Antibiotic Resistance in Urinary Tract Infection in a Tertiary Care Hospital in Bangladesh-A Follow-up Study

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Abstract

Introduction: Bacterial resistance to antibiotics is one of the most challenging global health threats. Urinary tract infections (UTIs) are a common infection. Regional surveillance programs are necessary to update knowledge on antimicrobial resistance pattern where empirical antibiotic treatment is the mainstay. The aim of this follow up study is to see the changing trends in bacteriology and antibiotic resistance pattern among urological pathogens in comparison to similar study 5 years back. Materials and Methods: We performed a prospective study in Comilla Medical College Hospital, Bangladesh during the period of July 2015- June 2016. Midstream clean-catch urine samples were collected from 658 suspected UTI patients with age more than 12 years and inoculated in MacConkey & Blood agar media for semi quantitative urine culture and sensitivity test. Antibiotic susceptibility pattern was done by Kirby-Bauer disc diffusion method following clinical laboratory science (CLS) program. Results: Culture positive were in 198 samples among 658 inoculated samples. E. coli was isolated from 171(86%) samples which was the most predominant bacteria followed by Klebsiella and Enterococcus. UTI with E. coli was significantly increased in the year 2016 in comparison to 2011. Meropenem, imipenem, amikacin, tazobactum, gentamycin nitrofurantoin, and mecillinum found resistance against 0% to 12% of the urological pathogens. Bacteria offered high degree of resistance against commonly used antibiotics - amoxycillin, amoxiclav, cephradine and cefixime ranging 60% to 86%. Comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone, amoxiclav and reduced resistance for nalidixic acid, mecillinum and cefuroxime. Conclusion: E. coli infection is significantly increasing in follow up study from 2011 to 2016 with no steady increase in resistance to all antibiotics. Imipenem, meropenem, tazobactum, amikacin and nitrofurantoin still remain more sensitive while comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone, and amoxiclave and reduced resistance for nalidixic acid, mecillinum, cefixime and cefuroxime.

Keywords: Urinary tract infection, Follow up comparative study, Changing trends, Culture, Sensitivity, Resistance.

Number of Tables:06; Number of References:27; Number of Correspondences:05

Introduction

Bacterial infection resistance to antibiotics is one of the most challenging global health threats faced in modern medicine. It has been estimated that by 2050, 10 million lives per year will be at risk from antibiotic-resistant infections 1. In September 2016, 193 countries agreed to prioritize reducing antimicrobial resistance at the United Nations General Assembly following a worldwide campaign by the UK Government2. Urinary tract infection (UTI) is a common bacterial infection globally and is a major public health problem in terms of morbidity and treatment cost which affecting 150 million people each year worldwide3,4. It also represent the most common antibiotic-resistant infections in primary care setting5,6. It is a leading cause of repeated physician consultations and antibiotic resistance and problem for clinicians in selecting appropriate antibiotic7,8.

Diagnosis and treatment of UTI are mostly empirical to initiate empirical treatment with appropriate antibiotic is necessary to have current knowledge regarding causative organisms and their antibiotic resistance pattern9. But alarming fact is that a large number of patient do not respond to conventional antimicrobial agents10.
Antibiotic use affects bowel flora acquiring drug resistance and may increase risk of urinary autoinoculation with antibiotic-resistant microbes. Antimicrobial resistance is a well known important emerging clinical and public health problem. There are various reports available in last two decades about changing pattern of pathogen and their sensitivity pattern to routinely used antibiotics which makes the situation miserable. An increasing antibiotic resistance among urological pathogens to commonly prescribed drugs has become a global reality. Resistance occurs in intestinal bacteria due to antibiotic therapy for treating infections outside the urinary tract. The irrational use of antibiotics has an influence in the spread of antimicrobial resistance among bacteria. Controlling antimicrobial resistance is a major issue confronting organized health care today. Therefore this is warranted to know information about rapidly changing sensitivity pattern of micro-organisms towards antibiotics in UTI. For updated proper therapeutic interventions, periodic evaluation and regional surveillance programs is necessary with antibiotic resistance data and analysis about antimicrobial resistance to uropathogens.

The present study was undertaken to find the current urological pathogens and their antibiotic resistance pattern in a tertiary hospital in Bangladesh to compare with previous pattern of study in 2011. It will be helpful for awareness and antibiotic use in UTI in this tertiary level hospital and country level.

Materials and Methods

It was a prospective study conducted during July 2015 to June 2016 on patients attending the outpatient and inpatient departments of in department of medicine, Comilla Medical College Hospital for culture within half an hour of collection. A modified semi-quantitative technique using a standard calibrated bacteriological loop of urine was performed to transfer 0.001 ml of sample on blood agar and MacConkey agar media. After allowing the urine to be absorbed into the agar, the plates were then inverted and incubated aerobically at 37°C for 24 hours. The plates were then examined macroscopically for bacterial growth. The colony count was done using semi quantitative method. Number of colonies obtained was multiplied by 1000 to obtain the colony forming units (CFU)/ml. A significant growth is considered if the number of colony is ≥ 105 CFU/ml. Colonial appearance and morphological characters of isolated bacteria was noted and gram staining was done for identification of the isolated organisms. The characteristic bacteria on the culture media were aseptically isolated.

Antimicrobial sensitivity tests were carried out by disc diffusion technique using Muller Hinton Agar. Interpretation of results was expressed in sensitive and resistant depending upon the size of the zone of inhibition. The antibiotics used for susceptibility testing in our study were amoxycillin, amoxyclyl, amikacin, cefixime, ceftazidine cefuroxime, cephadineciprofoxacin cotrimoxazole, cefotaxime, ceftriaxone, cephalxin, gentamycin, imipenem, meropenem, mexitilum, nalidexic acid, nitrofurantoain, and tazobactum. All the authors vouch for the completeness and accuracy of data and analyses presented.

Results

Total 658 patients urine samples were collected in 2016 and their baseline characteristics are shown below. The table I and II, the bacterial growth was positive in 198 patients out of total 658 patients included in the study. Most of the patients were from rural community, married, sexually active, middle class, had fever, abdominal pain, dysuria and comorbid condition as diabetes mellitus, hypertension. 50% patients took antibiotics before included in study.

Table-I: Base line characteristics in patients without growth in urine culture.

| Residence          | Frequency (n=460) | Percentage |
|--------------------|------------------|------------|
| Urban              | 136              | 30         |
| Rural              | 334              | 70         |

| Education          | Frequency (n=460) | Percentage |
|--------------------|------------------|------------|
| Educated           | 303              | 66         |
| Not educated       | 157              | 34         |

| Marital status     | Frequency (n=460) | Percentage |
|--------------------|------------------|------------|
| Married            | 338              | 73         |
| Unmarried          | 122              | 27         |

| Sexual activity    | Frequency (n=460) | Percentage |
|--------------------|------------------|------------|
| Active             | 285              | 62         |
| Not active         | 175              | 38         |

| Economical status  | Frequency (n=460) | Percentage |
|--------------------|------------------|------------|
| Lower class        | 49               | 11         |
| Middle class       | 393              | 85         |
| Higher class       | 18               | 4          |
Table-II: Base line characteristics in patients with growth in urine culture.

| Characteristic                  | Frequency (n=198) | Percentage |
|--------------------------------|-------------------|------------|
| Dysuria                        |                   |            |
| • Present                      | 321               | 68         |
| • Absent                       | 139               | 32         |
| Urgency                        |                   |            |
| • Present                      | 359               | 78         |
| • Absent                       | 101               | 22         |
| Fever                          |                   |            |
| • Present                      | 336               | 73         |
| • Absent                       | 124               | 27         |
| Abdominal pain                 |                   |            |
| • Present                      | 354               | 77         |
| • Absent                       | 106               | 23         |
| Treated with antibiotics       | 221               | 48         |
| • Yes                          | 239               | 52         |
| • No                           |                   |            |
| Co-morbid condition            |                   |            |
| • DM                           | 55                | 12         |
| • HTN                          | 15                | 3          |
| • ISD                          | 8                 | 2          |
| • Others                       | 34                | 7          |

Among 198 culture positive samples, E. coli was ranked highest 171(86%), simultaneously growth of Klebsiella pneumonia and Enterococcus was found in 17(9.6%) and 10(5%) samples. It was also observed from table III that the maximum numbers of isolates were distributed among the females 123 (62%).

Table-III: Frequency of Isolation of organism in relation to sex of patient and their overall percentage.

| SL No. Bacterial Isolates | Frequency Number (%) | Male (%) | Female (%) |
|---------------------------|----------------------|----------|------------|
| 01 E. coli                | 171 (86)             | 69 (35)  | 102 (51)   |
| 02 Klebsiella             | 17 (9.6)             | 4 (2)    | 13 (7)     |
| 03 Enterococcus           | 10 (5)               | 2 (1)    | 8 (4)      |
| Total                     | 198                  | 75 (38)  | 123 (62)   |

UTI with E. coli was found statistically significant increase in the year 2016 with p values <0.01(table - IV).

Table- IV: Comparative study between the common isolated urological pathogenic bacteria in the year 2016 and 2011.

| Name of organism       | No (%)       | No (%) | Chi-Square Value (x²) | P. value |
|------------------------|--------------|--------|-----------------------|----------|
| E. coli                | 171 (86)     | 98 (75)| 3.17                  | <0.01    |
| Klebsiella             | 17 (9.6)     | 14 (10.4)| .29                   | >0.1     |
| Enterococcus           | 10 (5)       | 8 (6)  | .38                   | >0.1     |
Study shows, meropenem, imipenem, amikacin, tazobactum, gentamycin, and mecillinum, were found to be most effective antibiotic against most of the urological pathogens. In vitro sensitivity of the isolates to these antibiotics was shown to be varied from 88% to 100%. Table V also shows high degree of resistance against commonly used antibiotics- amoxycillin, amoxiclav, cephradine and cefixime. In vitro resistance of the isolates to these antibiotics was varied from 60% to 86%.

Table-V: In vitro antibiotics resistance pattern of the bacteria (n=198).

| SL No. | Name of antibiotics | Total No Sensitive | Percentage |
|--------|---------------------|--------------------|------------|
| 01     | Meropenem           | 0                  | 0          |
| 02     | Imipenem           | 1                  | 0.5        |
| 03     | Amikacin           | 2                  | 1          |
| 04     | Tazobactum         | 2                  | 1          |
| 05     | Gentamycin         | 20                 | 10         |
| 06     | Nitrofurantoin     | 23                 | 12         |
| 07     | Mecillium          | 24                 | 12         |
| 08     | Colistin           | 31                 | 16         |
| 09     | Cefazidime         | 84                 | 47         |
| 10     | Ceftriazone        | 96                 | 55         |
| 11     | Cefotaxime         | 112                | 57         |
| 12     | Cefuroxime         | 114                | 58         |
| 13     | Nalidexic acid     | 190                | 55         |
| 14     | Cephalaxine        | 112                | 57         |
| 15     | Cefuroxime         | 114                | 58         |
| 16     | Cefotaxime         | 114                | 58         |
| 17     | Cefixime           | 118                | 60         |
| 18     | Cephradine         | 130                | 66         |
| 19     | Amoxiclav          | 149                | 76         |
| 20     | Amoxicillin        | 170                | 86         |

There was statistically significant increase in resistance pattern in year 2016 in comparison to 2011 was detected for ceftriazone, and amoxiclav with p value <0.001, which is shown in table VI. On the other hand significant reduced resistance was found for nalidexic acid, mecillinum, cefixime and cefuroxime. No statistically significant change in sensitivity pattern was shown for other antibiotics.

Table-VI: Comparative study between 2016 and 2011 of trend of antibiotic resistance pattern of uropathogenic bacteria.

| Antibiotic | 2016 (n=198) | 2011 (n=131) | Chi-Square Value (x²) | P value |
|------------|--------------|--------------|-----------------------|---------|
| Carbapenem |              |              |                       |         |
| Imipenem   | 1(0.5%)      | 0(0%)        | 0.04                  | 0.83ns  |
| Meropenem  | 0(0%)        | 3(2.0%)      | 2.39                  | 0.12ns  |
| Cephalosporins |     |              |                       |         |
| 1st Generation |         |              |                       |         |
| Cephradine | 130(66.0%)   | 83(63.0%)    | 0.18                  | 0.67ns  |
| Cephalaxine| 112(57.0%)   | 85(64.9%)    | 2.27                  | 0.13ns  |
| 2nd Generation |         |              |                       |         |
| Cefotaxime | 114(58.0%)   | 80(61.0%)    | 0.38                  | 0.52ns  |
| Cefazidime | 84(42.0%)    | -            | 72.41                 | <0.001* |
| Cefuroxime | 84(42.0%)    | 82(63.0%)    | 12.83                 | <0.001* |
| 3rd generation |         |              |                       |         |
| Cefotaxone | 102(51.5%)   | 31(24.0%)    | 25.39                 | <0.001* |
| Cefixime   | 80(40.0%)    | 91(70.0%)    | 26.37                 | <0.001* |
| Quinolones |              |              |                       |         |
| Nalidexic acid | 89(45.0%) | 98(75.0%)    | 28.65                 | <0.001* |
| Ciprofloxacin | 104(52.0%) | 86(65.5%)    | 5.6                   | 0.02s   |
| Aminoglycosides |          |              |                       |         |
| Amikacin   | 2(1.0%)      | 3(2.3%)      | 0.22                  | 0.63ns  |
| Gentamycin | 20(10.0%)    | 18(14.0%)    | 1.02                  | 0.31ns  |
| Penicillin |              |              |                       |         |
| Amoxiclav  | 149(76.0%)   | 31(24.0%)    | 84.67                 | <0.001* |
| Amoxicillin| 170          | 114(87.0%)   | 0.09                  | 0.76ns  |
| Mecillium  | 24(12.0%)    | 39(30.0%)    | 15.86                 | <0.001* |
| Colistin   | 31(16.0%)    | 17(13.0%)    | 0.45                  | 0.50ns  |
| Nitrofurantoin | 23(12.0%) | 12(9.0%)     | 0.50                  | 0.47ns  |
| Tazobactum | 2(1.0%)      | -            | 0.18                  | 0.66ns  |
| Cotrimoxazole | 93(47%)   | 81(62.0%)    | 6.98                  | 0.008s  |

Discussion
This study demonstrates the distribution and antibiotic resistance pattern of bacteria isolated from patients with suspected UTI from a tertiary care center. In our center only 31% had culture positive in patients with UTI.
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Tazobactum, amikacin and nitrofurantoin still remain more sensitive while comparative study of 2016 vs 2011 shows significant increased resistance for ceftriaxone and amoxiclav and reduced resistance for nalidixic acid, mecillinum, cefixime and cefuroxime.

Conflict of Interests: None.

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References

1. O’Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. May 2016 http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

2. UK Department of Health. UK Secures Historic UN Declaration on Antimicrobial Resistance. September 2016. https://www.gov.uk/government/news/uk-secures-historic-un-declaration-on-antimicrobial-resistance.

3. Gonzalez CM, Schaeffer AJ. Treatment of urinary tract infection: what's old, what's new, and what works. World J Urol. 1999; 6: 372-382. https://doi.org/10.1007/s003450050163

4. Stamm WE, Norby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis. 2001; 183 (Suppl 1):S1–S4. https://doi.org/10.1086/318850 PMid:1171002

5. Bryce A, Hay AD, Lanel F. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ. 2016; 352: i939. https://doi.org/10.1136/bmj.i939 PMid:26980184 PMCid:PMC4793155

6. Chin TL, Mac Gowan AP, Bowker KE. Prevalence of antibiotic resistance in Escherichia coli isolated from urine samples routinely referred by general practitioners in a large urban centre in South-west England. J Anti microbChemother. 2015; 70: 2167-9. https://doi.org/10.1093/jac/dkv050

7. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon. 2003; 49: 53–70. https://doi.org/10.1067/mda.2003.7 PMid:12601337

8. Petersen I, Hayward AC. Antibacterial prescribing in primary care. J Anti microbChemother. 2007; 60: 43–7. https://doi.org/10.1093/jac/dkm156 PMid:17656380
9. Allison ECK. Urises-becoming-untreatable-with-the-rise-of-antibiotic-resistance. Pbs. www.pbs.org/Mar 1, 2017.
10. Ram S, Gupta R, Gaheer M. Emerging antibiotic resistance among uropathogens. Ind J Med Sci. 2000; 54: 388.
11. Senewiratne B, Senewiratne K, Hettiarchchi, J. Bacteriology and antibiotic sensitivity in acute urinary tract infection in Ceylon. Lancet. 1973; 1: 222-225.
https://doi.org/10.1016/S0140-6736(73)93130-9
12. Ebrahimzadeh M.A., Mahdavee M.R., Vahedi M. Antibiotic resistance in E. coli isolated from urine: A 2-years study isolated from patient with urinary tract infections in Iran. J. Cell Tissue Res. 2005; 5(2): 445-448.
13. Udur G. Drug resistant cholera in India attributed to antibiotic misuse. BMJ. 2000; 321: 1368-1369.
https://doi.org/10.1136/bmj.321.7273.1368/a
14. M I Majumder, T Ahmed, D Hossain, S Begum. Bacteriology and antibiotic sensitivity patterns of urinary tract infections in a tertiary hospital in Bangladesh. Mymensingh Med J. 2014; 23 (1): 99-104.
PMid:24584381
15. Urine Cultures- General Procedure: University of Nebraska Medical Center Division of Laboratory Science Clinical Laboratory Science Program CLS 418/CLS 419
16. B H N Yasmeen, S Islam, S Islam, M MUddin, R Jahan. Prevalence of urinary tract infection, its causative agents and antibiotic sensitivity pattern: A study in Northern International Medical College Hospital, Dhaka. 2015; 7 (1): 105-109.
17. García-Morúa A, Hernández-Torres A, Salazar-de-Hoyos JL, Jaime-Dávila R, Gómez- Guerra I.S. Community acquired urinary tract infection etiology and antibiotic resistance in a Mexican population group. Revista Mexicana de Urología. 2009; 69: 45–48.
18. Boucher HW, Talbot GH, Bradley JS. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009; 48(1): 1–12.
https://doi.org/10.1086/595011
PMid:19035777
19. Henry Oladeinde B, Omorogie R, Olley M, Anunibe JA. Urinary tract infection in a rural community of Nigeria. North American Journal of Medical Sciences. 2011; 3(2): 75–77.
https://doi.org/10.4297/najms.2011.375
PMid:22540069 PMCid:PMC3336890
20. Ebie M, Kandakai-Olukemi YT, Ayanbadejo J, Tanyigna KB. Urinary tract infection in a Nigeria Military Hospital. Nig J Microbiol. 2001; 15(1): 31-37.
21. Kumar MS, Lakshmi V, Rajagopalan R. Related Articles, Occurrence of extended spectrum beta-lactamases among Enterobacteriaceae spp. isolated at a tertiary care institute. Indian J Med Microbiol. 2006; 24(3): 208-211.
PMid:16912442
22. Khan AU, Musharraf A. Plasmid mediated multiple antibiotic resistance in P. mirabilis isolated from the UTI patients. Medical Sci Mon. 2004; 10: 598-602.
23. Sleigh, J D, Timbury, M C. Notes on Medical Bacteriology. 2nd edition. Churchill Livingstone Inc., 1560 Broadway: New York; 1986.
24. Ebrahimzadeh M A, Mahdavee M R, Vahedi. M. Antibiotic resistance in E. coli isolated from urine: A 2-years study isolated from patient with urinary tract infections in Iran. J. Cell Tissue Res. 2005; 5(2): 445-448.
25. Prais D, Straussberg R, Avitzur Y, Nussinovitch M, Harel L, Amir J. Bacterial susceptibility to oral antibiotics in community acquired urinary tract infection. Archives of Disease in Childhood. 2003; 88: 215-218.
https://doi.org/10.1136/adc.88.3.215
PMid:12598381 PMCid:PMC1719471
26. Hossain MA, Sultana R, Islam F, Islam AH. Prevalence of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in an urban hospital in Dhaka, Bangladesh. Int. J Antimicrob Agents. 2004; 24(5): 508-510.
https://doi.org/10.1016/j.ijantimicag. 2004.05.007.
27. Colgan R, Williams M. Diagnosis and Treatment of Acute Uncomplicated Cystitis Am Fam Physician. 2011, 1; 84(7):771-776.