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RESEARCH ARTICLE

RECURRENT URINARY TRACT INFECTIONS IN IRAQI LEUKEMIC PATIENTS.

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Abstract

Background:- Despite significant advances in supportive care, infectious complications continue to be a significant cause of morbidity and mortality in leukemia patients. The development of effective chemotherapy regimens, incorporation of monoclonal antibodies, use of consolidation and maintenance strategies, and increased use of indwelling urinary catheters have increased susceptibility to urinary tract infections (UTIs) in patients with leukemia.
Multidrug resistant organisms have emerged; even under the optimal circumstances as on time diagnosis and application of proper therapy, infections in leukemia remain a therapeutic challenge. On the other spectrum any delayed recognition or poor application of proper therapy will lead to significant morbidity and mortality while potentially increasing the economic burden associated with the infections seen in this immunocompromised population.

Patients and Methods:- The present study was carried out in the teaching laboratories / medical city/ Baghdad through a period from beginning of May 2015 till the end of September 2015 applied upon 100 leukemic patients seeking the teaching hospital and complaining from recurrent urinary tract infections (UTIs) signs and symptoms during their chemotherapy taking courses. 74 specimens given a positive culture results from the total 100; while 26 specimens given no significant cultivation results. In addition at the same time took another 50 patients whom complaining also from urinary tract infections signs and symptoms as a control group, 23 given a positive culture results and the rest of 50 chosen attempted patients given a negative cultivation results.

Clean cached mid stream urine samples were taken in sterile sample containers from both groups and general urine examination were carried out upon them plus the biochemical assays through urinary dipsticks, then cultivate our specimens, incubate in ambient incubator at 35 ºC-37 ºC for 18-24 hours. The agents used in the present study were (Amikacin, Augmentin, Cefotaxime, Ceftriaxone, Cefoxitin, Cefepime, Ceftazidime, Ciprofloxacin, Levofloxacin, Gentamicin, Imipenem, Nitrofurantoin, Rifampicin, and Sulphamethoxazole-Trimethoprime).

Results:-The most distributable microbes among leukemia patients were gram-negative bacteria; Escherichia coli 21 isolates, Klebsiella pneumoniae 18 isolates, Enterobacter cloacae 8 isolates, Enterobacter aerogenes 7 isolates, Pseudomonas aeruginosa 6 isolates, Serratia marcescens 3 isolates, Proteus mirabilis 3 isolates. The gram-positive bacteria causative etiologies were; Enterococcus faecalis 6 isolates, Enterococcus faecium 2 isolates;

beside Candida albicans were so isolated from 14 cases from the chosen leukemic patients.

Regarding the included control group the predominant pathogenic microorganisms were Escherichia coli 9 isolates, Klebsiella pneumoniae 4 isolates , Enterobacter cloacae 3 isolates, Proteus mirabilis 2 isolates, and Pseudomonas aeruginosa one isolate; and the gram-positive bacteria causative etiologies were; Enterococcus faecalis 3 isolates, Staphylococcus saprophyticus one isolate.
The majority of the 66 gram-negative isolates were susceptible equally to Amikacin and Nitrofurantoin (43 isolates), Imipenem (41 isolates), (Gentamicin (38 isolates), Levofloxacin (29 isolates), Cefoxitin (16 isolates), Ceftriaxone (13 isolates), Sulphamethoxazole-Trimethoprime (10 isolates), Rifampicin (7 isolates). Lastly (3 isolates) were susceptible to the rest already used antimicrobial agents.

According to the isolated 8 gram-positive microbes; mostly was susceptible to Levofloxacin (6 isolates), then came Sulphamethoxazole-Trimethoprime (5 isolates), then Imipenem (4 isolates), Cefoxitin (3 isolates), and at last (one isolate) was susceptible to the rest already used antimicrobial agents.

The action of the antimicrobial agents regarding the microbial pathogens whom isolated from the control group was the same as occurred in the leukemia group.

Conclusions:- gram-negative bacteria Escherichia coli were the most common organisms isolated from leukemia patients gained recurrent UTIs, followed by Klebsiella pneumoniae. The antimicrobial susceptibility testing results that most of the isolated microorganisms were equally susceptible to Amikacin and Nitrofurantoin, then came Imipenem, Gentamicin, Levofloxacin, Cefoxitin, Ceftriaxone, Sulphamethoxazole-Trimethoprime, and Rifampicin

Introduction:-

Infectious complications have been known for many years to be a major cause of morbidity and mortality in leukemia patients. Indeed, they account for the leading cause of death in most series (Lee et al, 1987)

Patients with leukemia are predisposed to infections because of both the humoral immunodepression related to stage and duration of leukemia, and to a further immunosuppression related to therapy with steroids, cytotoxic drugs and monoclonal antibodies (Molica, 1994)

Fever in a neutropenic patient is usually defined as a single temperature more than 38.3 º C or a sustained temperature more than 38 º C for more than one hour (Chung et al, 2010)

Neutropenia is defined as an absolute neutrophil count of less than 500 cells / micro litter whereas absolute neutrophil count less than 100 cells / micro litter is indicative of profound neutropenia (Zaffanello et al, 2010)

Innate immunity represents the body's natural resistance. It provides the first line of defense against a variety of pathogens. Innate immunity is not disease or pathogen specific (Gorter et al, 2010)

Adaptive immunity which achieved by lymphocytes is highly specific response to antigen stimulation (Scholes et al, 2000)
B and T lymphocytes receive whole or partially processed antigens from antigen presenting cells from lymphoid tissue (lymph nodes and the spleen). These cells multiply at the site of infection to evoke a highly targeted antigenic response. B lymphocytes secrete antibodies, process and present antigens and transform into a pool of memory B

cells for future defense. Acute leukemia is characterized by the rapid proliferation of immature progenitor cells and includes acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL), while in chronic leukemia typically runs a more indolent course; This group includes chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL); so had accumulation and slow proliferation of mature appearing but functionally incompetent leukocytes (Scholes et al, 2005)

In leukemia normal hematopoiesis is replaced by abnormal maturation and proliferation of leukocytes, coupled with significant bone marrow infiltration, this leads to decreased production of normal granulocytes resulting in neutropenia and impaired granulocyte function. Also the presence of a large number of immature myeloid cells can inhibit antigen specific T cell response; therefore newly diagnosed leukemia patients often present with recurrent infections. The risk of severe infections is not uniform among these patients and is related to the degree and duration of neutropenia (Raup et al, 2015)

The polymorphonuclear leukocyte function may be adversely affected by several chemotherapeutic medications such as high dose glucocorticoids, vincristine, vinblastine, carmustine, cyclophosphamide and 6- mercaptopurine (Omar et al, 2014)

Patients and Methods:-

A case-control study was carried out in the teaching laboratories / medical city / Baghdad through a period from beginning of May 2015 till the end of September 2015 applied upon 100 leukemic patients seeking the teaching hospital and complaining from recurrent urinary tract infections (UTIs) signs and symptoms during their chemotherapy taking courses.

74 specimens given a positive culture results from the total 100; while 26 specimens given no significant cultivation results. In addition at the same time took another 50 patients whom complaining also from urinary tract infections signs and symptoms as a control group but are free from any immunosuppression conditions as confirmed by their CBC pictures, so 23 given a positive culture results and the rest of 50 chosen attempted patients given a negative cultivation results.

Clean cached mid stream urine samples were taken in sterile sample containers from both groups and general urine examination were carried out upon them plus the biochemical assays through urinary dipsticks, then cultivate our specimens onto blood agar plates and MacConkey's agar plates, incubate in ambient incubator at 35 ºC-37 ºC for 18-24 hours and the negative cultures were reincubate for another 24 hours to be then discarded permanently as a negative.

Thereafter the causative etiologies were accomplished their workflow via using API E 20 strips with API 20 Strep strips and API 20 Staph plus API 10 Candida (BioMereux, France) to gain their final diagnosis, and exposed them to the appropriate antimicrobial agents to view their susceptibility from resistance towards them depending upon the instructions supplied via the manufacturer (Bioanalyse, Turkey). The agents used in the current study were (Amikacin, Augmentin, Cefotaxime, Ceftriaxone, Cefoxitin, Cefepime, Ceftazidime, Ciprofloxacin, Levofloxacin, Gentamicin, Imipenem, Nitrofurantoin, Rifampicin, and Sulphamethoxazole-Trimethoprime).

Results:-

Actually the present study obtained that most frequent etiological agent (Table 1), which were gram-negative bacteria (66 isolates from the total positive 74 and 26 specimens gave no growth) illustrated as follows; Escherichia coli 21 isolates, Klebsiella pneumoniae 18 isolates, Enterobacter cloacae 8 isolates, Enterobacter aerogenes 7 isolates, Pseudomonas aeruginosa 6 isolates, Serratia marcescens 3 isolates, Proteus mirabilis 3 isolates.

Table 1: illustrate the gram negative isolates (66 from 74 positive cultures obtained) in leukemia patients group complaining from recurrent UTIs.

Microorganism	Number of isolates	Percentage
Escherichia coli	21	31.82
Klebsiella pneumoniae	18	27.27
Enterobacter cloacae	8	12.12
Enterobacter aerogenes	7	10.61
Pseudomonas aeruginosa	6	9.09
Serratia marcescens	3	4.55
Proteus mirabilis	3	4.55
Total	66	100%

Table 2: illustrate the gram positive isolates (8 from 74 positive cultures obtained) in leukemia patients group complaining from recurrent UTIs.

Microorganism	Number of isolates	Percentage
Enterobacter faecalis	6	75
Enterobacter faecium	2	25
Total	8	100%

On the other spectrum the gram-positive bacteria causative etiologies (Table 2) were (8 isolates from the total 74) illustrates as follows; Enterococcus faecalis 6 isolates, Enterococcus faecium 2 isolates; beside Candida albicans were so isolated from 14 cases from the total 74 chosen leukemic patients.

Regarding the included control group (Table 3) the predominant pathogenic microorganisms were Escherichia coli 9 isolates, Klebsiella pneumoniae 4 isolates , Enterobacter cloacae 3 isolates, Proteus mirabilis 2 isolates, and Pseudomonas aeruginosa one isolate; and the gram-positive bacteria causative etiologies were; Enterococcus faecalis 3 isolates, Staphylococcus saprophyticus one isolate.

Table 3: illustrate the gram negative isolates (19 from 23 positive cultures obtained) in non leukemia control group.

Microorganism	Number of isolates	Percentage
Escherichia coli	9	47.37
Klebsiella pneumoniae	4	21.05
Enterobacter cloacae	3	15.79
Proteus mirabilis	2	10.53
Pseudomonas aeruginosa	1	5.26
Total	19	100%

Table 4: illustrate the gram positive isolates (4 from 23 positive cultures obtained) in non leukemia control group

Microorganism	Number of isolates	Percentage
Enterobacter faecalis	3	75
Staphylococcus saprophyticus	1	25
Total	4	100%

In Table (5) the spectrum of antimicrobial agents testing; the results were as follows: the majority of the 66 gram-negative isolates were susceptible equally to Amikacin and Nitrofurantoin (43 from 66), Imipenem (41 from 66), (Gentamicin (38 from 66), Levofloxacin (29 from 66), Cefoxitin (16 from 66), Ceftriaxone (13 from 66), Sulphamethoxazole-Trimethoprime (10 from 66), Rifampicin (7 from 66), and finally (3 isolates from 66) were susceptible to the rest already used antimicrobial agents. The resistance pattern was variable accordingly.

Table 5: illustrate the gram negative isolates susceptibility pattern.

Antimicrobial agent name	Disc potency / mcg	Number of susceptible gram negative isolates from the total 66 positive cultures	Percentage from the total 66
Amikacin	30	43	65.15
Nitrofurantoin	300	43	65.15
Imipenem	10	41	62.12
Gentamicin	10	38	57.57
Levofloxacin	5	29	43.93
Cefoxitin	30	16	24.24
Ceftriaxone	30	13	19.69
Trimethoprim- Sulphamethoxazole	23.75/1.25	10	15.15
Rifampicin	5	7	10.6
Augmentin	30	3	4.54
Cefotaxime	30	3	4.54
Ceftazidime	30	3	4.54
Cefepime	30	3	4.54
Ciprofloxacin	5	3	4.54

According to the isolated 8 gram-positive microbes (Table: 6); their antimicrobial susceptibility testing was as follows: The majority was susceptible to Levofloxacin (6 isolates from 8), then came Trimethoprim-Sulphamethoxazole (5 isolates from 8), then Imipenem (4 isolates from 8), Cefoxitin (3 isolates from 8), and at last (one isolate from 8) was susceptible to the rest already used antimicrobial agents. The resistance pattern was variable accordingly also.

Table 6: illustrate the gram positive isolates susceptibility pattern.

Antimicrobial agent name	Disc potency	Number of susceptible gram positive isolates from the total 8 positive cultures	Percentage
Levofloxacin	5	6	75.0
Trimethoprim-Sulphamethoxazole	23.75/1.25	5	62.5
Imipenem	10	4	50.0
Cefoxitin	30	3	37.5
Ceftriaxone	30	1	12.5
Rifampicin	5	1	12.5
Augmentin	30	1	12.5
Cefotaxime	30	1	12.5
Ceftazidime	30	1	12.5
Cefepime	30	1	12.5
Ciprofloxacin	5	1	12.5

The action of the antimicrobial agents regarding the microbial pathogens whom isolated from the control group was the same as occurred in the leukemia group.

Discussion:-

Urinary tract infection is the infection that a typical individual acquires; the patient is diagnosed with uncomplicated cystitis if their midstream urine specimen has between 10^3 to 10^5 colony forming units / ml. In addition urinary tract infection is an infection in any part of the urinary system. Most infections will start in the lower urinary tract in the bladder and urethra or can affect the upper parts (kidneys) (Gupta et al, 2010)

The implementation of empiric antibiotic therapy in febrile neutropenia led to dramatic reduction in mortality and was hailed as a turning point in cancer treatment

Neutropenia and immunosuppression place patients on treatment for malignancies at a high risk for infections. As determine the prevalence of urinary tract infections in patients on treatment for cancer by using simple and

inexpensive screening methods, as included in this study 186 patients complaining of leukemia or lymphoma and after their clinical evaluation; urinalysis and culture and susceptibility were performed on all of them, Escherichia coli plus Klebsiella pneumoniae were responsible for 93.4% of UTIs cases, presence of pyuria as defined five or more leukocytes per high power field (Hooton and Stamm, 1997); this finding will be agree with the current study as the majority of isolated causative agents were also Escherichia coli plus Klebsiella pneumoniae

Like the present work another study had been applied upon leukemic patients whom complaining from recurrent urinary tract infections and the results were as 31.2% of the causative agents were due Escherichia coli while 22.2% were due to Klebsiella pneumoniae, then Enterobacter species, Pseudomonas aeruginosa. In addition the antimicrobial agents' response resembled the results gain from the current case-control study (Munyi et al, 1998)

Urinary tract infection patients have very different pathogen prevalence rates, which underlines the importance of diagnostic systems that are multiplexed. The patient population representing community-acquired UTIs (taken as a control group) have a pathogen E coli, K pneumoniae and Enterococcus species represent 74.2%, 6.2%% and 5.3%, respectively (Laupland et al, 2007); this situation data are clearly nearing by the data obtained from the ongoing work.

The overwhelming majority of uncomplicated UTIs are caused by members of the Enterobacteriaceae family with approximately 75% of occurrences associated with uropathogenic Escherichia coli (UPEC) (Foxman, 2010)

Fungal urinary tract infections are not as well documented as bacterial urinary tract infections. The prevalence rate varies significantly with the patient population from 11% among leukemia patients to 26.5% among catheterized patients. More recent estimates find 10-15% of nosocomial UTIs to be caused by Candida species (Platt et al, 1986; Rivett et al, 1986; Kauffman, 2005)

As is clarified in another study (Chi et al, 2010) deled with bacterial infections in leukemic patients; the concern is how to choose appropriate antibiotics with less cost, less toxicity, little collateral damage, and more effective antimicrobial agents for sepsis in oncologic patients are always an important issue and a great challenge. therefore all studies are focuses on antimicrobial susceptibility in bacteremic isolates from cancer patients with or without neutropenia. The results of the present work are clearly correlates with the mentioned work.

A high prevalence of Enterobacteriaceae infections in neutropenic cancer patients with urinary tract infections may be explained by breaking down of epithelium mucosal barrier; however, the prevalence of gram negative bacilli in neutropenic patients was 66 isolates from the total 74 positive cultivation results, three times that in non neutropenic control group. Such a causative species discrepancy highlights the precaution in choosing empirical antibiotics for cancer patients with and without neutropenia.

The antimicrobial agents' susceptibility testing which applied in the present study revealed that most of the incriminated etiologies were susceptible to Amikacin and nitrofurantoin plus Imipenem and to gentamicin beside Levofloxacin in the first line; then come cefoxitin and ceftriaxone and Sulphamethoxazole-trimethoprime in the second line. This finding is somewhat equal to the findings obtained by other studies carried out by (Del Favero et al, 2001; Wayne, 2005; Vardakas, 2005)

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