Impact the Antibiotics Resistance of *Enterobacter spp.* in Cancer patients

Fattma A Ali [1*], Ahmed Akil Khudhair Al-Daoody [2], Bashdar Mahmud Hussen [3], Shayma Hatam [4], Naba Mheddin Ekhlas [5], Sarhad, Rawan Sabir [6], Yaqub Aziz [7]

[1, 2, 4-7] College of Health Sciences/Hawler Medical University. Kurdistan Region, Erbil, Iraq

[3] Department of Clinical Analysis, College of Pharmacy, Hawler Medical University, Kurdistan Region, Erbil, Iraq

* Corresponding Author: **Fattma A Ali**

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Abstract

Background: Infection is a continuous problem in cancer patient especially in developing country, multi-drug resistance of *Enterobacter spp.* are among the most frequent complication in Immunocompromised cancer patients and pose the greatest risk to Immunocompromised cancer patient.

Objectives: Our study aimed to carry out a retrospective study on *Enterobacter spp*. isolated from various clinical samples among cancer patient in Erbil city and analyze its epidemiology and antibiotics susceptibility pattern test and multi-drug resistance.

Materials and Methods: A total of 467 from 2016 until 2020 *Enterobacter spp*. were isolated from 5 clinical samples (Urine, Wound and Ear swabs, Blood and Stool) from patient attending Nanakali Hospital and from both male and female. Only 32 cases had been identified as *Enterobacter spp.* isolates which was identified by using macroscopical, biochemical tests and Vitek 2 compact system. Also antibiotic susceptibility test was performed by Vitek 2 compact on 19 antibiotics.

Results: Only 32 Enterobacter isolates were isolated from 467 samples distribution according to their source of isolation in cancer patient. Urinary tract infections is the most common in our study followed by otitis media infection, and Skin-wound infection, Blood stream infection, the percentage of females infected with *Enterobacter spp*. were more than the males, females being 20/467(4.2%) and males being 12/467(2.5%), after 2016 infections by *Enterobacter spp.* was increased in over than 31 years old people being 9/15(60%) in total, from 2016-2020 *Enterobacter spp.* infected patients with solid tumor type was 16/32(50%) and leukemia was 9/32(28%) and multiple myeloma was 7/32(22%)for each, Although (Imipenem, Amikicin, Levofloxacin, Ticarcillin/clavulanic acid, Ceftazidime, Amoxicillin, Cephalexin) can be considered as effective agents toward multi-drug resistance strains for empirical antibiotic therapy in cancer patients, *Enterobacter Spp*. isolates had resistance to 11 antibiotics.

Conclusions: The study findings showed a significant distribution of multi-drug resistance *Enterobacter spp*. which may increase the burden of healthcare-associated infections in cancer patients. Moreover, mechanisms of resistance should also be investigated for better characterization antibiotic-resistant of *Enterobacter spp* isolates.

Keywords: *Enterobacter spp*., Cancer patient, multi-drug resistance

Introduction

Infection is a continuous and significant problem in cancer patients due to many factors that increase the susceptibility of immunosuppressed cancer patients to infection, such as neutropenia during chemotherapy, altered gut flora because of frequent antibiotic administration, and disruption of skin and damage of epithelial surfaces of the tissues by cytotoxic chemotherapeutic agents (Ashour and El-Sharif, 2009) [4]. Enterobacteriaceae bacteremia is a common complication in patients with neoplasm. The cancer itself, chemotherapy-induced immunosuppression, and other cancer-related procedures play a role as predisposing factors for this condition (Martinez *et al*., 2013) [41].

Enterobacter spp. are members of human gut microbiota. These facultative anaerobe Gram negative rods may cause opportunistic infections especially in immune compromised patients (Hong *et al*., 2018) [25]. Data from several large surveillance's studies conducted at major cancer centers both in the United States and Europe indicated that Enterobacteriaceae cause approximately 65% to 80% of documented gram-negative infections in cancer patients (Cattaneo *et al*., 2008) [12]. In recent years, a shift from Gram-positive to Gram-negative organisms has been documented in the etiology of BSI; however, these data vary depending on the geographic area. Gram-negative bacteria are most frequent in the U.S. and Latin America, while Gram-positive bacteria have been reported as the prevalent cause in Europe (Marín *et al*., 2014) [40]. *Enterobacter spp*. are increasingly recognized as important pathogens that induce nosocomial infections, such as These species are characterized by inducible antimicrobial resistance mediated by chromosomal AmpC β-lactamase which emerge rapidly during antimicrobial therapy (Choi *et al*., 2008) [14].

Studies suggest a high prevalence of extended spectrum β-lactamase (ESBL) production in these species (Ho *et al*., 2005). Limiting the choice of antimicrobial agents capable of treating invasive infection. The 2 most common *Enterobacter spp*. causing human infection are *Enterobacter cloacae and Enterobacter aerogenes*, comprising %90 to %99 of Enterobacter infections (Lee *et al*., 2002) [37]. Bacteria originating from the gastrointestinal tract are often responsible for infections in cancer patients with neutropenia. Broad-spectrum β-lactam agents are the cornerstone of treatment of cancer patients with suspected infection by Enterobacteriaceae. Therefore, the increasing prevalence in our healthcare system of carbapenem-pneumonia, UTI, surgical site infection and meningitis (Sanders and sanders, 1997) **[57]**.

Increasingly, there are fewer antimicrobial drugs available to effectively treat common as well as life-threatening infections. Annual deaths from untreatable infections may rise from estimated 700 000 in 2015 to 10 million by 2050 if antimicrobial resistance is not controlled (O'Neill, 2019). Cancer patients are particularly prone to nosocomial infections. This can be due to the negative effect of chemotherapy and other treatment practices on their immune system (Guinan *et al*., 2003) [24], resistant Enterobacteriaceae, also resistant to other β-lactams, poses an urgent threat (Rep, 2013) [65].

The choice of appropriate therapy is complicated by the fact that the majority *of Enterobacter spp*. is resistant to many antibacterial agents or can develop resistance during treatment. There are no data from Saudi Arabia regarding the trend in antibiotic resistance among *Enterobacter spp*. over time and the available data are related to the presence of extended-spectrum -lactamases in this organism (Kader *et al*., 2006) [30]. The misuse and abuse of β-lactam antibiotics has led to antibiotic selective pressure and the development of resistance to these drugs by most bacteria, particularly the Enterobacteriaceae, of which β-lactamase production remains the most important contributing factor to this resistance (Fair and Tor, 2014) [18].

Consequently, the clinical isolates collected in the patient during antibiotherapy show a serious loss in susceptibility to cephalosporin and carbapenems. This alteration of porin profiles is also often reported with a concomitant synthesis of degradative enzymes such as β -lactamases, cephalosporinases, or carbapenemases, which generate a worrying level of β -lactam resistance (Valade *et al*., 2014) [64]. Enzymatic barriers and epidemiology. In most *Enterobacter spp.*, the production of β -lactamases is the prominent mechanism responsible for β -lactam resistance, and *E. aerogenes and E. cloacae* have a broad ability to modulate these mechanisms of resistance. Importantly, these bacteria are able to produce a low level of a chromosomal Amp β -lactamase-type cephalosporinase that generates a resistance to first-generation cephalosporins (Carter *et al*., 2017) [11].

Lastly, MDR has recently been described in Enterobacter isolates (*E. cloacae and E. aerogenes)* and in MDR-associated porin alteration, target mutation β -lactamase production, and efflux overexpression that are accumulated during antibiotic treatment**.** Some mechanisms are intertwined and controlled by regulators in a complex genetic cascade. MDR and genetic regulation. MDR and genetic regulation. Recently, several chemical inducers that are able to modulate the expression of Enterobacter membrane transporters, including porins and/or efflux pumps, have been described, e.g., salicylate, chloramphenicol, etc (Davin-Regli and Pagès, 2015).

The extensive emergence of multidrug-resistant (MDR) bacteria has increased the burden of morbidity and mortality among cancer patients with BSI (Marín *et al*., 2014) [40]. Pre-ventive measures to stop the spread of these potential pathogens clearly are warranted (Verhoeven, 2000) [39].

Current prophylactic and empiric antibiotic regimens is compromised by the emergence of gram-negative bacteria that exhibit multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) phenotypes (Magiorakos *et al*., 2012) [38]. The wide spread of extended-spectrum β -lactamase-producing Enterobacteriaceae (ESBL-E) is of special importance since it raises doubts about the efficacy of some noncarbapenem β -lactams as first-line treatment in cancer patients (Montes *et al*., 2014) [44].

Sample collection

A total of (476) samples were collected from five different sources (Urine,Wound swab,Ear swab, blood and Stool samples) from hospitalized patients with cancer cancer (Acute amyloid or chronic myeloid Leukemia, Multiple myloma, Breast cancer, Cervix cancer, Prostate cancer, Chronic lymphoid Leukemia) from January 2016-November 2020 all isolated bacterial from patients attending in Nanakali hospital in Erbil city confirmed by confirmed tests. For isolation of microorganisms, the specimen was directly inoculated on culture media; Blood culture and macConkey agar plates were incubated aerobically at 37°C 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 (18).

Vitek2 compact system

The newly redesigned colorimetric Vitek 2 compact system figure (2.2), 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 resistance (Nakasone *et al*., 2007) [47].

Principles of the Vitek 2 is an automated microbiology system utilizing growth-based technology. This system accommodate the colorimetric reagent cards that are

incubated and interpreted automatically. Overall, the Vitek 2 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 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 (Kasse *et al*.,2009) [32].

Antimicrobial susceptibility test by Vitek 2 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 (Kollef, 2003). With its ability to provide accurate "fingerprint" recognition of bacterial resistance mechanisms and phenotypes, the AES is a critical component of Vitek 2 technology (Tenover *et al*., 2007) [62].

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 (Wiegand *et al*., 2007) [66].

Statistical Analysis

Data analysis were showed as the mean and standard deviation (SD) by using Microsoft Excel. Chi-square tests (Regression), Fisher's exact tests and student's *T*-tests (two samples assuming unequal variances used to determine any significant differences among the groups, if $P < 0.05$ it is considered significant.

Results

Incidence of *Enterobacter spp.* isolated from cancer patients.

The investigation study between 2016-2020 out of 476 isolates only 32(7%) were positive from cancer patients as in Table (1) and Figure (1). Results showed that we had 4(5.6%) positive cases out of 71 in 2016 and 5(5%) positive cases and out of 99 in 2017 and in 2018 we had 8(7%) positive cases and out of 116 and 15(10%) positive cases and out of 153 in 2019 and we had not any positive cases out of 37 in 2020.

Statistical analysis showed that significant correlation between the *Enterobacter spp*. and years ($P < 0.05$) as seen in Table (1) and figure (1).

Table 1: Incidence of *Enterobacter spp*. isolated from cancer patients.

Years	Positive	%	Negative	%	Total	%
2016	4	5.6	67	94.3	71	100
2017	5	5	94	95	99	100
2018	8	7	108	93	116	100
2019	15	10	138	90	153	100
2020	-	-	37	100	37	100
Total	***32***	6.7	444	92.3	476	***100***
***P*-value <0.00009**						

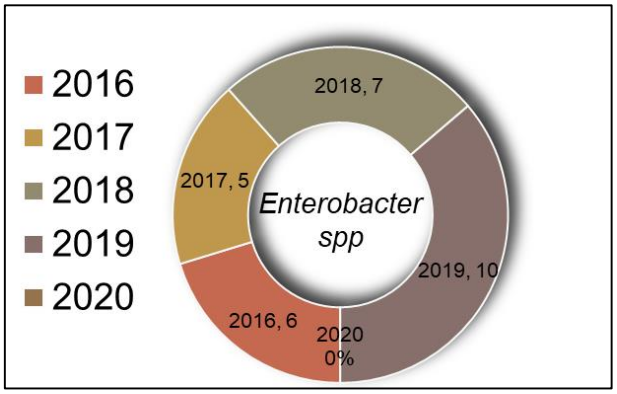

Fig 1: Incidence of Enterobacter *spp*. isolated from cancer patients.

Incidence of *Enterobacter spp*. among gender

In 2016 out of 71 samples the female ratio was more than the males, for males we hadn't any positive cases and 19(26.8%) negative cases and for the females we had 4(5.6%) positive cases and 48(67.6%) negative cases. In 2017 out of 99 samples the female ratio higher than the males for males we had 1(1%) positive case and 34(34%) negative cases and for females we had 4(4%) positive and 60(60.6%) negative. As for 2018 we had 116 Samples and 2019 we had 153 Samples, for 2018 for males we had 3(2.6%) positive and 35(30%) negative and for females .5(4%) positive cases and 73(63%) negative cases, as for 2019 for the males we had 8(5%) positive and 51(33%) negative as for females 7(4.5%) positive and 87(57%) negative. And for 2020 we didn't have sample for positive for both male and female just we have sample for negative as for male we have 14(38%) and for female we have 23(62%).

Statistical analysis showed that significant correlation ($P < 0.05$) as in Table (2).

Table 2: Incidence of *Enterobacter spp*. among gender.

Years	Male		Female		Total
	P (No %)	N (No %)	P (No %)	N (No %)	No (%)
2016	-	19(26.8)	4(5.6)	48(67.6)	71(100)
2017	1(1)	34(34)	4(4)	60(60.6)	99(100)
2018	3(2.6)	35(30)	5(4)	73(63)	116(100)
2019	8(5)	51(33)	7(4.5)	87(57)	153(100)
2020	0	14(38)	0	23(62)	37.8(100)
Total	12(2.5)	153(32)	20(4.2)	291(61)	476(100)
p-value <0.002					

P=positive, N=negative, No=number,%=percentage

Distribution of *Enterobacter spp*. in different clinical samples

From 2016 until 2020 *Enterobacter spp*. were isolated from 5 clinical specimens (Urine, wound Swab, ear swab, blood, stool)in 2016 urine become the major source of infection by Enterobacter, urine 4 per 71(4.6%) but we didn't have any wound swab, Ear swab, blood or stool samples. In 2017 we had 3 major sources of *Enterobacter spp*. which Urine 3 per 99(3%), wound swab 1 per 99(1%), Ear swab 1 per 99(1%) but we didn't have any other samples like blood and stool samples. In 2018 we had urine and stool samples for Urine 7 per 116(6%) and Stool 1per 116(1%) but we did not have any other samples like wound swab, ear swab, and blood samples. In 2019 Urine, wound swab and blood were the major source of infection. Urine 9 per 153(6%) and wound swab 1 per 153(0.6%), and blood 5 per 153(3.3%) but we didn't have any samples for ear swab and Stool samples. In 2020 we had not

any samples or sources for *Enterobacter spp*.
Statistical analysis showed that significant correlation (P < 0.05) as in Table (3) and Figure (2).

Table 3: Distribution of *Enterobacter spp*. in different clinical samples

Years	+ve or -ve	Urine (N)	Wound swab (N)	Ear swab (N)	Blood (N)	Stool (N)	Total
2016	+(%)	4(4.6)	-	-	-	-	4(5.6)
	-(%)	64(90)	-	-	3(4.3)		67(94.3)
2017	+(%)	3(3)	1(1)	1(1)	-	-	5(5)
	-(%)	85(86)	6(6)	1(1)	-	2(2)	94(95)
2018	+(%)	7(6)	-	-	-	1(1)	8(7)
	-(%)	83(71.5)	7(6.1)	-	12(10.3)	6(5.1)	108(93)
2019	+(%)	9(6)	1(0.6)	-	5(3.3)	-	15(10)
	-(%)	124(81)	3(2)	2(1)	6(4)	3(2)	138(90)
2020	+(%)	-	-	-	-	-	-
	-(%)	29(78.4)	4(11)	-	2(5)	2(5)	37(100)
Total		408(85.7)	22(4.6)	4(1)	28(6)	14(3)	476(100)
p-value <0.0002							

N=number of samples, %=percentage

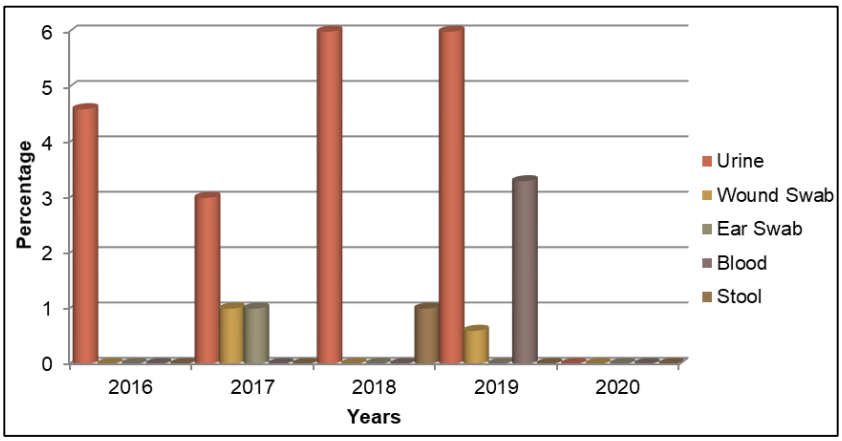

Fig 2: Distribution of *Enterobacter* spp. in different clinical sample

Incidence of *Enterobacter spp*. among age

From 2016 to 2020 More than 31 became the major the major source of infection it means 18/32(56.25%). in 2016 was seen under 18 years of age means minor(law) it means 2/4(50%), in 2017 like 2016 it was seen under 18 years means minor(law) ages having 3/5(60%). Also in 2018 it was seen mostly in more than 31 it (31 or elderly) means 6/8(75%) and lastly in 2019 like 2018 it was seen in more than 31 (31 or older than 31) it means 9/15(60%). In 2020 we had not any ages that infected by *Enterobacter spp*. Statistical analysis showed that significant correlation between bacteria and age (P < 0.05) as in Table (4) and Figure (3).

Table (4): Incidence of *Enterobacter spp*. among ages

Years	Under 18 No. (%)	19-30 No. (%)	31≤ No. (%)	Total
2016	2(50)	1(25)	1(25)	4(100)
2017	3(60)	-	2(40)	5(100)
2018	-	2(25)	6(75)	8(100)
2019	4(27)	2(13)	9(60)	15(100)
2020	-	-	-	-
Total	9(28)	5(15.6)	18(56.25)	32(100)
p-value <0.0002				

No.=number of positive, %=percentage

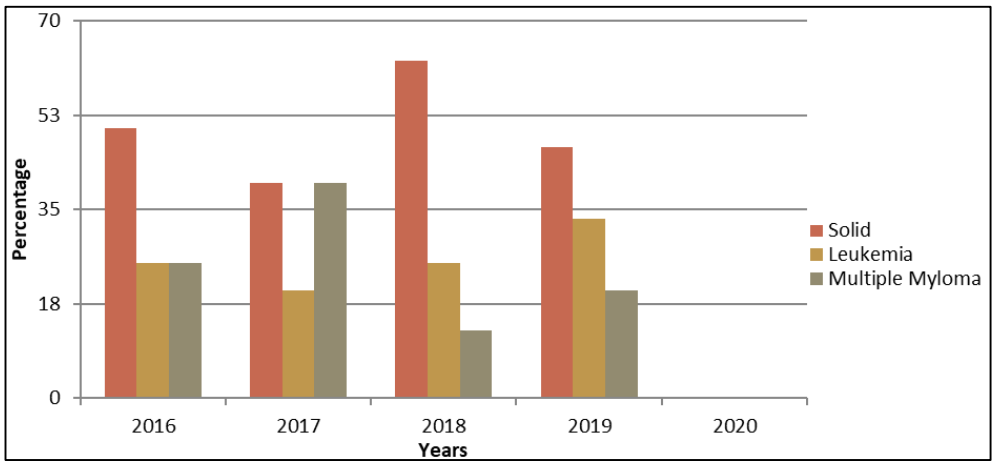

Fig 3: Incidence of *Enterobacter spp*. among ages

Types of cancer among *Enterobacter spp*. in infected patients

In 2016 *Enterobacter spp*. was present mostly in patients with solid means 2/4(50%), Leukemia and Multiple myeloma 1/4(25%) for each. In 2017 *Enterobacter spp*. was present mostly in patients with Multiple myeloma and solid which multiple myeloma 2/5(40%) for each and leukemia become second. In 2018 5 were Solid means (62.5%) and in Leukemia 2(25%) and lastly in Multiple myeloma become the least 1(12.5%). Lastly in 2019 *Enterobacter spp*. occurred the mostly in patients with Solid 7/15(46.6%) and in Leukemia become second and Multiple myeloma become the least. In 2020 There are not any Infection occur in cancer patients. Statistical analysis showed that significant correlation between types of cancer and *Enterobacter spp*. (P < 0.05) as in Table (5).

Table 5: Types of cancer among *Enterobacter spp*.in infected patients

Types	Solid	Leukemia	Multiple Myeloma	Total
	No (%)	No (%)	No (%)	No (%)
2016	2(50)	1(25)	1(25)	4(100)
2017	2(40)	1(20)	2(40)	5(100)
2018	5(62.5)	2(25)	1(12.5)	8(100)
2019	7(46.6)	5(33.3)	3(20)	15(100)
2020	-	-	-	-
Total No (%)	16(50)	9(28)	7(22)	32(100)
p-value <0.0002				

Multi-resistance antibiotics among *Enterobacter spp* (2016-2019)

In 2019 out of 153 samples 15 were positive and antibiotic susceptibility test performed on all isolated bacteria and resulted show that Bacteria got resistance to most of antibiotic in 2019 more than 50% resistance to more than 7 antibiotics and all isolates resistance against Norfloxacin or Vancomycin as show in Table 3-6 and table 7 it means resistance nearly to more than 50% of trhe isolates resistance against 11 antibiotics.

Table 6: Multi-resistance antibiotics among *Enterobacter spp*. in 2019

Antibiotics	No.(percentage)(N total=15)
Ceftazidime	2(13.4)
Amoxicillin / Clavulanic acid	2(13.4)
Oxacillin	6(40)
Trimethoprim	9(60)
Erythromycin	11(73)
Vancomycin	15(100)
Cephalothin	12(80)
Imipenem	-
Levofloxacin	1(6.66)
Chloramphenicol	12(80)
Ticarcillin/clavunic acid	1(6.66)
Ciprofloxacin	7(46.6)
Cefoxitin	13(86.6)
Cehalexin	2(13.4)
Ertapenem	7(46.6)
Cefepime	14(93.3)
Piperacillin	11(73)
Norfloxacin	15(100)
Amikicin	-

R=resistance, I=intermediate, S=sensitivity, N=number of patients, %=percentage

Table 7: Number and percentage of antimicrobials susceptibility tests among *Enterobacter spp*

	2016(N=4)			2017(N=5)			2018(N=8)			2019(N=15)		
Antibiotics	**R N (%)**	**I N (%)**	**S N (%)**	**R N (%)**	**I N (%)**	**S N (%)**	**R N (%)**	**I N (%)**	**S N (%)**	**R N (%)**	**I N (%)**	**S N(%)**
Ceftazidime	2(50)	1(25)	1(25)	2(40)	-	3(60)	4(50)	2(25)	2(25)	2(13.4)	6(40)	7(46.66)
Amoxicillin / Clavulanic acid	3(75)	1(25)	-	3(60)	2(40)	-	6(75)	2(25)	-	2(13.4)	3(20)	10(66.6)
Oxacillin	1(25)	2(50)	1(25)	3(60)	-	2(40)	1(12.5)	1(12.5)	6(75)	6(40)	2(13.4)	7(46.6)
Trimethoprim	2(50)	-	2(50)	4(80)	-	1(20)	8(100)	-	-	9(60)	1(6.66)	5(33.4)
Erythromycin	2(50)	-	2(50)	5(100)	-	-	5(62.5	-	3(37.5)	11(73)	4(26.6)	-
Vancomycin	3(75)	-	1(25)	3(60)	2(40)	-	8(100)	-	-	15(100)	-	-
Cephalothin	2(50)	1(25)	1(25)	2(40)	2(40)	1(20)	3(37.5)	2(257	3(37.5)	12(80)	2(13.4)	1(6.66)
Imipenem	-	2(50)	2(50)	-	3(60)	2(40)	2(25)	-	6(75)	-	2(13.4)	13(86.6)
Levofloxacin	-	-	4(100)	-	4(80)	1(20)	1(12.5)	1(12.5)	6(75)	1(6.66)	-	14(93.3)
Chloramphenicol	3(75)	-	1(25)	-	5(100)	-	8(100)	-	-	12(80)	-	3(20)
Ticarcillin/clavumic acid	4(100)	-	-	4(80)	1(20)	-	6(75)	-	2(25)	1(6.66)	-	14(93.3
Ciprofloxacin	3(75)	1(25)	-	3(60)	-	2(40)	1(12.5)	3(37.5)	4(50)	7(46.6)	4(26.6)	4(26.6)
Cefoxitin	1(25)	1(25)	2(50)	3(60)	2(40)	-	1(12.5)	4(50)	3(37.5)	13(86.6)	2(13.4)	-
Cephalexin	-	-	4(100)	1(20)	1(20)	3(60)	-	2(25)	6(75)	2(13.4)	-	13(86.6)
Ertapenem	-	3(75)	1(25)	-	-	45(100)	1(12.5)	2(25)	562.5)	7(46.6)	-	8(53.4)
Cefepime	1(25)	2(50)	1(25)	-	3(60)	2(40)	2(25)	-	6(75)	14(93.3)	1(6.66)	-
Piperacillin	4(100)	-	-	2(40)	2(40)	1(20)	4(50)	-	4(50)	11(73)	2(13.4)	2(13.4)
Norfloxacin	3(75)	1(25)	-	3(60)	-	2(40)	-	3(37.5)	562.5)	15(100)	-	-
Amikicin	4(100)	-	-	-	3(60)	2(40)	-	1(12.5)	7(87.5)	-	3(20)	12(80)

Discussion

Incidence of *Enterobacter spp*. isolates in cancer patient.

Many studies have been performed to determine the interaction between bacteria and cancer. However, there has been no attempts to demonstrate a possible relationship between *Enterobacter spp*. and cancer. Therefore, in the present study, it was aimed to investigate the effects of *Enterobacter* group of microorganisms on cancer. Determination of the interaction between strains of *Enterobacter spp*. and cancer will lead to new approaches to cancer initiation and mechanism. Identification of a possible interaction between colon cancer and strains of *Enterobacter spp*. may also be for development of pro-phylaxis and new treatment strategies. Studies also showed that, similar to tumor promoters, bacterial toxins can interfere with the regulation of cell growth or induction of inflammation Proliferation, apoptosis, and differentiation processes are affected by those toxins. Some of those, directly damage

Deoxyribonucleic acid (DNA) by enzymatic attack, these are the toxins that mimic carcinogens and tumor promoters. Bacterial products can also affect DNA repair mechanisms (Yurdakul *et al*., 2015) **[67]**.

A total of (476) samples were collected from five sources (urine, blood, wound swab, stool, ear swab) from hospitalized patient with cancer (Acute myeloid leukemia, Chronic myeloid leukemia, Acute lymphocytic leukemia, Chronic lymphocytic leukemia, Breast cancer, prostate cancer) in Nanakali hospital in Erbil city from January 2016-November 2020.After collection all bacterial isolates were subjected to a series of confirming tests. *Enterobacter spp*. are gram-negative bacteria that are classified as facultative anaerobes, which means that they can thrive in both aerobic and anaerobic environments. Many species possess flagella and thus are motile. Features such as motility, as well as certain biochemical properties, including the ability to synthesize an enzyme known as ornithine decarboxylase, are used to distinguish *Enterobacter spp.* from the very similar and closely related *Klebsiella* bacteria. *Enterobacter spp*. are named for the organisms' predominant natural habitat, the intestines of animals (Rogers, 2020) [52].

Our 2016 results 4/71(5.6%) isolates of *Enterobacter spp.* was less than results recorded by (Nadir *et al*, 2016) [46] that was from 186 Enterobacteriaceae isolates only (28.2%) positive *Enterobacter spp.* detected in 2 teaching hospitals in Dakar, Senegal. In 2017 our result 5/99(5%) were less than data recorded by (Ghonaim and Elgohay, 2017) [21] which were 3/32(9.37%) *E.clocae* at faculty of medicine, Zagazig University, Egypt.In 2018 we had only 8/116(7%) isolates of *Enterobacter spp*. Which was more compared to (Kamel *et al*., 2018) [31] which out of 171 total samples 5(2.9%) were positive at children cancer hospital, Cairo university, Cairo, Egypt. In 2019 we had only 15/153 (9.8%) isolates of *Enterobacter* which was less to (Jawad, 2019) study, which out of 60 total samples 12(20%) were positive at university of kufa in Iraq.

Relation between *Enterobacter spp.* and gender

The percentage of females infected with *Enterobacter spp*. were more than the males, females being 20/439(5%) and males being 12/439(2.7%) from 2016 to 2019, statistical analysis showed that highly significant correlation (P < 0.0002) between bacteria and gender from cancer patients as in Table (3-2). Our results agreed with that reported by (Gebremichael *et al*., 2020) [20] who founded that females infected with *Enterobacter spp*.were more than males but was higher than ours, a total of 11 patients infected with *Enterobacter spp*. 8(5.7%) were females and 3(1.5%) were males isolated from clinical specimens at International Clinical Laboratories, Addis Ababa University, Addis Ababa, Ethiopia. Also, in the same year in the university of Gondar in Gondar, Ethiopia there were out of 120 cancer patients only 50(41.7%) were males and the remaining were females 70(58.3%) conducted by (Tigabu *et al*., 2020) **[63]**. But disagreed with results reported by (Kim *et al*., 2014) **[33]** in which from 203 episodes of *Enterobacter* spp. More than half of the study patients were male (113/203) 55.7% and the remaining patients were females (90/203) 44.3%, conducted from The Korean Association of Internal Medicine.

Distribution of *Enterobacter spp. a*ccording to source of infection

The *Enterobacter spp.* are known to cause a number of infections including urinary tract infections (UTIs), central nervous system (CNS) infection, endocarditis, lower respiratory tract infections, bacteremia, skin and soft tissue infection, intra-abdominal infection, ophthalmic infection, septic- arthritis and osteomyelitis (Fraser, 2019) [19].

Statistical analysis showed that highly significant correlation (p <0.0002) between the bacteria and clinical samples from cancer patient as in Table (3-3). This shows that from 2016-2020 patient with *Enterobacter spp.* had urinary tract infections followed by wound and otitis media infection then BSI. Urinary tract infection is the most common in our investigation study which is 23/439(5.2%) followed by wound infection 2/439(0.4%) and ear infection and Gastrointestinal infection 1/439(0.2%), blood stream infection 5/439(1.1%) between different clinical sample as showed in (Table 3-3). That disagrees with the results reported by (Eldomany and Abdelaziz, 2011) **[17]** in which BSI is the most infection caused by *Enterobacter spp*. in cancer patients being 9/343(2.6%) followed by Wound infection having 3/343(0.8%) and UTI 2/343(0.5%) which was conducted in the National cancer institute (Cairo, Egypt) but disagrees with the results reported by (Ashour *et al*., 2009) [4] in which BSI 5/772(0.6%) was the most infection caused by *Enterobacter spp*. in patients followed by Urinary tract infection 4/772(0.5%) and Wound infection 17/772(2.2%) and BSI 5/772(0.6%) in hospitalized cancer patients (Cairo, Egypt).

Urinary tract infection in our study caused by *Enterobacter spp*. (86%) was higher than results done by (Ashour *et al*., 2009) [4] in which Urinary tract infection caused by *E. coli* 37(37.8%) and *Enterobacter spp.* was 4(0.5%), and higher than the results records by (Zorgani *et al*., 2012) [68] in which UTI in *Enterobacter cloacae* was 3.0% (n=6) out of 196 total samples in central hospital in Libya.

In our study, it shows that UTI is the most type of infection caused by *Enterobacter spp*. and this may be to the fact that after 2016 there was a rise in using indwelling urinary catheter among the population. The Urinary tract infection (UTI) is the most common hospital acquired infection. The major associated cause is indwelling urinary catheters. Currently there are many types of catheters available. complications in long-term catheterized patients, over years, cause is bladder cancer (Schumm *et al*., 2008) [58].

Incidence of *Enterobacter spp*. among ages

This shows that after 2016 infections by *Enterobacter spp*. was increased in 31 years old and older being 18/32(56.25%) in total and 9/32(28.1%) under 18 years old and 5/32(15.6%) were between 19-30 years old, and agreed with results recorded by (Tigabu *et al*.,2020) [63] in total of 120 cancer patients infected with *Enterobacter aerogenes* 17(14.2%) under 20 years old and 15(12.5%) were between 21-30 and 31 years old and older being 88(73.3%) conducted at school of Biomedical and laboratory Sciences, University of Gondar, Gondar, Ethiopia.

Monitoring cancer occurrence in young adults, often under 50 years, is informative because it often reflects relatively recent changes in exposure to carcinogenic factors. Worldwide, younger generations face a greater and longer-lasting exposure to excess adiposity than previous generations have faced. Numerous cancers are related to excess body weight, and evidence from laboratory studies of murine models indicates that obesity and an obesogenic diet accelerate the transition from normal tissue to invasive

malignancy and metastatic disease. So, rise in the cancer 31 years old and older may be due to obesity and smoking (Sung *et al*., 2019) [60].

Types of cancer among *Enterobacter spp*. in infected patients.

From 2016-2019 the total of *Enterobacter spp* infected patients with solid tumor type was16/32(50%) and leukemia 9/32(28.1%) and multiple myeloma having 7/32(21.8%) this rise in solid type tumor is due to high number of female infected with Breast cancer and prostate cancer for males which were more predominant at 2019 than both leukemia and multiple myeloma, our result agrees with the results recorded by (kim *et al*., 2014) [33] in which in total 255 patients with the solid type 21(8.2%) and Hematological malignancies having 11(4.3%). Also disagrees with results recorded by (Ashour *et al*., 2009) [4] which showed that *Enterobacter spp*. Was found in patients with leukemia having 63/772(8.1%) and with the solid type having 26/772(3.3%).

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 (Rolston and Bodey, 2020; Safdar and Armstrong, 2001) [55]. Most infections in cancer patients are nosocomial in nature because of their prolonged and frequent contact with hospital environment (Kurtaran *et al*., 2010) [36]. In many institutions in developed countries, more Gram-positive bacteria, mainly staphylococci, than Gram-negative bacteria are isolated from cancer patients (Morris *et al*., 2008; Rolston *et al*., 2006; Safdar *et al*., 2006) [45, 53, 56]. 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 (Klastersky and Aoun, 2004) **[34]**.

Distribution of multi resistance drug among *Enterobacter spp* isolates.

The rise of antimicrobial resistance has become a major concern worldwide in recent years, and cancer patients are among those affected by it. Treatment of multidrug-resistant infections (MDR) Bacteria pose a clinical challenge, especially in the case of Gram-negative bacilli, as the treatment options are often very limited (Gudiol and carratala, 2014) [23]. Gram-negative bacilli infections are normal in patients with cancer during intensive therapy. In recent years the incidence of antibiotic resistance against gram-negative bacilli has increased markedly (Eldomany and Abdelaziz, 2011) [17].

Multi resistance drug among *Enterobacter spp*. in 2019 out of 153 samples 15 were positive and antibiotic susceptibility test performed on all isolated bacteria and resulted show that Bacteria drive resistance to most of antibiotic they had resistance to 11 antibiotics. study done by (Eldomany and Abdelaziz, 2011) [17] who recorded that out of 343 isolates (95.8%) were found to be resistance to antibiotics, with the study done by (Ashour *et al*., 2009) [4] who recorded that 64% of *Enterobacter spp*. are resistance to antibiotics. On the other hand, the most effective antibiotics were (Imipenem, Amikicin, Levofloxacin, Ticarcillin/clavulanic acid, Ceftazidime, Amoxicillin, Cephalexin) showing sensitivity to more than (85%) to these 8 antibiotics as seen in Table (7).

Treatment of *Enterobacter spp*. infection is complicated due to its intrinsic resistance to cephalosporins. Recent use of a third-generation cephalosporin, older age, tumor progression at last evaluation, recent surgery, and nosocomial acquisition were associated with ESC-resistance Enterobacter bacteremia (Huh *et al*., 2014, Ali *et al*., 2020) [26]. Bacterial infection is one of the most frequent complications in cancer patients and hematopoietic stem cell transplant recipients. In recent years, the emergence of antimicrobial resistance has become a significant problem worldwide, and cancer patients are among those affected (Gudiol and Carratala, 2014, Bakir and Ali, 2016, Ali *et al*., 2022) [23, 8]. These pathogens are frequently associated with a multidrug resistance (MDR) phenotype, mainly due to their adaptation to the hospital environment and their ability to easily acquire numerous genetic mobile elements containing resistance and virulence genes. These species have an intrinsic resistance to ampicillin, amoxicillin, first-generation cephalosporins, and cefoxitin due to the expression of a constitutive AmpC β-lactamase. Moreover, the production of extended-spectrum β-lactamases has been reported in these bacteria, which make their treatment difficult (Davin-regil *et al*, 2019, Ali, *et al*, 2019, Ahmad and Ali, 2019) [15].

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