table 5: Antimicrobial Resistance Properties in *Staphylococcus spp, Streptococcus spp and Enterococcus spp* isolated from clinical infections.

Antibiotics	*Urine %*	*Sputum %*	*Blood %*	*Throa Swab %*	*Wound %*	*Total %*
Amoxicillin (AX)	30.2	22	31	0	0	25
Cefotetan (CN)	24.8	31	23	0	0	26
Levofloxacin (DO)	35	45	40	44	54	39
Imipenem (IPM)	4	12	15	18	0	8.9
Meropenem (MEM)	11	18	5	46	0	15
Tetracycline (TE)	48	50	49	32	104	50
Ticarcillin clavulanic acid (TIM)	32	36	40	32	53	34
Vancomycin (VAN)	31	33	49.2	90	5	35.2

Table 6: Resistance rate of *Staphylococcus spp, Streptococcus spp and Enterococcus spp* isolates.

	No.and % of Resistance							
	S.epidermidis	***S.saprophyticus***	***S. aureus***	***S.homins***	***S.haemolyticus***	***Streptococcus pyogens.***	***Streptococcusviridance***	***Enterococcus spp***
Amoxicillin	30 57.6%	20 54%	10 77%	/ /	/ /	15 34%	/ /	20 77%
Cefotetan	15 29%	9 24.3%	5 38.4%	/ /	7 100%	13 27.6%	1 50%	8 34.7%
Levofloxacin	35 67.3%	18 48.6%	11 84.6%	/ /	/ /	30 64%	2 100%	12 46%
Imipenem	11 1.2%	/ /	5 38.4%	6 66.6%	/ /	10 21.2%	2 100%	9 34.6%
Meropenem	9 17.3%	8 21.6%	6 46.1%	4 44.4%	/ /	10 21.2%	1 50%	6 23%
Tetracycline	30 57.6%	31 83.7%	8 61.5%	9 100%	7 100%	20 42.5%	/ /	10 38.4%
Ticarcillin-clavulanic acid	21 40.3%	14 37.8%	9 69.2%	5 55.5%	3 43%	9 19.1%	1 50%	11 42.3%
Vancomycin	19 6.5%	13 35.1%	5 38.4%	8 88.8%	5 71.4%	21 44.6%	2 100%	13 50%

Discussion

Frequency of isolated gram-positive bacteria in cancer patient

In most hospitals nowadays, there is a shift of the microbial spectrum of cancer patients from Gram-negative to Gram-positive, compared with the predominance of Gram-negative species in the 1960s and 1970s. There are factors that account for this surge in Gram-positive infections. For example, intensive chemotherapy leads to damage of the mucosal barriers, which increases the risk of infection with Gram-positive oral and Gastrointestinal flora [23]. Gram positive bacteria will grow on general culture media such as Blood therefore can be isolated from direct plating of clinical specimens. The *S. Aureus* strains were cultured on commercial blood agar plates. The bacteria were cultured at 35°C in an atmosphere containing 5% CO_2 (v/v) for 24 h and then underwent serial passage. The hemolytic phenomenon was then observed it appears as grape like clusters when viewed through microscope, and has large round golden yellow colonies, often with beta hemolysis, when grown on blood agar plates, while *S. Epidermidis* is non pigmented, non-hemolytic colonies and coagulase negative Staphylococci on blood agar and *S. saprophyticus* produce either a bright yellow or white pigment colony, *S. Epidermidis and S. saprophyticus* are always nonhemolytic [24]. Out of 720 samples that were subjected to Nanakali Hospital in Erbil city, 193 were positive for *Staphylococcus spp*., *Streptococcus spp* and Enterococcus spp. isolates distributed according to their source of isolation, Results showed that *S. epidermids* isolates are the most frequent encountered 52(7.2%), *S. saprophyticus* isolates were 37(5%), *S. Aureus* 13(1.8%), *S. homins* 9(1.25%), *S. haemolyticus* 7(0.97%) followed by *S. pyogenes* isolates were 47(6.5%), *S. viridance* 2(0.3%), Enterococcus spp were 26(3.6%) respectively. Our result higher than that recorded by (Ashour and El-Sharif, 2007) [25] in which out of 752 samples collected in a 2007, *Staphylococcus spp* isolates were 254(51.8%), S. *saprophyticus* 4(0.8%), *S. Aureus* 140(28.6%), *S. Epidermidis* 58(11.8%), *S. haemolyticus* 34(6.9%) followed by Streptococcus spp. isolates were 237(31.54%), non-haemolytic Streptococcus 9(1.2%), Enterococcus spp. were 13(1.7%) this research were collecting samples from throat swabs, pus blood, urine, chest tube, BAL, sputum while our study we had throat swab, sputum, urine, wound and blood samples. Our result lower than other studies done by (3) showed that out of 493 presence of *Staphylococcus spp*. as 161(32.3%), *S. Aureus* 72(15%) and Streptococcus spp. was 58(11.8%) and Enterococcus spp. 41(8%). A systematic analysis of bacteremia studies published since 2008 among all cancer patients found that *Staphylococcus aureus* accounted for between 1.3% and 12% of all cases. A systematic analysis of bacteremia studies published since 2008 among all cancer patients found that *S. Aureus* accounted for between 1.3% and 12% of all cases [26]. *Staphylococcus aureus* accounts for 20%-30% of nosocomial blood stream isolates in the general patient population [27] and 11% of blood stream isolates in patients with cancer [12]. Statistical analysis showed that highly significant ($p<0.01$) correlation between different species isolated from cancer patients. In addition, the use of implantable intravenous catheters with cancer patients can facilitate the entry of organisms colonizing the skin into the bloodstream, and thus increase the rate of Staphylococcal infections. Moreover, prophylactic antibiotics, which are active against Gram-negative enteric bacilli, exert a selective pressure that contributes to this increase in the rate of Gram-positive infections [23]. Although the prevalence of *Staphylococcus aureus* as a cause of infection in cancer patients varies widely depending on the specific population, the type of infection studied, and geographic location, *S. Aureus* has a major clinical impact on patients with malignancy [28]. This variation might have been either due to sample size, the prevalence of bacterial varies widely among different areas and communities within the country also the various prevalence may be because of various reasons such as differences in economic status and educational background, study population and method used for diagnosis of bacterial differences.

The incidence of gram-positive bacteria in different clinical specimens

Data from several cancer treatment centres/organizations indicate that Gram-positive organisms are the predominant pathogens isolated from different clinical samples in cancer patients. The Staphylococci (CoNS, *S. Aureus)* and streptococci are isolated most often, with the Enterococci becoming increasingly common *S. Aureus* commonly causes infections in the skin and soft tissue, bones, joints, and the respiratory system. It also is a frequent cause of surgical site and to a lesser degree, endovascular infections [12]. A total (720) samples were collected from five different sources (urine, sputum, Blood, swab, wound). After the final confirmation using vitek2 a mong a total of 193 samples in our study, we found that the highest number of isolates were in urine sample (61.8%), then (13.9%) in sputum, (20%) in blood, (1.4%) in swab and (2.8%) in wound. Our results higher than results recorded by [29] which had the rate of 14(23%) urine, 13(21.3) sputum but our results lower than results recorded by which had 299(39.8) sputum, 177(23.5) throat swab, 139(18.5) blood. Only looking at bloodstream infections may lead to significant underestimation of the impact of *S. Aureus*. For example, among nonneutropenic cancer patients in 9 Asian countries, skin and soft tissue infection (26.7%) and pneumonia (25.4%) were the most common types of infections caused by *S. Aureus*, whereas bacteremia only accounted for 14.0% [30]. Having pneumonia was an independent risk factor for mortality, and the observed 30-day mortality rate of both pneumonia and bacteremia approached 50%, which is substantially higher than that observed in patients who do not have cancer [26]. In general, the largest densities of Staphylococci are found in sweat glands and on mucous membranes surrounding body openings. *S. Epidermidis* which is known as a coagulase-negative and Gram-positive Staphylococcus, is one of the five significant microorganisms that are located on human skin and mucosal surfaces with the ability of causing nosocomial infections due to the wide usage of medical implants and devices, hence until 1980 *S. Epidermidis* was considered as an opportunistic microorganism, while in accordance to various infections increasement such as cardiovascular, CNS shunts, joints, blood stream infections, etc. The mentioned bacteria is regarded as one of the main cause of nosocomial infections. Most infections in cancer patients are nosocomial in nature as a result of their prolonged and frequent contact with hospital environment [4]. In the general patient population, most common complications of *S. Aureus* Bacteremia (SAB) are infective endocarditis, septic arthritis, deep tissue abscess, and septic thrombophlebitis. Predictors of complications in this group include community acquisition of the infection, persistent fever 72 hours after the initial positive blood culture, and positive follow-up blood culture results 48-96 hours after the initial positive blood culture) [31]. In many institutions in developed countries, more Gram-positive bacteria, mainly Staphylococci, than Gram-negative bacteria are isolated from cancer patients. Infections remain a part of the natural course of cancer. During the course of their disease,

patients with cancer frequently present with an infection that can ultimately be fatal. *S. Aureus* continues to be a dangerous pathogen for both community-acquired as well as Hospital acquired infections [5].

Relation between gram-positive bacteria species and gender in cancer patient

In this study, the highest rate of Gram-positive bacteria in cancer patient was found in female 123(64%) while only 70(36%) found in males, our result disagreed with that reported by [3] who founded that 192(39%) of isolates from female and 301(61%) from male. Also, our result disagreed with [32] which had 173(40.2%) female and 255(59.6%) male. The differences of number of gram-positive bacteria isolates in male and female might due to sample size were more in female (123) than in male (70) respectively because our target populations only patient attending the hospital randomly in Erbil city. Statistical analysis showed that highly significant ($p<0.01$) correlation between different species and Gender from cancer patient.

Antibiotic susceptibility pattern for gram-positive bacteria in cancer patients

Similarly, the high rate of antibiotic use and antimicrobial resistance in cancer patients means implementation of antimicrobial stewardship efforts are needed to mitigate the rise of drug resistant pathogens [33]. Finally, characterization and manipulation of the host microbes may offers promising hope for pre-emptive therapeutics and prevention of gram-positive infections [34]. From the total 193 samples of Staphylococcus spp., Streptococcus and Enterococci we collected in Erbil city, antibiotic susceptibility test were performed on antibiotics and our study results showed resistance to Tetracycline followed by Vancomycin and Levofloxacin revealed the highest percentage of resistance which were (100%, 88.8%, 84.6%) respectively and Imipenem, Amoxicillin, Meropenem, Ticarcillin-clavulanic acid a the highest percentage of susceptible which were (100%, 77%, 69.2%, 50%,) respectively. *S. Epidermids*. resistance to Levofloxacin followed by, Tetracycline and Amoxicillin and ticarcillin-clavulanic acid revealed the highest percentage of resistance which were (67.3%, 57.6%, 57.6%, 40.3) respectively. For *Staphylococcus saprophyticus* showed resistance to Tetracycline followed by Levofloxacin and Amoxicillin revealed the highest percentage of resistance which were (83.7%, 54%, 48.6%) respectively. Statistical analysis showed that highly significant ($p<0.01$) correlation between Gram positive bacteria and different types of antibiotics while *Staphylococcus aureus* were resistance to Ciprofloxacin 1(1.8%) in study done by [35]. A report by the National Nosocomial Infections Surveillance (NNIS) system in the USA indicated the similar result as in our study according to Vancomycin Resistance Enterococci (VRE) by having 30% of all enterococci isolates from cancer patients infected in ICUs [36]. Besides the spread and dissemination of VRE, the emergence of ampicillin-resistant, vancomycin-susceptible *E. Faecium* in Europe is also worrisome, since it may presage the emergence of vancomycin-resistant enterococci. In recent decades, antimicrobial resistance in *S. Aureus* isolates has emerged worldwide. Multi-drug resistance in *S. Aureus* is defined by the existence of methicillin resistance or lack of susceptibility to greater than or equal to one active agent in greater than or equal to three antimicrobial categories [37]. However, none of our Enterococci isolates were resistance to Cefotetan nor Imipenem. A study in Libya done by [38] showed resistance to Tetracycline was observed in 7(70%) Streptococci isolates while in our study Streptococci have a greater resistance to Tetracycline which we observed is that 33.3%. While in our study Imipenem and Meropenem showed excellent anti-Staphyloccocal spectrum which has the lowest percentage of resistance against Staphylococcal by 2.3%. Antimicrobial agents have been the only easily and widely used therapeutic option available to counter the infections caused by diverse microbial agents. However, microbial populations have developed various strategies to overcome these antimicrobial agents a major contributing factor in the development of antimicrobial resistance world-wide [39]. The indiscriminate use of antimicrobials over prolonged periods has led to the emergence of Multi Drug Resistant (MDR) strains [39]. Whenever a new and effective antibiotic is introduced, bacteria after exposure to this antimicrobial, acquire resistance through different mechanisms, commonest being the production of lactamases. To combat these MDR strains new and more effective [40]. The current study revealed a multi-resistance in Gram positive isolates in cancer patients, highlighting the necessity for local or country-based investigations to characterize and monitor multi-resistant antibiotic and to develop strategies that will accelerate, management and control. In addition, the application of antibiotic combination therapy against multi-resistant and maintenance of proper hygiene by hospitalized patients and staff could effectively reduce the rate and dissemination of such cases. Differences in antibiotic resistance patterns can result from the ecology and physiology of the bacteria and may suggest distinct modes and mechanisms of resistance acquisition.

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