Research Article

Fluoroquinolones resistance among uropathogens at a tertiary-care hospital, Ahmedabad

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Received November 18, 2015. Accepted November 24, 2015

Abstract

Background: Urinary tract infection (UTI) is one of the most common infections in both outpatients and hospitalized patients. The progressive increase in antimicrobial resistance among patients with UTIs is of great concern.

Objective: To determine the resistance patterns of fluoroquinolones in UTIs.

Materials and Methods: This study was conducted at NHL Municipal Medical College, Ahmedabad, Gujarat, India, from October, 2013 to March, 2015. A retrospective analysis of data taken from all urine samples (6,545 patients suspected of UTI) was analyzed. A total of 1,744 isolates were found for which fluoroquinolones susceptibility was analyzed. Cultures with *Candida* growth were excluded from this analysis. Antimicrobial susceptibility was done by Kirby–Bauer's disc diffusion method as per Clinical and Laboratory Standards Institute guidelines.

Result: *Escherichia coli* (55.1%) was the leading uropathogen, followed by *Klebsiella* spp. (22.3%), *Pseudomonas aeruginosa* (11.9%), *Acinetobacter* spp. (3.2%), *Enterobacter* spp. (2.3%), *Citrobacter* spp. (1.3%), *Enterococcus* spp. (1.2%), *Proteus mirabilis* (1.0%), and others (1.7%). Overall resistance to ciprofloxacin (85.5%) when compared with levofloxacin (53.8%) was higher. The levofloxacin resistance increased minimally from 55.6% overall in October 2013–March 2014 to 55.8% in October 2014–March 2015, whereas resistance to ciprofloxacin increased from 79.5% overall in October 2013–March 2014 to 90.3% in October 2014–March 2015.

Conclusion: Levofloxacin is still active against major pathogenic organisms, whereas ciprofloxacin has become largely inactive. So, it is time to reconsider the use of fluoroquinolones and develop clear strategies to counteract the development of further resistance.

KEY WORDS: Fluoroquinolones, urinary tract infection, antimicrobial resistance

Introduction

Urinary tract infection (UTI) is one of the most common infections in both outpatients and hospitalized patients.[1] In the majority of the cases, broad-spectrum antimicrobials such as cephalosporins, fluoroquinolones, and aminoglycosides are usually started before the urine culture results are available.[2] However, the indiscriminate use of such antimicrobial agents was the main reason behind the emergence and spread of antimicrobial resistance among microorganisms.[3–7] Therefore, antimicrobial resistance has become a worldwide problem[8] affecting all and uniting all to fight against this menace.

Expenses on UTI are huge not only in the hospitalized patients but also in the community.[9] Early diagnosis and prompt treatment are required to decrease complications such as permanent renal damage.[10] The fluoroquinolones have assumed an important role in the therapy of these infections because of their lesser side effects and convenient oral dosages. Above all, they have a broad spectrum of activity, including Gram-positive and, in particular, Gram-negative bacteria.[11–15] Among fluoroquinolones, levofloxacin is widely used in clinical practice because of its established efficacy

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2016.18112015257	

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and safety.[16,17] Levofloxacin shows better activity against Gram-positive bacteria and is less likely to select resistant strains compared with older quinolones.[18–20]Because the initiation of antimicrobial therapy in UTI is empirical, knowledge of the antimicrobial resistance patterns of common uropathogens is essential to provide clinically appropriate and cost-effective therapy and achieve both a favorable clinical outcome and a reduction in antimicrobial resistance.[21,22]This study was conducted to determine the progressive fluoroquinolones resistance pattern in UTI over a one-and-a-half year period. This study was conducted at NHL Municipal Medical College, Ahmedabad, Gujarat, India, from October, 2013 to March, 2015. A retrospective analysis of data taken from all urine samples (6,545 patients suspected of UTI) was analyzed, and an antimicrobial susceptibility test for commonly usable antimicrobial agents was performed for the isolates using the Kirby–Bauer's standard disc diffusion method.

The findings of this study indicate that *Escherichia coli* (55.1%) is the predominant pathogen of UTI, followed by *Klebsiella* spp. (22.3%), *Pseudomonas aeruginosa* (11.9%), *Acinetobacter* spp. (3.2%), *Enterobacter* spp. (2.3%), *Citrobacter* spp. (1.3%), *Enterococcus* spp. (1.2%), *Proteus mirabilis* (1.0%), and others (1.7%). Moreover, levofloxacin (46.2%) is far more effective then ciprofloxacin (14.5%) against the uropathogens, but there is an increasing resistance to both of them.

Materials and Methods

Sample Collection and Analysis

A retrospective observational analysis was performed on all bacterial urine samples (6,545 patients suspected of UTI) sent to the bacteriology laboratory at NHL Municipal Medical College, Ahmedabad, Gujarat, India, from October 2013 to March 2015. Midstream urine samples were collected in a sterile, wide-mouthed container, properly labeled and cultured. The cultures were done on quality control (QC) checked nutrient agar and MacConkey agar and were incubated for 24 h at 37°C. The growth was identified on the next day, and, for identification, biochemical reactions and sensitivities were placed in an incubator for 24 h at 37°C. A total of 1,744 isolates were found for which sensitivity was determined using the Kirby–Bauer's standard disc diffusion method with Mueller–Hinton agar, and zones were determined by Clinical and Laboratory Standards Institute (CLSI) guidelines. Cultures with *Candida* growth were excluded from this analysis.

The susceptibility was analyzed for ciprofloxacin (5 μg) and levofloxacin (5 μg) antimicrobials as per CLSI recommendations. For QC, *E. coli* American type culture collection (ATCC) 25922 and *P. aeruginosa* ATCC 27853 strains were used as standard.

Result

Different bacterial uropathogens were isolated from patients as shown in Table 1.

From Table 2, following results can be noted:

All of the organisms were more resistant to ciprofloxacin (85.5%) when compared with levofloxacin (53.8%), clearly indicating the effectiveness of the higher generation fluoroquinolones.

There is increase in the overall fluoroquinolones resistance among different uropathogens, the magnitude of which is more for ciprofloxacin (10.8%) when compared with levofloxacin (0.2%).

Moreover, there is a constant increase in levofloxacin resistance among *E. coli* over the period from 47.2% to 47.5% but there is higher magnitude of increase in ciprofloxacin resistance among this group (i.e., from 79.8% to 90.5%).

There is a constant increase in levofloxacin resistance among *P. aeruginosa* over the period from 76.2% to 80.3%, but there is higher magnitude of increase in ciprofloxacin resistance among this group (i.e., from 82.5% to 92.4%).

It was prominent that *P. aeruginosa* (76.2%) was highly resistant to levofloxacin in October 2013–March 2014 when compared with *Acinetobacter* spp. (41.7%) and *Enterococcus* spp. (66.7%), but, as the study progressed (i.e., from October 2014–March 2015), it was found that *Acinetobacter* spp. (82.6%) and *Enterococcus* spp. (88.9%) developed much higher resistance than *P. aeruginosa* (80.3%).

Discussion

The fluoroquinolones susceptibility of urine pathogens, changing over the years, is influenced by factors such as the changing patient population and the extensive use and misuse of the antimicrobial agent, which contribute to alterations in the microbial profile of urine isolates.[23] Therefore, the overuse of fluoroquinolones may increase the risks of resistance, side effects, and the cost of medical care.[22]

Moreover, there are huge geographical differences in the patterns of bacterial resistance properties based on local practices of antimicrobial prescriptions.[24] The highest regional fluoroquinolones resistance rate in gram-negative bacilli was observed in Latin America at 38.7%, but resistance was as high as 70% in one hospital in Panama and more than 40% from three sites in Puerto Rico and Mexico. The highest fluoroquinolone resistance rates in this study were seen in India, where 75% of all UTIs were nonsusceptible to the fluoroquinolones. The average for the Asian countries was 33.2%. Fluoroquinolone resistance rates for Canada and the United States were 22% and 24%, respectively. In our study too, it was observed that there is 53.8% resistance for levofloxacin and 85.5% resistance among ciprofloxacin antimicrobials.

In a study[25] there was up to 62% resistance for fluoroquinolones among gram-negative uropathogens in different parts of the world, which is clearly indicated in our study too as resistance for ciprofloxacin is 85.5% overall, and, for levofloxacin, it is 53.8%.

For *E. coli* isolates, in the study done by Karlowsky,[26] the ciprofloxacin resistance was 15.8%; moreover, 5.1% resistance for levofloxacin was reported in the same study.[7] In another study,[27] levofloxacin resistance among uropathogens was 17%.

Table 1: Prevalence (percentage and frequency) of bacterial urinary tract infections

Isolates	Percentage	Number of isolates
E. coli	55.1	961
Klebsiella spp.	22.3	389
Pseudomonas aeruginosa	11.9	208
Acinetobacter spp.	3.2	56
Enterobacter spp.	2.3	40
Citrobacter spp.	1.3	23
Enterococcus spp.	1.2	21
Proteus mirabilis	1.0	18
Others	1.7	28
Total	100	1744

Table 2: Different isolates from urine samples with their respective percentages of resistance (R) for levofloxacin and ciprofloxacin

Organism	Oct 13–Mar 14		Apr 14–Sep 14		Oct 14–Mar 15	
	Levofloxacin	Ciprofloxacin	Levofloxacin	Ciprofloxacin	Levofloxacin	Ciprofloxacin
E. coli	47.2	79.8	44.7	85.2	47.5	90.5
Klebsiella spp.	68.7	83.8	48.4	87.3	57.9	89.5
Pseudomonas aeruginosa	76.2	82.5	78.5	86.1	80.3	92.4
Acinetobacter spp.	41.7	66.7	72.7	90.9	82.6	95.7
Enterobacter spp.	36.4	81.8	33.3	66.7	50	96.2
Citrobacter spp.	55.6	55.6	0	50	37.5	50
Enterococcus spp.	66.7	66.7	77.8	88.9	88.9	88.9
Proteus mirabilis	80	100	33.3	66.7	60	80
Others	46.2	53.8	62.5	87.5	66.7	100
Overall	55.6	79.5	50.7	85.6	55.8	90.3

Yet, in another study,[28] there was 69% resistance for *E.coli* isolates in India alone. However, in our study, the resistance for *E. coli* isolates were 53.7% and 85.4% for levofloxacin and ciprofloxacin, respectively.

For *Enterococci* isolates, in "Antimicrobial resistance trends in the province of British Columbia," AMR Trends Report, 2009,[29] nonsusceptibility to ciprofloxacin decreased progressively from a peak of 47.0% in 2002 to 24.8% in 2011. However, in another study,[28] there was 59% resistance recorded for *Enterococci*. In our study, the resistance increased from 66.7% to 88.9% for both ciprofloxacin and levofloxacin for *Enterococci* isolates from October 2013 to March 2015, respectively.

For *P. aeruginosa* isolates, in the study done by Karlowsky,[25] the ciprofloxacin and levofloxacin resistance was 26.5% and 27%, respectively. In our study, the resistance for *P. aeruginosa* isolates was 78.4% and 87.0% for levofloxacin and ciprofloxacin, respectively.

For *Acinetobacter* spp. isolates, in the study done by Akram et al.,[30] all isolates were fluoroquinolone sensitive. However, in our study, the resistance for *Acinetobacter* spp. isolates was 66.7% and 87.7% for levofloxacin and ciprofloxacin, respectively.

Moreover, owing to overuse of levofloxacin and ciprofloxacin, there is a constant increase in the resistance of *E. coli*, *P. aeruginosa*, *Acinetobacter* spp., and *Enterococcus* spp. indicating the importance of the acquired resistance in the form of mutation or resistant gene transfer between microorganisms or both.[31]There are three mechanisms that operate in a microorganism showing resistance to the fluoroquinolones group: decreased uptake, altered target-mutational changes in the subunit of the DNA gyrases enzyme which is the target of quinolone activity, and increased efflux mechanisms. In gram-negative bacteria, the first two mechanisms operate dominantly, whereas in gram-positive bacteria, the third mechanism predominates, especially in *Staphylococci* spp.[32]

Conclusion

Although levofloxacin is clearly far effective then ciprofloxacin for uropathogens, both gram-positive and gram-negative bacteria, the resistance among microorganisms are on the increase. The results presented in this study indicate that it is time to reconsider the frequent use of fluoroquinolones and stop its indiscriminate use to treat patients before getting the sensitivity pattern of the isolate. It is also very clear to develop clear strategies to counteract the development of further resistance. Because antimicrobial resistance patterns may vary in different regions, it is mandatory to formulate their

antimicrobial policy according to their local resistance pattern, which must be assessed in hospital and laboratory-based surveillance studies.

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How to cite this article: Gupta A, Chauhan B, Pethani J, Shah P. Fluoroquinolones resistance among uropathogens at a tertiary-care hospital, Ahmedabad. Int J Med Sci Public Health 2016;5:1583-1587

Source of Support: Nil, **Conflict of Interest:** None declared.