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ORIGINAL ARTICLE

Incidence, Causative Organisms and Pattern of Drug Resistance of Nosocomial Urinary Tract Infection in Patients with Liver Cirrhosis

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ABSTRACT

Background: *The nosocomial urinary tract infections (UTIs) creates a major health problem in hospitals all over the world.* ***Objectives:*** *We aimed in this study to determine the incidence of nosocomial UTIs in our cirrhotic patients, identification of the most common pathogens responsible for nosocomial UTIs and identification of the pattern of drug resistance.* ***Methodology:*** *366 cirrhotic patients were studied within one year. Patients with apparent clinical manifestations of any UTI at time of admission were excluded. All patients were subjected to clinical evaluation, abdominal ultrasound examination, and laboratory investigations including complete blood picture, renal function tests, liver function tests and urine analysis at time of admission. Urine samples were collected from the infected patients for both bacterial and fungal cultures and drug sensitivity testing.* ***Results:*** *The frequency of nosocomial UTIs in cirrhotic patients was 7.1%. The most significant risk factor was urinary catheterization (OR=189.0). Gram negative bacilli were the first cause (46%) of nosocomial urinary tract infection followed by fungi (36%). The sensitivity revealed that the most sensitive antibiotic for both Gram positive and Gram negative cocci was Gatifloxacin. The most sensitive antifungal for candida albicans was Nystatin.* ***Conclusion:*** *The frequency of nosocomial UTIs in cirrhotic patients was not low. Malnutrition and urinary catheterization were the most significant risk factors. Urinary fungal infection was not rare and must be in mind. Both bacterial and fungal cultures and their sensitivity to antibacterial and antifungal drugs were very important to improve the survival rate of patients.*

INTRODUCTION

A nosocomial infection is an infection that becomes clinically evident after 48 hours of hospitalization and is not present or incubating the patient at time of admission[1]. Patients admitted to intensive care units (ICUs) have a higher risk of nosocomial UTIs than those admitted to other units[2].

Hospitalized patients with cirrhosis are at greater risk of contracting infections than others, especially those with gastrointestinal (GI) hemorrhage. Bacterial infections occur in 32 -34% of admitted patients with cirrhosis and 45% of those with GI hemorrhage[3]. The most prevalent infectious complications are spontaneous bacterial peritonitis (SBP) (25%-31%), urinary tract infections (UTIs) (20%-25%), pneumonia (15%-21%), bacteremia (12%), and soft tissue infection (11%)[4].

Cirrhotic patients are susceptible to infections because of impaired immune response and bacterial translocation, causing disruption of normal flora equilibrium and thereby excessive growth of other pathogenic microorganisms[5]. The phagocytosis process is impaired in patients with liver cirrhosis, with deleterious effects on the cellular and humoral immune resposes[6].

The nosocomial UTIs is a major health concern in hospitals worldwide. Many risk factors are known to facilitate a bacterial infection like hepatic disease stage, malnutrition, impairment of cutaneo-mucous barrier, associated pathology (diabetes mellitus, neoplasia), upper GI hemorrhage, and invasive diagnostic or therapeutic procedures such as intravenous or urethral catheters[7].

Infections can be serious leading ultimately to renal failure, encephalopathy and shock with negative impacts on survival. Infection is directly responsible for 30–50% of deaths in cirrhosis and increases mortality rates of cirrhotic patients four times. Approximately, 30% of cirrhotic patients die within the first month after infection, and additional 30% die within the first year[8].

Consequently, prevention, early diagnosis, and appropriate management of these infections are mandatory to improve survival. Proper choice of empiric antimicrobial therapy is thus critical to improve

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the prognosis of patients[9]. So, we aimed in this study to determine the incidence of nosocomial UTI in cirrhotic patients, the most common causative bacteria and their antibiotic susceptibility patterns.

METHODOLOGY

In a prospective study, all cirrhotic patients admitted to Tropical Medicine and Gastroenterology Department, Assiut University Hospital within one year was included in the study. Patients with any apparent clinical manifestations of UTIs at the time of admission were excluded from the study.

At time of admission, all included patients were subjected to complete history taking, thorough physical, and urinary system examination; including examination of kidneys and urethra for signs of inflammation. Investigations included complete blood picture, renal function tests, liver function tests, urine analysis and abdominal ultrasonographic examination. Patients were classified according to Child -Pugh classification. Patients were followed up after three days of admission to identify any clinical manifestations of UTIs with repeated blood pictures and urine analysis. The diagnosis of UTIs was based on clinical symptoms and signs [dysuria and fever], >15 leukocytes in urinalysis, and/or positive urine culture [> 10^5 CFU/ml] .

Sample collection:

Midstream clean catch or catheter urine samples were collected from the infected patients by the infection control nurses under complete aseptic conditions. All samples were subjected, as soon as possible, to both bacterial and fungal cultures, biochemical reactions and antibiotic susceptibility testing at the infection control research lab of Assiut University Hospitals. Bacterial viability was estimated by CFU counts.

Isolation and phenotypic identification of isolates:

All specimens were cultured on blood agar and incubated at 37 °C for 24 hrs and isolates were initially identified by Gram's stain. Bacterial colonies were sub-cultured on Mannitol salt agar, bile-esculin azide agar with and without 6 µg/ml of Vancomycin, MacConkey agar and Eosin methylene blue (EMB) agar (Oxoid, Cambridge, UK). Suspected Staphylococci were further characterized by catalase, deoxyribonuclease, coagulase tests and Oxacillin Resistance Screen Agar Base (ORSAB) test.

Also subcultures on TSI, Motility Indole Ornithine Medium (MIO Medium) together with IMVC (Indole, Methyl red, Voges-Proskauer & Citrate), oxidase and urease tests were done to identify the different Gram negative bacilli isolates.

Antibacterial susceptibility of the isolates was determined by disc diffusion method using Muller Hinton Agar (HiMedia, Mumbai, India), and antibacterial Susceptibility discs (for Gram negative bacilli: Gatifloxacin (5µg), Norfloxacin (10µg), Lomefloxacin (10µg), Ciprofloxacin (5µg), Trimethoprim-Sulphamethoxazole (1.25/23.75µg), Ceftriaxone (30 µg), Cefipime (30 µg), Cefoperazone (75µg), Cefaclor (30µg), Cefpodoxime (10µg), Ampicillin (10 µg), Amoxicillin-clavulinc acid (30 µg), Carbenicillin (100 µg) and Aztreonam (30µg). For Gram positive cocci: Gatifloxacin (5µg), Norfloxacin (10µg), Lomefloxacin (10µg), Ciprofloxacin (5µg), Trimethoprim-Sulphamethoxazole (1.25/23.75 µg), Ceftriaxone (30 µg), Cefazolin (30 µg), Cefipime (30 µg), Ampicillin (10 µg), Amoxicillin-clavulinc acid (30 µg), Cloxacillin (1 µg) and Carbenicillin (100 µg) (Oxoid limited United Kingdom).

For detection of fungi, samples were cultured onto Sabouraud's Dextrose Agar (SDA) (HiMedia, Mumbai, India) supplemented with chloramphenicol. Suspected *Candida* colonies were identified phenotypically by the conventional methods including: Gram's staining, germ tube test, morphological characters and chlamydospore production on Corn meal-tween 80 agar[10], culture on CHROMagar Candida medium[11] (CHROMagar Company, Paris, France), urease utilization and sugar assimilation test[12].

As shown in table (1), the genotypes of *Candida* isolates were recognized by a seminested PCR (snPCR) using universal and species-specific primers for detection of Candida species. DNA extraction from liquid *Candida* cultures and snPCR was then accomplished[13]. Initial amplification was done using universal primers amplifying the 3' end of 5.8S rDNA and the 5' end of 28S rDNA; CTSF (5'-CGCATCGATGAAGAACGCAGC-3'), and CTSR (5'-TCTTTTCCTCCGCTTATTGATATGC-3') (metabion international AG, Germany). Then 1 µl of the product was further amplified using the reverse primer (CTSR) and species specific forward primers to amplify the intervening internally transcribed spacer 2 (ITS2) region of *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei* and *C. dubliniensis* in six separate tubes[14-16].

Table 1: Species specific primer sequence used for the seminested PCR

Primer	Sequence	Amplicon size	Species
CADET	5'-ATTGCTTGCGGCGGTAACGTCC-3'	105 bp	C. albicans
CGDET	5'-TAGGTTTTACCAACTCGGTGTT-3'	142 bp	C. glabrata
CTDET	5'-AACGCTTATTTTGCTAGTGGCC-3'	106 bp	C. tropicalis
CPDET	5'-ACAAACTCCAAAACTTCTTCCA-3'	88 bp	C. parapsilosis
CKDET	5'-GGCCCGAGCGAACTAGACTTTT-3'	132 bp	C. krusei
CDDET	GCTAAGGCGGTCTCTGGCGTCG-3'	100 bp	C. dubliniensis

Antifungal susceptibility of the isolates was determined by disc diffusion method using Muller Hinton Agar (HiMedia, Mumbai, India) containing 2% Glucose and 0.5µg/ml Methylene Blue Dye, and Antifungal Susceptibility discs (Fluconazole (10 µg), Fluconazole (25 µg), Ketoconazole (10 µg), Nystatin (50 µg), Itraconazole (10 µg), Voriconazole (1 µg) and Clotrimazole (10 µg) (HiMedia, Mumbai, India).

Ethical Considerations:

Written informed consent was obtained from each eligible patient who participated in the study. The study protocol was approved by the ethical committee of the Faculty of Medicine, Assiut University (IRB no 17101101). It was conducted in accordance with the provisions of the Declaration of Helsinki. Data collection was obtained through in-depth interview with participants taking into consideration data confidentiality.

Statistical Analysis:

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS- version 17). All data were expressed as mean ± SD or frequencies. Student T-test was used to compare between groups. *P*-value was considered significant if <0.05.

RESULTS

This study included 366 cirrhotic patients admitted to Tropical Medicine and Gastroenterology Department, Assiut University Hospital (112 ICU patients and 254 ward patients) during the period of one year. Results revealed that the frequency of nosocomial UTIs in cirrhotic patients was 26/366 (7.1%); 12/112 ICU patients (10.7%) and 14/254 Ward patients (5.5%). As shown in table (2) the mean age of cirrhotic patients with nosocomial UTI was 56.4 ± 12 years and the percentage of infection was higher in male patients, <60 years old than other groups but the difference was not statistically significant (p-value >0.05).

Table 2: Demographic data of cirrhotic patients with nosocomial UTIs

Personal characteristics	Patients with infection (n=26)	Patients without infection (n=340)	p-value
Age:			
< 60 years	16 (61.5%)	222 (65.3%)	0.7
≥ 60 years	10 (38.5%)	118 (34.7%)	
Mean ± SD	56.4 ± 12		
Sex:			
Male	20 (76.9%)	234 (68.8%)	0.6
Female	6 (23.1%)	106 (31.2%)	

Table (3), showed that the most significant risk factor for development of this infection was Malnutrition (OR=20.5, p<0.0001) followed by urinary catheterization (OR=4.5, p<0.00001), diabetes mellitus and obesity (OR=4.2, p<0.0001 and OR=3.6, p=0.001). Regarding Child-Pugh classification, the infection was higher in patients classified as Child grade C then grades B and A (53.8% versus 38.5% and 7.7%, respectively).

Table 3: Risk factors in cirrhotic patients with nosocomial UTIs

Risk factors	Patients with infection # (n= 26)	Patients without infection # (n= 340)	OR	*P*-value
Malnutrition	25 (96.2%)	187 (55%)	20.5	<0.0001*
Urinary catheter	18 (69.2%)	114 (33.5%)	4.5	<0.0001*
Diabetes mellitus	15 (57.7%)	83 (24.4%)	4.2	<0.0001*
Obesity	13 (50%)	74 (21.8%)	3.6	0.001*
Anemia	25 (96.2%)	286 (84.1%)	4.7	0.2
Intravenous cannula	22 (84.6%)	253 (74.4%)	1.9	0.2
Hypertension	2 (7.7%)	17 (5.0%)	1.6	0.9
Child-Pugh classification				
A	2 (7.7%)	27 (7.9%)	0.97	0.96
B	10 (38.5%)	146 (42.9%)	0.8	0.7
C	14 (53.8%)	167 (49.1%)	1.2	0.6

***:** statistically significant,[#] Number (percentage), OR: odds ratio

According to culture results of urine samples, 18 patients (69.2%) showed single organism and 8 (30.8%) had mixed infections. As shown in table (4), most of the isolates were one of the Gram negative bacilli (18 isolates) followed by fungi (14 isolates) then Gram positive cocci (7 isolates). *E. coli* was found to be the commonest bacterial cause followed by *klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (table 4).

Table 4: Percentages of different isolates in nosocomial UTIs

Type of organism	Number of isolates (n=39)	Percentages (%)#
Gram negative bacilli	**18**	**46%**
E. coli	7	18%
Klebsiella pneumoniae	5	12.8%
Psudomonas aeruginosa	4	10.3%
Proteus	2	5%
Gram positive cocci	**7**	**18%**
Staphylococcus aureus	4	10.3%
Enterococci	3	7.7%
Fungi	**14**	**36%**
C. albicans	10	25.6%
C. tropicalis	3	7.7%
C. glabrata	1	2.6%

percentages are calculated from the total number of isolates

Candida species were the most common isolates in both ICU and Ward patients (9 and 5 isolates, respectively) followed by *E. coli* in ICU patients (5 isolates) and *Klebsiella pneumoniae* in ward patients (4 isolates).

Three of the four *Staphylococci* isolates were methicillin resistant, all *Enterococci* isolates were resistant to Vancomycin (VRE) and 12 of the 18 Gram negative bacilli were potential extended spectrum beta lactamase (ESBL) producers. The sensitivity revealed that both Gram positive and Gram negative isolates were most sensitive to Gatifloxacin followed by Trimethoprim-Sulphamethoxazole, Lomefloxacin and Cefipime in Gram negative bacilli and Carbenicillin in Gram positive cocci. All isolates were resistant to Ampicillin, Amoxicillin-Clavulinic acid, Ceftriaxone and Ciprofloxacin (tables 5, 6).

Table 5: Antibiotic susceptibility patterns of gram-negative isolates in nosocomial UTIs in cirrhotic patients

Antibiotic	Percentage of sensitive isolates	Percentage of resistant isolates
Gram-negative bacilli % (n= 18 isolates)		
Gatifloxacin	58.3	41.7
Trimethoprim sulphamethoxazole	33.3	66.7
Lomefloxacin	33.3	66.7
Cefipime	33.3	66.7
Norfloxacin	15.4	84.6
Carbenicillin	13.3	86.7
Cefopodxime	12	66.6
Ampicillin	0.0	100.0
Amoxicillin clavulanic acid	0.0	100.0
Cefoperazone	0.0	100.0
Cefaclor	0.0	100.0
Ceftriaxone	0.0	100.0
Aztreonam	0.0	100.0
Ciprofloxacin	0.0	100.0

Table 6: Antibiotic susceptibility patterns of gram-positive isolates in nosocomial UTIs in cirrhotic patients

Antibiotic	Percentage of sensitive isolates	Percentage of resistant isolates
Gram-positive cocci % (n= 7 isolates)		
Gatifloxacin	50	50
Carbenicillin	33.3	66.7
Norfloxacin	14.3	85.7
Ampicillin	0.0	100.0
Amoxicillin-clavulinic acid	0.0	100.0
Cloxacillin	0.0	100.0
Cefipime	0.0	100.0
Cefazolin	0.0	100.0
Ceftriaxone	0.0	100.0
Trimethoprim sulphamethoxazole	0.0	100.0
Lomefloxacin	0.0	100.0
Ciprofloxacin	0.0	100.0

Phenotypic and genotypic detection methods showed that *C. albicans* was the most common *Candida spp.* isolated from Cirrhotic patients with UTIs followed by *C. tropicalis and C. glabrata* (table 4).

Culture and sensitivity against most common fungi causing nosocomial UTIs revealed that *Candida spp.* were most sensitive to Nystatin followed by Fluconazole (25 µg). All Candida isolates were resistant to Voriconazole and Clotrimazole (table 7).

Table 7: Antibiotic susceptibility patterns of fungi isolates in nosocomial UTIs in cirrhotic patients

Antibiotic	Percentage of sensitive isolates	Percentage of resistant isolates
Fungi % (n=14 isolates)		
Nystatin	100.0	0.0
Fluconazole (25 µg)	60	40.0
Fluconazole (10 µl)	44.4	55.6
Ketoconazole	27.3	72.7
Itraconazole	9.1	90.9
Voriconazole	0.0	100.0
Clotrimazole	0.0	100.0

As shown in table (8), Cefotaxime was the most common prophylactic antibiotic associated with nosocomial UTIs in cirrhotic patients (7 *Candida spp*., 4 *E. coli*, 4 *Klebsiella pneumoniae*, 2 *Proteus*, 2 *Enterococci* and 1 *Pseudomonas aueruginosa* isolates). This was followed by Amoxicillin-clavulinic acid (4 *Candida* spp., 4 *E. coli*, 2 *Proteus* and 2 *Enterococci* isolates). Cefipime was the least prophylactic antibiotic accompanied by development of UTIs (2 Candida isolates)

Table 8: Common pathogens isolated in nosocomial urinary tract infection in relation to prophylactic antibiotics used in cirrhotic patients

Antibiotic	Isolates type (number)
Cefotaxime	*Candida spp.* (7) *E. coli* (4) *Klebsiella pneumoniae* (4) *Proteus* (2) *Enterococci* (2) *Pseudomonas aeruginosa* (1)
Amoxicillin-clavulinic acid	*Candida spp.* (4) *E. coli* (4) *Proteus* (2) *Enterococci* (2)
Cefipime	*Candida spp.* (2)

Follow up of the 26 Cirrhotic patients who developed nosocomial UTIs revealed that 12 patients improved (46%), six developed complications (23%) and the mortality rate was 31% (8 patients).

DISCUSSION

Besides being immune-compromised, Cirrhotic patients are more prone to undertake invasive diagnostic or therapeutic procedures making them at highest risk of acquiring nosocomial infections[17]. UTI is the most frequent complication in patients with cirrhosis and comprises about 40% of nosocomial bacterial infections[18]. The frequency of nosocomial UTIs in cirrhotic patients in our study was (7.1%); (10.7%) in ICU patients and (5.5%) in Ward patients. Higher levels of UTIs were detected among cirrhotic patients in previous studies[19]. In disagreement with previous researchers[3], in the current study, nosocomial UTIs was more common in males than females. This may be due to the higher rate of cirrhosis in males in our locality[20].

Regarding risk factors, malnutrition was the most frequent risk factor detected for the development of nosocomial UTIs in our patients followed by urinary catheterization, diabetes and obesity. Malnutrition is very common in chronic hepatic disorders and is an important risk factor for developing infections in cirrhotic patients[21]. Additionally, in an earlier study[22], UTI was the most frequent infection detected in cirrhotic patients with malnutrition. As in the non-cirrhotic individuals, cirrhotic individuals with indwelling catheters are highly prone to develop UTIs. Generally, risk of UTIs seemed to by greater in higher Child-Pugh classes. Similarly, Rosa et al[23] reported that infections and mortality are more common in patients with Child-Pugh C compared to A or B stage, yet no significant differences were observed between the three classes in our study.

Collectively, results of our work revealed that Gram negative bacilli were the most common causative agents followed by fungi then Gram positive cocci. Among bacteria, *E.coli* was the commonest bacterial cause followed by *Klebsiella pneumoniae*, *pseudomonas aeruginosa* and *staphylococcus aureus*. Moreover, *Candida* was the only type of fungi isolated. *Candida* species were the commonest isolates in both ICU and Ward patients followed by *E. coli* in ICU patients and *Klebsiella pneumoniae* in ward patients.

Earlier studies mentioned that the commonest bacteria found in nosocomial UTIs were *E. coli* and *Klebsiella pneumoniae*[24-25].

Cirrhotic patients are especially in danger of acquiring infections by multidrug resistant (MDR) bacteria due to prolonged hospitalization with frequent exposure to invasive procedures and broad-spectrum antibiotics[26]. As was previously described, most of our Gram negative isolates were potential ESBL producers and nearly all *Staphylococci* isolates were methicillin resistant, all *Enterococci* isolates were VRE. As MDR is a key predictor of inappropriate therapy, the antimicrobial treatment in cirrhosis should be guided by the antibiotic susceptibility results, taking into

consideration the site of infection, rates of resistance and local epidemiology[27].

The antimicrobial susceptibility results in our study revealed that both Gram positive and Gram negative isolates were most sensitive to Gatifloxacin followed by Trimethoprim-Sulphamethoxazole, Lomefloxacin and Cefipime in Gram negative bacilli and Carbenicillin in Gram positive cocci. All isolates were resistant to Ampicillin, Amoxicillin-Clavulinic acid, Ceftriaxone and Ciprofloxacin. Others[28] reported that the use of quinolones should be restricted due to their high possibility for selection of antimicrobial resistant strains. Inconsistent with our results, an earlier research[29] found that *E. coli*, *Klebsiella pneumoniae* and *Enterococcus spp*., the commonest organisms causing UTIs, were sensitive to ciprofloxacin or amoxicillin clavulanic acid.

Fungal infections in cirrhotic patients are principally caused by *Candida spp.* and could be a cause of treatment failure if not appropriately recognized[30]. *Candida spp.* were the only fungi isolated in our patients and *C. albicans* was the most common spp. detected followed by *C. tropicalis and C. glabrata*. In a previous work [31], *Candida spp.* were responsible for about 67% of nosocomial fungal UTI among which *Candida tropicalis* and *Candida albicans* were the most prevalent isolates followed by *Candida glabrata*. Early treatment of fungal infection has been accompanied by improved outcomes, especially in severe cases[32]. All *Candida spp.* in our study were sensitive to Nystatin followed by Fluconazole (25 µg) and resistant to Voriconazole and Clotrimazole. Despite the wide use of Fluconazole due to its satisfactory tolerability and pharmacokinetics, a shift towards non-albicans strains with a lower susceptibility to Fluconazole has been described[33].

Anastasiou and Williams[34] suggested the restriction of the use prophylactic antibiotics in cirrhotic patients to lessen the spread of MDR bacteria. Our results revealed that cefotaxime was the most common prophylactic antibiotic associated with nosocomial UTIs in cirrhotic patients followed by Amoxicillin-clavulinic acid. Cefipime was the least prophylactic antibiotic accompanied by development of UTIs. Cefepime, a fourth generation broad spectrum cephalosporin, that act against Gram negative and Gram positive bacteria, in addition, some has antipseudomonal activity[35]. Our results indicate that cefepime prophylaxis in cirrhotic patients displays the lowest rate of UTIs and is recommended for prophylactic use in those patients.

About 23% of our patients developed complications and the mortality rate was 31%. A preceding study[36] stated that the average length of hospital stay and costs of hospitalizations for a cirrhotic patient with UTIs were significantly higher than that in the non-UTIs group with 1.46 times higher mortality than without UTIs. Moreover, septic shock and mortality rate were higher in infections caused by MDR strains in cirrhotic patients[37].

CONCLUSION

UTI is a frequent complication in cirrhotic patients with increased morbidity and mortality. Malnutrition is the major risk factor for developing UTI. Incidence of fungal UTI is increasing. Proper antibiotic treatment guided by antimicrobial susceptibility testing is mandatory to lessen the high rates of multi-drug resistance. Cefipime is the least prophylactic antibiotic accompanied by development of UTI in cirrhotic patients.

Authors' contributions statement:

Prof Ehab F Mostafa designed and supervised the study and drafted the manuscript. Dr Mohamed AA Ghaliony and dr Sahar M Hassany collected and analyzed the data and performed the background literature review for the manuscript. Dr Omnia El-Badawy and dr Hebatallah M. Hassan carried out the laboratory work, conducted the statistical analyses and drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

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- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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