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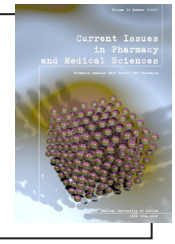

Pathogen profile of urinary tract infections in Nephrology Unit

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ABSTRACT

Introduction. Urinary tract infection (UTI) is one of the most common types of infection in both hospitalized and outpatient settings. The etiology is mostly bacterial, and the typical causative agent is uropathogenic *Escherichia coli*. There is a noticeable increase in drug resistance of pathogenic microorganisms.
The aim of the study was retrospective analyses of etiological agents of UTI and their antibiotic resistance patterns in Nephrology Unit patients.
Material and methods. An infection was diagnosed based on the patient's symptoms and positive results of urine culture, carried out over 26 months. The clinical material was tested by using the VITEK system, the drug susceptibility of the emerged pathogens was identified.
Results. The most common etiological agents of UTI were Gram-negative rods: *Escherichia coli* (51.23%), *Klebsiella* spp. (19.3%) and *Proteus* spp. (13.68%). The analysis of drug resistance profiles of these pathogens showed a high percentage of strains resistant to broad-spectrum penicillins and fluoroquinolones. At the same time, it seems that *E. coli* isolates presented the most favorable pattern of drug susceptibility in this comparison.
Conclusions. The alarming tendency of increasing drug resistance among pathogens causing UTIs to antibiotics such as penicillins or fluoroquinolones prompts a careful choice of drugs in empirical therapies. The most appropriate practice in this regard seems to be meticulous control of nosocomial infections and making therapeutic decisions based on the knowledge of local microbiological data.

INTRODUCTION

Urinary tract infections (UTIs) are considered to be one of the most common infections both among hospitalized and outpatient patients [1,2]. It is estimated that they constitute about $^{1}/_{3}$ of all cases of nosocomial infections [3]. The etiology is most often bacterial (much less often fungal or viral) - definitely dominant Gram-negative rods, mainly *Escherichia coli*. Subsequently, bacteria of the genus *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Pseudomonas* spp. or Gram-positive cocci *Staphylococcus saprophyticus* and *Enterococcus* spp., are mentioned [2,4,5]. The diagnosis of infection should be based on a positive urine microbial culture, the titer of microbial growth, and the method of specimen collection, in correlation with the patient's symptoms and risk factors. The current state of knowledge has determined that the urinary tract above the level of the bladder sphincter was considered sterile, but the latest scientific research indicates the existence of a "urine microbiome". According to this hypothesis, UTI can also be perceived as a dysbiosis of microorganisms within the bladder, and not only as the presence of a pathogenic microorganism [6]. Detection of bacteria in a significant amount exceeding 10^5 CFU/ml does not always determine the clinical form [7] – the infection may take the form of asymptomatic bacteriuria, acute or chronic cystitis, acute or chronic pyelonephritis [4,6]. Many patient-dependent variables must be considered in determining the type of complications. A different classification distinguishes the division into complicated UTIs (concerning people with anatomical or functional disorders in the urinary outflow, more common in hospitalized patients and requiring long-term catheterization of the urinary bladder) and uncomplicated UTI (concerning people without such disorders, more common in outpatients) [8,9].

AIM

The aim of this study was to retrospectively analyze the frequency of UTI , etiological agents, and the drug

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susceptibility profile of the most commonly cultured pathogens in Nephrology Unit patients.

MATERIALS AND METHODS

The study included patients hospitalized in the Department of Nephrology and Hypertension of the Provincial Specialist Hospital in Lublin (Poland). The observation period was 26 months (from January 2016 to February 2018). Microbiological tests results were analyzed in the indicated period. Clinical material was collected from patients with suspected infection. In general, for microbiological analysis in the Unit, the urine, blood, fragments of soft tissues, ear swabs, body cavity fluids, pus and wound materials were sent to the laboratory. The collection procedure was performed with due care and following the principles of asepsis. On this basis, infection was diagnosed in approximately 9.5% of all hospitalized patients (309 out of 3,258 people): 164 women (53.07%) and 145 men (46.93%).

Analysis of urine samples revealed the presence of microbes in 244 patients (7.5% of all hospitalized patients), and in some cases, more than one pathogen was detected in the clinical specimen as a potential etiological agent. Diagnostics and evaluation of drug susceptibility were performed with the use of automatic methods (VITEK® system: ID, AST). The interpretation of the obtained results was carried out following the EUCAST 9.0 recommendations. The marked pattern of the antibiogram was in some cases different between individual urine samples containing pathogens of the same species/genus.

RESULTS

Types of infections

The analysis of the location from which clinical materials were collected for microbiological tests allowed to determine the frequency of occurrence of particular types of infections in the patients of the Unit (Figure 1). Urinary tract infections (UTIs), found in 244 patients (78.96% of all patients with confirmed infection), dominated over bloodstream infections/ bacteremia (BSIs; 97 patients – 31.39%) and soft tissue infections (STIs; 18 patients – 5.82%).

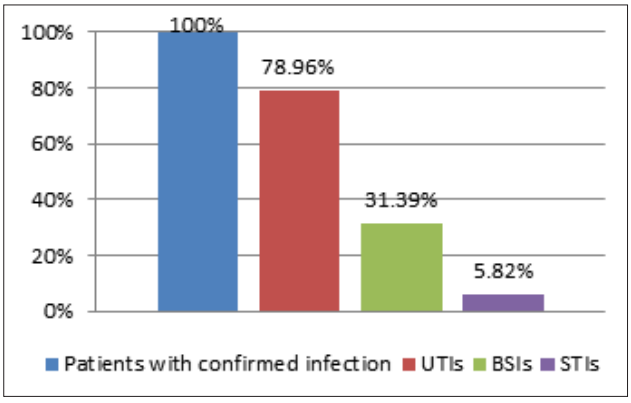

Figure 1. Types of infections in Nephrology Unit patients

Etiological agents of UTIs

The study also focused on the species and types of pathogens detected in the urine (Table 1). A total of 285 microorganisms were isolated in the collected samples of clinical material. A clear predominance of Gram-negative rods from the *Enterobacteriaceae* family as etiological factors of the UTI was found – *Escherichia coli*, *Klebsiella* spp. and *Proteus* spp. bacteria (together constituting 84.21% of all isolates). In the group of women, the percentage of *E. coli* cases was almost twice as high as that of men (65.22% *vs*. 33.06%).

Table 1. Ethiological agents of UTIs

Pathogen	Men	[%]	Women	[%]	Total	[%]
Escherichia coli	41	33.06	105	65.22	146	51.23
Klebsiella spp.	34	27.42	21	13.04	55	19.30
Proteus spp.	18	14.52	21	13.04	39	13.68
Enterococcus spp.	10	8.06	3	1.86	13	4.56
Pseudomonas spp.	7	5.65	2	1,24	9	3.16
Enterobacter spp.	4	3.23	3	1,86	7	2.46
Acinetobacter spp.	3	2.42	0	0	3	1.05
Others	7	5.65	6	3.73	13	4.56
Total	124	100	161	100	285	100

Drug resistance profile of *Escherichia coli*

Patterns of drug resistance have been developed for the 3 most common UTI etiological agents found in the urine samples. During the observation period, 146 diverse *E. coli* strains were isolated (Table 2). As previously mentioned, the profiles of the antibiograms determined could differ between the isolated bacteria, hence the variable number of strains for which the degree of susceptibility was not determined for a particular drug (column "N" in Table 2, Table 3, and Table 4). The percentages given in the tables for each category are calculated concerning the total number of isolates for which a pattern of resistance to a given antibiotic has been determined (same in Table 2, Table 3, and Table 4).

The highest percentage of susceptible *E. coli* strains was found to be to the following antibiotics: all marked from the carbapenem group (100%), tigecycline (100%), colistin (100%), ceftriaxone (94.66%), piperacillin/tazobactam (93.84%). However, the highest degree of drug resistance was observed to: ampicillin (69.57%), norfloxacin (51.11%), amoxicillin/clavulanic acid (34.48%), and ciprofloxacin (34.25%).

Drug resistance profile of *Klebsiella* spp.

During the reporting period, 55 infections with *Klebsiella* spp. were detected (Table 3), among them, the dominant species was *Klebsiella pneumoniae*.

The highest percentage of susceptible strains was found to be to the following antibiotics: colistin (100%), all marked from the carbapenem group (97.62-100%), gentamicin (67.27%) and ceftriaxone (66.67%). The highest degree of drug resistance was observed to: ampicillin (100%), ciprofloxacin (67.27%), tobramycin (62.50%), and amoxicillin/clavulanic acid (62.26%).

Table 2. Drug resistance profile of *Escherichia coli*

Antibiotic	The number of strains			
	S	I	R	N
Ampicillin	14 (30.43%)	-	32 (69.57%)	100 (68.49%)
Piperacillin/ Tazobactam	137 (93.84%)	1 (0,68%)	8 (5.48%)	-
Amoxicillin/ Clavulanic acid	95 (65.52%)	-	50 (34.48%)	1 (1.46%)
Cephalexin	38 (84.44%)	-	7 (15.56%)	101 (69.17%)
Cefuroxime	116 (79.45%)	-	30 (20.55%)	-
Ceftazidime	129 (88.36%)	-	17 (11.64%)	-
Cefotaxime	127 (86.99%)	-	19 (13.01%)	-
Ceftriaxone	124 (94.66%)	-	7 (5.34%)	15 (10%)
Cefepime	129 (88,36%)	6 (4,11%)	11 (7.53%)	-
Meropenem	146 (100%)	-	-	-
Imipenem	101 (100%)	-	-	45 (30.82%)
Ertapenem	57 (100%)	-	-	89 (60.95%)
Gentamicin	130 (89.04%)	-	16 (10.96%)	-
Amikacin	136 (93.15%)	9 (6,16%)	1 (0.68%)	-
Tobramycin	88 (87.13%)	-	13 (12.87%)	45 (30.82%)
Ciprofloxacin	96 (65.75%)	-	50 (34.25%)	-
Norfloxacin	22 (48.89%)	-	23 (51.11%)	101 (69.17%)
Trimetoprim/ Sulfamethoxazole	101 (69.18%)	-	45 (30.82%)	-
Nitrofurantoin	40 (90.91%)	-	4 (9.09%)	102 (69.86%)
Tigecycline	101 (100%)	-	-	45 (30.82%)
Colistin	95 (100%)	-	-	51 (34.93%)

List of shortcuts: **S** – sensitive, standard dosage regimen; **I** – increased exposure; **R** – resistant; **N** – strains for which the degree of susceptibility was not determined

Table 3. Drug resistance profile of *Klebsiella* spp.

Antibiotic	The number of strains			
	S	I	R	N
Ampicilin	-	-	11 (100%)	44 (80%)
Piperacillin/ Tazobactam	23 (41.82%)	1 (1.82%)	31 (56.36%)	-
Amoxicillin/ Clavulanic acid	20 (37.74%)	-	33 (62.26%)	2 (3.63%)
Cephalexin	5 (38.46%)	-	8 (61.54%)	42 (76.36%)
Cefuroxime	22 (40.00%)	-	33 (60.00%)	-
Ceftazidime	26 (47.27%)	1 (1.82%)	28 (50.91%)	-
Cefotaxime	23 (41.82%)	-	32 (58.18%)	-
Ceftriaxone	24 (66.67%)	-	12 (33.33%)	19 (34.54%)
Cefepime	26 (47.27%)	-	29 (52.73%)	-
Meropenem	54 (98.18%)	-	1 (1.82%)	-
Imipenem	41 (97.62%)	1 (2.38%)	-	13 (23.63%)
Ertapenem	23 (100%)	-	-	32 (58.18%)
Gentamicin	37 (67.27%)	-	18 (32.73%)	-
Amikacin	27 (49.09%)	28 (50.91%)	-	-
Tobramycin	9 (37.50%)	-	15 (62.50%)	31 (56.36%)
Ciprofloxacin	16 (29.09%)	2 (3.64%)	37 (67.27%)	-
Norfloxacin	5 (38.46%)	-	8 (61.54%)	42 (76.36%)
Trimetoprim/ Sulfamethoxazole	29 (52.73%)	1 (1.82%)	25 (45.45%)	-
Tigecycline	21 (51.22%)	10 (24.39%)	10 (24.39%)	14 (25.45%)
Colistin	36 (100%)	-	-	19 (34.54%)

S – sensitive, standard dosage regimen; I – sensitive, increased exposure; R – resistant; N – strains for which the degree of susceptibility was not determined

Table 4. Drug resistance profile of *Proteus* spp.

Antibiotic	The number of strains			
	S	I	R	N
Ampicilin	5 (62.5%)	-	3 (37.5%)	31 (79.48%)
Piperacillin/ Tazobactam	36 (94.74%)	-	2 (5.26%)	1 (2.56%)
Amoxicillin/ Clavulanic acid	29 (74.36%)	-	10 (25.64%)	-
Cephalexine	5 (62.5%)	-	3 (37.5%)	31 (79.48%)
Cefuroxime	27 (69.23%)	-	12 (30.77%)	-
Ceftazidime	32 (82.05%)	4 (10.6%)	3 (7.69%)	-
Cefotaxime	28 (71.79%)	-	11 (28.21%)	-
Ceftriaxone	28 (90.32%)	-	3 (9.68%)	8 (20.51%)
Cefepime	29 (74.36%)	3 (7.69%)	7 (17.95%)	-
Meropenem	39 (100%)	-	-	-
Imipenem	24 (77.42%)	7 (22.58%)	-	8 (20.51%)
Ertapenem	14 (100%)	-	-	25 (64.1%)
Gentamicin	26 (66.67%)	1 (2.56%)	12 (30.77%)	-
Amikacin	32 (82.05%)	1 (2.56%)	6 (15.38%)	-
Tobramycin	22 (70.97%)	-	9 (29.03%)	8 (20.51%)
Ciprofloxacin	17 (43.59%)	6 (15.38%)	16 (41.03%)	-
Norfloxacin	4 (50.00%)	-	4 (50.00%)	31 (79.48%)
Trimetoprim/ Sulfamethoxazole	20 (51.28%)	-	19 (48.72%)	-
Tigecycline	1 (5.26%)	1 (5.26%)	17 (89.47%)	20 (51.28%)
Colistin	-	-	14 (100%)	25 (64.1%)

S – sensitive, standard dosage regimen; I – sensitive, increased exposure; R – resistant; N – strains for which the degree of susceptibility was not determined

Drug resistance profile of *Proteus* spp.

During the reporting period, 39 pathogens of the genus *Proteus* spp. were detected. (Table 4), among them, the species *Proteus mirabilis* dominated.

The highest percentage of susceptible strains was found to be to the following antibiotics: meropenem (100%), ertapenem (100%), piperacillin/azobactam (94.74%) and ceftriaxone (90.32%). The highest degree of drug resistance was observed in: colistin (100%), tigecycline (89.47%) and norfloxaicin (50.00%).

DISCUSSION

Our study confirmed that UTI is a common type of infection found in hospital conditions. The percentage of this infection type turned out to be significantly higher than indicated by the scientific data quoted in the introduction (UTI as 1/3 of nosocomial infections) [3], but this should be considered as a result of a specific group of patients from the Nephrology Unit. Hospitalized individuals are often undergoing dialysis treatment and are burdened with multiple UTIs risk factors such as female gender, diabetes, obesity, anatomical and functional disorders in the urinary outflow, history of previous UTIs, history of urological, and gynecological procedures [4,10]. Moreover, during a hospital stay, the requirement for long-term use of urinary catheters becomes a very important risk factor for many serious complications [3].

When analyzing more broadly the topic of nosocomial infections, it should be realized that an unambiguous

determination of the out-of-hospital or in-hospital origin of infection can be very difficult, sometimes even impossible [11]. The risk of infectious complications during hospitalization consists of many factors (not always modifiable) depending on the hospital infrastructure, medical staff, medical procedures performed, and depending on the patient [12]. It follows that the risk of nosocomial infection, as well as its type and the most common etiological agents of infection and their drug resistance, may significantly differ between hospitals and hospitals units. It should be noted that this outcome is related to the specificity of the department, the patient's clinical condition, and the scope of medical procedures performed (especially invasive ones) [13]. The indicated aspects generating the potential diversity of the pathogens, as well as possibly influencing the differences in the patterns of bacterial drug resistance, encourage individual administration and scrupulous conduct of infection control programs and antibiotic management programs in each hospital ward that are based on the latest treatment guidelines and recommendations [14]. It is also worth taking actions aimed at preventing the occurrence of nosocomial infections, such as: interrupting pathogen transmission routes from medical personnel (especially through appropriate hand hygiene), and the environment, and proper management of medical waste [14].

When comparing the drug resistance profiles of the pathogens included in the study, it can be seen that *E. coli* seems to show the most favorable pattern of antibiotic susceptibility. There are a high percentage of cephalosporin-sensitive strains (for example, cefuroxime from 2nd generation – 79,45%), compared to *Klebsiella* spp. (percentage of cefuroxime sensitive strains - 40%) and compared to *Proteus* spp. (69,23%). The profile of drug susceptibility to antibiotics from the aminoglycoside and fluoroquinolone groups is similar – in the overall summary of these 3 pathogens, *E. coli* is the most favorable in terms of percentages of susceptible strains. High sensitivity to carbapenems has been demonstrated for all of the bacteria indicated. Nevertheless, it should be taken into account that carbapenems are one of the strongest antibiotics currently used in medicine and are administered primarily for the treatment of infections caused by multi-drug-resistant pathogens [9].

When discussing drug resistance of pathogens, it should be noted that this problem has grown to a global scale in recent years, and it is no different from bacteria that cause UTIs [2,9,15]. The problem was caused by excessive and/or irrational antibiotic use [16,17]. This led to the selection of strains with new, acquired resistance mechanisms transmitted between bacteria via plasmids [18]. The likely risk factors for the occurrence of multi-drug-resistant pathogens (MDR) of UTIs are the earlier use of antibiotics during the previous year and catheterization of the urinary bladder [19], and for complicated UTI, also male sex and the occurrence of UTI during the previous year [9].

The collective analysis of our studies has shown a worrying tendency to increase resistance to antibiotics such as that to beta-lactams (broad-spectrum penicillins, some cephalosporins) and fluoroquinolones. Similar patterns of drug resistance have been demonstrated in many scientific studies – for *E. coli* and *K. pneumoniae* causing complicated UTI [20], *E. coli* causing uncomplicated UTI [21], and MDR strains of *E. coli* [15]. The cited studies also indicate the high effectiveness of fosfomycin and nitrofurantoin as first-line therapy, discouraging the use of cotrimoxazole and fluoroquinolones for this purpose [15,21]. According to the data presented above, there is a discussion about the appropriate choice of empirical therapy from among the options included in the treatment recommendations for UTIs. The most rational approach seems to be the selection of a drug adapted to local microbiological data and commonly detected uropathogens [22,23]. Also, the choice of empirical antibiotic therapy should be considered individually for each patient and constantly controlled [15,23].

In recent years, scientists have suggested the direction of scientific development in the diagnostics and treatment of UTIs. The researchers are dictated by the increasing pathogens drug resistance to commonly used antibiotics and the problem of recurrent infections [2,6]. In the field of diagnostics, attempts are made to search for biomarkers that would allow supplementing the standard microbiological testing. Nevertheless, Masajtis-Zagajewska A. and Nowicki M., upon analyzing the data on many potential markers (such as leukocyte esterase or interleukins), indicate that there is currently no sufficiently strong scientific evidence that would allow the introduction of determinations of these biomarkers into routine clinical practice [24]. The future in the treatment of UTI caused by uropathogenic strains of *E. coli* may be molecular drugs targeting surface adhesion factors (facilitating the binding of bacteria to the urinary tract epithelium) or virulence factors [6]. The search for appropriate antigenic patterns against which a vaccine could be developed is also in progress [6]. Nevertheless, despite the identification of potential molecular targets, the current scientific research has not allowed for the development of an effective vaccine [2]. A very promising alternative and complement to antimicrobial drugs, especially in the face of increasing MDR pathogens, seems to be phage therapy with the use of bacteriophages that destroy only bacterial cells in a highly specific manner [25,26]. All the above-described innovative solutions in the diagnosis and/or treatment of UTIs require further, extensive research.

CONCLUSIONS

Urinary tract infections are the most common type of infection in patients of the Nephrology Unit. In the aspect of nosocomial infections, it is worth remembering the risk factors for their occurrence and about possible preventive measures. In our study, we found a disturbingly high percentage of resistance to broad-spectrum penicillins and fluoroquinolones among the etiological factors of UTI, which may translate into the limited effectiveness of these drugs in empirical therapies. The phenomenon of increasing drug resistance of pathogens has become a global health problem in recent years, resulting from the abuse and irrational use of antibiotics. In a hospital setting, infection control programs and antibiotic management policies are strongly recommended. Awareness of the possibility of a huge variation in patterns of drug resistance of pathogens between hospital departments or geographic regions

should encourage therapeutic decisions based on local microbiological data (so-called "hospital microbiological mapping"). Scientific evidence shows new opportunities for development in the diagnosis and/or treatment of UTIs, but more extensive research is needed prior to introducing these innovative solutions into clinical practice.

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