Antibiotic Susceptibility and Resistance Patterns in Urine Cultures - A Single Center Experience

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Author’s Contribution

1 Conception of study
2 Experimentation/Study conduct
3,5 Analysis/Interpretation/Discussion
3,5 Manuscript Writing
4,6 Critical Review
4,6 Facilitation and Material analysis

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Abstract

Introduction: Antimicrobial resistance is a threatening global medical challenge. Its prevalence is on the rise, more so in developing countries like Pakistan. It is pivotal to know and follow the local drug sensitivity and resistance pattern for effective empirical treatment of urinary tract infections.

Objectives: To evaluate antibiotic susceptibility and resistant patterns of different urinary pathogens in cultures among patients presented in a tertiary care hospital.

Materials and Methods: A Descriptive Cross-sectional study was carried out at the Department of Nephrology and Microbiology Holy Family Hospital, Rawalpindi Medical University from January 2018 to July 2018. All the samples from patients suspected to be suffering from UTI that were ordered a urine culture by attending doctors were recruited for the study and were sent to the central pathology laboratory of the hospital. All urine cultures performed in HFH were recruited for the study including both inpatient and outpatient departments. Data were collected in a structured performa and were entered and analyzed in SPSS version 21.0.

Results: 402/1216 (33.0 %) urine samples had positive bacterial growths. Females accounted for the majority of 61.6% of cases. E.coli was the most common isolate 42.7%, followed by Klebsiella spp. 17.5%. E.coli exhibited high antimicrobial resistance, with the least resistance to fosfomycin 13.6%. E.coli, Klebsiella spp. and pseudomonas showed significant coreistance to Ceftazidime and ciprofloxacin.

Conclusion: Emergence of high AMR in a developing country like Pakistan can have grave clinical and economic implications. It adversely impacts all aspects of patient care. It limits therapeutic options and leads to treatment failure.

Keywords: Antimicrobial resistance, Healthcare-associated UTI, healthcare-associated infections, uropathogenic E. coli, extended-spectrum beta-lactamases, multidrug-resistant.
Introduction

Urinary Tract Infections (UTI) are a major global public health issue as they are the most prevalent bacterial infections both in the community and in hospitals. Every year 150 million people suffer from UTI worldwide with considerable economic burden. UTI can arise anywhere in the urinary tract, females being afflicted mostly in the form of uncomplicated cystitis. One in three women will develop an antibiotic requiring UTI during their lifetime. Clinical spectrum of urinary tract infections includes asymptomatic bacteria, uncomplicated UTI, complicated UTI, recurrent UTI and antibiotic-resistant UTIs. HAUTI accounts for approximately 40% of nosocomial infections. The diagnosis of UTI can be made based on a combination of symptoms and a positive urine culture. Gram-negative Enterobacteriaceae are common causes of both community-acquired and HAUTIs. Uropathogenic E.coli (UPEC) a normal gut commensal is responsible for almost 80% of uncomplicated community-acquired UTIs. UTI is one of the most prevalent indications for antibiotic prescription globally. UTI's account for the most common antibiotic-resistant infections in primary health care (PHC). Major antibiotic consumption is in PHC, accounting for 75%-80% of all antibiotics prescribed. Antimicrobial resistance (AMR) arises when bacteria survive exposure to an antimicrobial that would normally kill or inhibit growth. Consequently, these strains continue to proliferate and spread, due to a lack of competition from other strains. This has led to the emergence of superbugs. More than two million infections in the US annually are caused by bacteria resistant to first-line antibiotics. By 2050, 10 million lives per year will be at risk from antibiotic-resistant infections. AMR is an emerging global menace endangering efficacy of antibiotics. AMR reduces the effectiveness of antibiotics, leading to increased morbidity, mortality, length of stay and health care expenditure. In developing countries, a paucity of expensive second-line antibiotics could worsen the situation. Similarly in outpatients resistance to commonly prescribed antibiotics for UTI in children is increasing, more so in developing countries. Non-adherence to as well as non-availability of local antibiotic sensitivity pattern, OTC antimicrobial availability, recent antibiotic exposure, routine and injudicious use of antibiotics all are contributing to AMR. Previous antibiotic use in primary health care increased the subsequent risk of E.coli resistance to that particular antibiotic. For an antibiotic to be considered a first-line empirical treatment for UTI, resistance should not exceed 20% in the most likely infecting strain. To combat AMR, regular surveillance, new effective drugs, and global public awareness campaigns are mandatory. Effective empirical antibiotics can only be prescribed if local epidemiologic data regarding the common bacteria and antibiotic sensitivity is available.

Materials and Methods

Descriptive cross-sectional study: Samples from patients suspected to be suffering from UTI were collected and sent to the central pathology laboratory of the hospital. All urine cultures performed in HFH were recruited for the study including both inpatient and outpatient departments. Quantitative urine cultures were performed by the calibrated loop technique delivering approximately 0.01 ml of sample onto Mueller Hinton agar plates followed by incubating the plates at 35-37°C for 24 hours. The isolates were further identified using standard microbiological methods and subjected to antibiotic susceptibility and resistance against antibiotics by Kirby-Bauers disc diffusion method according to Clinical Laboratory Standards Institute (CLSI). The diameters of inhibition zones were in millimeters and interpreted according to the manufacturer’s guidelines. Significant bacteriuria was defined as isolation of more than 10^5 CFU/ml. Also positive culture with no more than 2 species of organisms, at least one of which is a bacterium of ≥ 10^5 CFU/ml. Samples with three or more pathogens were discarded as contamination. Antimicrobials used for antibiotic susceptibility/resistance testing were amoxicillin/clavulanic acid, amikacin, cefixime, cefotaxime, ceftazidime, cefepime, cotrimoxazole, cefoperazone-sulbactam, fluoroquinolones (ciprofloxacin/levofloxacin/moxifloxacin), fosfomycin, gentamicin, carbapenems (imipenem/meropenem), nitrofurantoin, and piperacillin/tazobactam. Gram-positive bacteria were also tested against cefoxitin, clindamycin, fusidic acid, linezolid, and vancomycin. Data was collected in a structured performa and was entered and analyzed in SPSS version 21.0.
Results

Out of a total of 1216 urine samples submitted, 680 samples had no growth. Candida was positive growth in 60, mixed growth present in 74. A total of 402 samples exhibited positive bacterial growth. Single growth was positive in 376 samples, whereas 26 cultures plates exhibited a growth of two organisms. So a total of 428 organisms were tested for antibiotic susceptibility and resistance patterns. Out of positive samples, females accounted for majority 264/428 (61.68%) cases, whereas specimens from males were about 164/428 (38.31%).

Gram-negative bacteria were the most common isolate 360/428 (84.11%), whereas Gram-positive bacteria accounted for 68/428 (15.88 %). Overall the most common organism isolated was E.coli accounting for 183/428 (42.76%), followed by Klebsiella spp. 75/428 (17.5%). Enterococcus spp. was the third most common organism 56/428 (13.06%). Acinetobacter accounted for 41/428 (9.58%). Coliform spp. comprised of 33/428 (7.71 %). Pseudomonas aeruginosa was 25/284 (5.84 %). MRSA accounted for 11/428 (2.57%). Proteus mirabilis 2/284 (0.47%), whereas S.aureus and Serratia marcescens each accounted for one case (0.23%) respectively.

Table 1: Age Demographics

| No of Cases | 430 |
| Mean        | 47.4488 |
| Std. Deviation | 12.19369 |
| Minimum    | 16.00 |
| Maximum    | 75.00 |

Table 2: Gender demographics

<table>
<thead>
<tr>
<th>Gender</th>
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<th>Percent</th>
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<tbody>
<tr>
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<tr>
<td>Female</td>
<td>264</td>
<td>61.7</td>
</tr>
<tr>
<td>Total</td>
<td>428</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Discussion

In our study E.coli was the most common isolate from urinary specimens, this is consistent with almost all studies reviewed.23,24,25 E.coli is emerging as an MDR pathogen worldover.26,27,28 In the past, MDR bacteria were prevalent in nosocomial/healthcare-associated infections. But now they are being increasingly found in community sources of infection. This will have dire consequences as AMR is associated with the poor patient outcomes with increased health care costs.29 Fluoroquinolones proved to be very effective for UTI for many years, as resistance was very low initially. Unfortunately, progressive escalation in global quinolone resistance is a crucial development.30 WHO has declared E.coli as one of the major antibiotic-resistant human pathogens from data collected from 17 countries and documented ciprofloxacin resistance of UPEC from 8% to 65%. In October 2015 WHO took the initiative to establish the Global Antimicrobial Resistance Surveillance System (GLASS) to monitor AMR worldwide.31 E.coli is the most common uropathogen producing ESBL,32 an enzyme produced by bacteria inactivating β-lactam antibiotics (penicillins, cephalosporins, and aztreonam).33 The global increase in the prevalence of ESBL producing E.coli is critical, reported higher in Asia compared to Europe.34 ESBL producing E.coli also harbor various other antimicrobial resistance genes rendering them resistant to other clinically important alternatives like aminoglycosides, cotrimoxazole, fluoroquinolones, trimethoprim. This significantly reduces therapeutic options and increases therapeutic failure.35,36,37 Another worrisome aspect increases in Carbanapemase producing E.coli, especially in healthcare-associated infections, rendering carbapenems ineffective.38

In our study, E.coli exhibited high resistance to all available oral antibiotics with the least resistance to fosfomycin 13.8%, a drugless used in our population. Resistance to commonly used drugs for empiric treatment of UTI is as follows: amoxicillin-clavulanic acid 87.5%, cotrimoxazole 82.1%, ciprofloxacin 74.3%, cefuroxime 88.9%, cotrimoxazole 82.1% nitrofurantoin 31.7%. Resistance to 3rd and 4th generation cephalosporins was above 85% Overall resistance observed is much higher than what has been reported previously. E.coli, Klebsiella spp. and pseudomonas exhibited significant co-resistance to ciprofloxacin and ceftazidime. In our study overall resistance is much higher than what has been reported previously in Pakistan. Ibrahim et al (2012) from Sudan reported 92.7% MDR-UPEC, ESBL positivity 32.7%, resistance to cotrimoxazole 88.3%, ciprofloxacin 58.4%, nitrofurantoin 22.4%, cefotaxime 92.5%.38 Oluwasola et al (2013) from Nigeria reported UPEC with MDR (36.5% resistant to 10 out of 11 antimicrobials), with fluoroquinolone resistance ranging from 65.7–89.9%. Lowest resistance was observed for nitrofurantoin (7.3%).39 Daoud et al (2015) reported resistance as follows ciprofloxacin 41%, cotrimoxazole 41.6%, ceftazidime 30.2% nitrofurantoin 4.1%, fosfomycin 0.4% with progressive increase in ESBL positivity, increasing from 1.3% in 1997 to 25.3% in 2012 in UPEC in Lebanese population.40 Jena et al (2016) observed UPEC with MDR 68.7%, having resistance to ofloxacin 93.5%, cotrimoxazole 67.5%, cefepime/ceftriaxone 96.1%, ceftazidime 100%, nitrofurantoin 24.6% and ESBL genes in 59.4%.36 Alizade et al (2018) E.coli fluoroquinolone resistance between 5–64.7% cotrimoxazole 4.2–88.2%, third-generation cephalosporins 15 to 87%, and ESBL positivity ranging between 17.45 – 66.2% from different regions of Iran.36,37,38 Woldai et al (2016) documented E.coli resistance to ciprofloxacin 30%, ceftriaxone 7% in community antibiogram from Texas USA.23 Fazae et al (2018) reported ESBL genes in 5.9 % of UTI’S in ED.40,41 Tandogdu et al reported 20% resistance to all antimicrobials in HAUTI.41 In 2014 Ali et al from Pakistan observed UPEC resistance as follows cotrimoxazole 86%, ciprofloxacin/ceftazidime 57.5%, cefixime 53.7%, and nitrofurantoin 3.7% in outpatients.42 CDDEP reported a higher Drug Resistance Index in developing countries because of higher disease burden and higher consumption of antibiotics.43 In 2017 CDDEP E.coli resistance map for Pakistan reported resistance as follows: aminopenicillins 97%, carbapenems 10%, cephalosporins (3rd Gen) 86%, fluoroquinolones 59%.43 Overall worldwide AMR shows considerable geographical variation.41,43,44 AMR is coupled with a degree of exposure to a particular antimicrobial; selection pressure. This has been observed with fluoroquinolones and cotrimoxazole.44 Areas with high prescription rates for these antimicrobials developed correspondingly high resistance rates to these drugs. Avoidance or decreased exposure to a certain antimicrobial over years/decades can probably increase susceptibility.3,44 This necessitates the appropriate use and disposal of antimicrobials in the health sector as well as in the food industry (animal health and agriculture). WHO recommends a global strategic plan involving all countries to increase.
awareness, global AMR surveillance, and infection prevention, and antibiotic stewardship, development of new antibiotics, vaccines and diagnostic tools. This study focused on single-center experience. Patient records were not available, so the distinction between asymptomatic bacteriuria and true infection could not be made. Also, the distinction between inpatient and outpatient samples was not possible. Data from HAUTI tends to exaggerate AMR.

**Conclusion**

High antibiotic resistance observed in our study can have far-reaching public health implications. AMR is a serious national and global public health challenge that needs continuous surveillance and resolute management. We need multicenter and larger-scale prospective studies from all over Pakistan to collect data and establish a central national registry. AMR can vary from region to region even in the same country. Documentation susceptibility and resistance patterns and adhering to them are imperative. All measures have to be taken to minimize community antibiotic exposure.

**Acknowledgments**

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