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Intensive care unit-acquired urinary tract infections in patients admitted with sepsis: etiology, risk factors, and patterns of antimicrobial resistance

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Summary
Objectives: The objective of the present study was to evaluate the etiology, risk factors, and patterns of antimicrobial resistance of intensive care unit (ICU)-acquired urinary tract infections (UTIs) in patients admitted with sepsis.
Methods: In this observational study, 100 septic patients hospitalized in a general ICU were selected. Demographic, clinical, and outcome data were obtained by chart review. Antibiotic resistance/susceptibility was determined using the minimal inhibitory concentration (MIC) technique.
Results: A UTI was present in 28 (28%) patients; the male to female ratio was 19:9 and the mean age of the patients was 58.71 $\pm$ 19.45 years. From the total of 28 isolates, 27 were resistant to ciprofloxacin, 23 to amikacin, 27 to meropenem, 28 to cefepime, 26 to ceftazidime, and 27 to ceftriaxone.
Conclusions: On the basis of our results, the rate of multidrug-resistant UTIs may be very high in some ICUs in patients admitted with sepsis. This antimicrobial susceptibility/resistance should be determined, and a special antimicrobial treatment protocol should be planned based

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on the results for each ICU. The use of antibiotics for treating UTIs should be guided only through this protocol because of the different spectra of pathogens and susceptibility patterns in each ICU.

Introduction

Hospital-acquired urinary tract infections (UTIs) are the most frequent nosocomial infections[1] and are responsible for 20—30% of nosocomial infections in medical or surgical intensive care units (ICUs).[2,3] The overall incidence density of ICU-acquired UTIs may be as high as 9.6—11.3 per 1000 ICU days.[4,5]

Nosocomial UTIs have been associated with a three-fold increased risk for mortality in hospital-based studies (including in ICUs), and may involve urosepsis, which carries a mortality rate that may be as high as 25—60%. Nosocomial UTIs often occur in patients with an indwelling urinary catheter.[4,6,7] Furthermore, several studies have associated nosocomial UTIs with an increased length of hospital stay and cost.[4,8,9]

In previous studies, the development of ICU-acquired UTIs has been found to be more common in women[4,5] and in medical (9%) compared with non-cardiac surgical (6%) and cardiac surgical patients (2%). It has also been shown to be associated with the length of ICU stay[4] and length of bladder catheterization.[10] Patients aged over 50 years, diabetic patients, or patients who are immunocompromised are more likely to develop a hospital-acquired UTI.[11—13]

Several microbial agents have been found to be responsible for ICU-acquired UTIs such as Escherichia coli, Pseudomonas spp, Proteus mirabilis, Klebsiella spp, Enterobacter spp, Staphylococcus spp, Enterococcus faecalis, Candida spp, and Enterococcus spp.[4,14] Antimicrobial resistance is a growing problem worldwide, especially in hospitals, where resistant organisms are often first detected in ICUs. Previous studies have demonstrated that the rates of antimicrobial resistance are greater in bacteria isolated from ICUs compared with other hospital wards and outpatient clinics,[15] and that hospitalization in ICUs may be an independent risk factor for acquiring infection by multidrug-resistant strains.[16] Moreover, ICU patients are often colonized with endemic, multidrug-resistant strains, which often spread to other wards.[17] In one study, approximately 75% of Klebsiella pneumoniae, 87% of Enterobacter spp, 55% of Pseudomonas aeruginosa, and 75% of methicillin-resistant Staphylococcus aureus (MRSA) strains were drug-resistant to at least three different classes.[18]

The incidence of resistance to antibiotics in bacteria isolated from hospital-acquired infections varies among bacterial species, clinical settings, and even countries, and may be related to local epidemic spread of a few colonies.[19] Despite the importance of nosocomial UTIs in ICU patients, there is a paucity of related data in the existing literature. It is noteworthy that sepsis has been shown to be associated with a high mortality rate of 30—50% and significant morbidity despite advances in current medical care.[20] This study focused on septic patients as they may be at increased risk for acquiring antimicrobial resistant UTIs because of prior exposure to various types of antibiotics, a factor that is known to play an important role in the generation of antimicrobial resistance. The objective of the current study was to evaluate the etiology, risk factors, and patterns of antimicrobial resistance of ICU-acquired UTIs in patients admitted with sepsis.

Materials and methods

Setting and patients

In this observational study, 100 septic patients with symptoms of systemic inflammatory response syndrome (SIRS) hospitalized in the general ICU of Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran between March 2004 and March 2005 were selected.

Patients older than 18 years of age with two or more SIRS symptoms were included in the study. All the patients had an indwelling urinary catheter. Figure 1 depicts the study design.

Definitions

Patients with a positive urine culture (in catheterized patients, one urine culture with a bacterial count $>10^3$ colony-forming units (CFU)/ml and no more than two bacterial species) first identified on ICU day 3 (48 hours) or later were defined as having an ICU-acquired UTI. Patients with positive urine cultures within 48 hours of ICU discharge were also considered to have an ICU-acquired UTI. SIRS was defined as the presence of fever or hypothermia ($38\ ^\circ C < T < 36\ ^\circ C$), leukocytosis or leukopenia ($12 \times 10^9/l <$ leukocyte count $< 4 \times 10^9/l$ or band cell >10%), tachypnea (respiratory rate >20/min or PCO_2 <32 mmHg), and tachycardia (heart rate >90 bpm). Sepsis was defined as SIRS with a proven or suspected microbial etiology. Urosepsis was defined as sepsis in the setting of a UTI with a concomitantly positive blood culture with the same organism within a 48-hour period.

Clinical evaluation

The following data were collected: demographic data (age, sex), length of stay in ICU, indwelling catheter duration, and fasting blood glucose (FBS). The score on the acute physiology and chronic health evaluation (APACHE) II[21] at admission

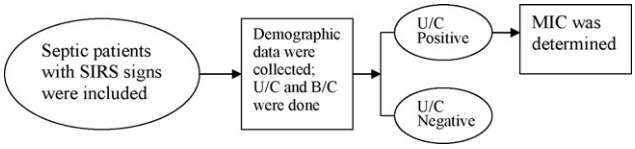

Figure 1 Study design.

was evaluated and recorded for all the patients. Arterial blood pressure (BP) was assessed by means of a manual sphygmomanometer in the early morning. Heart rate (HR) was measured by heart auscultation for 1 min.

In order to control urinary output, a urinary catheter was inserted for each patient. A closed prolonged urinary drainage (indwelling catheter) system was used. The insertion of the indwelling urethral catheter was performed after surgical hand washing, wearing sterile gloves, a facemask, and a cap, and using sterile drapes. All the urine samples were sterilely aspirated via the catheter lumen and were immediately sent to the microbiology laboratory. A blood sample was obtained from each patient and was sent to the laboratory for culture.

Laboratory evaluation

Blood cultures were done as routine. Urine culture was performed quantitatively, and uropathogens were identified according to routine laboratory methods.

Pathogen identification

In order to isolate and identify the pathogens, the urine specimens were streaked onto nutrient agar plates in the form of four-phase streaking patterns, and all the culture plates were then incubated at 37 °C for 24—48 hours. After colony formation, a second culture of each colony was done in the same way in order to obtain a pure bacterial colony. Bacterial species were identified by performing Gram staining and microscopic examination for each pure bacterial colony. For Gram-negative bacteria their specific culture medium was used. In order to identify *P. aeruginosa*, pure Gram-negative bacteria were streaked onto a specific cetrimide agar plate and were then incubated at 37 °C for 24 hours. Colonies appearing bluish green or fluorescent yellow were considered positive for *P. aeruginosa*. For identifying *K. pneumoniae* and *E. coli*, the specimens were cultured separately on eosin methylene blue (EMB) media and were examined after being incubated at 37 °C for 24 hours. *K. pneumoniae* was identified by the production of red-colored colonies and observation of the following biochemical results: fermentation of glucose and lactose to acid and gas; positive results in the Voges—Proskauer (VP), citrate, and urease tests; negative results in methyl red, indole, and SH2 tests; and gelatin liquefaction, where the growth of colony with metallic sheen was considered *E. coli*.

For Gram-positive cocci, a catalase test was performed. In order to distinguish *S. aureus* from coagulase-negative Staphylococcus (CoNS), catalase-positive cocci were selected and tested for mannitol fermentation and coagulation activity. The selected organism was considered *S. aureus* if the results were positive and it was considered CoNS if the results were negative.

Antibiotics

Antibiotic susceptibility was determined for the following antibiotics: cefepime, ceftriaxone, ceftazidime, amikacin, ciprofloxacin, and meropenem.

Antimicrobial susceptibility testing

Antibiotic resistance/susceptibility was determined by using the minimal inhibitory concentration (MIC) technique. For this purpose, the broth microdilution method, which is a known method in referral microbiology laboratories, was utilized.[22] Ten tubes, each containing 1 ml liquid Mueller—Hinton broth (MHB) medium, were allotted for each bacterial isolate; the exception was the first tube, which contained 2 ml. Antibiotic concentrations were prepared using a two-fold method, as follows: (μg/ml) 64, 32, 16, 8, 4, 2, 1, and 0.5. The two last tubes were considered as controls for the antibiotic and culture medium.

For the next step, 1 ml of microbial suspension equal to 0.5 McFarland standard was added to 100 ml liquid MHB, and inoculum density of 10^5—10^6 CFU/ml of isolate was prepared. One ml of microbial suspension obtained from the culture media was then added to all the tubes except for the controls, and all the tubes were subsequently incubated at 37 °C for 24 hours before evaluation. The results were recorded.

Evaluating MIC results

Turbidity due to organism growth was evaluated for each tube and was compared with the controls after the incubation time was completed. MIC endpoints were defined as the lowest concentration of antibiotic that resulted in no bacterial growth as indicated by the absence of turbidity. Susceptibility classification was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) criteria.[23]

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 for Windows. The obtained data on APACHE, length of stay in ICU, duration of catheterization, and FBS were analyzed with an independent sample *t*-test. Cross-tabulation (Chi-square test) was used to analyze gender and age. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographics and correlations

A total of 100 septic patients with symptoms of SIRS hospitalized in the ICU were investigated during the 12-month study period. UTI (bacteriuria) and urosepsis were present in 28 (28%) and six (6%) of the patients, respectively. For the patients with a UTI (bacteriuric patients, $N = 28$), the male to female ratio was 19:9 and the mean age was 58.71 ± 19.45 years. For the non-bacteriuric patients ($N = 72$), the male to female ratio was1.6/1 and mean age was 54.44 ± 20.19 years.

The differences in the male to female ratio and age between the bacteriuric and non-bacteriuric patients were not statistically significant ($p = 0.61$ and $p = 0.34$, respectively). The ICU length of stay and mean APACHE score showed no significant differences between the two groups ($p = 0.164$ and $p = 0.57$, respectively). UTI was not significantly correlated with the duration of catheterization ($p > 0.05$). There were significantly higher levels of FBS among the non-bacteriuric patients when compared with the bacteriuric patients (mean = 169.57 ± 91.63 mg/dl vs. 133.36 ± 36.31 mg/dl, $p = 0.04$).

Table 1 Antimicrobial resistance patterns of isolates

	MIC result[a]	Urine isolate count				Total
		Klebsiella pneumoniae	CoNS	*Pseudomonas aeruginosa*	*Escherichia coli*	
Ciprofloxacin	S	0	0	0	0	0
	RR	1	0	0	0	1
	R	11	5	5	6	27
Amikacin	S	3	0	0	0	3
	RR	1	0	0	1	2
	R	8	5	5	5	23
Meropenem	S	0	0	0	0	0
	RR	1	0	0	0	1
	R	11	5	5	6	27
Cefepime	S	0	0	0	0	0
	RR	0	0	0	0	0
	R	12	5	5	6	28
Ceftazidime	S	2	0	0	0	2
	RR	0	0	0	0	0
	R	10	5	5	6	26
Ceftriaxone	S	1	0	0	0	1
	RR	0	0	0	0	0
	R	11	5	5	6	27

CoNS, coagulase-negative Staphylococcus.
[a] S: susceptible; RR: relatively resistant; R: resistant.

Microbiology

A total of 28 strains were identified in the urine cultures. *K. pneumoniae* was the most common organism isolated from the urine specimens ($n = 12$). Other organisms isolated were *E. coli* ($n = 6$), CoNS ($n = 5$), and *P. aeruginosa* ($n = 5$). All the infections due to CoNS and *P. aeruginosa*, except for one of the pseudomonal infections, occurred after seven days of catheterization.

All the isolates, except for one *K. pneumoniae* isolate that showed a relative resistance ($1 < \text{MIC} < 4$), were resistant to ciprofloxacin (MIC ≥ 4). All the isolates, with the exception of four *K. pneumoniae* isolates of which three were susceptible (MIC ≤ 16) and one was relatively resistant ($16 < \text{MIC} < 64$), and one *E. coli* that was relatively resistant, demonstrated resistance to amikacin (MIC ≥ 64). From the total of 28 isolates, 27 were resistant to meropenem and cefepime (MIC ≥ 16 and MIC ≥ 32, respectively). All the CoNS, *P. aeruginosa*, and *E. coli* isolates were resistant to ceftazidime (MIC ≥ 32). Of the 12 *K. pneumoniae* isolates, two were susceptible (MIC ≤ 8) and the others were resistant to ceftazidime (MIC ≥ 32). All the isolates, except for one *K. pneumoniae* isolate that was susceptible (MIC ≤ 4), showed resistance to ceftriaxone (MIC ≥ 64). The antimicrobial resistance patterns of the isolates are presented in Table 1.

Discussion

A UTI was present in 28 (28%) of our patients. Leone et al. showed a 12% occurrence of catheter-associated UTI (CAUTI) among ICU patients requiring an indwelling urinary catheter.[24] The higher incidence observed in our study may be due to the difference in the definition of bacteriuria where we considered 10^4 CFU/ml density of isolate also as catheter-associated bacteriuria; this factor was not included in the latter study. A prospective study in which catheterized patients were cultured daily via a technique capable of detecting very low-level bacteriuria, as low as 1 CFU/ml,[25] showed that the isolation of any microorganisms from an intraluminal specimen, even 3—4 CFU/ml, is highly predictive of CAUTI. If intercurrent antimicrobial therapy is not given, the level of bacteriuria almost uniformly increases to $>10^5$ within 24—48 hours, demonstrating the vulnerability of the catheterized urinary tract to infection once any microorganisms gain access to the lumen of the catheter and the bladder. Thus, most authorities consider concentrations $>10^2$ or 10^3 CFU/ml in urine collected with a needle from the sampling port of the catheter, to be indicative of true CAUTI. This concentration can be reproducibly detected in the laboratory, and this definition is useful for therapeutic decisions and epidemiologic research.[26—28]

The development of urosepsis in our patients was an infrequent event, occurring in 6% of the cases. Previously, Rosser et al.[7] demonstrated the same result in their retrospective study on critically ill patients with a urinary catheter where the occurrence rate was reported as 15.8% of cases. The lower frequency observed in our study may be due in part to the difference in the evaluation of the patients for urosepsis where we did not include patients with positive urine culture and all other cultures negative, a criterion considered by Rosser et al. in their study. In the Laupland et al. study,[4] 1.37% of ICU-acquired UTIs demonstrated association with a positive blood culture with the same organism. This small difference in results may be due in part to the difference in the study population.

Gender was not a risk factor for catheter-associated bacteriuria in our septic patients, and the male to female ratio showed no significant difference between the bacteriuric and non-bacteriuric patients. A number of studies in general hospitals and some ICUs[29,30] have shown that nosocomial UTIs are more common in women, but this risk factor has not been shown in most studies specific to ICU patients.[7,13]

No differences were observed between the patients who developed an ICU-acquired UTI and those patients who did not with regard to either mean age or APACHE II score. Similar results were observed in ICU patients in the Laupland et al. studies.[4,5]

The ICU length of stay was not correlated with developing ICU-acquired UTI in our septic ICU patients, which is in contrast with results reported from previous studies on non-selected ICU patients.[4,5,30]

Although diabetes mellitus has been previously reported as a risk factor for CAUTI,[26] the mean FBS levels did not show such a correlation in our study. In fact, the mean FBS levels were significantly higher in the non-bacteriuric compared with the bacteriuric patients. Although this could be due to more intensive care probably offered to the bacteriuric as compared with non-bacteriuric patients, it may be a bias caused by the small number of our cases.

One of the risk factors for CAUTI identified in previous studies is prolonged catheterization.[13,30] The duration of catheterization was not present as a risk factor for UTI in our septic patients; nevertheless, all the infections due to CoNS and *P. aeruginosa*, except for one of the pseudomonal infections, occurred after seven days of catheterization.

In total, the most common organism isolated from the urine specimens of our patients was *K. pneumonia*, followed by *E. coli*, CoNS, and *P. aeruginosa*. A national survey of nosocomial UTIs in the USA found *E. coli*, *Pseudomonas* and *Klebsiella* species among the top five pathogens,[31] and many authors have reported that Gram-negative bacteria have greater isolation rates than other microorganisms in nosocomial UTIs, as was seen in our study.[32] *Klebsiella* species have also been demonstrated to be among the top three UTI causative agents in our country.[33,34] However, unlike in our study, most investigators have reported *E. coli* as the most prevalent strain.[4,35,14]

We used the MIC method via the broth microdilution technique to evaluate antimicrobial resistance. Good correlation between this micro-technique and the standard agar dilution method has been previously obtained. This method of susceptibility testing is economically feasible to perform on even a small number of isolates, and the endpoints are easily interpretable.[36]

Interestingly in our study, all the 28 isolates were resistant or relatively resistant to both meropenem and cefepime. These two drugs are among the most common antibiotics in ICU protocols. In the Savas et al. study, the resistance rate against meropenem was determined as 20% for *P. aeruginosa*.[37] The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) study group reported an incidence of 19% in 10 medical centers.[38]

Inhibitor resistance is an emerging problem making therapy with cephalosporins a more difficult problem day by day. Inhibitor-resistant organisms are also being increasingly reported from various parts of the world.[39,40] In addition to cefepime, resistance to ceftazidime and ceftriaxone was significant in our study (26 and 27 of the isolates, respectively). Previous studies have suggested that the selective pressure from the use of antimicrobial agents is a major determinant for the emergence of resistant strains.[41,42] Recently, increased resistance has been observed against third-generation cephalosporins for Gram-negative bacilli.[43]

High resistance rates to ciprofloxacin as a drug considered highly effective in the treatment of UTIs was another finding of our study. A study conducted on a pediatric population of 50 hospitalized patients with UTI showed 100% susceptibility of *E. coli* to ciprofloxacin.[44] However, with the widespread use of fluoroquinolones, there have been reports of evolving bacterial resistance to ciprofloxacin ranging from 10% to 53%.[45] The very high rate of ciprofloxacin resistance among organisms (27 of the isolates) observed in our study warrants special attention and possibly is explained by the fact that this is a setting with ciprofloxacin constituting one of the commonly prescribed drugs.

Resistance to amikacin has been shown to be increasingly progressive in Turkey.[37] Resistance of Gram-negative aerobic bacteria to aminoglycoside antibiotics differs according to region and country. Resistance to aminoglycosides was found to be higher in Southern Europe than in Central Europe and Northern Europe.[46] In the present study, the rate of aminoglycoside resistance was found to be high (23 of the isolates were resistant to amikacin).

The present study included 100 septic patients, 28 of whom had a UTI. Therefore, the number of cases was very small and did not allow statistical comparisons with significant power. It could also be a possible answer to the question of why we could not confirm the risk factors described in the literature, although to our knowledge, no study has thus far evaluated these risk factors in septic patients. A further limitation of our study is that we did not consider some factors such as prior use of antibiotics, admission reasons, and prior hospitalization, which may play important roles in developing antimicrobial resistance.

The susceptibility data collected from our septic patients showed high resistance rates among CAUTI causative agents to antibiotics commonly used in ICUs in these patients. The high resistance rates observed in our study may be in part due to the design of our study, as only septic patients were included. These patients generally undergo various empiric antimicrobial regimens and are, therefore, prone to develop antimicrobial resistance. Another contributing factor could be the poorly controlled antibiotic prescription and lack of a well-defined antimicrobial treatment protocol in pre-ICU as well as ICU settings in our country. Thus, antimicrobial susceptibility/resistance should be determined and a special antimicrobial treatment protocol should be planned based on the results for each ICU. The use of antibiotics in the treatment of UTIs should be guided only through such a protocol because of the different spectra of pathogens and the susceptibility patterns in each ICU.

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