بسم الله الرحمن الرحيم

Sudan University for Science & Technology

College of Graduate studies

Isolation, Identification and A ntimicrobial Sensitivity of Common Bacteria in Different Clinical Specimens from Cancer Patients under Chemotherapy in Shendi City-Sudan.

عزل وتحديد البكتيريا الشائعة واختبار مقاومة المضادات الحيوية في العينات السريرية المختلفة من مرضى السرطان الخاضعين للعلاج الكيميائي في شندي- السودان

A Theies Submitted for Partial Fulfillment of the Requirement for M.S.C. Degree inMedical Laboratory Sciences (Microbiology).

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الاية

قالتعالى :

(وَلَقَدْ ءَاتَيْنَا دَاوُۥدَ وَسُلَيْمَٰنَ عِلْمًاۖ وَقَالَا ٱلْحَمْدُ لِلَّهِ ٱلَّذِى فَضَّلَنَا عَلَىٰ كَثِيرٍ مِّنْ عِبَادِهِ ٱلْمُؤْمِنِينَ)

صدق الله العظيم

سوره النمل الآية (15)

Dedication

I dedicatethis work to my loving father and mother whom affection, love, encouragement, and prays of day and night make me able to get such success and honour.

Acknowledgement

First of all we praise and thank Allah. I wished to thanks the faculty of MLS. I'm also graduate to all the staff at the department for provision of experiences and technical supported. In particular, I'm grateful to my supervisor DR. Nasr Mohamed for skillful guidance, enthusiasm and never-ending patience and supported.

Abstract

Patients with cancer are highly susceptible to almost any type of bacterial infection. This cross sectional descriptive study(February to May 2022) was aimed to isolate common bacteria in patients under chemotherapeutic drug. Isolation of bacteria and their antibiotic sensitivity were made by cyctine lactose electerolyte deficient agar (CLED) , biochemical media, muller Hinton agar and single disk of antibiotic. Out of 100 samples(urine ,swab) that collected from patients under chemotherapeutic drug were found 10 types of bacteria. Of 70 urine sample 46(65.7%) show growth, while 24(34.3%) show no growth and 30 swabs samples, 23(76.7%) show growth while 7(23.3%) show no growth, the distribution of isolated organism were *klebsiellappneumoniae*(*Kpneumonia)*15(32.6%),*Escherichiacoli(E.coli)*9 (19.6%), *proteus mirabilis(P.mirabilis)*7(15.2%), *proteus vulgaris(P.vulgaris)* 6(13%), *Staphylococcus.aureus* (*S.aureus*) 7(15.2%) and *citrobacterfreundii (C.freundii*)2(4.3%)*pseudomonas.aeurginosa(Ps aeurginosa).* 3 (13%), *Streptococcus pyogens* (*S.pyogens)* 2 (8.7%), *Enterococcus faecalis* (*E faecalis)*3(13%), *Streptococcus. pneumoniae* 1 (0.1%). Total of 69 sample show growth in males constitutes 30(43.5%) while female constitutes 39(56.5%), there was statically significant association between gender and bacterial growth (P value 0.05), and no statically significant association between age and bacterial growth (P value 0.09). The most sensitive antibiotic areimpenem and ciprofloxacin and resistant are ciftazidimcefexime and ceftriaxone.

المستخلص

المرضى المصابون بالسرطان معرضون بشدة لأي نوع من أنواع العدوى البكتيرية. هدفت هذه الدراسة الوصفية المقطعية (من فبراير إلى مايو 2022) إلى عزل البكتيريا الشائعة في المرضى الذين يخضعون للعلاج الكيميائي. تم عزل البكتيريا وحساسيتها للمضادات الحيوية بواسطة أجار السيكتين اللاكتوز الناقص بالكهرباء (CLED) ، والوسائط البيوكيميائية ، وأجار مولر هينتون ، وقرص واحد من المضادات الحيوية. تم العثور على 10 أنواع من البكتيريا من بين 100 عينة (بول ، مسحة) تم جمعها من المرضى تحت العلاج الكيميائي. من 70 عينة بول أظهرت 46 (65.7٪) نموًا ، بينما أظهرت 24 (34.3٪) عدم نمو و 30 عينة مسحة ، 23 (76.7٪) أظهرت نموًا بينما أظهرت 7 (23.3٪) عدم نمو ، وكان توزيع الكائن الحي المعزول klebsiellap الرئوية (الالتهاب الرئوي K) 15 (32.6٪) ، الإشريكية القولونية (E.coli) 9 (19.6٪) ، البروتينات الرائعة (P. mirabilis) 7 (15.2٪) ، البروتيوس الشائع (P. citrobacter freundii) و (C suerua.succocolyhpatS (suerua.S) 7 (15.2٪) iidnuerf) 2 (4.3٪) Ps aeurginosa (pseudomonas.aeurginosa). 3 (13٪) ، Enterococcus faecalis (E ، (8.7٪) 2 (snegoyp.S) snegoyp succocotpertS (silaceaf) 3 (13٪) ، العقدية. الرئوية 1 (0.1٪). إجمالي 69 عينة أظهرت نمو الذكور 30 (43.5٪) بينما شكلت الإناث 39 (56.5٪) ، كان هناك ارتباط ذو دلالة إحصائية بين الجنس والنمو البكتيري (قيمة P 0.05) ، ولا يوجد ارتباط ذو دلالة إحصائية بين العمر ونمو البكتيريا (قيمة P 0.09). أكثر المضادات الحيوية حساسية هي الإيمبينيم والسيبروفلوكساسين والمقاومة هي سيفتازيديم سيفكسيم وسيفترياكسون.

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List of abbreviations

AMR	Anti microbial resistant
BSI	Blood stream infection
CLED	Cystine Lactose Electrolyte Deficient
E.coli	: Escherichia coli
GNB	: Gram negative bacteria
GPB	: Gram positive bacteria
MATE	: Multi drug and toxic extrusion
MBL	: Metallo beta lactamase
MDR	: Multi drug resistant
NaCl	: Sodium chloride
PBP	: Penicillin binding protein
PDR	: Pan drug resistant
PSMR	: Paired small multi drug resistant
PSMR	: Paired small multi drug resistant
RBCs	: Red blood cells
TTCRC	: Tumor therapy and cancer research
UTI	: Urinary tract infection
WBCs	: White blood cells

CHAPTER I

INTRODUTION

Chapter I

1.Introduction

1.1 Background

Major advances in the care of cancer patients over the past several decades have led to significant improvement in patient survival. Despite these advances, cancer patients are prone to serious infection complications with substantial morbidity and mortality. In this patient population, infection risk results from a complex interplay between the host's underlying immunodeficiency and the nature of treatment practices they experience (like surgery, radiation therapy, chemotherapy), prophylaxis use, and application of invasive procedures (central venous catheter and urinary catheter)(Dominique, 2015). The symptoms of infection in cancer patients could be masked by the cancer treatment modalities, that is an indicator for considering asymptomatic infections(Kate *et al*, 2010).

Factor that are associated with elevated risk of cancer are tobacoo use (22%of cancer deaths), lack of physical activity ,alcohol use ,low vegetable and fruit intake,and high body mass index. These factor are thought to be reseponsible for approximately one third of cancer deaths, Breast, cervical, and colorected, lung, thyroid, and colorectal cancers are the most common types of cancer in woman while prostate, lung, colorectal, liver and stomach cancer are most common among men. Despesitethe fact that there are several different methods of cancer treatments including radiation theraby, surgery, immunotherapy, endocrine therapy, and gene therapy,chemotherapy still remain the most common method of cancer healing.(Bukowaski and kontek ,2020).

Therefore, patients with both type of cancer(solid and fluid) are highly susceptible to almost any type of bacterial infection. Among Gram positive bacteria (GPB) genus Staphylococcus and from Gram negative bacteria (GNB): *Escherichia coli*, *Klebsiellapneumoniae*, and *Pseudomonas aeruginosa* are frequently associated(Mims *etal*, 2005). Moreover, frequent prescription of broad-spectrum antibiotics as prophylaxis among cancer patients may potentially alter the composition of endogenous flora and select multidrug resistant pathogens. As a result, empirical

antibiotic treatments of cancer patients are continually challenged by the change in frequency of Gram-positive and Gram-negative bacteria and the emergence of new antimicrobial resistant pathogens(Forbes *et al*, 2002).

Multidrug resistance (MDR) in tumor cells is a significantobstacle to the success of chemotherapy inmany cancers. Multidrug resistance is a phenomenon whereby tumorcells in vitro that have been exposed toone cytotoxic agent develop cross-resistance to a rangeof structurally and functionally unrelated compounds.The drug resistance that develops in cancer cells oftenresults from elevated expression of particular proteins,such as cell-membrane transporters,which can result in an increased efflux of the cytotoxic drugs from the cancercells, thus lowering their intracellular concentrations.1,2 In addition, MDR occurs intrinsically in somecancers without previous exposure to chemotherapyagents.3 The cytotoxic drugs that are most frequentlyassociated with MDR are hydrophobic, amphipathicnatural products, such as the taxanes (paclitaxel,docetaxel), vinca alkaloids (vinorelbine, vincristine, vinblastine),anthracyclines(doxorubicin, daunorubicin,epirubicin), epipodophyllotoxins (etoposide, teniposide),topotecan, dactinomycin, andmitomycin C(Thomas *et al* 2003).

1.2 Rationale

Previous studies on bacterial infection and drug resistance pattern among cancer patients were mainly focused on bloodstream infection (BSI) with hematologic malignancies. However, cancer patients who have solid tumors might have a tendency to undergo surgery to remove the tumor or sometimes due to other medical reasons. This, thus, increases the potential of acquiring bacterial infection either by endogenously normal flora near the operative sites or exogenously from the hospital environments, such as in the air, hospital staff, inanimate objects, and medical equipment, as a result of their prolonged and frequent contact.

1.3 Objectives

1.3.1 General objective

To isolate and identify common bacteria in different clinical specimens from cancerpatient's under chemotherapy in shendi.

1.3.2 Specific objectives

- To determine the frequency of bacteria isolated from patient under chemotherapeutic drugs.
- To isolate and identify bacterial species from cancer patients with conventional methods.
- To detect the drug sensitivity and resistant of each bacteria isolated by using single disk diffusion method.
- To detect association between isolated bacterial species and patients according to gender and age.

CHAPTER II
LITERATURE REVIEW

Chapter II

2.0 Literature review

2.1 Background on chemotherapy

Chemotherapy treatment can be used for the following intents: curing, prolonging survival, or palliation, Cancer treatment depends on the type and stage of cancer along with patient characteristics (Kate *et al*, 2010).

2.1.1 Principle of chemotherapy

Chemotherapy employs systemically administered drugs that directly damage cellular DNA (and RNA). It kills cells by promoting apoptosis and necrosis. There is narrow therapeutic window between effective treatment of the cancer and normal tissue toxicity, because the drugs are not cancer specific. The dose and schedule of the chemotherapy is limited by the normal tissue's tolerance, all tissues can be affected however, depending upon the pharmacokinetics of the drug and affinity for particular tissues. The therapeutic effect on the cancer is achieved by a variety of mechanisms which seek to exploit differences between normal and transformed cells. Toxicity to the normal tissue can be limited in some instances by supplying growth factors or by the infusion of stem cell preparations to diminish myelotoxicity (Kumar and Clark, 2003).

2.1.3 Side-effect of chemotherapy

Although chemotherapy kills cancer cells, it can damage normal cells and cause significant side effects, the side effect varies depending on the particular drug, dosage, route of administration and patient characteristics (Kate *et al*, 2010).

2.1.3.1 Damage and irritation on cells lining the digestive tract This may cause Nausea, vomiting or diarrhea. The severity of Vomiting side-effect varies with the cytotoxic and can be eliminated in 75% of 11 patient by using modern antiemetic (Kumar and Clark, 2003; Kate *et al*, 2010).

2.1.3.2 Hair loss:

Many but not all cytotoxic drugs are capable of causing it. Scalp cooling can some time use to reduce it (Kumar and Clark, 2003).

2.1.3.3 Bone marrow suppression and immunosuppression

Suppression of the production of red blood cells, white blood cells and platelets occur with the most cytotoxic drug and dose related phenomenon, Anaemia and thrombocytopenia are managed by red cell or platelet transfusions but the WBCs have not been successful until the advent of peripheral blood stem cell harvesting (Kumar and Clark, 2003).

Neutropenic patients are at high risk of bacterial and fungal infection often from enteric flora; this managed by immediately introduction of broad-spectrum antibiotics intravenously (Kumar and Clark, 2003).

2.1.4 The problem that related with receiving chemotherapy in cancer patient

The treatment of the malignant diseases requires the use of combination chemotherapy in multiple cycles administered to achieve adequate tumor cell kill without life threatening toxicity or the development of tumor cell resistance. The dose of drug needed to achieve adequate tumor cell kill often causes toxicity to normal tissues. Infection is the major cause of morbidity and mortality in patients undergoing antineoplastic chemotherapy (Tanchev*a et al*, 2009). These include defects in humoral and cell mediated immunity mucosal damage resulting from chemotherapy and impairment of central nervous system reflexes, and The most common sites of infection in neutropenic patients include the lung, oropharynx, blood, urinary tract, skin, and soft tissues, including the perirectal area. Several of the cancers chemotherapeutics drugs are used today as immunosuppressant for the treatment of severe systemic autoimmune diseases. (Laurence *et al*, 2008).

2.2 Example of complication in cancer patients receive chemotherapy

patients with colon and rectum cancer who were candidates for chemotherapy with FU-5 or capacitabine-based bases, they were followed up and treated continuously during the study, a group of complications of treatment were prospectively tracked and recorded.In this study, after 468 chemotherapy and complication registrations during the first 6 periods, and 55 cases of grade 3 and 4 complications, in total 11.6% of the patients had significant complications.In sum, the most complicated complications were neutropenia (5.3%) among all regimens, followed by

complications of GI including nausea and diarrhea (1.5% and 1.3% respectively) (33) (Madmoli and Mostafa 2018).

2.2 Enterobacter Species:

Enterobacter species are gram negative rode and have many features in common with those of genus klebsiella but readily distinguished by their motility a although non motile variant occurs occasionally, several species are recognized. Enterobacter erogenous and Enterobacterceloacae are the most important (Greenwood *et al.,* 2007). Normal habitat of Enterobacter species is probably soil and water but organisms occasionally found in human faces and respiratory tract. Enterobacter are much less important cause of hospital infection than klebsiella species, most infections of the urinary tract although member of the genes are important cause of bacteraemia (Greenwood *et al.,* 2007).

2.3 *Escherichia coli*:

Escherichiacoli is most common cause of acute uncomplicated urinary tract infection outside hospital as well as causing hospital associated urinary tract infection (Greenwood *et al*.,2007). Strains that cause urinary tract infection often originate from the gut of the patient with infection occurring in ascending manner, the ability of Escherichia coli may be associated with fimbriae that specifically mediated adherence to uroepithelial cells (Greenwood *et al.,* 2007). The most of urinary tract infections are thought to be caused by organisms originating from the patient's own faecal flora, however prevalence of varies serotypes of *Escherichiacoli* in urinary tract infection varies with geographical location (Greenwood *et al*.,2007).

2.4*Klebsiella*species:

The taxonomic status of *klebsiella* species is ill defined there is no general agreement of the species composition of the genus also differentiation within the species is difficult as many of the biochemical reactions are indeterminate the main feature of these bacteria that they are capsulated non motile and vogesproscauer (v-p) is positive (Balows*et al*.,1991). Greenwood et al.,2007 Divided klebsiella to four sub species all of which belong to one species and so the genus klebsiella contain the species *pneumoniae,* sub species *aeruginosa, ozaena, pneumoniae* and rhinocerotic (cheesbrough.,2000) defined *klebsiellapneumoniae* as V-P variable, indole negative, H2S negative, lactose fermented and citrate positive.

2.5 *proteus* species:

2.5.1 *proteus* morphology:

In general, these bacteria appear as straight or slightly curved rods 1-2.5 μm in length, pairs and short chains, ovoid forms are common, hoe ever long curved filamentous in actively swarming culture (Free man., 1979).

Proteus is actively motile by peritrichous flagella and from neither capsule nor spore (free man., 1979). These bacilli stain readily with the usual aniline dyes and are gram negative (freeman., 1970).

2.6 *Pseudomonas* species:

2.6.1 Morphology and structure:

Pseudomonas species are Gram negative rod, it is general slimmer and more pale staining than members of Enterobacteriaceaeit's length is 0.5-2.5 μm polar flagellum (Sherris*et al.*,1984).

2.7 *Staphylococci*:

The name of staphylococci is now used as the genus name for a group facultative anaerobic, catalase positive, Gram-positive cocci (Greenwood *et al*., 2007). They are resistant to dry conditions, and are well suited to their ecological niche, which is the skin (Greenwood *et al*., 2007). The coccus forms tend to be much more uniform in size than others morphological types of bacteria, and the staphylococci are consistently slightly less than 1μm in diameter they tend to be in grape like clusters (Freeman., 1979). Growth on agar mediums is abundant and the colonies are opaque, smooth and glistening in appearance (freeman., 1979). Some staphylococci form carotenoid pigments (Hammand and White., 1970) which give the golden yellow or lemon-yellow color, while other don't and are white (Freeman., 1979). The staphylococci are facultative anaerobes, although growth is best under aerobic conditions (Freeman., 1979). The optimum temperature for growth is 35o-37o C they are not highly fastidious in their nutrition requirement and grow readily on the usual meat extract – peptone mediums (Freeman., 1979).

Staphylococci are strongly Gram positive, do not form spores, non-motile, and few strains are known to form capsule (Freeman.,1979). They are relatively more resistant to heat it require high temperature and long time to kill such as 80oC for 1hour they resistant to drying, may remain infectious for extend periods, and are able to grow in up to 15% NaCl (Greenwood *et al.,* 2007).

2.8 Bacterial Resistance:

2.8.1. Introduction:

Antimicrobial resistance (AMR) is defined as the resistance of microorganisms to an antimicrobial agent to which they were at first sensitive. This natural evolutionary phenomenon, enhanced by the misapplication of antimicrobial medicines and the global spread of AMR mainly affects unhealthy and debilitated patients, giving rise to superbugs. AMR inflicts high costs in the public health sectors of all countries, and many researchers are involved in searching for greater understanding of resistance and ways to mitigate it. A wide range of antibiotics have been faced with the threat of resistance in recent decades, and this resistance may be generated and transmitted in many different ways (Jindal et al., 2015). Through horizontal gene transfer, for example, mobile integrins carried on transposons permit pathogens to share resistance mechanisms. For organisms resistant to one antibiotic, the gaining of a transposon that transports several antibiotic resistance cassettes offers the organism resistance to numerous other antibiotics (Bradley, 2014). Another case of natural resistance is measured frequently by the incidence of natural mutations within chromosomally located genes that later are spread vertically as the bacteria replicate (Martinez &Baquero, 2000).

2.8.2 Mechanisms of Antibacterial Resistance:

There are many mechanisms of resistance in bacteria. Of these, five are the most frequently observed, showing high prevalence in clinical isolates. They are enzymatic inhibition, penicillin binding protein (PBP) modifications, porin mutations, efflux pumps, and target changes (Bhullar et al., 2012).

2.8.2.1 Enzymatic inhibition:

Resistance to beta-lactams in Enterobacteriaceae is mainly conferred by betalactamases. These enzymes inactivate beta-lactam antibiotics by hydrolysis. Two classifications of beta-lactamases are known, namely the Ambler and the Bush-Jacoby-Medeiros. The Ambler classes are based on the amino acid homology, where they are clustered in four molecular classes namely, A, B, C and D. Molecular classes A, C, and D include the beta-lactamases with serine at their active site, whereas molecular class B stands for metallo-beta-lactamase's (MBLs), enzymes with zinc molecule in the active-site. The Bush Jacoby-Medeiros classification grouped the beta-lactamases in three major groups and 16 subgroups. This classification is based on the substrates and inhibitors of the enzymes (Bush & Fisher, 2011).

2.8.2.1.1 AmpC type beta-lactamases:

AmpC beta-lactamases are mainly chromosomally encoded in Enteorbacteriaceae and they confer resistance to cephalothine, cefazoline, cefoxitin, most penicillins and to beta-lactamase inhibitor (clavulanic acid). ChromsomalAmpC enzymes are inducible and can be expressed at high levels by mutation in ampD leading to AmpChyperinducibility or constitutive hyper production (Schmidtke& Hanson, 2006).

Over expression confers resistance to extended-spectrum cephalosporins including cefotaxime, ceftazidime and ceftriaxone. AmpC enzymes located on transmissible plasmids are usually constitutively expressed and appear in bacteria lacking or poorly expressing a chromosomal AmpC gene, such as E. coli, K. pneumoniae, and P. mirabilis. AmpC enzymes encoded by both chromosomal and plasmid genes are capable to hydrolyze broad-spectrum cephalosporins more efficiently (Jacoby, 2002).

2.8.2.1.2 Extended spectrum beta-lactamases (ESBLs):

ESBLs are beta-lactamases capable of conferring bacterial resistance to the penicillins, early and extended-spectrum cephalosporins, and aztreonam (but not to cephamycin's or carbapenems) by hydrolysis of these antibiotics, and are inhibited by beta-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam (Bush & Fisher, 2011). The most common ESBLs are SHV-, TEM-, and CTX-M. Each of these enzymes derives from its own progenitor. Interestingly, SHVs are more prevalent in Europe; TEMs are dominantly present in the USA while the CTX-Ms are being increasingly detected worldwide (Paterson, 2005).

2.8.2.1.3. Carbapenems:

Carbapenems are beta-lactamases with a wide hydrolytic spectrum. These enzymes inactivate almost all hydrolysable beta-lactams including the carbapenems as a unique, additional substrate (Queenan& Bush, 2007). Carbapenems are among beta-lactamases from Ambler classe A, B and D .In class A, the dominant carbapenems is KPC (Klebsiella. Pneumoniacarbapenems) which was mainly detected on plasmids of K. pneumoniae (Yigit*et al*., 2001).

The IMI 21 (imipenem hydrolysing beta-lactamase), NMC (non-metallo-carbapenems) and SME (Serratiamarcescens enzyme) carbapenems belong also to Ambler class A and 2f in Bush-Jacoby-Medeiros classification. These enzymes are

chromosomal located in Enterobacterspp, and in S. marcescens while they are closely related to each other as IMI and NMC have 97% amino acid similarity and they are homolog 70% to SME (Rasmussen, *et al*., 1996). All the three enzymes have a broad hydrolysis spectrum that includes the penicillins, early cephalosporins, aztreonam, and carbapenems (Queenan& Bush, 2007).

2.8.2.2. PBP modification:

Penicillin binding proteins (PBPs) are important proteins involved in the construction of peptidoglycan, which is the major constituent of bacterial cell walls. These enzymes catalyse the glycan strand (trans glycosylation) and the cross-linking between glycan chains (transpeptidation) (Sauvage *et al*., 2008). However, some PBP classes did not have trans glycosylation activity, such as B PBPs and low molecular-mass PBPs (Sauvage*et al*., 2008). The transpeptidase active site is the target of β-lactam agents (Yoneyama& Katsumata, 2006). These compounds mimic the D-Ala-D-Ala dipeptide in peptidoglycan and form a very stable acygl-enzyme complex, leading to enzyme inactivation (Yoneyama& Katsumata, 2006). Among the different modified PBPs, some of them have high prevalence, including PBP4 and PBP5, which confer resistance to penicillins; and PBP2x and PBP1a, which are responsible for conferring variable resistance to penicillins and other β-lactams, both of chromosomal origin (Rossolini*et al*., 2010).

2.8.2.4. Efflux pumps:

A highly efficient mechanism of resistance is the production of an efflux pump, a proton-dependent system that effects an active removal of the antibiotic from inside the cell (Wright, 2011). There are five families of membrane-spanning efflux proteins, including major facilitators (MFs), small multidrug resistance (SMR), resistance nodulation division (RND), ATPbinding cassette (ABC), and multidrug and toxic compound extrusion (MATE) (Nishino & Yamaguchi, 2001). On the one hand, drug efflux from Gram positive bacteria is commonly mediated by a single cytoplasmic membrane-located transporter of the MF, SMR, or ABC families. On the other hand, Gram-negative bacteria are more complex due to the presence of an outer membrane (Stavri et al., 2007). The MF family consists of membrane transport proteins, with 12_14 Trans membrane domains (TMDs) (Morita *et al*., 1998). Implicated in the antiport, symport, or uniport of many substances. In MF and SMR family transporters,

the propulsion force for drug efflux appears to be an electrochemical potential of H1 over the cell membrane (Morita *et al*., 1998).

2.9 Previous studies:

Tanchevaet.al(2009) reported that treatment of the malignant diseases requires the use of combination chemotherapy in multiple cyclesadministered to achieve adequate tumor cell kill without life-threatening toxicity or the development of tumorcellresistance. As opposed to many other classes of drugs, the therapeutic plan for chemotherapeutic agents isvery narrow, The dose of drug needed to achieve adequate tumor cell kill often causes toxicity to normal tissues. Infection is themajor cause of morbidity and mortality in patientsundergoing antineoplastic chemotherapy. The mostimportant risk factor for infection in patientswithhematologic diseases is absolute neutropenia. On theothere hand, most common sites of infection in neutropenicpatients include the lung, oropharynx, blood, urinary tract skin, and soft tissues, including the perirectal area.Infections are generally caused by organismsalreadycolonizing the patient, although some of these organismsare acquired after admission to the hospital (Tanchev*a et.al,* 2009).

Among the total 540 analyzed patient,208(38.5%)developed a LUTI. *E. coli* was the main microorganism involved in LUTIs(102,49.04%)with 8 cases of acombination between *E. coli* and another germ.In conclusion, a risk of urinary infections in cancer patients treated with pelvicradiotherapy was observed ,in order to reduce the use of antibiotic resistance , preventive treatment with non-antibiotic agents 5 are warranted.*E. coli* 102(49%),*Enterococcusfaecalis*46(22.1%),*Proteus mirabilis* 10(4.8%),*Pseudomonas aeruginosa* 6(2.9%) (GiandomenicoRoviello2018) .

In total 195 patients were included. The postoperative wound infection was detected in 115 patients (59%). In average, the swabs were taken 8 days after the surgery. The similar bacterial species from all three sites were detected in 24 patients (12,3%). In comparison, we found that there was statistically significant difference in the bacteria abundance from all three sites (p=0,031). There were significantly more bacteria in the wounds of the neck than cannula (p=0,007) and in the wounds in the oral cavity than cannula (p=0,002). No statistically significant difference between the wound on the neck and in the oral cavity was found. The most frequently isolated bacterial family was *Enterobacteriaceae.* Other more commonly isolated bacteria species were

Staphylococcus spp. (G+), *Pseudomonas aeruginosa* (G- *Corynebacteruim* spp. (G +) and *Acinetobacterbaumanii* (G-).(MargitaBelusic-Gobic*et al*, 2020)

Total of fifty(n=50) urine specimens were aseptically collected fromchemotherapytic patients. Where then cultured on Cystine- Lactose Electrolyte Deficiency media (CLED) Agar, blood agar for growth of bacteria. The identification of isolated bacteria was done by colonial morphology, Gram stain and biochemical tests. The result revealed that 46% (23) out of 50 urine specimens were positive for bacterial growth and 54% (27) were negative. The bacteria isolated were *S. aureus*(26.1%), *E.coli*(21.7%), *S.epidermidis*(17.4%), *K. pneumoniae*(13%), *p. mirabilis* (13%) and *Ps. aeruginosa*(8.7%). It's concluded that *S. aureus*was the most common causative agent among chemotherapeutic patient.*(HajerAbdalmhmoud, 2014).*

out of 150 urine sample that collected from patients under chemotherapeutic drug were found five type of bacteria .the causative agents were identified of these groups under their distribution in age , sex , type of cancer and type of chemotherapy drug .identified bacteria included *E.coli*(37%) , *staphylococcus aureus*(30%) , *proteus vulgaris* (18%) , *proteus mirabilis* (9%).the infection is more prevalent in females the study confirmed *Escherichia coli* to be the major cause of UTI.*Mohammed Tag Eldin, 2016).*

Of totally 292 urine samples tested, eighteen (6.3%) were culture positive cases, *Escherichiacoli* (44.4%) was the highest proportion isolated uropathogen followed by *Klebsiellapneumoniae*(22.2%) and *Citrobacterdiversus*(16.7%). The antibiotic susceptibility resultsshowed meropenem and nitrofurantoin as the most effective antibiotics for *E. coli*, *K. pneumoniae,*and *Citrobacterdiversus*isolates. The rate of multidrug resistant (MDR) isolateswere33.3% (6/18), and meropenem and nitrofurantoin were the most effective antibioticagainst MDR isolates. The current research established P value <0.05 as an indicator of statical*significancewondewosenTseagyeSime et al 2020*

CHAPTER III

Materials and Methods

CHAPTER III

MATERIALS AND METHODS

3.1Methodology:

3.1.1 Study design:

Descriptive Cross- sectional laboratory-based study.

3.1.2 Study area:

This study was performed in the Tumors therapy and cancer research Center-Shendi.

3.1.3 Study population:

Patients with suspected urinary tract infection ,eye ,ear and wound infecations which were attending the tumors therapy.

3.1.3.1 Inclusion criteria:

Patient under chemotherapy treatment

3.1.3.2 Exclusion criteria:

People not under chemotherapy treatment or patients refuse to participate in study

3.1.4 Sample size and sampling tech :

The total of sample size was100.

3.1.5 Data collection tools:

The data was collected by using a questionnaire, was designed to include all needed information.

3.1.6 Ethical consideration:

Ethical clearance of the study was taken from the ethical committee of the Sudan of science and technology university, verbal constant was taken from patients.

3.2 laboratory examination:

3.2.1Collection of samples:

The patients were given a sterile, dry, wide-necked, leak proof container and requested for collection of Midstream urine (MSU) 10-20 ml specimen, a swab from eye, ear and wound were also taken in sterile containers.

3.2.2 Culture Media:

3.2.2.1Cystine lactose electrolyte deficient (CLED) agar:

medium Used for culturing of urine sample; because it gives consistent results, can differentiate between lactose fermenting from non

lactose fermenting bacteria (the indicator is bromothymol blue) (Cheesbrough, 2009).

3.2.2.2MacConkeyagar:is differential and low selectivity medium used to distinguish lactose fermenting from non lactose fermenting bacteria .bacteria which grow onMacConkey agar include member of entrobacteriaceae pseudomonas aeruginosa ,klebsiella pneumonia and Escherichia coli (Cheesbrough, 2009).

3.2.2.3 blood agar: is used to grow wide range pathogen particularly those that are more difficult to grow such as *H. influenza*.it also required to detect and differentiate haemolytic bacteria ,especially streptococcus species (Cheesbrough, 2009).

3.2.2.4 Mueller-Hinton agar:

Use for sensitivity test with pH 7.2-7.4 (Cheesbrough, 2009).

3.2.3 Gram stain:

A drop of normal saline was placed on slide. The suspected colonies were emulsified and smeared. The smears should be fixed by dry heat and then cover with crystal violet stain for 30-60 seconds. The stain rapidly washed by tap water and tipped the side. Stained smear then cover with lugoṡs iodine for 30-60 seconds. Iodine immediately washed off and the smear was decolorized with ethanol for few seconds. Suffranin was added to the smear for 2 minutes. The red stain then washed off with tap water and smear preparation subsequently air dried and microscopically examined using high resolution objective power (Cheesbrough, 2009).

3.2.3.1 Identification of Gram positive cocci.

3.2.3.1.1 Catalase test

The differentiation between staphylococci (which produce catalase) from streptococci (non catalase production) was made by catalase test. Catalase acts as catalyst in the breakdown of hydrogen peroxide to oxygen and water. Using sterile wooden stick, suspected colonies were immersed in tube containing 2ml of 3% hydrogen peroxide (Cheesbrough, 2009; Collee et al, 1996) A Positive result was indicated by production of air pubbling. A negative result indicated by no change in tube

3.2.3.1.2DNase test

Using sterile loop to inoculate the suspected colonies under a septic condition into DNA media, after overnight, aerobic incubation at 37◦c 17 hydrochloric acid (1% HCL) was to the spots of an organism. Clear zone around the colonies mean positive result (Cheesbrough, 2009).

3.2.3.1.3Mannitol salt agar (MSA)

It is a useful media for identifying staphylococci species, which are able to grow on agar containing 70-100 g/l sodium chloride. Some species of staphylococci are able to

ferment mannitol and other cannot ferment mannitol. The test done by inoculating the organism under test in MSA media which contain phenol red indicator, and then incubated the plate at 37c for 24 hours, and then change in color is observed (Cheesbrough, 2009).

3.2.3.2 Identification of gram negative rods

3.2.3.2.1Indole test

In this test the tested organism produce tryptophanase enzyme which breakdown tryptophan and produce indole, which react with kovac´s reagent and give pink ring. The tested organism was inoculated into peptone water and incubated at 37◦c for overnight, the kovac̀s reagent was added . If there is pink ring the result was indicated as positive. If there is no pink ring in the surface the result was indicated as negative (Cheesbrough, 2009; Colleeet *al*, 1996).

3.2.3.2.2 Citrate utilization test

In this test organism has ability to use citrate as only source of carbon. By straight loop apart of tested colonies was emulsified in kosser′s citrate media and incubated at 37◦c for 24 hours. A blue color with growth indicated as positive, no change in color indicated the negative result (Cheesbrough, 2009).

3.2.3.2.3 Urease test

In this test organism produce urease enzyme which breakdown urea and produce ammonia, which make the pH of media alkaline, in the presence 18 of phenol red indicator, the tested organism inoculated in Christensen's urea agar. Positive: pink color. Negative: no change in color (Cheesbrough, 2009; Collee et al, 1996).

3.2.3.2.4Kligler iron agar (KIA)

A tested organism inculcated by sterile straight loop by stepping on the butt then blocked the pore and streaked the slop of the media and incubated at 37◦c for 24 hour. Glucose fermentation indicated by yellow butt, yellow slop indicated the lactose fermentation, gas produce in the end of the tube and H2S produce blacking in the media (Cheesbrough, 2009 and Collee et al, 1996).

3.2.4. Sensitivity testing:

3.2.4.1 On Muller Hinton

Use sterile wire loop, touch 3-5 colonies of overnight isolated organism and emulsify in 3ml of normal saline to prepare the suspension, then compared the turbidity of the suspension with the standard. Use sterile swab and socked with the bacterial suspension, excess fluid was removed by pressed the swab against the side of the tube

and streaked over MullerHinton agar (M.H) on the three directions rotating the plates approximately 60 degree to ensure even distribution. Then allow for 3-5 minute, using a sterile forceps the appropriate antimicrobial discs was placed; the disc should be 15mm from the edge and 25 mm from the next disc (Cheesbrough, 2009; colleeet *al*, 1996). plate was incubated aerobically at 35˚c - 37˚c for 16-18hr, after incubation period the zone of inhibition is measured by using ruler, then using interpretative chart the zone of each disc was measured and reported as sensitive or resistant or intermediate (Cheesbrough, 2009; colleeet *al*, 1996).

Table3.1 show Antibiotics drugs used in the study

			Diameter of zone of inhibition(mm)		
Antimicrobial agent	symbol	Discpotency	Susceptiable	intermediate	Resistance
Imipenem	IPM	10mcg	≥19	16-18	≤15
Meropenem	MRP	10mcg	≥23	20-22	≤19
Cefexime	CFM	5mcg	≥19	16-18	≤15
Fetariaxone	CRO	30mcg	≥23	20-22	≤19
Ciproflaxacin	CIP	5mcg	≥22	20-22	≤19
Cefazidime	CAZ	30mcg	≥22	20-21	≤19

Statistical analysis: Data collected was analysed by using the Statistical Package for the Social Science software. (Version 16)

CHAPTER IV

RESULTS

CHAPTER IV

RESULTS

A total of 100 cancer patients were included in the study out of these 42% male and 58% female.

The sociodemographic data of the patients included gender, residency and age were expressed in **Figures (4.1) (4.2) (4.3)** respectively.

Of 70 urine sample 46(65.7%) show growth, where 24(34.3%) show no growth, the distribution of isolated organism were *Klebsiella* 15(32.6%), *E. coli* 9(19.6%), *Proteus mirabilis* 7(15.2%), *Proteus Vulgaris* 6(13%), *S.aureus* 7(15.2%) and *Citrobacter* 2(4.3%). Out of 30 swabs samples, 23 show growth (76.7%) where 7(23.3%) show no growth, The distribution of isolated organism wereE. *coli*6 (26.1%), *P.aeurginosa*3 (13%), *Klebsiella*2 (8.7%),*P.mirabilis*2 (8.7%), *S.aureus* 5 (21.7%), *S.pyogens*2 (8.7%), *E. faecalis* 3 (13%), *S. pneumoniae* 1 (0.1%).Out of 20 wound swabs ,18 show growth (90%) ,and 2 show no growth (10%), The distribution of isolated organism were E. *coli*5 (27.7%)*P.aeurginosa*2 (11.1%) *Klebsiellapneumoniae*2 (11.1%)*S. aureus*4 (22.2%)*S.pyogens*1 (5.5%)*proteus vulgaris* 1 (5.5%)*E. faecalis* 3 (16.6%). 5 eye swabs ,2 show growth(40%) 3 show no growth (60%)The distribution of isolated organism were*S. pneumonia* 1(50%) *S. aureus*1(50%) .5 ear swabs ,3 show growth (60%),2 show no growth (40%)The distribution of isolated organism were E. *coli* 1 (33.3%) ,*P.aeurginosa*1 (33.3%),*S.pyogens* 1 (33.3%)as in **(Table 4.1).**

Total of 69 sample show growth males constitutes 30(43.5%) while female constitutes 39(56.5%) as demonstrated in **(Table 4.2).**

Allsample was tested for sensitivity for ciprofloxacin,cefexime, ipenem, meropenem, ceftriaxone and ceftazideme.as showed in (**Table 4.3).**

Regarding to this study.**Table (4.4)** show the association between gender and infection with significant value (0.02), **Table (4.5)** show the association between age and infection with insignificant value (0.009).

The bacterial infection was higer in female (56.5%) than male (43.5%) and according to age more than 60 years are more infected (24.6%) than 41-60 years (15.9%).

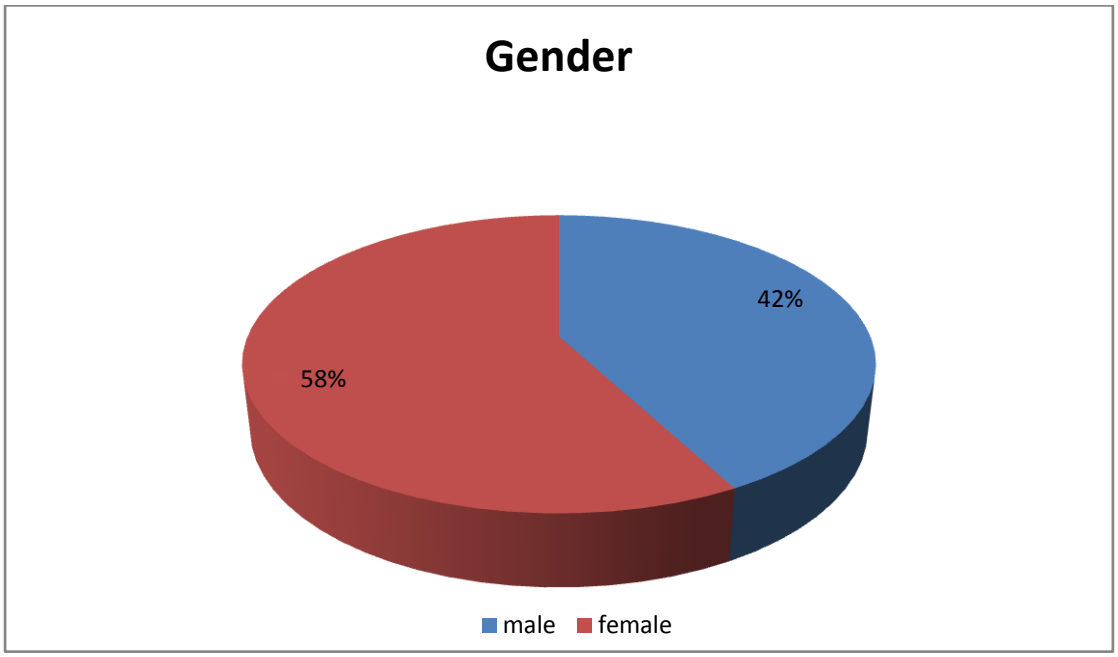

Figure (4.1) The distribution of study group according to gender

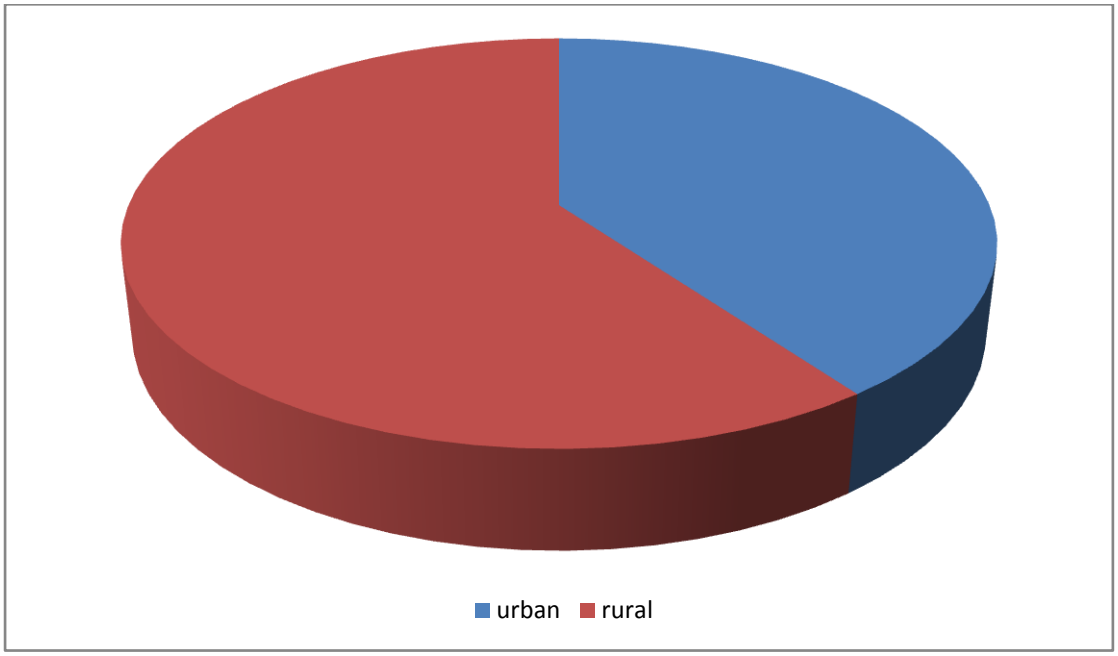

Figure (4.2)The distribution of patients according to residency

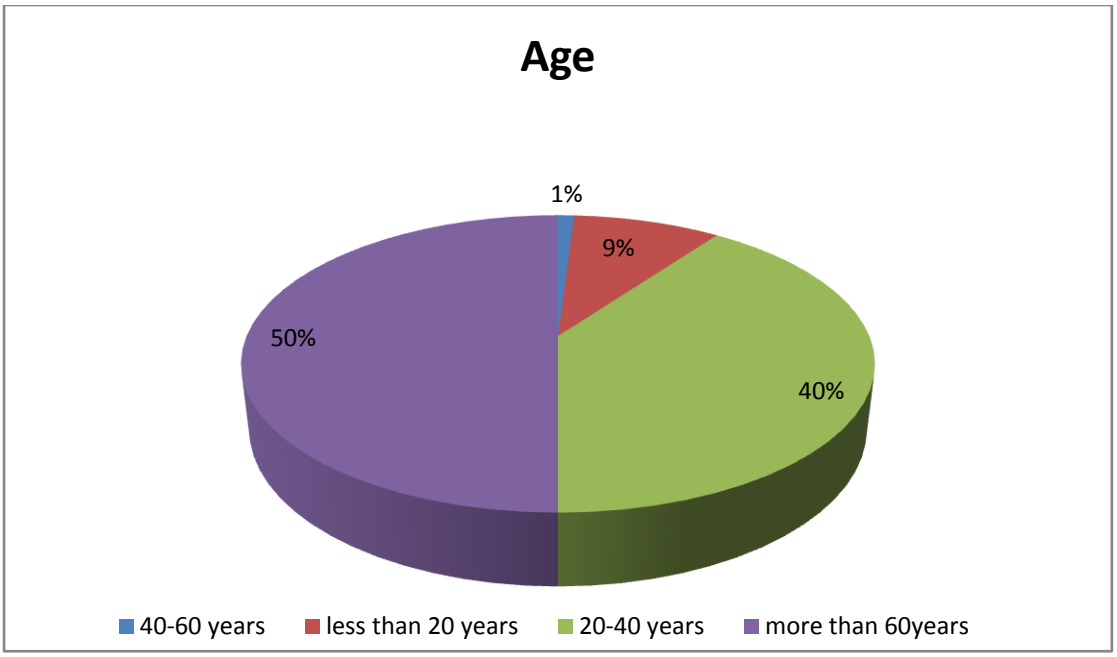

Figure (4.1) The distribution of patients according toage groups

Table 4.1The frequency and percentage of organisms isolated.

Organisms	Frequency	Percent
Klebsiella	17	24.6%
E.coli	15	21.7%
S. aureus	12	17.4%
P.mirablis	7	10.1%
p.vulgaris	7	10.1%
E. faecalis	3	4.3%
P.aeurginosa	3	4.3%
citrobacter	2	2.9%
S.pyogens	2	2.9%
S. pneumoniae	1	1.5%
Total	69	100%

Distribution of bacterial isolation from different clinical specimens among cancer patient at shendi hospital

Bacteria isolates	Type of samples			
	Urine	Wound	Ear	Eye
Klebsiella	32.6%	0	0	0
E.coli	19.5%	27.7%	33.3%	0
S. aureus	15.2%	22.2%	0	50%
P.mirablis	15.2%	0	0	0
p.vulgaris	13%	5.5%	0	0
E. faecalis	0	16.6%	0	0
P.aeurginosa	0	11.1%	33.3%	0
citrobacter	4.3%	0	0	0
S.pyogens	0	5.5%	33.3%	0
S. pneumoniae	0	0	0	50%
Total	70	20	5	5

Table (4.3) show the antibiotic sensitivity of isolated bacteria:

	Impenem		**Cefexime**		**CRO**		**Meropenem**		**CIP**		**CAZ**	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
E.coli	5	10	6	9	7	8	5	10	5	10	4	11
Kellebeshila	9	8	2	15	2	15	6	11	8	9	3	12
proteus vulgaris	2	5	0	6	1	6	1	6	2	5	4	3
proteusmirrabilis	0	7	0	7	0	7	1	6	1	6	2	5
s.aureus	6	6	0	7	9	3	6	6	4	8	3	10
Citrobacter	0	2	0	2	0	2	0	2	1	1	0	2
E. fecalis	3	0	1	2	3	0	2	1	2	1	3	0
S.pyogens	2	0	0	2	2	0	1	1	2	0	0	2
P.aeruginosa	2	1	3	0	2	1	3	0	3	0	1	2
S.pneumoniae	1	0	1	0	1	0	1	0	1	0	1	0

Table (4.4) Association between gender of patients and bacterial growth:

Gender	Frequency	Percent	P-value
Male	30	43.5%	0.02
Female	39	56.5%	

Table (4.5) Association between age group of patients and bacterial growth:

Age	Frequency	Percent	P-value
Less than 20 years	17	31.8%	0.09
20-40 years	19	27.5%	
41- 60 years	11	15.9%	
More than 60 years	22	24.6%	

CHAPTER V

DISCUSSION

CONCLUSION AND RECOMMENDATIONS

Chapter V

Discussion, conclusion and recommendations

5.1 Discussion

The main objective of the present study was to isolation and identification the main common bacteria among patients under chemotherapeutic drug. 100 specimens were collected from patients, prepared and adopted different standardized tools and methods for the realization of the problem through isolation and identification of bacterial strains.

In this study the frequency of UTI in patients under chemotherapeutic drug treatment was (65.7%) this study was found to be similar to the findings of Tanchevа*etal* (2009) whom found the prevalence rate (68%),on the other hand,the prevalence in the present study was higher than the report from Poland by GiandomenicoRoviello (2018) .The variation in results might be explained due to increase rate of multidrug resistant bacteria .

Also statistical analysis of the result of this study should(significant association between gender and bacterial growthP.value 0.02 that show female more affected than male ,that agree with wondewosenTseagyeSime et al 2020 P value less than 0.05 , and there is no significant association between age and bacteril growth P value 0.09 that may be due to small sample size or due to dietary intake for people) revealed that the distribution of disease among female higher than male this result was found to be similar to the findings of (Tanchevaetal 2009) whom found that about (66.6%) were female and (33.4%)were males,HajerAbdalmhmoud who found (72%) were females and (28%) were males and Mohammed tag Eldin who found (74%) were females and (26%) were males. The similarity of the results can be explained by the urethera is shorter in females and continually contaminated with pathogens from the vagina and the rectum .

In this study the frequency of bacteria according to age group was found higher in old age (>60) was (24.6) this result was found to be lower than MohmmadTag Eldin who (37%) of Cases were more than 60 years. These results might be explained due to low immunity in this group of patients.

Also, this study revealed that gram negative pathogens are commonly isolated from the patients and *klebsiella*spp was predominant microorganism recovered. disagree with Tanchevaetal(2009) whom found that *E. coli* is the common pathogen isolated,MohmmedTag Eldin who found (37%) of isolated pathogens was *E.coli* and HajerAbdalmhmoud who found (26.6) of isolated pathogens was *S.aureus*, The variation in results might be explained due to different areas were studies performed.

In this study the frequency of wound infection in patients under chemotherapeutic drug treatment was (90%).the prevalence in the present study was higher than the report by Margita et al 2020 (57%). In the both studies foundthat most frequently isolated bacterial family was*Enterobacteriaceae.*

In this study susceptibility test of *klebsiella*spp show that impenem is active followed by ciprofloxacin.disagree with HajerAbdalmhmoud that report activity of ciprofloxacin was (100%) and agreeArchana and Harsh,2011 that report activity of ciprofloxacin was (90%).

Susceptibility test for *E. coli* show that ciprofloxacin is active not similar to HajerAbdalmhmoud that found the activity of ciprofloxacin was low.

The variation in results might be explained due to different antibiotic used and increase rate of multidrug resistant bacteria.

5.2 Conclusion

Bacterial infection remains an important health problem in cancer patients .in the present study we found the prevalence of infection was (65.7%).the most common bacterial isolated *klebsiella* and *E. coli* are the most frequency. Females are more infected than males. Old patients are more infected than young patients.The most sensitive antibiotic areimpenem and ciprofloxacin and resistant are ciftazidimcefexime and ceftriaxone.

5.3 Recommendations

- Patients should also be followed for bacterial infection at regular time.
- To control drug resistance, the use of antibiotic should be restricted and be given only after doing culture and sensitivity test.
- For more accurate description on patients whom receive chemotherapeutic drug further well designated studies are needed with increased number of samples.
- There are no previous studies in ear and eye swabs in chemotherapy patients so I suggest to make studies about that.
- It is important to use advance techniques to detect the bacterial species.
- Routine bacterial surveillance and study of the resistant pattern.
- Strict regulation of antibiotic and infection control programmes should be considered.

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APPENDIXES

Appendix (1)

بسم الله الرحمن الرحيم

Sudan University for Science & Technology

Collage of Graduate studies

Faculty of Medical Laboratory Science

Guestionnaire About:

Identification and isolation of common bacteria clinical specimens and antimicrobial resistance in patient under chemotherapy

1.Age:

( )≤20years

( )21-40years

( )41-60years

( )<60years

2.Sex:

( )Male

( )Female

3.Residence:

( )Urban ( )Rural

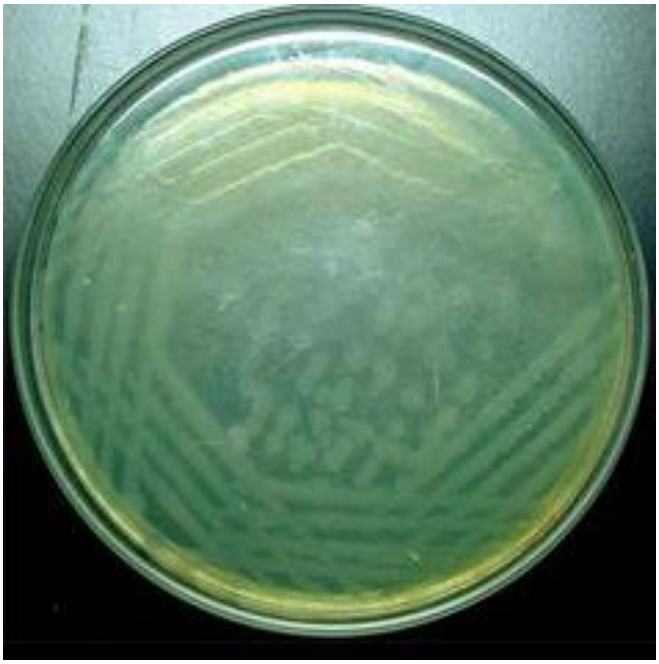
4.Type of infection:

5.Type of sample collection

……
……

Treatment

Appendix (2)



CLED show growth

Appendix (3)

Biochemical tests

Appendix (4)

Antibiotic sensitivity