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Urosepsis among Sudanese Patients: A Paradigm from Limited Resources Country

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Abstract

Background: Urosepsis is life-threatening sepsis that leads to organ dysfunction and results from a defective response to a urinary tract infection; the major precipitating is obstructive uropathy in the upper or lower urinary tract (UT). The magnitude and burden of bacteria that caused uropathy were reported to increase annually. In 30% of all septic patients who were diagnosed with urosepsis, 1.5% of them were found in urology and a quarter due to hospital-acquired urinary tract infections (HAUTIs). This study aims to determine the clinical pattern and the frequency of commonly used antibiotics against bacteria associated with urosepsis among Sudanese patients. **Methods:** This was a cross sectional laboratory-based study, study subjects were recruited from patients attended to Gezira Hospital for Renal diseases and surgery (GHRDS) and was diagnosed, on clinical and laboratory basis, to have urosepsis. Hundred (n = 100) urine samples were collected and inoculated on cysteine lactose electrolyte deficient agar (CLED) media and identify using the suitable biochemical test and performed antimicrobial susceptibility testing (AST) by Kirby Bauer disc diffusion technique for selected antimicrobial agents, according to clinical laboratory standard institute (CLSI) guidelines. **Results:** Amongst urosepsis infection the frequency of *E. coli*, *S. aureus*, *Proteus mirabilis*, *Klebseilla pneumonia* and *Pseudomonas aeruginosa* were (37%,

21%, 10%, 6%, 4% respectively). Resistance to commonly prescribed antibiotics was high, ranging from 17% for meropenem to 100% for cefepime. *P. aeruginosa* was multidrug resistant compared with other isolates. **Conclusions:** There was high rate of antibiotic resistance against the common causes of urosepsis in GHRDS, and this reflects the importance of culture and sensitivity test and necessitates adoption of guidelines for selection of suitable antibiotic.

Keywords

Urosepsis, Antimicrobial Susceptibility, Gezira Hospital for Renal Diseases and Surgery, Sudan

1. Introduction

Urinary tract infections (UTI) are a group of common diseases that occur predominantly by ascension of normal enteric flora through the urethra into the bladder [1]. The consequence of UTI when associated with a sepsis is denoted as urosepsis, which is characterized by physiological, biological and biochemical abnormalities caused by a deregulated host response to infection [2]. Many causes are contributed to urosepsis; benign prostatic hyperplasia (BPH), tumors, anatomical abnormalities and renal colic's [3]. However it was noted that, upper and lower obstructive uropathy are frequently reported causes [4]. Some diseases associated with the severity of urosepsis include disseminated intravascular coagulopathy (DIC), acute kidney injury and acute respiratory distress syndrome (ARDS) [2]. Most of patients diagnosed with urosepsis either community-acquired or healthcare associated infections remain in hospital, starting antimicrobial therapy and other necessary medications [5].

Worldwide among all sepsis cases, an estimated of 9% - 31% were urosepsis, represented in up to 1.6 million deaths [5]. In developed countries such as Germany urosepsis was demonstrated to be a commonest health problem with rates of infection in intensive care units (ICU) of 30.8% [6] [7]. Data regarding urosepsis in Africa in general and Sudan in particular there was few studies or event absent. Urosepsis is usually mono-microbial, with the predominant bacterial causes being Gram-negative bacilli, and to a lesser extent, Gram-positive bacteria and yeasts. [8]. The most isolated bacterial species were *Escherichia coli* followed by *Proteus, Enterobacter*, *Klebsiella*, *Pseudomonas aeruginosa* and gram-positive bacteria [2] [9].

Appropriate management of patients with urospesis includes recommendations for guidelines for acute sepsis and septic shock as well as specific treatment for sepsis and treatment process after early diagnosis, including broad-spectrum antimicrobials and control of identified complications [10]. Selection of antimicrobial therapy guided according to geographical susceptibility patterns and pre antimicrobial used, a combination of antimicrobials may also preferable, timeframe is a critical in treatment of urosepsis after one hour of diagnosis to decrease

the rates of mortality, before initiation of antimicrobial therapy, urine and blood for microbiological cultures are recommended [11]. According to policy of antibiotics prescription inurology department of GHRDS the commonest Abcs used were ceftriaxone, meropenem, ciprofloxacin, gentamicin, ceftizoxime and cefepime. Recently, there is increase in the incidence of multi-drug resistance (MDR) of microorganisms that causes urosepsis had been reported [12] [13] [14]. From which *E. coli* alone accounted for up to 45% of extended-spectrum beta-lactamases (ESBL) producers [15]. There was no study conducted in Sudan to determine the incidence of urosepsis among Sudanese patients, but the records of 2020 in urology department at GHRDS showed that 10% - 20% of admitted patients suffered from urosepsis, so this study aimed to focus on the problem of urosepsis and to determine the bacterial causes and their antimicrobials response.

2. Methods

2.1. Study Design and Settings

This study was set as cross-sectional laboratory-based. It was conducted between 2019 to 2020 at Gezira Hospital for Renal diseases and surgery (GHRDS) in Wad Medani, Sudan. Wad Medani city is a capital of Gezira State while GHRDS consider as the only specialized referred centre outside Khartoum.

2.2. Case Definition, Operational Definition and Sample Size

Urosepsis characterized by physiological, biological and biochemical abnormalities caused by a deregulated host response to infection. Recruitment of subjects for this study was from all patients attended to GHRDS and diagnosed in urology department and exclude patients in nephrology department, on clinical and laboratory basis, to have urosepsis from January to June in this period collected 100 urine samples from all admitted patients in urology department. Clinical diagnosis by a presence of two or more of systemic inflammatory response syndrome (SIRS) beside UTI indicated urosepsis. Observed symptoms were fever or hypothermia, tachycardia more than 90 beats/minutes, tachypnea more than 20 breaths/minutes and leukocytosis of more than 12×10^9/L or leucopenia of less than 4×10^9/L. In the current study the operational definition was taken according to the presence of obstructive uropathy; benign prostatic hyperplasia (BPH), bilateral renal stone, ureteric stricture, urethral stricture, prostate cancer, bladder mass, posterior urethral valves (PUV), neurogenic bladder and etc.,were considered as obstructive uropathy, while post-operative urosepsis and other certain cases of BPH considered as non-obstructive uropathy. A purposeful sampling technique was adopted to collect 100 urine samples from study participants.

2.3. Sample Collection and Bacterial Identification

Catheter urine samples were collected from the catheter valve after disinfection clamping of the catheter below the part of urine collection. In cases of non-ca-

theterized patient mid-stream urine (MSU) was obtained. Sterile, leakproof, wideneck containers were used. Streaking method used for Loopful inoculation of specimens on cysteine lactose electrolyte deficient agar (CLED). After overnight incubation at 37˚C growing isolates were identified by colonial morphology, lactose fermentation and gram's stain. Biochemical tests used were catalase, coagulase, indole, urease, citrate and Kligler's iron agar (KIA). Confirmation of *S. aureus* was completed by mannitol salt agar sub culture.

2.4. Antimicrobial Susceptibility Testing

Isolated bacterial species were tested against vancomycin (30 µg), meropenem (10 µg), gentamicin (30 µg), ciprofloxacin (5 µg), ceftriaxone (30 µg), ceftizoxime (30 µg) and cefepeme (30 µg). Kirby Bauer disc diffusion technique for selected antimicrobial agents according to CLSI guidelines was followed. The procedure used 0.5 McFarland standards as standard turbidity to adjust the bacterial inoculums size, then spread on Mueller-Hinton agar and incubated overnight at 37˚C for 24 hours. Susceptibility interpretation was accomplished according to the diameter of inhibition zones and reported as sensitive, intermediate-resistant and resistant according to the antimicrobials manufacture instructions.

2.5. Ethical Approval

The ethical approve was obtained from the Faculty of Medical Laboratory Sciences, University of Gezira and Ministry of Health, Gezira State, Sudan.

3. Results

A total of 100 urosepsis cases were tested during the study period, 70% were males and 30% were females, ages ranged between 17 - 75 years with median age of 45 years shown in (Table 1). Clinical classification revealed that 91% of cases were due to obstructive uropathy causes, BPH showed most common cases (Table 2). When culture performed under aerobic conditions for non-fastidious bacteria results, revealed that 15% (15/100) of samples gave no growth, 7% (7/100) gave mixed growth (Candida species with gram positive bacteria). The majority of urine cultures 78% (78/100) showed single growth of bacteria; 73% (57/78) isolates were gram negative and 27% (21/78) isolates were gram positive. *E. coli* was predominated with frequency of 47.4% (37/78), followed by *S. aureus* 26.9% (21/78), *P. mirabilis* 12.8% (10/78), *K. pneumonia* 7.7% (6/78) and *P. aeruginosa* 5.1% (4/78) (Table 3). The antimicrobial susceptibility testing for isolated bacteria showed that the effective drug against all isolated except *P. aeruginosa* was meropenem with sensitivity of 83% (65/78), followed by ceftizoxime 54% (42/78), on the other hand, isolated species expressed full resistant against cefepime (Table 4). *E. coli* recorded resistance to meropenem, ceftizoxime and gentamicin of 11% (4/37), 35% (13/37) and 43% (16/37) respectively, 3 and 4 strains of *S. aureus* showed resistance against meropenem and vancomycin respectively (Table 5).

Table 1. Baseline data of urosepsis subject. No 100.

		Frequency	Percentage %
Gender	Male	70	70
	Female	30	30
	Total	100	100
Age	1 - 16 Years	7	7
	17 - 40 Years	18	18
	41 - 60 Years	31	31
	>61 Years	44	44
	Total	100	100
Residence	Wad Medani	21	21
	South of Gezira	35	35
	East of Gezira	10	10
	Alhasahisa	3	3
	Sinnar	11	11
	Elqadarif	7	7
	Eldamazin	10	10
	Others	3	3
	Total	100	100

Table 2. Distribution of urosepsis causes among study subject.

Causes		Frequency	%
Obstructive uropathy	BPH	38	42
	Renal stone	23	26
	Uretic structure	5	5
	Urethral structure	6	7
	Ca prostate	10	11
	Bladder mass	5	5
	PUV	1	1
	Neurogenic bladder	3	3
	Total	91	100
Non-obstructive uropathy	Post operative	6	67
	Post URS	3	33
	Total	9	100

BPH: benign prostatic hyperplasia, PVU: posterior urethral valves, URS: ureteroscopy.

4. Discussion

Urosepsis is a health problem with global concern, the magnitude and burden of bacteria caused uropathy were reported to increase annually. Researches that carried out in Sudan in the field of urology discussed the problems of UTIs and their complications, but there was no data about urosepsis, whichis a health problem with global concern. It was found that 30% of sepsis cases are suffered from urosepsis and mainly due to obstruction in various urogenital tract [16] [17] [18]. Microorganisms such as *E. coli* and *Klebsiella*, *Proteus mirabilis, P. aeruginosa* and Gram-positive cocci are among the frequent pathogens associated

Table 3. Characters and species of isolated bacteria from urosepsis participants.

Gram reaction/isolates species		Frequency	%
Gram reaction	Gram negative	57	57
	Gram positive	21	21
	Mixed growth	7	7
	No growth	15	15
	Total	100	100
Isolated species	*E. coli*	37	47.4
	S. aureus	21	26.9
	P. mirablis	10	12.8
	K. penumoniae	6	7.7
	P. aeruginosa	4	5.1
	Total	78	100

Table 4. Results of selected antimicrobials against all isolated bacterial species from urosepsis subject.

Antibiotics	Sensitive		Intermediate-resistant		Resistant	
	F	%	F	%	F	%
Meropenem	65	83	0	0	13	17
Vancomycin	30	38	6	8	42	54
Gentamicin	36	46	2	3	40	51
Ceftizoxime	42	54	6	7	30	39
Ceftriaxone	11	14	7	9	60	77
Cefepime	0	0	0	0	78	100
Ciprofloxacin	17	22	12	15	49	63

F: frequency.

with urosepsis [2]. The current findings showed that urosepsis is more frequently in male than female [18], although females were more affected by UTIs and complications. Certain urological obstruction are related to male only and this include; benign prostatic hyperplasia, prostate cancer and urethral stricture [19]. Moreover urine acute and chronic retention were found to be commonly occurs in males. In general medications done for management of obstructive uropathy such as suprapubic catheter (SPC) or indwelling catheter (IDC), percutaneous nephrostomy (PCN) [20], should be adopted; the long duration and insertion techniques of catheter may increase chance of post-operative urine retention reported by Zhao [21], because it creates a suitable environment for bacterial growth by ascending infections [22].

From our results the age group of those above 61 years represented 44% of urosepsis patients, same finding were in agreement, which could be explain by many factors contributed to elderly; anatomical abnormality, decline immune cells and chronic conditions due to immunocompromised and most of them underwent transurethral prostatectomy (TURP), transurethral resection of bladder

Table 5. Susceptibility pattern of selected antimicrobial drugs against common urosepsis pathogens; *E. coli*, *S. aureus*, *P. mirablis*, *K. pneumonia* and *P. aeruginosa*.

	Sensitive		Intermediate-resistant		Resistant	
	Frequency	%	Frequency	%	Frequency	%
			E. coli			
Meropenem	33	89	0	0	4	11
Vancomycin	13	35	5	14	19	51
Gentamicin	20	54	1	3	16	43
Ciprofloxacin	9	24	8	22	20	54
Ceftizoxime	20	54	4	11	13	35
Ceftriaxone	4	11	4	11	29	78
Cefepime	0	0	0	0	37	100
			S. aureus			
Meropenem	18	86	0	0	3	14
Vancomycin	17	81	0	0	4	19
Gentamicin	10	48	0	0	11	52
Ciprofloxacin	7	33	0	0	14	67
Ceftizoxime	12	57	1	5	8	38
Ceftriaxone	5	24	2	9	14	67
Cefepime	0	0	0	0	21	100
			P. mirablis			
Meropenem	9	90	0	0	1	10
Vancomycin	0	0	1	10	9	90
Gentamicin	2	20	1	10	7	70
Ciprofloxacin	1	10	1	10	8	80
Ceftizoxime	6	60	1	10	3	30
Ceftriaxone	2	20	0	0	8	80
Cefepime	0	0	0	0	10	100
			K. pneumonia			
Meropenem	5	83	0	0	1	17
Vancomycin	0	0	0	0	6	100
Gentamicin	4	67	0	0	2	33
Ciprofloxacin	0	0	3	50	3	50
Ceftizoxime	4	67	0	0	2	33
Ceftriaxone	0	0	1	17	5	83
Cefepime	0	0	0	0	6	100
			P. aeruginosa			
Meropenem	0	0	0	0	4	100
Vancomycin	0	0	0	0	4	100
Gentamicin	0	0	0	0	4	100
Ciprofloxacin	0	0	0	0	4	100
Ceftizoxime	0	0	0	0	4	100
Ceftriaxone	0	0	0	0	4	100
Cefepime	0	0	0	0	4	100

tumor (TURBT), bladder neck obstruction (BNO) and direct vision internal urethrotomy (DVIU) [23] [24].

In this study 15 urine samples showed no bacterial growth although the microscopical examination revealed significant pyuria, this false-negative results mostly could be explained by appropriate antimicrobials admonition. Poly-microbial growth in UTI cases had been documented [25] and we observed 7% of studied urosepsis specimens as mixed growth of more than one bacterium beside yeasts. *E. coli* was dominated as urosepsis pathogens [2] [26] and this attributed to many reasons. Firstly, it is the most members of normal microbiota of intestine and skin that can spread via the perineal, vaginal and periurethral area to the lower urinary tract. Secondly, it has a number of virulent strains that enhances invasion mechanism of urinary tract e.g. extra intestinal pathogenic *E. coli* (ExPEC) also uropathogenic *Escherichia coli* (UPEC). On the other hand, UPEC isolated from urosepsis patients or hospital-acquired (HA-UTI) have ability to translocate from the gut to the blood stream due to the presence of multiple virulence genes (VGs); include fimbriae, iron-acquisition systems, flagella and adhesins toxins, its located on transmissible genetic elements (plasmid) and/or on the chromosome [27] [28] [29].

Studies of nosocomial infection remarked *S.aureus* as usual cause of UTI [30], hence this study detected *S. aureus* as second common pathogen of urosepsis and higher percentage compare with Porat study [2], the transmission could be via indwelling catheter in septic conditions or/and come from distance site via bloodstream [31]. *Proteus mirabilis* which is a causative agent of cystitis and pyelonephritis primarily in individuals with indwelling catheters or structural abnormalities and *K. penumoniae* is frequently opportunistic pathogens implicated in UT and catheter associated UTIs of hospitalized patients it has been suggested to involve the formation of biofilms on this surface include adherence factors. Each of *Proteus mirabilis* and *K. penumoniae* are pathogens implicated in catheter associated UTI and had been isolated from urosepsis patients in the present study, in study of Jessica reported same frequencies of *Proteus mirabilis* [32] and Dimitrijevic *et al.* reported 11.7% of *K. penumoniae* causes urosepsis while in this study finding showed 7.7% [33].

Finally; *P. aeruginosa* recognized as a multidrug-resistant or extensively drug-resistant (MDR/XDR), it's due to molecular structures. It's commonly causing nosocomial in origin; catheter-associated urinary tract infections [34] [35]. In this study showed 5.1% this result agrees with Guliciuc *et al.* [36]. All isolated species from urosepsis subjects were included in the WHO list as a serious organisms requiring antibiotic intervention [37].

Increased the incidence of MDR organisms in the last few decades that causing UTI, makes the treatment process more complicated [7], this is due to empirical broad spectrum antibiotics prescription among hospitalization patients [36], it's observed that in GHRDS, the selection of antibiotics base on culture and sensitivity (C/S) wasn't usually followed.

Meropenem was the most effective antibiotics against all bacterial isolates, except *P. aeruginosa* showed fully resistant to all classes of antimicrobial used in this study, this event was consistent with Tospon and might be show the effectiveness if used in large dose [38]. Unlike cefepime was fully resistant to all isolates compare with Yarlagadda study showed susceptible to cefepime [39], it's may due to excessive used.

Although the effectiveness of the ceftizoxime classified as the third-generation cephalosporin than ceftriaxone, it may be due to the ceftriaxone most prescribe antibiotics, and the fourth generation has proven ineffective.

Treatment of Urosepsis

The main goal of treatment of urosepsis decreased the complication in order to decreased mortalityrate used empirical injectable antimicrobial immediately after diagnosed; the urologist should kept in mind patient status such as previous (urological intervention, UTI) and hospitalization associated with previous antimicrobial administration and the presence of a urinary catheter, furthermore, the selection of empirical antibiotics depend on geographical variability of resistance rate [8], in case of indwelling catheters change the catheter in case of prolong used, monitoring output of urine, furthermore; used antibiotics as a prophylaxis before [40].

5. Conclusion

Urosepsis is life threatening complication of infection originating from the UT may be due to obstructive urophathy or foreign bodies like urethral catheters with high mortality rate and its management depends on antimicrobial with specific sepsis therapy. The dominated pathogens was *E. coli* and increased rate of antibiotic resistance against the common causes of urosepsis in GHRDS, and this reflects the importance of culture and sensitivity test and necessitates adoption of guide lines for selection of antibiotics. The empiric meropenem is the drug of choice.

6. Study Limitation

This study is limited in data on previous urological intervention, UTI and hospitalization associated with previous antimicrobial administration. It is also limited in clinical symptoms of SIRS, brief patient treatment and ultra sound report.

Conflicts of Interest

The authors interest for publication of this paper only.

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