Original Article

Current Urology

OPEN

Decreasing susceptibility of bacteria to ampicillin/ sulbactam and third generation cephalosporins in urinary tract infections

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Abstract

Background: Urinary tract infections (UTIs) are among the most common bacterial infections worldwide and have become more difficult to treat over the years. Inappropriate antibiotic use has led to increased antibiotic resistance.

Materials and methods: We examined 1921 urine culture samples from a single hospital and analyzed them for bacterial spectrum and antibiotic susceptibility. We further analyzed changes in the rates of detected bacteria and of the sensitivity of these uropathogens to antibiotics over the years.

Results: In our hospital-based analysis, cystitis was the most frequently diagnosed UTI in women (76%) and men (79%). *Escherichia coli* (48%) was the most commonly identified uropathogen. Samples demonstrated an increase in the proportion of *E. coli* ($p < 0.001$) and a decrease in *Enterococcus faecalis* ($p < 0.001$) over the study time period. Antimicrobial susceptibility analysis showed an increase over time in the number of isolates with resistance to ampicillin/sulbactam ($p < 0.001$) and to third-generation cephalosporins cefotaxime ($p = 0.043$) and ceftazidime ($p < 0.001$).

Conclusions: Ampicillin/sulbactam and third-generation cephalosporins are antibiotics frequently used in the treatment of UTIs. When selecting an optimal antimicrobial treatment regimen for patients with UTIs, it is imperative to understand regional and timedependent differences in the prevalence of various uropathogens and antimicrobial resistance patterns. Therefore, continuous surveillance of local pathogen and antimicrobial susceptibility patterns for frequently used antibiotics should be prioritized.

Keywords: Ampicillin/sulbactam; Resistance; Third generation cephalosporin; Urinary tract infection

1. Introduction

Urinary tract infections (UTIs) refer to symptomatic bacterial colonization of the urinary tract and are among the most common infectious diseases worldwide ranking just below upper respiratory tract infections.[1] In most cases, uncomplicated lower UTIs can resolve spontaneously without sequellae; however, antibiotic therapy is significantly more likely than placebo to result in clinical cure and a significantly reduced risk of recurrence.[2] When considering long-term consequences of UTIs, it should be borne in mind that chronic inflammation can be a risk factor for the development of malignancy. Furthermore, in susceptible patients such as those with impaired immune function, urosepsis can develop, potentially leading to multiorgan dysfunction and even death. It is worth noting that nearly 25% of all sepsis cases originate from the urogenital tract, and the prevalence of sepsis appears to be increasing over the last 40years.[3]

Successful treatment of UTIs has become more difficult over the years, with this trend being attributed to increasing antibiotic resistance.[4,5] Inappropriate antibiotic use has been associated with an increase in the rate of bacteria with antibiotic resistance.[6] While antimicrobial management is straightforward for most UTIs, the increasing prevalence of resistant *Escherichia coli,the* most frequently detected uropathogen, and other commonly detected bacteria necessitates continuous re-evaluation of appropriate empiric antibiotic regimens.[7] Knowledge of local bacteria spectrum and antibiotic resistance surveillance data is essential for empirical treatment of UTIs, as antibiotic-resistance rates may vary significantly between regions and over time.[8] The aim of this retrospective study was to analyze the spectrum of bacteria causing UTIs and the sensitivity rates of the isolates to frequently used antibiotics in a single hospital in Germany.

2. Materials and methods

Urine cultures collected at our hospital were analyzed retrospectively from 2011 to 2015. In total, 1921 urine

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Current Urology, (2022) 16, 94–98

Received January 31, 2021; Accepted March 11, 2021.

http://dx.doi.org/10.1097/CU9.0000000000000079

cultures were included for review. A clinically significant positive culture was defined as a culture taken from a midstream urine sample with more than $\geq 10^5$ colonies of a single bacterial pathogen. Isolates were included for analysis if the patients had a symptomatic bacterial infection. The following most common UTIs were analyzed (cystitis, pyelonephritis, epididymitis, and prostatitis). We analyzed the frequency of clinical diagnoses (cystitis, pyelonephritis, epididymitis, and prostatitis in males and cystitis and pyelonephritis in females), frequency of pathogenic bacteria and their association with these diagnoses, and antimicrobial susceptibility patterns. We further analyzed changes of the rates of detected bacteria and sensitivity of these uropathogens to antibiotics over the study time period. To accomplish this, we assigned a similar number of positive urine cultures to two groups, the first group consisting of isolates from 2011 to 2013, and the second group of those from 2014 to 2015.

The antibiotics most often included in susceptibility testing were ampicillin/sulbactam, piperacillin/tazobactam, ciprofloxacin, levofloxacin, imipenem, gentamicin, nitrofurantoin, cefuroxime, cefotaxime, and ceftazidime. Therefore, these antibiotics were chosen for further statistical evaluation.

Statistical analysis was performed using the Biometric-Statistical Program BiAS Version 11.06 (Biometric Analysis of Samples). Statistically significant differences were assessed using the Pearson Chi-square test. The level of statistical significance was defined as a p-value < 0.05.

3. Results

The most common diagnosis among male patients was cystitis, with 481 positive urine cultures, representing 79% of UTIs in men in this study. Among female patients, 363 patients (76%) had cystitis (Table 1). Pyelonephritis was diagnosed in 56 (9%) of males and 115 (24%) of females. In addition, epididymitis and prostatitis were diagnosed in 51 (8%) and 23 (4%) men, respectively (Table 1).

E. coli (48%) was the most commonly detected bacteria, and it was detected at a significantly higher proportion in patients with pyelonephritis compared to all UTIs (60% pyelonephritis vs. 48% all UTIs, $p = 0.006$). Additional frequently detected pathogens included *Enterococcusfaecalis* (9%), *Klebsiella pneumoniae* (9%), *Pseudomonas aeruginosa* (7%), and *Proteus mirabilis* (6%) (Table 2).

Out of 805 samples tested, 454 (56%) isolates were found to be sensitive to ampicillin/sulbactam, with a range between 51% of epididymitis and 57% of cystitis cases (Table 3). Out of 780 samples tested, 619 (79%) isolates were sensitive to piperacillin/ tazobactam, with a range between 69% of epididymitis and 87% of prostatitis cases (Table 3). Isolates were sensitive to ciprofloxacin and levofloxacin in 79% and 78% of cases, respectively, with sensitivity rates between 74% in prostatitis and 84% in epididymitis (Table 3). The overall sensitivity rate of all identified bacterial pathogens to imipenem was 96%, to gentamicin 89%, and to nitrofurantoin 70% (Table 3). Only 45% of isolates were sensitive to the second-generation cephalosporin cefuroxime, whereas 78% and 86% of isolates were sensitive to third-generation cephalosporins cefotaxime and ceftazidime, respectively (Table 3). No statistical difference was found between the sensitivity rates of bacterial isolates to ciprofloxacin, levofloxacin, imipenem, gentamicin, nitrofurantoin, cefuroxime, cefotaxime, and ceftazidime among the different clinical diagnoses included in this study (Table 3).

An increase in the rate of infections caused by *E. coli* ($p < 0.001$) and a decrease in the rate of infections caused by *E. faecalis* ($p < 0.001$) was detected during the time period under study. The rates of other common bacteria, namely *K. pneumoniae, P. mirabilis, and P. aeruginosa,* did not significantly change (Table 4). Furthermore, significant changes were found in the antimicrobial susceptibility pattern of isolates over the study time period, with a reduced susceptibility to ampicillin/ sulbactam ($p < 0.001$) and the third-generation cephalosporins cefotaxime ($p = 0.043$) and ceftazidime ($p < 0.001$) in 2014–2015 as compared to 2011–2013 (Table 5).

Table 1

Urinary tract infections between 2011 and 2015.

Diagnosis	Male	Female
Cystitis	481/611 (79%)	363/478 (76%)
Pyelonephritis	56/611 (9%)	115/478 (24%)
Epididymitis	51/611 (8%)	–
Prostatitis	23/611 (4%)	–

4. Discussion

For optimal treatment of UTIs, it is imperative to have precise information about local bacterial pathogen prevalence and antimicrobial resistance patterns. The most appropriate choice of antibiotics in the local setting can only be made if regional data that identify possible emerging resistance patterns of prevalent bacteria are available.[9] Therefore, in this study we aimed to describe the spectrum and frequency of uropathogens

Table 2

Uropathogens associated with urinary tract infections.

Uropathogen	Cystitis	p	Pyelonephritis	p	Epididymitis	p	Prostatitis	p	Average (total)
Escherichia coli	374/844 (44%)	0.123	101/171 (60%)	0.006*	29/51 (57%)	0.208	17/23 (74%)	0.123	521/1089 (48%)
Enterococcus faecalis	71/844 (8%)	0.920	14/171 (8%)	0.878	7/51 (14%)	0.201	1/23 (4%)	0.920	93/1089 (9%)
Klebsiella pneumoniae	84/844 (10%)	0.476	10/171 (6%)	0.171	3/51 (6%)	0.444	1/23 (4%)	0.476	98/1089 (9%)
Pseudomonas aeruginosa	64/844 (8%)	0.505	10/171 (6%)	0.644	0/51 (0%)	0.054	0/23 (0%)	0.505	74/1089 (7%)
Proteus mirabilis	60/844 (7%)	0.553	7/171 (4%)	0.236	2/51 (4%)	0.472	1/23 (4%)	0.553	70/1089 (6%)
Other bacteria	191/844 (23%)	0.515	29/171 (17%)	0.184	10/51 (20%)	0.761	3/23 (13%)	0.515	233/1089 (21%)

* Indicates a statistically significant difference.

Table 3

Antibiotic susceptibility according to urinary tract infection type.

Antibiotic	Cystitis	p	Pyelonephritis	p	Epididymitis	p	Prostatitis	p	Average (total)
Ampicillin/sulbactam	344/600 (57%)	0.726	75/137 (55%)	0.719	23/45 (51%)	0.487	12/23 (52%)	0.687	454/805 (56%)
Piperacillin/tazobactam	454/570 (80%)	0.896	110/136 (81%)	0.684	35/51 (69%)	0.070	20/23 (87%)	0.373	619/780 (79%)
Ciprofloxacin	500/639 (78%)	0.856	115/145 (79%)	0.855	38/45 (84%)	0.352	17/23 (74%)	0.586	670/852 (79%)
Levofloxacin	471/607 (78%)	0.785	109/137 (79%)	0.720	38/45 (84%)	0.321	17/23 (74%)	0.624	635/812 (78%)
Imipenem	734/763 (96%)	0.915	155/161 (96%)	0.989	50/51 (98%)	0.516	23/24 (96%)	0.906	962/999 (96%)
Gentamicin	605/687 (88%)	0.760	138/154 (90%)	0.703	40/45 (89%)	0.946	22/23 (96%)	0.288	805/909 (89%)
Nitrofurantoin	370/555 (76%)	0.221	103/133 (78%)	0.075	37/46 (80%)	0.126	18/22 (82%)	0.226	528/756 (70%)
Cefuroxime	322/742 (43%)	0.489	84/168 (50%)	0.236	26/49 (53%)	0.273	11/24 (46%)	0.941	443/983 (45%)
Cefotaxime	444/575 (77%)	0.592	123/155 (79%)	0.799	34/40 (85%)	0.322	21/23 (91%)	0.137	622/793 (78%)
Ceftazidime	494/579 (85%)	0.881	132/154 (86%)	0.972	37/43 (86%)	0.936	21/23 (91%)	0.441	684/799 (86%)

Table 4

Uropathogen detection rates between 2011 and 2015.

Uropathogen	2011	2012	2013	2014	2015	p
Escherichia coli	75/211 (36%)	144/415 (35%)	132/414 (32%)	225/461 (49%)	238/477 (50%)	<0.001*
Enterococcus faecalis	39/211 (18%)	78/415 (19%)	68/414 (16%)	32/461 (7%)	36/477 (8%)	<0.001*
Klebsiella pneumoniae	12/211 (6%)	39/415 (9%)	33/414 (8%)	34/461 (7%)	37/477 (8%)	0.675
Pseudomonas aeruginosa	15/211 (7%)	26/415 (6%)	29/414 (7%)	29/461 (6%)	26/477 (5%)	0.429
Proteus mirabilis	15/211 (7%)	30/415 (7%)	32/414 (8%)	31/461 (7%)	24/477 (5%)	0.170
Others	55/211 (26%)	98/415 (24%)	120/414 (29%)	110/461 (24%)	116/477 (24%)	0.270

* Indicates a statistically significant difference.

Table 5

Antibiotic susceptibility in urinary tract infections between 2011 and 2015.

Antibiotic	2011	2012	2013	2014	2015	p
Ampicillin/sulbactam	132/207 (64%)	158/285 (55%)	153/284 (54%)	188/372 (51%)	178/387 (46%)	<0.001*
Piperacillin/tazobactam	165/185 (89%)	172/236 (73%)	241/310 (78%)	311/395 (79%)	293/400 (73%)	0.148
Ciprofloxacin	140/209 (67%)	227/305 (74%)	254/316 (80%)	313/400 (78%)	315/407 (77%)	0.154
Levofloxacin	140/209 (67%)	221/301 (73%)	229/281 (81%)	284/369 (77%)	291/380 (77%)	0.319
Imipenem	159/208 (76%)	287/329 (87%)	319/346 (92%)	382/425 (90%)	392/437 (90%)	0.175
Gentamicin	197/207 (95%)	376/385 (87%)	364/383 (95%)	417/434 (96%)	423/447 (95%)	0.420
Nitrofurantoin	53/94 (56%)	227/305 (74%)	173/285 (61%)	262/372 (70%)	272/385 (71%)	0.440
Cefuroxime	113/209 (54%)	121/341 (35%)	171/368 (46%)	203/458 (44%)	225/472 (48%)	0.411
Cefotaxime	133/157 (85%)	202/261 (77%)	215/292 (74%)	323/424 (76%)	302/432 (70%)	**0.043***
Ceftazidime	149/160 (93%)	228/262 (87%)	249/293 (85%)	357/426 (84%)	333/436 (76%)	<**0.001***

* Indicates a statistically significant difference.

and associated antimicrobial susceptibility patterns from the urine culture results of UTI patients inourhospital (Tables 2 and 3). Furthermore, weevaluated changes over time in the bacterial spectrum and antimicrobial susceptibility patterns (Tables 4 and 5).

We analyzed retrospective data for potential differences in the bacterial spectrum of various UTI clinical diagnoses in this cohort. Cystitis, the most commonly diagnosed UTI, is often associated with a more indolent clinical presentation and sometimes can be self-limited. In contrast, UTIs of parenchymal organs, such as the kidney, epididymis, and prostate, usually present with more severe infections. These infections may develop into life-threatening disease — urosepsis.[10] Therefore, delayed or inappropriate management can lead to severe consequences, including renal failure, septic shock, and death.[3]

E. coli is the most frequently detected bacteria in UTIs worldwide, with previous studies of patients with acute uncomplicated UTIs reporting rates of 68.1%–83.8%.[11–13] In the current study, *E. coli* was only detected in 48% of all urine samples (Table 3), but there was a significant increase in the percentage of UTIs caused by *E. coli* over time (Table 4). The most recent data demonstrated a frequency in our hospital quite similar to the average rate of *E. coli* generally reported in Germany.[11] There is also evidence that the bacterial spectra differs between uncomplicated and complicated UTIs.[7,14,15] Therefore, one reason for the relatively low number of *E. coli* infections at our hospital might be that uncomplicated UTIs were underrepresented in our cohort. For example, in our region, many young women with uncomplicated cystitis are treated by their general practitioners and some might not even seek medical care, leading to a smaller proportion of uncomplicated UTIs among urine cultures analyzed at our hospital.

The rate of infections with *E. faecalis* (9%) in this study is comparable to several previous studies, which reported rates of 2% –20%.[16,17] We detected a decrease of infections with *E. faecalis* over the last years. In contrast to our study, Magyar et al. found an increase in *E. faecalis* infections from 2004 to 2015 in Hungary.[18] Different geographical incidence rates of bacteria might be a possible reason for this finding.[8]

K. pneumoniae was responsible for 9% of the UTIs in this study, which is higher than the 2.5% described in the Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) study.[17] The rate of *P. mirabilis* was the same as that reported in the ARESC study,[17] although higher rates have been reported in Portugal and Greece in the ECO.SENS study (16.9% and 11.6%).[13]

P. aeruginosa was detected in 7% of urine cultures in this study. This rate is in line with previous reports of nosocomial UTIs.[19,20] Shigemura et al. described that *P. aeruginosa* infections are more frequentin complicated than uncomplicated UTIs.[21] This is clinically relevant since *P. aeruginosa,* commonly found in nosocomial infections, frequently displays resistance to several antimicrobial agents. Antibiotic therapy against *P. aeruginosa* is complex, since most antibiotics cannot penetrate the outer membrane of the bacteria. According to the literature, only imipenem and 3rd and 4th generation cephalosporins are effective.[16]

Information about antibiotic resistance patterns with regard to the treatment of UTIs in different regions of Germany is limited and therefore it is difficult to compare the results of antibiotic resistance from this study with other studies because of a dynamic situation which changes over time and between different regions. Furthermore, it is noteworthy that the studies referenced above primarily focused on resistance patterns of *E. coli,* since *E. coli* causes most UTIs. However, antimicrobial resistance of other bacteria should also be considered in order to determine an appropriate treatment plan.

One of the largest multinational studies that dealt with the bacterial spectrum of UTIs and the emergence of antibiotic resistance in uncomplicated UTIs is the ARESC study by Schito et al.[17] In the ARESC study, country-specific bacterial spectrum was reported and associated antimicrobial resistance patterns were described. Patients from nine European countries and Brazil were enrolled in the study between the years of 2003 and 2006. The results of the study from Germany were reported by Wagenlehner et al.[11]

The use of gyrase inhibitors has decreased tremendously in Germany and world-wide in recent years due to increasing resistance patterns and new information about possible side effects of these medications.[22] The overall sensitivity rate of bacteria to ciprofloxacin was 79% in our study. In the data from Germany in the ARESC study, it was even higher, with 92.3% of the bacteria being sensitive to ciprofloxacin.[11]

Susceptibility to cefuroxime was only found in 45% of cases in our study. Therefore, cefuroxime susceptibility was significantly lower in our cohort compared to a susceptibility of 89.6% in Germany between the years 2003 and 2006 reported by Wagenlehner et al.[11] This information of decreasing sensitivity to cephalosporins should be an alarming signal concerning our prescribing habits, since these antibiotics have become standard of care for empiric therapy and for preoperative single dose prophylactic use in many urology departments. While our study showed a decrease in sensitivity to third generation cephalosporins over time (Table 5), uropathogens were still more susceptible to third generation cephalosporins than to second generation cephalosporins. Based on these results, we modified our clinical protocols and use now third generation cephalosporins for first-line empiric therapy and prophylactic use.

One limitation of the current study is that some relevant antibiotics such as trimethoprim or fosfomycin were not analyzed in detail in this study, as these antibiotics were not as frequently tested as would be necessary for a detailed analysis. Furthermore, patients with infections such as epididymitis or prostatitis rarely presented to our hospital during the study time period. Therefore, data on these infections were inadequate to conduct a robust analysis for statistical significance.

We would like to emphasize that this study focused on local uropathogen and antibiotic sensitivity rates in one hospital. Different spectra and sensitivity rates might be found elsewhere.

The study was designed to reflect the pragmatic approach to pathogen analysis of UTIs and common antibiotic treatment in Bad Homburg, Germany.

5. Conclusions

We conclude that in the current study, bacteria showed a reduced susceptibility to several antibiotics including ampicillin/sulbactam and the third generation cephalosporins cefotaxime and ceftazidime, which are frequently used worldwide. Therefore, it is necessary to enhance continuous monitoring of the prevalence of uropathogens and antimicrobial resistance rates in local contexts.

Acknowledgments

We thank the Department of Hospital Hygiene of the Hochtaunuskliniken. (Bad Homburg, Germany) for providing us pseudonymized data of detected uropathogens and antibiotic susceptibility.

Statement of ethics

The study was accepted by the local ethics committee on 13th June 2016. According to the local institutional regulations, there'sa waiver of the written consent since only pseudonymized data was used. All procedures performed in study involving human participants were 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.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

SV: Participated in research design, writing of the paper, performance of the research and data analysis;
PW: Participated in research design, performance of the research, data analysis;
AK: Participated in the performance of the research;
ON: Participated in writing of the paper;
LN: Participated in writing of the paper;
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How to cite this article: Vallo S, Wirth P, Kukic A, Nafez O, Neagoe L, Nestler S, Jones J. Decreasing susceptibility of bacteria to ampicillin/sulbactam and third generation cephalosporins in urinary tract infections. *Curr Urol* 2022;16(2):94–98. doi: 10.1097/CU9.0000000000000079