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Changes in Bacterial Spectrum and Resistance Patterns Over Time in the Urine of Patients with Neurogenic Lower Urinary Tract Dysfunction Due to Spinal Cord Injury

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Keywords

Neurogenic lower urinary tract dysfunction · Spinal cord injury · Bacteriuria · Multidrug resistance · Urinary tract infection

Abstract

Introduction: Urinary tract infections (UTI) are among the most common complications in persons with neurogenic lower urinary tract dysfunction (NLUTD) due to spinal cord injury (SCI). As both asymptomatic bacteriuria and UTI are frequently treated with antibiotics, concerns about multidrug resistance arise. Therefore, we analyzed the bacterial spectrum in the urine and the resistance patterns of the strains over time in patients with NLUTD due to SCI. ***Methods:*** In a systematic chart review, we identified all microbiologic urine test results including resistance patterns of persons with SCI in a tertiary referral hospital at 2 time periods (2010–2011 and 2017–2018). We assessed the frequency of the bacterial strains, the resistance patterns of the 5 most frequent bacteria, and the use of antibiotics for in- as well as for outpatients. ***Results:*** From 2010 to 2011, 1,308 (outpatients) and 2,479 (inpatients) bacterial strains were detected in the urinalyses performed; these numbers rose to 3,162 and 6,112 during 2017–2018, respectively. The most frequently detected bacteria during both time periods were *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae/variicola*, *Streptococcus viridans*, *Pseudomonas aeruginosa*, and coagulase negative Staphylococci. Fluoroquinolones were the most frequently used antibiotics during both time periods. Despite its frequent use, no relevant increase in resistance against fluoroquinolones was detected. The most prominent increase in resistance appeared in *E. coli* against amocixillin/clavulanic acid in inpatients (from 26.0 to 38.5%). ***Discussion and Conclusions:*** Although fluoroquinolones were used frequently, we did not observe an increased resistance against these antibiotics over time in the urine of patients with SCI.

Introduction

Virtually every patient with a spinal cord injury (SCI) suffers from neurogenic lower urinary tract dysfunction (NLUTD). The impaired storage and voiding functions of the lower urinary tract urinary tract are not only risk

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factors for renal damage [1] but also for bacteriuria and urinary tract infections (UTI) [2]. Besides the NLUTD itself, using catheter-assisted voiding [3, 4], or morphologic alterations, like bladder stones, foreign bodies, and elevated residual urine, are risk factors for UTI.

UTI are among the most common morbidities in individuals with NLUTD [5]. Recurrent UTI are associated with a considerable morbidity and mortality and affect the quality of life substantially [6].

Despite its importance, the diagnosis of UTI in persons with NLUTD is not easy. Based on the recent guidelines, a UTI is defined as the combination of bacteriuria, leukocyturia, and clinical symptoms [7]. As symptoms are often unspecific due to the underlying neurologic disorder and differ from those recognized by able-bodied persons, the differentiation between asymptomatic bacteriuria (ABU) and UTI is challenging. As a consequence, both ABU and UTI are frequently treated with antibiotics [8], raising concerns about an increased rate of multidrug-resistant bacteria in the urine [9]. In 2015, we initiated initial steps of an antibiotic stewardship program. Therefore, we analyzed the bacterial spectrum in the urine and the resistance patterns of the strains over time in patients with NLUTD due to SCI.

Materials and Methods

In 2015, we undertook first steps toward an antibiotic stewardship program. We established a regular interdisciplinary infectiology board, documented and reported the consumption of antibiotics, implemented cross-checking of antibiotic prescriptions of the residents by attendants, and strictly refrained from treating UTI prior to susceptibility testing whenever clinically justifiable.

We systematically evaluated all urine specimens that were analyzed in the laboratory of our hospital during the time period 2010–2011 (implementation of electronic documentation of urinalysis and microbiologic testing results) and compared the results with the most recent urinalyses (time period 2017–2018). All data were extracted anonymously without patient-related health data. The local Ethics Committee approved the retrospective data collection.

Sample processing and susceptibility tests were performed according to the recent guidelines at the respective time intervals (Clinical and Laboratory Standards Institute [CLSI] in 2010/2011; European Committee of Antimicrobial Susceptibility Testing [EUCAST] in 2017/2018). By standard microbiologic testing, urine specimens with $>10^3$ cfu/mL urine were identified. The bacteria were spread on Müller-Hinton Agar plates. Antimicrobial susceptibilities of isolated strains were determined using Kirby-Bauer disc diffusion method [10] and fully automated systems in compliance with the recommendations of the respective standards (2010/2011: CLSI; 2017/2018: EUCAST). For resistance testing, antibiotics used were penicillin, amikacin, ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, ertapenem, imipenem/cilastatin, meropenem, cefoxitin, cefepime, ceftazidime, ceftriaxone, gentamicin, tobramycin, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, colistin, teicoplanin, vancomycin, tigecyclin, linezolid, erythromycin, clindamycin, and nitrofurantoin. Standardized resistance testing is not feasible for amoxicillin/clavulanic acid against Pseudomonas and for trimethoprim/sulfamethoxazole against Streptococci.

Using the electronic documentation system of our hospital pharmacy, we anonymously evaluated how frequently the antibiotics listed were used in our hospital and distinguished between in-house use and the frequency of prescription by the urology outpatient clinic.

For analysis, the results were subdivided into specimens from outpatients and inpatients for the 2 different time periods. Descriptive statistics were applied.

Results

Regarding outpatients, 1,308 bacterial strains were detected in the urinalyses performed from January 2010 to December 2011, whereas 3,162 bacterial strains were detected in the urinalyses performed from January 2017 to December 2018, respectively (Table 1). Within the mentioned time intervals, we isolated 2,479 bacterial strains in the samples of inpatients in the 2010/2011 period and 6,112 strains in the probes in the 2017/2018 period (Table 1).

Bacterial Strains

In outpatients, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae/variicola*, *Streptococcus viridans*, and *Pseudomonas aeruginosa* were the 5 most frequently detected bacteria. Their relative frequency and the rank order did not vary between the 2 time periods except for *Klebsiella pneumoniae/variicola*, which appeared less frequently in the more recent time period (13.5 vs. 9.5%).

Similar to the findings in outpatients, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae/variicola*, and *Pseudomonas aeruginosa* were among the 5 most frequent bacteria in inpatients as well. The 5th most common strain were coagulase negative Staphylococci instead of *Streptococcus viridans*. Comparing the 2 time periods for inpatients, *Escherichia coli* (27.8 vs. 22.1%) and coagulase negative Staphylococci (8.4 vs. 3.7%) appeared less frequently in 2017/2018, whereas *Enterococcus faecalis* was found more often (12.4 vs. 16.7%).

Antibiotic Use

In the time period 2017–2018, the 5 most frequently used antibiotics for inpatients were amocixillin/clavulan-

Table 1. Incidence of bacterial strains in urine over time

Germ		2010–2011 (n = 1,308)		2017–2018 (n = 3,162)	
		n	%	n	%
a	**Outpatients**				
1	*Escherichia coli*	384	29.4	855	27.0
2	*Enterococcus faecalis*	160	12.2	421	13.3
3	*Klebsiella pneumoniae/variicola*	176	13.5	301	9.5
4	*Streptococcus viridans*	87	6.7	209	6.6
5	*Pseudomonas aeruginosa*	77	5.9	207	6.5
Germ		2010–2011 (n = 2479)		2017–2018 (n = 6,112)	
		n	%	n	%
b	**Inpatients**				
1	*Escherichia coli*	689	27.8	1,351	22.1
2	*Enterococcus faecalis*	307	12.4	1,018	16.7
3	*Klebsiella pneumoniae/variicola*	300	12.1	848	13.9
4	*Pseudomonas aeruginosa*	189	7.6	442	7.2
5	Coagulase negative Staphylococci	209	8.4	224	3.7

Table 2. Antibiotic use over time

Antibiotic	2010–2011, %	Antibiotics	2017–2018, %
a Outpatients			
Norfloxacin	54.5	Ciprofloxacin	30.1
Cotrimoxazol	20.2	Amocixillin/clavulanic acid	25.1
Amocixillin/clavulanic acid	11.9	Cotrimoxazol	17.2
Ciprofloxacin	7.5	Cefuroxim	13.2
Nitrofurantoin	2.2	Nitrofurantoin	9.2
b Inpatients			
Ciprofloxacin	18.9	Amocixillin/clavulanic acid	19.4
Amocixillin/clavulanic acid	16.3	Piperacillin/tazobactam	15.0
Norfloxacin	10.9	Ciprofloxacin	12.1
Imipenem	7.8	Cotrimoxazol	11.3
Cotrimoxazol	5.8	Imipenem	8.9

ic acid (19.4%), piperacillin/tazobactam (15%), ciprofloxacin (12.1%), cotrimoxazol (11.3%), and imipenem/cilastatin (8.9%), whereas in the outpatient setting, the 5 most frequently applied drugs were ciprofloxacin (30.1%), amocixillin/clavulanic acid (25.1%), cotrimoxazol (17.2%), cefuroxime (13.2%), and nitrofurantoin (9.2%) (Table 2a, b). The use of fluoroquinolones decreased over time from 62% in the first period to 30.1% in the second period and from 29.8 to 12.1% in inpatients. Thus, fluoroquinolone use was reduced by >50% in both groups of patients over time.

Resistance Patterns

Escherichia coli

Escherichia coli were resistant against fluoroquinolones in >30% of the specimens from inpatients as well as from outpatients (Table 3). Noteworthy, we did not observe a relevant increase in fluoroquinolone-resistant strains over time. The resistance against amocixillin/clavulanic acid increased markedly in inpatients (Tables 3, 4).

Enterococcus faecalis

Resistance against enterococci did not change greatly in outpatient samples over time, whereas in inpatient

Table 3. Resistance patterns of the 5 most frequent bacteria versus the 5 most frequently used antibiotics in outpatients

Bacteria	Resistance to antibiotics, %				
	ciprofloxacine	amocixillin/ clavulanic acid	cotrimoxazol	cefuroxime	nitrofurantoin
Escherichia coli					
2010/11	39.4	25.1	38.8	k.A	16.3
2017/18	33.4	33.2	36.7	k.A	2.3
Enterococcus faecalis					
2010/11	12.9	1.0	100	na***	6.0
2017/18	13.8	1.4	100	na***	kA
Klebsiella pneumoniae					
2010/11	14.8	10.0	14.3	kA	40.3
2017/18	18.8	13.8	21.4	kA	kA
*Streptococcus viridans**					
2010/11	na	0	na	na	na
2017/18	aa	0	na	na	na
Pseudomonas aeruginosa					
2010/11	35.1	na**	100	na**	na****
2017/18	26.6	na**	100	na**	na****

* For *Streptococcus viridans*, no resistance testing was performed. ** *Pseudomonas aeruginosa*: natural resistance against amocixillin/clavulanic acid and cephalosporins. *** *Enterococcus faecalis*: natural resistance against cephalosporins. **** Nitrofurantoin: ineffective against Pseudomonas due to primary resistance.

Table 4. Resistance patterns of the 5 most frequent bacteria versus the 5 most frequently used antibiotics in inpatients

Bacteria	Resistance to antibiotics, %				
	amocixillin/ clavulanic acid	piperacillin/ tazobactam	ciprofloxacin	cotrimoxazol	imipenem
Escherichia coli					
2010/11	26.0	6.9	40.7	38.0	0.1
2017/18	38.5	4.4	36.0	38.3	0.1
Enterococcus faecalis					
2010/11	1.3	0.3	22.9	100	1.8
2017/18	2.6	2.6	10.2	100	4.4
Klebsiella pneumoniae					
2010/11	16.9	18.8	16.9	22.3	1.9
2017/18	14.7	7.7	22.9	21.8	0.8
Pseudomonas aeruginosa					
2010/11	na	13.7	32.7	99.5	21.4
2017/18	na	15.1	15.5	100	15.0
Coagulase negative Staphylococci***					
2010/11	na	na	na	na	na
2017/18	67.2	67.2	72.5	56.4	67.2

*** In 2010/2011, no resistance testing of coagulase negative Staphylococci was performed.

samples, resistance rate doubled for amocixillin/clavulanic acid and increased even more for imipenem/cilastatin and piperacillin/tazobactam, but remained <5% (Tables 3, 4).

Klebsiella pneumoniae

In all samples, resistance rates remained stable over time, with a maximum of roughly 20% resistive strains against cotrimoxazol (Tables 3, 4).

Streptococcus viridans

Due to the known natural resistance patterns, susceptibility of streptococci was assessed merely against amocixillin/clavulanic acid and no resistant strains were detected (Tables 3, 4).

Pseudomonas aeruginosa

Merely fluoroquinolones were effective against *Pseudomonas aeruginosa* in outpatients, and the resistance rate did not increase markedly over time (Table 3). For the most frequently applied antibiotics in inpatients, resistance rates remained unchanged between the 2 time periods (Table 4).

Coagulase Negative Staphylococci

These bacteria demonstrated high resistance rates against all evaluated antibiotics (Tables 3, 4).

Discussion

We evaluated the resistance development in bacteria found in the urine of the patients treated at our institution. Evaluating a large number of urine samples from in- and outpatients, surprisingly, we did not observe a dramatic increase in resistance rates over time. A possible reason for this result are different patient groups at the 2 time periods. It is unlikely, however, that there was a relevant change in patient groups between 2010 and 2018, as the specimens all derived from patients with SCI presenting at a specialized SCI rehabilitation center with a life-long follow-up of these patients.

Another possible cause could be a change in bladder management over time. We did not analyze the mode of bladder management, as the goal of our study was not to assess the association between bladder management and UTI, but to analyze if there is an association between use of antibiotics, spectrum of bacterial strains, and resistance patterns over time. A recent study provides an insight in the bladder management in our hospital. It demonstrated that the most common bladder evacuation method was intermittent catheterization [11].

In our study and according to the literature, *E. coli* are the most frequently detected bacterial strains in the urine of patients with NLUTD and UTI [9]. A recent meta-analysis demonstrated that quinolone-resistant *E. coli* spread widely and developed rapidly [12]. Among the risk factors for this development are urinary catheter use, prior use of antibiotics, and the NLUTD itself [12]. Although virtually all of our patients had at least one of the mentioned risk factors, and we used quinolones frequently, we did not observe an increase in resistance rates against quinolones in our population. Our observation is based on a large sample size, and the reason for this observation is not clear.

Merely a few studies have compared the urine bacterial spectrum and susceptibility rates in patients with SCI from outpatients and inpatients, and we did not find another study evaluating these factors over time. In a study comparing urine samples from patients being transferred from another hospital to a specialized SCI care center (n = 235) to those from patients coming from the community (n = 189), Pseudomonas, Acinetobacter, and Enterococcus species were more frequently observed in hospital-dwelling patients. The isolates from hospital-dwelling patients showed lower susceptibility to ampicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, and cephalosporins. Susceptibility to fluoroquinolones was <50% but did not differ between the different types of residence [13].

Kang et al. [14] analyzed bacteriuria rates in patients with SCI over time but restricted their analysis to hospitalized patients. Of 2.629 routine urine cultures from patients with SCI admitted to a specialized care center between 2001 and 2013, 73.4% demonstrated relevant bacteriuria with *E. coli*, Pseudomonas, and Klebsiella being the most frequent strains. The prevalence of MDR organisms gradually increased over time to 4.7% in 2013 [14].

One limitation of our study is the change of antibiotic susceptibility testing guidelines from CLSI to EUCAST between the first and the second observation period. In line with many European clinical laboratories [15], this change took place in June 2011. A study evaluating the influence of this change on the reported results that was performed in close proximity to our hospital (German-speaking part of Switzerland) demonstrated that these changes may influence a hospital's cumulative antibiogram in various ways which cannot be easily predicted and may differ between hospital units [15]. The most prominent changes of susceptibility rates due to guideline changes, however, did not affect the bacteria and antibiotics assessed in our study (*E. coli* against cefepime, *E. cloacae* against cefepime, and *P. aeruginosa* against meropenem).

Antibiotic resistance can get acquired through different mechanisms, which often occur due to the acquisition of resistance genes via mobile genetic elements such as plasmids, transposons, gene cassettes in the integrons, or changes in regulatory locus on the chromosome of the bacteria [16]. Irrespective of the underlying mechanism, an increased use of antibiotics correlates with the emergence of multidrug resistive organisms [17, 18]. Thus, any unnecessary use of antibiotics should be strictly avoided. All relevant guidelines point out that ABU should not be treated in patients with NLUTD [7, 19, 20]. Nonetheless, even in specialized SCI rehabilitation centers, overtreatment of ABU in persons with SCI is common [8]. This is partly due to the difficulties in correctly diagnosing UTI in patients with NLUTD as bacteriuria in these patients is common and symptoms are often unspecific [21]. Thus, to avoid unjustified use of antibiotics and to alert the treating clinicians, antibiotic stewardship programs (ASP) have been established. These programs include prospective audits with intervention and feedback, and formulary restriction and pre-authorization [22]. A recent study in outpatients with SCI and UTI demonstrated that antimicrobial stewardship interventions decreased the use of antibiotics in this cohort of patients [23]. Even today, the awareness and knowledge regarding ASP is scarce, and there is substantial need for advanced training, regardless of the medical specialty [24]. In our hospital, the concept of ASP is established since 2015, which may at least partially explain the paucity of changes in the resistance pattern over time. The 50% reduction of fluoroquinolone use over time is one of the results of establishing an ASP in our institution, which may have significantly contributed to the stable resistance rates toward these antibiotics.

Conclusion

Evaluating a large number of urine samples from in- and outpatients treated at our institution, we did not observe a dramatic increase in resistance rates over time. This also applies for fluoroquinolones although they were used most frequently in our patients. The most probable cause for this finding is the introduction of antibiotic stewardship, which led to a decreased use of this class of antibiotics.

Statement of Ethics

The authors certify that the research complies with the guidelines for human studies and should include evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This retrospective data collection was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The local Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz) approved the retrospective data collection.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J. Pannek: project development and manuscript writing. C. Kurmann: data collection. J. Krebs: data management and manuscript editing. V. Habermacher: data collection. J. Wöllner: manuscript editing.

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