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# PREVALENCE OF MULTIDRUG RESISTANCE GRAM NEGATIVE BACTERIA IN HOSPITALIZED CANCER PATIENTS

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**ABSTRACT**

Infection is a continuous problem in cancer patient especially in developing country. Multidrug-resistant gram negative bacteria are among the most frequent complication in immunocompromised cancer patients and pose the greatest risk to immunocompromised cancer patient. Our study aimed to carry out a retrospective study on Gram negative bacteria isolated from various clinical samples among cancer patient in Erbil city and analyze its epidemiology, antibiotics susceptibility pattern test and multi-drug resistance. A total of 588 samples were collected from eight sources (urine, stool,blood,abscess and wound swab, throat and tonsil swab, CSF, sputum and ear swab) from patient attending Nanakaly Hospital and from both male and female from Jun 2017 to November 2018. Only 83 cases had been identified as Gram negative bacteria isolates which isolated and identified by using macroscopically, microscopically, biochemical tests and Vitek 2 compact system . Also antibiotic susceptibility test were performed by Vitek 2 compact on fifteen antibiotics. Only eighty three Gram negative bacteria isolates isolated from 588 samples distribution according to their source of isolation in cancer patient, Our results showed that the highest percent of the isolates belong to genus *E.coli* 61(10.4%) followed by *Klebsiella spp*. 14(2.4%), *Enterobactor spp*. 6(1%), *Acinetobactor spp*. 1(0.2%) and *Pseudomonas spp*. 1(0.2%), urinary tract infection isolates are the most frequent in our study which is 56 (67.5%) followed by Respiratory tract infection 8 (9.6%),Blood stream infection 7 (8.4%), Gastrointestinal infection and Skin-wound infection 6 (7.2%),the highest percentage of *E.coli* was isolated from female samples 45(7.7%) while only 16(2.7%) from male and when performing antibiotics susceptibility test, bacteria showed highest resistance to Ceftriaxone and Amoxicillin 39(47%), followed by Ticarcillin-clavulanic acid 37(44.6%), Vancomycin 36(44.4%) and Doxycycline 34(40.96%) respectively,in contrast the highest effective antibiotics were Amikacin 81(97.6%), Gentamicin 80 (96.4%), Meropenem and Imipenem 79(95.2%), in which the highly resistance of *E.coli* in urine sample has been noticed to Ceftriaxone and Amoxicillin which are 24(54.5%) and in blood has been showed to Amoxicillin is 5(83.3%), followed by stool that has been noticed to Ticarcillin-clavulanic acid which is 3(60%) and in wound has been noticed to Ceftriaxone 4(66.7%), in contrast the highly sensitivity for *E.coli* in urine has been showed to Amikacin which is 43(97.7%), and in blood has been showed to Cefepime, Ertapenem, Gentamicin, Amikacin, Imipenem and Levofloxacin which are 6(100%), in stool has been noticed to Cefepime, Amoxicillin, Ertapenem, Gentamicin, Amikacin, Imipenim, Meropenem, Levofloxacin and Ciprofloxacin which are 5(100%) and for wound sample has been noticed to Gentamicin and Meropenem which are 6(100%).In general 72(86.7%) isolates of Gram negative bacteria were multidrug resistance to more than three antibiotics, in which urinary tract infection are the most frequent isolated multi-drug resistance which is 50(60.3%). The study findings showed a significant distribution of MDR Gram-negative bacteria which may increase the burden of healthcare-associated infections in cancer patients. Although, Carbapenem can be considered as effective agents toward MDR strains for empirical antibiotic therapy in cancer patients in our region. Moreover, mechanisms of resistance should also be investigated for better characterization of multi-drug resistance and antibiotic-resistant of Gram-negative isolates.

**Keywords:** Gram negative bacteria, Cancer patient, Multidrug resistant.

## Introduction

Cancer is a significant cause of death worldwide, Bacterial infections are frequent complications among patients treated for cancer. The type, severity, and treatment of bacterial infections vary and depend upon the specific malignancy, associated chemotherapies, and transplantation Stosor and Zembower, *et al*. (2014). It has been demonstrated that chronic bacterial infections, including toxin production, disrupt the cell cycle leading to abnormal cellular growth, inducing DNA damage, apoptosis and stimulating host immune responses contributing to carcinogenesis Shurin, *et al*.,(2015). Gram-negative bacteria significantly promoted lung cancer development including growth and metastasis in dose dependent manner Ye *et al*., (2018), the incidence of infections caused by Gram-negative bacteria (GNB) in cancer patients has increased in recent years, a consequence of injury to the mucosal surface of the gastrointestinal tract

from cancer treatment .The most commonly reported GNB include *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species, with rates ranging from 40 to 60% .Particularly worrisome is the emergence of carbapenem-resistant *Enterobacteriaceae* (*CRE*), extended-spectrumbeta-lactamase *Enterobacteriaceae* (ESBL-E), multidrug-resistant *Pseudomonas* species, and *Acinetobacter* species. HSCT patients are at increased risks for GNB infections because of their extended hospitalization, the frequent use of indwelling devices (central venous catheter or urinary catheter), and routine exposure to broad-spectrum antibiotics. The reported mortality rates of CRE and ESBL-E bacteremia in patients with hematologic malignancies can be as high as 56% and 40%, respectively, especially during periods of extended neutropenia Babady *et al*. (2016). The overall frequency of Gram-negative infection has decreased over the past decade, but data from several large surveillances studies conducted at major cancer centers both in the United States and Europe indicate that *Enterobacteriaceae* cause approximately 65% to 80% of documented Gram-negative infections in these patients. However, *Pseudomonas aeruginosa* is also associated with significant morbidity and mortality in immunocompromised hosts Saghir *et al*., (2009).Throughout the 1960s and 1970s, Gram-negative organisms were the most frequent causative agents of BSI in neutropenic cancer patients Gudiol and Carratala, (2016). In the hematology and oncology population there appears to be a steady increase in proportion of invasive infections caused by MDR bacteria, with rates as high as 70% reported in some centres. In adult patients, these MDR infections are associated with increased intensive care unit requirements and mortality. Although fewer pediatric studies are available, a similarly concerning increase in intensive care unit admission and mortality among children with cancer and antibiotic resistant bacteraemia is described (HaeuslerG and Levene, 2015 ).

Physicians must familiarize themselves with local antibiograms for their particular hospitals and choose drugs accordingly. Notably, among 1148 episodes of bacteremia in cancer patients from a prospective multicenter study in Spain, 392 (34 %) were caused by ESKAPE (*Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter species*) pathogens (*E. coli* and *Stenotrophomonas* excluded in this study), and 54 episodes (4.7 %) were due to antibiotic-resistant ESKAPE strains (Rapoport *et al.*, 2016). The use of older quinolones (norfloxacin, ofloxacin, and ciprofloxacin) may also have led to the increased frequency of infections caused by drug-resistant, nonfermentative gram-negative bacilli, such as *Alcaligenes species*, *Pseudomonas species* other than *P. aeruginosa*, and *Stenotrophomonas maltophilia*. Rates ESBL producing isolates among *E. coli* and *Klebsiella species* are increasing Rolston *et al*. (2005).

## Materials and Methods

### Study population and specimens

A total of (588) samples were collected from seven sources (urine, stool, blood, abscess and wound swab, throat and tonsil swab, CSF 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 June 2017 -November of 2018 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 Vitek 2 system (10).

### Antimicrobial susceptibility test by Vitek 2 system

All isolates of were screened for their susceptibility to 15 used antibiotics (such Amoxicillin, Amikacin, Cefepime, Ceftriaxone, Ciprofloxacin, Doxycycline, Ertapenem, Gentamicin, Imipenem, Levofloxacin, Meropenem, Piperacillin, Tetracycline, Ticarcillin-clavulanic acid, Vancomycin) by using Vitek 2 system with its ability to provide accurate "fingerprint" recognition of bacterial resistance mechanisms and phenotypes, the AES is a critical component of Vitek 2 technology .The Vitek 2 card contains 64 microwells. Each well contains identification substrates or antimicrobial. Vitek 2 offers a comprehensive menu for the identification and antibiotic susceptibility testing of organisms. The Vitek 2 test card is sealed, which minimizes aerosols, spills, and personal contamination. Disposable waste is reduced by more than 80% over microtiter methods (10).

## Results

### Incidence of Gram negative bacteria isolated from cancer patient

A total of (588) samples were collected from eight different source from cancer patient. After collection all bacterial isolates were subjected to a series of confirmed tests. Out of 588 only (83) of Gram negative bacteria isolated from cancer patient (Acute myeloid leukemia, Chronic myeloid leukemia, Acute lymphocytic leukemia, Chronic lymphocytic leukemia) as in (Figure 1). Results showed that among GNB, *E. coli* isolates are the most frequent encountered 61 (10.4%), while *Klebsiella spp* isolates were 14 (2.4%), *Enterobacter spp* were 6 (1%), *Acinetobacter spp* was 1 (0.2%), *Pseudomonus spp* was 1 (0.2%) respectively. Statistical analysis showed that highly significant correlation ($P < 0.01$) between different species isolated from cancer patients.

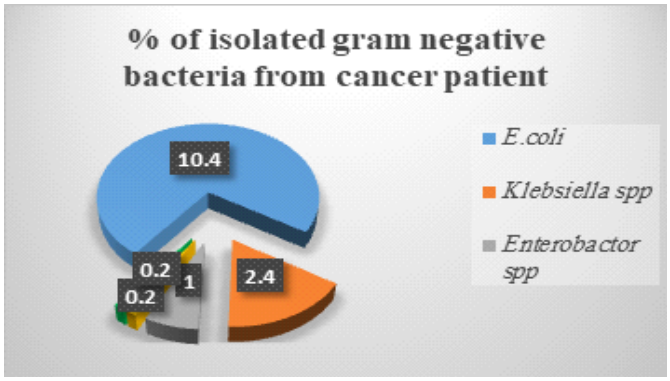


**Fig. 1**: The incidence of gram negative bacteria.

### The incidence of gram negative bacteria in different clinical specimens

Eighty three samples among 588 collected samples were positive. Urine was the major source of bacterial isolates collected comprising 350/588 and among them 56

were positive, for *E.coli* 44(12.6%), *Klebsiella spp*. 7(2%), *Enterobactor spp*. 5(1.4%) were positive. Statistical analysis showed that highly significant correlation (P < 0.01) between different clinical sample and different species of Gram-negative bacteria. For stool 32/588 isolated, which only 6 were positive, includes *E.coli* 5(15.6%), *Enterobactor spp*. 1(3.1%).However for blood 92/588 isolated in which 7 were positive, includes *Ecoli* 6(6.5%) and *Acinetobactor spp* 1(1.1%). While for sputum 83/588 isolated and among this 83 samples 7 were positive, for *Klebsiella spp* 6(7.2%) and *Pseudomonus spp* 1(1.2%), for Wound samples were 20/588 andspp 1(14.3%) was isolated .Finally here were not any positive samples from CSF among 4/588 isolates, as in (Table 2).

**Table 2 :** Distribution of Gram negative bacteria in different clinical samples according to gender.

| Gram negative bacteria | | No. and % of *GNB* | | | | | | | Total N=588 | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | UrineN=350 | Stool N=32 | Blood N=92 | Abscess and wound N=20 | Sputum N=83 | Throat N=7 | CSF N=4 | | |
| | | No.% | No.% | No.% | No.% | No.% | No.% | No.% | No.% | |
| *E.coli* | + | 44 | 5 | 6 | 6 | / | / | / | 61 | |
| | | 12.6% | 15.6 | 6.5 | 30% | / | / | / | 10.4% | |
| | - | 306 | 27 | 86 | 14 | 83 | 7 | 4 | 527 | |
| | | 87.4% | 84.4% | 93.5% | 70% | 100% | 100% | 100% | 89.6% | |
| *Klebsiella spp.* | + | 7 | / | / | / | 6 | 1 | / | 14 | |
| | | 2% | / | / | / | 7.2% | 14 | / | 2.4% | |
| | - | 343 | 32 | 92 | 20 | 77 | 6 | 4 | 574 | |
| | | 98% | 100% | 100% | 100% | 92.8% | 86 | 100% | 97.6% | |
| *Enterobactor spp.* | + | 5 | 1 | / | / | / | / | / | 6 | |
| | | 1.4% | 3.1% | / | / | / | / | / | 1% | |
| | - | 345 | 31 | 92 | 20 | 83 | 7 | 4 | 582 | |
| | | 96.8% | 96.9% | 100% | 100% | 100% | 100% | 100% | 99% | |
| *Acinetobactor spp* | + | / | / | 1 | / | / | / | / | 1 | |
| | | / | / | 1.1 | / | / | / | / | 0.2% | |
| | - | 350 | 32 | 91 | 20 | 83 | 7 | 4 | 587 | |
| | | 100% | 100% | 98.9% | 100% | 100% | 100% | 100% | 99.8% | |
| *Pseudomonas spp* | + | / | / | / | / | 1 | / | / | 1 | |
| | | / | / | / | / | 1.2% | / | / | 0.2% | |
| | - | 350 | 32 | 92 | 20 | 82 | 7 | 4 | 587 | |
| | | 100% | 100% | 100% | 100% | 98.8% | 100% | 100% | 99.8% | |
| Total | + | 56 | 6 | 7 | 6 | 7 | 1 | / | 83 | 0.00001 |
| | | 16% | 18.8% | 7.6% | 30% | 8.4% | 14.3% | / | 14.2% | |
| | - | 294 | 26 | 85 | 14 | 76 | 6 | 4 | 505 | |
| | | 84% | 81.3% | 92.4% | 70% | 91.6% | 85.7% | 100% | 85.9% | |

### 3.4. Distribution of Gram negative bacteria according to gender

Out of 588 samples, 83(14.2%) samples were diagnosed positive for Gram negative bacteria, the percentage of Gram negative bacteria in female 57 (9.7%), was higher than those in male patients 26 (4.4%). Statistical analysis showed that significant correlation (P < 0.05) between Gender (male and female) and frequency Gram-negative bacteria. On the other hand 505(85.8%) samples were diagnosed as Negative, in which the percentage of Gram negative bacteria in Female258 (43.9%), was higher than those in male 247(42%) samples. Except *Pseudomonus spp*. all other species of Gram negative bacteria showed higher number in female. The number of isolated *E. coli* was highest in both male and female which was 16 (2.7%) in male and 45 (7.7%) in female. Other species showed lower number as for *Klebsiella spp* was 6 (1.02%) in male and 8 (1.4%) in female, *Enterobactor spp* was 3 (0.5%) in male and 3(0.5%) in female. It is important to notice that there was no any isolated *Acinetobactor spp* in male, but the number of this bacterium in female was 1 (0.2%). The number of isolated *Pseudomonas spp* in male was 1 (0.2%) and in female was 0(0%) as in (Figure 2) and table 3.

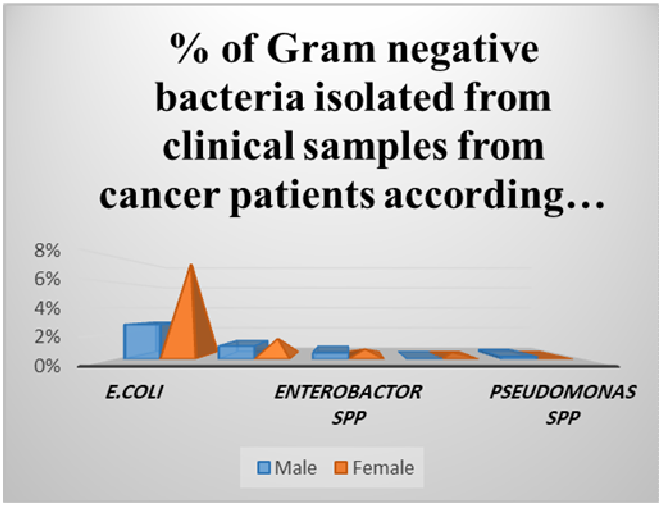


**Fig. 2 :** Distribution of Gram negative bacteria according to gender.

**Table 3 :** Distribution of Gram negative bacteria in different clinical samples according to gender.

| | | | No. and % of *GNB* | | | | | | | Total N=588 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Urine N=350 | Stool N=32 | Blood N=92 | Abscess and wound N=20 | Sputum N=83 | Throat N=7 | CSF N=4 | |
| | | | No.% | No,% | No.% | No.% | No,% | No.% | No% | No.% |
| *E.coli* | + | ♀ | 34 (5.2) | 2 (6.3) | 4 (4.3) | 5 (25) | / | / | / | 45 (7.7) |
| | | ♂ | 10 (2.9) | 3 (9.4) | 2 (2.2) | 1 (5) | / | / | / | 16 (2.7) |
| | - | ♀ | 182(52) | 10 (31.3) | 36 (39.1) | 8 (40) | 29 (35) | 3 (42.9) | 2 (50) | 270 (46) |
| | | ♂ | 124(35.4) | 17 (53) | 50 (54.3) | 6 (30) | 54 (65) | 4 (57.1) | 2 (50) | 257 (43.7) |
| *Klebsiella spp.* | + | ♀ | 6 (1.7) | / | / | / | 2 (2.4) | / | / | 8 (1.4) |
| | | ♂ | 1 (0.3) | / | / | / | 4 (4.8) | 1 (14.3) | / | 6 (1.02) |
| | - | ♀ | 210 (60) | 12 (37.5) | 40 (43.5) | 13 (65) | 27 (32.5) | 3 (42.9) | 2 (50) | 307 (52.2) |
| | | ♂ | 133 (38) | 20 (62.5) | 52 (56.5) | 7 (35) | 50 (60.24) | 3 (42.9) | 2 (50) | 267(45.4) |
| *Enterobactor spp.* | + | ♀ | 3 (0.9) | / | / | / | / | / | / | 3 (0.5) |
| | | ♂ | 2 (0.6) | 1 (3) | / | / | / | / | / | 3 (0.5) |
| | - | ♀ | 213 (60.9) | 12 (37.5) | 40 (43.5) | 13 (65) | 29(35) | 3 (42.9) | 2 (50) | 312 (53.1) |
| | | ♂ | 132 (37.7) | 19 (59.4) | 52 (56.5) | 7 (35) | 54(65) | 4 (57.1) | 2 (50) | 270 (46) |
| *Acinetobactor spp* | + | ♀ | / | / | 1 (1.1) | / | / | / | / | 1 (0.2) |
| | | ♂ | / | / | / | / | / | / | / | 0 |
| | - | ♀ | 216 (61.7) | 12 (37.5) | 39 (42.4) | 13 (65) | 29 (35) | 3 (42.9) | 2 (50) | 314 (53.4) |
| | | ♂ | 134 (38.3) | 20 (62.5) | 52 (56.5) | 7 (35) | 54 (65) | 4 (57.1) | 2 (50) | 273 (46.2) |
| *Pseudomonas spp* | + | ♀ | / | / | / | / | / | / | / | 0 |
| | | ♂ | / | / | / | / | 1 (1.2) | / | / | 1 (0.2) |
| | - | ♀ | 216 (61.7) | 12 (37.5) | 40 (43.5) | 13 (65) | 29 (35) | 3 (42.9) | 2 (50) | 315 (53.8) |
| | | ♂ | 134 (38.3) | 20 (62.5) | 52 (56.5) | 7 (35) | 53 (63.9) | 4 (57.1) | 2 (50) | 272 (46.3) |
| Total | + | ♀ | 43 (12.3) | 2 (6.3) | 5 (5.4) | 5 (25) | 2 (2.4) | / | / | 57 (9.7) |
| | | ♂ | 13 (3.7) | 4 (12.5) | 2 (2.2) | 1 (5) | 5 (6) | 1 (14.3) | / | 26 (4.4) |
| | - | ♀ | 173 (49.4) | 10 (31.3) | 35 (38) | 8 (40) | 27 (32.5) | 3 (42.9) | 2 (50) | 258 (43.9) |
| | | ♂ | 121 (34.6) | 16 (50) | 50 (54.3) | 6 (30) | 49 (59) | 3 (42.9) | 2 (50) | 247 (42) |
| P value | | | | | | | | | | 0.03 |

**Number and percentage of antimicrobials susceptibility patterns tests**

The antibiotics resistance pattern of (83) isolates of Gram negative bacteria were screened for their resistance to fifteen antibiotics, widely used antibiotics. Gram negative bacteria isolates showed high resistance for Ceftriaxone and Amoxicillin 39(47%), Ticarcillin-clavulanic acid 37(44.6%), Vancomycin 36(44.4%) and Doxycycline 34(40.96%) respectively, On the other hand the lowest resistance of Gram negative bacteria were for Amikacin 2(2.4%), Gentamicin 3(3.6%) and also Meropenem 3(3.6%) as in (figure 3). and the highly sensitive has been noticed for other antibiotics, Statistical analysis showed that highly significant correlation ($P < 0.01$) between frequencies of different species of GNB isolated from cancer patients and antibiotics.

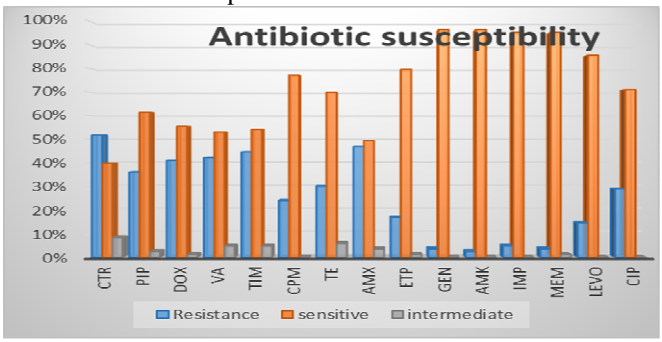


**Fig. 3 :** Total percentage of antimicrobials susceptibility patterns

**Resistance rate of *E.coli* to different clinical specimens**

Out of (588) of different clinical samples in which CSF, Urine, Blood, Stool, Sputum, Throat, Abscess and Wound are collected from cancer patients (61) isolated of *E.coli* has been noticed to distributed between Urine (44), Blood (6), Stool (5), Wound and abscess (6). The highest resistance in Urine has been noticed to Ceftriaxone and Amoxicillin are 24(54.5%), lowest resistance has been noticed to Amikacin which is 1(2.3%).The highest resistance in Blood has been showed to Amoxicillin is 5(83.3%), and the highly sensitive to Cefepime, Ertapenem, Gentamicin, Amikacin, Imipenem and Levofloxacin have been noticed. The highest resistance in stool has been noticed to Ticarcillin-clavulanic acid which is 3(60%), and the highly sensitive has been noticed to Cefepime, Amoxicillin, Ertapenem, Gentamicin, Amikacin, Imipenim, Meropenem, Levofloxacin and Ciprofloxacin. The highest resistance in wound has been noticed to Ceftriaxone 4(66.7%), and the highly sensitive to Gentamicin and Meropenem have been noticed, as in (**Table 4**).

Table 4 :

| Antibiotics | Urine(N=44) Resistance N(%) | Blood(N=6) Resistance N(%) | Stool(N=5) Resistance N(%) | Wound(N=6) Resistance N(%) | Total(N=61) Resistance N(%) |
|---|---|---|---|---|---|
| Ceftriaxone | **24 (54.5)** | **3 (50)** | **1 (20)** | **4 (66.7)** | **32 (52.5)** |
| Piperacillin | **16 (36.4)** | **4 (66.7)** | **1 (20)** | **3 (50)** | **24 (39.3)** |
| Doxycycline | **13 (30)** | **4 (66.7)** | **2 (40)** | **2 (33.3)** | **21 (34.4)** |
| Vancomycin | **15 (34.1)** | **3 (50)** | **2 (40)** | **3 (50)** | **23 (37.7)** |
| Ticarcillin-clavulanic acid | **15 (34.1)** | **4 (66.7)** | **3 (60)** | **2 (33.3)** | **24 (39.3)** |
| Cefepime | **16 (36.4)** | **/** | **/** | **2 (33.3)** | **18 (29.5)** |
| Tetracycline | **8 (18.2)** | **1 (16.7)** | **1 (20)** | **2 (33.3)** | **12 (19.7)** |
| Amoxicillin | **24 (54.5)** | **5 (83.3)** | **/** | **2 (33.3)** | **31 (51)** |
| Ertapenem | **8 (18.2)** | **/** | **/** | **2 (33.3)** | **10 (16.4)** |
| Gentamicine | **3 (7)** | **/** | **/** | **/** | **3 (4.9)** |
| Amikacin | **1 (2.3)** | **/** | **/** | **1 (16.7)** | **2 (3.3)** |
| Imipenem | **3 (7)** | **/** | **/** | **1 (16.7)** | **4 (6.6)** |
| Meropenem | **2 (4.5)** | **1 (16.7)** | **/** | **/** | **3 (4.9)** |
| Levofloxacin | **9 (20.5)** | **/** | **/** | **1 (16.7)** | **10 (16.4)** |
| Ciprofloxacin | **15 (34.1)** | **2 (33.3)** | **/** | **2 (33.3)** | **19 (31.1)** |

Fourteen samples of *Klebsiella spp* have been collected distributed between Urine (7), Sputum (6) and throat (1). The highest resistance in Urine has been showed to Doxycycline and Ticarcillin-Fourteen samples of *Klebsiella spp* have been collected distributed between Urine (7), Sputum (6) and throat (1). The highest resistance in Urine has been showed to Doxycycline and Ticarcillin-clavulanic acid 5(71.4%), the highly sensitive to Piperacillin, Levofloxacin, Ciprofloxacin, Cefepime, Gentamicin, Amikacin, Imipenem and Meropenem have been noticed. The highest resistance in sputum has been noticed to Piperacilin, Vancomycin and Ciprofloxacin which are 4(57%), the highly sensitive to Cefepime, Gentamicin, Amikacin, Imipenem and Meropenem have been noticed .The highest resistance in throat has been noticed to Vancomycin, Ticarcillin-clavulanic acid and Tetracyclin are 1(100%), and the highly sensitive to other antibiotics have been showed, as in Table (6) clavulanic acid 5(71.4%), the highly sensitive to Piperacillin, Levofloxacin, Ciprofloxacin, Cefepime, Gentamicin, Amikacin, Imipenem and Meropenem have been noticed. he highest resistance in sputum has been noticed to Piperacilin, Vancomycin and Ciprofloxacin which are 4(57%), the highly sensitive to Cefepime, Gentamicin, Amikacin, Imipenem and Meropenem have been noticed. The highest resistance in throat has been noticed to Vancomycin, Ticarcillin-clavulanic acid and Tetracyclin are 1(100%), and the highly sensitive to other antibiotics have been showed, as in Table (5)

**Table 5:** Resistance rate of *Klebsiella spp.* to different clinical specimens

| Antibiotics | Urine(N=7) Resistance N (%) | Sputum(N=6) Resistance N (%) | Throat(N=1) Resistance N (%) | Total (N=14) Resistance N (%) |
|---|---|---|---|---|
| Ceftriaxone | **2 (28.6)** | **3 (50)** | **/** | **5 (35.7)** |
| Piperacillin | **/** | **4 (57)** | **/** | **4 (28.6)** |
| Doxycycline | **5 (71.4)** | **2 (33.3)** | **/** | **7 (50)** |
| Vancomycin | **3 (43)** | **4 (57)** | **1 (100)** | **8 (57.1)** |
| Ticarcillin-clavulanic acid | **5 (71.4)** | **3 (50)** | **1 (100)** | **9 (64.3)** |
| Tetracycline | **2 (28.6)** | **3 (50)** | **1 (100)** | **6 (42.9)** |
| Amoxicillin | **3 (43)** | **3 (50)** | **/** | **6 (42.9)** |
| Ertapenem | **1 (14.3)** | **2 (33.3)** | **/** | **3 (21.4)** |
| Levofloxacin | **/** | **2 (33.3)** | **/** | **2 (14.3)** |
| Ciprofloxacin | **1 (14.3)** | **4 (57)** | **/** | **5 (35.7)** |
| Cefepime | **/** | **/** | **/** | **/** |
| Gentamicin | **/** | **/** | **/** | **/** |
| Amikacin | **/** | **/** | **/** | **/** |
| Imipenem | **/** | **/** | **/** | **/** |
| Meropenem | **/** | **/** | **/** | **/** |

Six samples of *Enterobacter spp* have been noticed to Urine (5) and Stool (1). The highest resistance in Urine has been showed to Tetracycline 5(100%), the highly sensitive to Cefepime, Ertapenem, Gentamicin, Amikacin, Imipenem, Meropenem , Levofloxacin and Ciprofloxacin have been noticed. The highest resistance in stool has been noticed to Piperacillin, Vancomycin, Ticarcillin-clavulanic acid and Tetracycline which are 1(100%) and the highly sensitive to amoxicillin, doxyxyclin and seftryaxone have been showed, **as in Table 6.**

**Table 6:** Antibiotic resistance of *Enterobactor spp*. and incidences of resistance in isolated clinical specimens

| Antibiotics | Urine(N=5) Resistance N (%) | Stool(N=1) Resistance N (%) | Total (N=6) Resistance N (%) |
|---|---|---|---|
| Ceftriaxone | **2 (40)** | / | **2 (33.3)** |
| Piperacillin | **1 (20)** | **1 (100)** | **2 (33.3)** |
| Doxycycline | **4 (80)** | / | **4 (66.7)** |
| Vancomycin | **3 (60)** | **1 (100)** | **4 (66.7)** |
| Ticarcillin-clavulanic acid | **3 (60)** | **1 (100)** | **4 (66.7)** |
| Tetracycline | **5 (100)** | **1 (100)** | **6 (100)** |
| Amoxicillin | **1 (20)** | / | **1( 16.7)** |
| Cefepime | / | / | / |
| Ertapenem | / | / | / |
| Gentamicin | / | / | / |
| Amikacin | / | / | / |
| Imipenem | / | / | / |
| Meropenem | / | / | / |
| Levofloxacin | / | / | / |
| Ciprofloxacin | / | / | / |

One sample of *Acinetobacter spp* hase been noticed to only blood in which the highest resistance to Doxycycline and Vancomycin 1(100%) has been observed and the highly sensitive has been showed to other antibiotics, as in (Table 7).

**Table 7**: Antibiotic resistance of *Acinetobactor spp*. and incidences of resistance in isolated clinical specimens

| Antibiotics | Blood(N=1) Resistance N (%) | Total (N=1) Resistance N (%) |
|---|---|---|
| Doxycycline | 1 (100) | 1 (100) |
| Vancomycin | 1 (100) | 1 (100) |
| Ceftriaxone | / | / |
| Piperacillin | / | / |
| Ticarcillin-clavulanic acid | / | / |
| Tetracycline | / | / |
| Amoxicillin | / | / |
| Cefepime | / | / |
| Ertapenem | / | / |
| Gentamicin | / | / |
| Amikacin | / | / |
| Imipenem | / | / |
| Meropenem | / | / |
| Levofloxacin | / | / |
| Ciprofloxacin | / | / |

One sample of *Pseudomonas spp* has been examined only for sputum specimen which the highest resistance has been showed to Amoxicillin, Doxycycline, Tetracycline, Ertapenem 1(100%), while the highly sensitive has been noticed to other antibiotics, as in Table 8.

**Table 8:** Antibiotic resistance of *Pseudomonus spp*. and incidences of resistance in isolated clinical specimens

| Antibiotics | Sputum (N=1) Resistance N (%) | Total (N=1) Resistance N (%) |
|---|---|---|
| Amoxicillin | 1 (100) | 1 (100) |
| Doxycycline | 1 (100) | 1 (100) |
| Tetracycline | 1 (100) | 1 (100) |
| Ertapenem | 1 (100) | 1 (100) |
| Gentamicin | / | / |
| Ticarcillin-clavulanic acid | / | / |
| Imipenem | / | / |
| Meropenem | / | / |
| Levofloxacin | / | / |
| Ciprofloxacin | / | / |

| | | |
|---|---|---|
| Ceftriaxone | / | / |
| Piperacillin | / | / |
| Vancomycin | / | / |
| Amikacin | / | / |
| Cefepime | / | / |

**Distribution of Gram-negative isolates according to sources of infections and incidence of Multi-drug resistant.**

Eighty three sample of gram negative bacteria are isolated which are remarkable variable to their resistance to antibiotic use, but in general (86.7%) isolates of Gram negative bacteria were multidrug resistance to more than three antibiotics. Urinary tract infection is the most common site of infection which is (67.5%) followed by Respiratory tract infection (9.6%),Blood stream infection (8.4%), Gastrointestinal infections and Skin and wound infection (4.8%).The incidence of multi drug resistance is more common in Urinary tract infection which is 50(60.3%) followed by Respiratory tract infection 7(8.4%), Blood stream infection 5(6%), Gastrointestinal infection 4(4.8%) and Skin and wound infection 6(7.2%).as in(Table 9) Out of 61 sample of *E.coli*, 44(88.5%) sample were Multi drug resistance as in (Table 9, Figure 4). Out of 14 sample of *Klebsiella spp*, 11(78.6%) sample were Multi drug resistance as in (Table 9, Figure 5). Out of 6 sample of *Enterobacter spp*., 6(100%)sample were Multi drug resistance as in (Table 9, figure 6). Out of 1 sample of *Pseudomonas spp*, 1(100%) was Multi drug resistance as in (Table 9,Figure 7). Out of 1 sample of *Acinetobacter spp*, 0(0%) was Multi drug resistance as showed in (Table 9,Figure 8). Statistical analysis showed that highly significant correlation ($P < 0.01$) between Gram negative bacteria isolated from different clinical sample and multi-drug resistance.

**Table (3-10):** Distribution of Gram-negative isolates according to sou Table (9): Distribution of Gram-negative isolates according to sources of infections and incidence of Multi-drug resistance

| Source of infection. | *E.coli* (n=61) | | *Klebsiella spp*(n=14) | | *Enterobactor spp*(n=6) | | *Acinetobactor spp*(n=1) | | *Pseudomonas spp*(n=1) | | Total (n=83) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total N (%) | MDR N (%) | Total N (%) | MDR N (%) | Total N (%) | MDR N(%) | Total N (%) | MDR N (%) | Total N (%) | MDR N (%) | Total N (%) | MDR N (%) | P - value |
| **UTI** | 44 (72) | 40 (65.6) | 7 (50) | 5 (35.7) | 5 (83.3) | 5 (83.3) | 0 | 0 | 0 | 0 | 56 (67.5) | 50 (60.3) | |
| **RTI** | 0 | 0 | 7 (50) | 6 (43) | 0 | 0 | 0 | 0 | 1 (100) | 1 (100) | 8 (9.6) | 7 (8.4) | |
| **BSI** | 6 (9.8) | 5 (8.2) | 0 | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 | 7 (8.4) | 5 (6) | |
| **GIT** | 5 (8.2) | 3 (5) | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 0 | 0 | 0 | 6 (7.2) | 4 (4.8) | |
| **SWI** | 6 (9.8) | 6 (9.8) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 (7.2) | 6 (7.2) | |
| **Total** | 61 (100) | 54 (88.5) | 14 (100) | 11 (78.6) | 6 (100) | 6 (100) | 1 (100) | 0(0) | 1 (100) | 1 (100) | 83 (100) | 72 (86.7) | 0.0001 |

All data presented as n (%), b UTI: Urinary tract infection, WI: wound infection, RTI: Respiratory tract infection, BSI: Bloodstream infection, GTI: Gastrointestinal infection, MDR: Multiple-drug-resistant

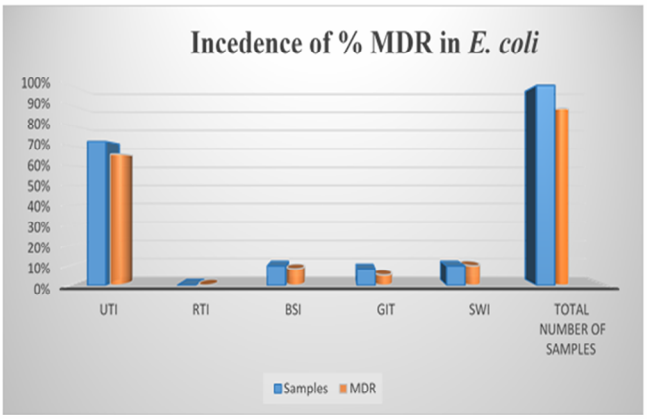


**Fig. 4 :** Distribution of *E.coli* isolates according to sources of infections and incidence of MDR.

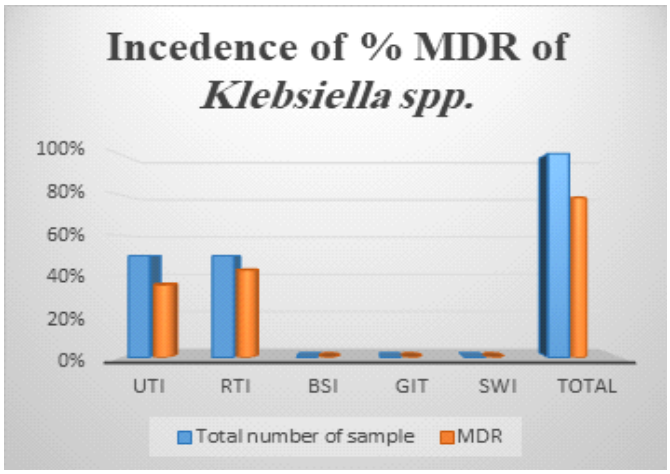


**Fig. 5 :** Distribution of *Klebsiella spp.* isolates according to sources of infections and incidence of MDR

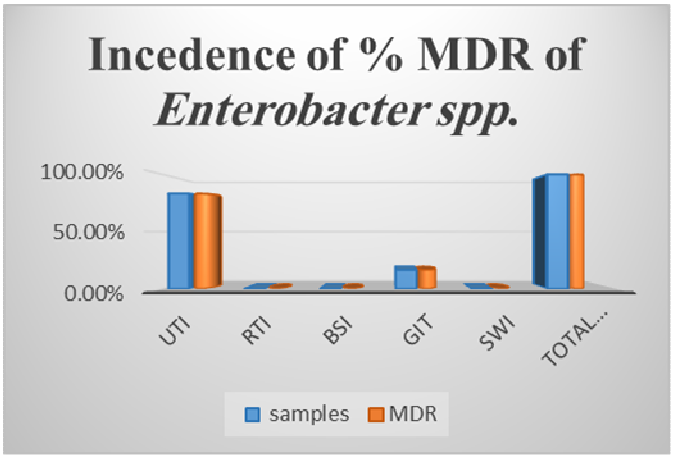


**Fig. 6 :** Distribution of *Enterobacter spp.* isolates according to sources of infections and incidence of MDR.

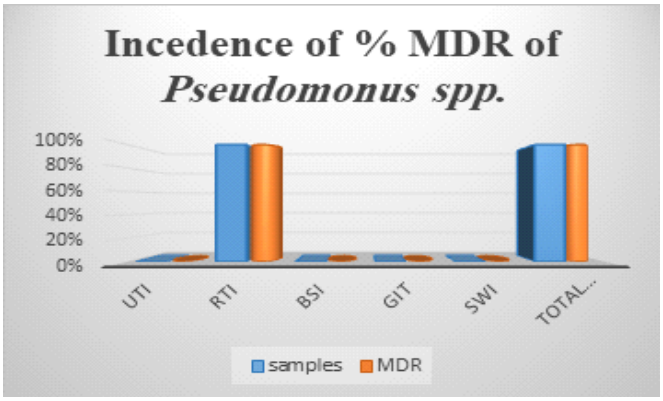


**Fig. 7 :** Distribution of *Psedomonas Spp.* isolates according to sources of infections and incidence of MD

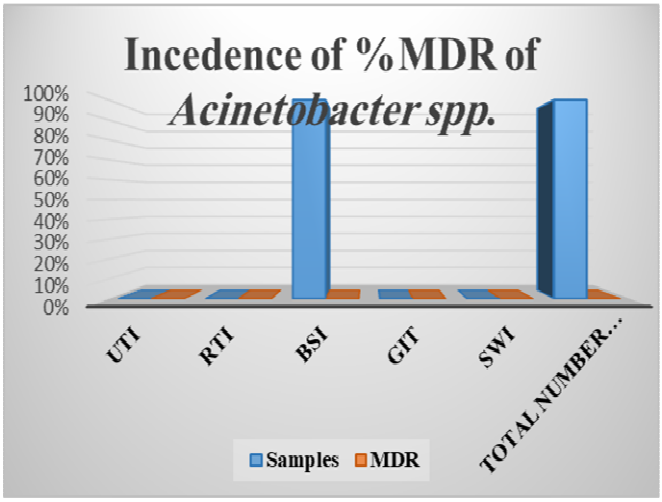


**Fig. 8 :** Distribution of *Acinetobacter* isolates according to sources of infections and incidence of MD

## Discussion

The incidence of infections caused by Gram-negative bacteria (GNB) in cancer patients has increased in recent years, a consequence of injury to the mucosal surface of the gastrointestinal tract from cancer treatment .The most commonly reported GNB include *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species, with rates ranging from 40 to 60% Babady, *et al.*,(2016). A total of (588) samples were collected from eight different source from cancer patient,only 83(14.2%) isolated were indicated as positive of Gram negative bacteria.All Gram negative bacteria isolated are identified by using macroscopically, microscopically, biochemical tests and Vitek 2 compact system.In our study All gram negative bacteria isolated are classified into two grouped based on fermentation of lactose which are lactose fermented gram negative rods which is family *Enterobacterieaceae* include ( *E.coli, klebsiella spp* and *Enterobcter spp*), and none lactose fermented gram negative bacteria (*Pseudomonas spp* and *Acinetobacter spp*),our results lower than (11) study, that was from total 256 clinical sample 196 (76.6%) samples of gram negative bacteria were positive at the African Oncology Institute (AOC) in Sabrata in Libya country. And in our study the *Enterobacterieaceae* cause approximately 81(%98) from 83 of documented gram negative infection in cancer patient, which is higher than Data from several large surveillances studies that conducted at major cancer centers both in the United States and Europe indicated that *Enterobacterieaceae* cause approximately 65% to 80% of documented gram-negative infections in cancer patients Eldomany and Abdelaziz, *et al.*,(2011).

**Distribution of gram negative bacteria according to different clinical sample.**

Our results showed that from 83(14.2%) isolated positive gram negative bacteria,the highest percent belong to genus *E.coli* 61(10.4%) followed by *Klebsiella spp.* 14(2.4%), *Enterobactor spp.* 6(1%), *Acinetobactor spp.* 1(0.2%) and *Pseudomonas spp.* 1(0.2%) and statistical analysis showed that highly significant correlation ($P < 0.01$) between different species isolated from cancer patients disagree with the studies of Eldomany and Abdelaziz, (2011) which showed that,from out of 343(100%) samples of Gram negative bacteria isolates collected from different clinical sample *E.coli* were the most frequent isolates 103(30%) followed by *Pseudomonas spp.* 88(25.7%), *Acinetobactor spp.* 69 (20.1 %) and *Klebsiella spp.* 38(11.1%) respectively. This variation in the prevalence of Gram-negative bacteria may arise from the differences in sample size, the source of infection, type of cancer, and geographical distribution and 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.

**Distribution of gram negative bacteria according to source of infection**

Urinary tract infection is the most common in our study which is 56 (67.5%) followed by respiratory tract infection 8 (9.6%),blood stream infection 7 (8.4%),gastrointestinal infection and Skin-wound infection 6 (7.2%) and statistical analysis showed that highly significant correlation ($P< 0.01$) between different clinical sample and different species of Gram-negative bacteria that's disagree with (13) study in incidence of infection in which out of 259 total sample isolates gram negative bacteria,the incidence of urinary tract infection was 170(65.6%) and followed by skin soft tissue infection 61(23.6%), respiratory tract infection 16(6.2%) and Blood stream infection 8(3.1%)respectively .

Blood stream infection (BSIs) due to Gram-negative bacilli are common in cancer patients during aggressive therapy. In recent years, there has been marked increase in the incidence of antibiotic resistance against Gram-negative bacilli. The overall frequency of Gram-negative infection has decreased over the past decade (5).Blood stream infections in our study caused by GNB were mainly due to *E.coli* 6(30%)

and *Acinetobactor species* 1(1.1%), but in study done by by (Eldomany and Abdelaziz, 2011) particularly blood stream infections caused by Gram-negative bacteria were mainly due to *Acinetobacter species* 14(27.5%) and *Pseudomonas species* 12(23.5%), and also with the study done by (13)in which blood stream infection caused by *E.coli* 6(%75) and *Klebsiella species* was 2(25%). In the present study, *E. coli*, followed by *K. pneumoniae* and *P.aeruginosa* were the most common Gram negative bacteria identified. It should be noted that most of Gram negative bacteria strains examined were from urine specimens. This may explain the predominance of *E. coli* and *K. pneumoniae* amongst our gram negative bacteria isolates Ashour and El-Sharif, *et al*.,(2009), in Egypt, reported similar findings. They found that Gram negative bacteria causing urinary tract infection s in both leukemic and solid-tumor patients were mainly *E. coli* and *K. pneumoniae*. Contrary to recent reports from developed countries, our findings and those reported by other investigators indicate that GNB are the predominant organisms associated with infections in cancer patients in developing countries. This observation may have important implications in selecting the appropriate treatment for such patient Zorgani *et al*., (2012)our results lower with those reported by (13) who found that *E.coli* causing urinary tract infection was 94(55%) and *Klebsiella* was 47(27.6%), and from total 259 Gram negative bacteria only 4 sample isolated from Gastrointestinal infection which are only 2(50) *Salmonella spp* and 2(20) *Shigella spp*.

**Relation between Gram negative bacteria Species and Gender**

In this study, the highest rate of Gram negative bacteria was found in female 57 (9.7%) while only 26 (4.4%) found in males and statistical analysis showed that significant correlation ($P < 0.05$) between Gender (male and female) and frequency Gram-negative bacteria, our result agreement with that reported by (13) from Iran who founded that out of 259 total gram negative bacteria, 142 (54.8%) belonged to female and 117(45.2%) were from male. The sex distribution of patients in our study is consistent with those of other reported studies, showing a statically predominance of females with urinary tract infection. This result is similar to those reported from many other centers. The higher rate of *E.coli* was found in females 45(7.7%) compared to 16(2.7%) males urine..The differences of number of GNB in male and female might due to sample size were more in female than in male(57, 26) respectively,because our target populations only patient attending the hospital randomly in Erbil city.

**Number and percentage of antimicrobials susceptibility patterns tests**

The most effective antimicrobial agent in this study for total gram negative bacteria are Amikacin 81(97.6%), Gentamicin 80(96.4%), Meropenem and Imipenem 79(95.2%) statistical analysis showed that highly significant correlation ($P<0.01$) between frequencies of different species of GNB isolated from cancer patients and antibiotics which is similar with(15)study in Anderson cancer center in which resistance among gram-negative bacilli at their center, increased to third generation Cephalosporins, quinolones, β-lactams and aminoglycosides. They suggested that Meropenem, Cefepime, Imipenem and Piperacillin/ tazobactam were appropriate choices for febrile neutropenic patients in their hospital.Our study is similar with other study such as the study done by Eldomany and Abdelaziz, *et al*.,(2011) who mentioned that *E.coli* and *Klebsiella spp*. isolates showed multi drug resistance and were only susceptible to Imipenem (94.2%84.2%respectively), Cefotetan (87.4, 76.3% sussceptibility respectively) and Amikacin (85.4%, 71, 1% susceptibility respectively). *Enterobactor spp* isolates were resistant to most antibiotics tested, with Imipenem being the most active against *Enterobactor spp* (58.3% susceptibility).*Pseudomonus spp* isolates were resistant to most antibiotics tested, with ciprofloxacin,Amikacin and Levofloxacin being the most active against *Pseudomonas spp* (67,4%, 64% and 58.2% susceptibility respectively) . *Acinetobactor spp* showed increased resistance to more antibiotic. And have susceptible to Tetracycline, Levofloxacin and Gatifloxacin (49,3 %, 36,3 % and 36,2% susceptibility respectively). This information can help clinicians to choose effective empirical therapies and provide good epidemiological profile to compare our situation with others.

**Distribution of MDR among GNB in cancer patient.**

Treatment of infections due to MDR bacteria represents a clinical challenge, especially in the case of Gram-negative bacilli, since the therapeutic options are often very limited .The emergence and rapid spread of carbapenem-resistant GNB (especially *Enterobacterieaceae* and particularly *K. pneumoniae*), across the globe is of special concern. Carbapenem resistance among *Enterobacterieaceae* is due either to a carbapenem-hydrolyzing enzyme (carbapenemase), the most common mechanism, or to changes in outer membrane porins combined with overproduction of AmpC b-lactamases or ESBLs (6).Most infections in cancer patients are nosocomial in nature as a result of their prolonged and frequent contact with hospital environment. In many institutions in developed countries, more Gram-positive bacteria, mainly staphylococci, than Gram-negative bacteria are isolated from cancer patients. Use of indwelling catheters, oral mucositis, and prophylactic and empirical treatment directed mainly against Gram-negative bacteria are reasons, among others, that have been given for this phenomenon (11) .From the total 83 samples of GNB we collected in nanakli hospital in Erbil city, antibiotic susceptibility test were performed by Vitek 2 compact on fifteen antibiotics and the high level of bacterial resistance was seen to Ceftriaxone and Amoxicillin 39(47%), Ticarcillin-clavulanic acid 37(44.6%), Vancomycin 36(44.4%) and Doxycycline 34(40.96%) respectively, which Ceftriaxone and Amoxicillin were less effective than Ticarcillin-clavulanic acid and Vancomycin against isolated bacteria, On the other hand the lowest resistance of Gram negative bacteria were screened for Amikacin 2(2.4%), Gentamicin 3(3.6%) and also Meropenem 3(3.6%) and statistical analysis showed that highly significant correlation ($P < 0.01$) between frequencies of different species of GNB isolated from cancer patients and antibiotics, this is different to previous studies in Libya (Zorgani *et al*., 2012)(11)in which the high resistance rates were observed among total GNB to Ampicillin (73.1%), Amoxicillin-clavulanic acid (36.2%), Piperacillin (46.4%), Tetracycline (46.9%) and Trimethoprim-sulfamethoxazole (36.7%), on the other hand, low resistance rates were detected for Imipenem (3.1%), Meropenem (1.5%), Piperacillin/tazobactam (3.6%), Amikacin (3.6%), and Colistin (2.6%)and (16)observed high resistance rates against Cephalosporins in *P. aeruginosa* and

*Enterobacteriaceae*. *Enterobacter species* exhibited 95.8% resistance to both antibiotics *Pseudomonas species* exhibited 87.6% and 66.3% resistance to Cefotaxime and Ceftazidime, resistance was high in *Escherichia coli* and *Klebsiella species*, which is consistent with a study from Egypt that reported high resistance levels to Cefotaxime (74.4%) in gram-negative rods Talaat *et al*. (2010). High resistance to Ciprofloxacin has been reported for gram-negative bacilli collected in United States, Canada, and Latin America in SENTRY Antimicrobial Surveillance Programs and in Turkey Pfaller *et al*. (2010). Fluoroquinolones resistance against *E. coli* in cancer patients was found with a resistance rate of more than 50% among *E. coli*. Kern *et al*. (2005),which is similar with our study that showed 36(43.3%) resistance to Fluoroquinolones (Ciprofloxacin and Levofloxacin) .In recent years, the emergence of antimicrobial resistance has become a significant problem worldwide, and cancer patients are among those affected. Treatment of infections due to MDR bacteria represents a clinical challenge, especially in the case of Gram-negative bacilli, since the therapeutic options are often very limited Gudiol and Carratala *et al*. (2014). Infections due to gram-negative bacilli are common in cancer patients during aggressive therapy . In recent years, there has been marked increase in the incidence of antibiotic resistance against gram-negative bacilli Eldomany and Abdelaziz *et al*. (2011), Fattma *et al*. (2020) reported that in total, from 2016-2019 Klebsiella infected patients with solid tumor type was24/70(34.4%) and leukemia and lymphoma were 23/70 (32.8%) for each, Klebsiella isolates had resistanceto more than three classes of antibiotics mostly (72%) of isolates.Multidrug-resistance organisms (MDRO) such as *P. aeruginosa*, *K. pneumoniae* and the other *Enterobacterieaceae* species with emerging resistance, is an important cause of morbidity and mortality in hospitalized critically ill patients and patients with underlying medical condition such as neutropenia and immunosuppressant. The return to the pre-antibiotic era has become a reality in many parts of the world. MDR microorganisms were recently named as the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*), indicating their 'escape' from the effects of antibacterial agents or the non-existence of newer active antibiotics. Similarly anti-microbial resistance pattern among bloodstream infection isolated from SENTRY antimicrobial Surveillances Program (1997-2002) showed high prevalence of multidrug resistant *P. aeruginosa* in America Eldomany and Abdelaziz *et al*. (2011).

Gram negative bacteria remarkable variable to their resistance to antibiotic use, but in general from 83 total gram negative bacteria 72(86.7%) isolates of Gram negative bacteria were multidrug resistance to more than three antibiotics and statistical analysis showed that highly significant correlation ($P < 0.01$) between Gram negative bacteria isolated from different clinical sample and multi-drug resistance,our finding is similar and some lower than study done by (13) who recorded that out of 259 isolates (91.5%%) were found to be Multi-drug resistance. The indiscriminate use of antimicrobials over prolonged periods has led to the emergence of multi drug resistant (MDR) strains. Whenever a new and effective antibiotic is introduced, bacteria after exposure to this antimicrobial, acquire resistance through different mechanisms, commonest being the production of β-lactamases. To combat these MDR strains new and more effective

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