Analysis of Therapy of Uncomplicated Urinary Tract Infection Based on Effectiveness and Improvement in Quality of Life

Mathew George[1], Lincy Joseph[2], Leena P.N[3], Ann Mary Kurian[4]*

1. Department of Pharmacology, Pushpagiri College of Pharmacy, Thiruvalla, India.

2. Department of Pharmaceutical Chemistry, Pushpagiri College of Pharmacy, Thiruvalla, India.

3. Department of Pharmacognosy, Pushpagiri College of Pharmacy, Thiruvalla, India.

4. Department of Pharmacy Practice, Pushpagiri College of Pharmacy, Thiruvalla, India.

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ABSTRACT

Urinary Tract Infection (UTI) is one of the most common diseases encountered in humans today, especially in women and children. *E.coli* has consistently been reported to be the major cause of this disease. Nitrofurantoin, Fluoroquinolones, and Trimethoprim-Sulfamethoxazole are the most commonly used classes of drugs for the therapy of Urinary tract infection. However, uropathogens have become greatly resistant to these drugs, as reports from all over the world suggest. As such, it has become necessary that we address the effectiveness of each pharmacological management strategy, taking into consideration the side effects and resistance reported when any of these are used so that the results may enable clinicians to practice rational prescribing. In this study, 14 studies were reviewed to assess the effectiveness, resistance to drugs reported and side effects as well as to determine the change in Quality of Life trends upon contacting urinary tract infection. Overall, Nitrofurantoin appears to be the best option to manage UTI, in light of the increasing reports of Fluoroquinolone resistance. *E.coli* continues to be the major pathogen responsible which increases the chances of resistance development. The fact that UTI tends to recur makes this an even bigger problem. This disease is not to be taken lightly as the associated decrease in quality of life is quite significant. Thus, it is the need of the hour to use the most rational antibiotic therapy to manage UTI.

INTRODUCTION

Urinary Tract Infection is one of the most common diseases encountered in medical practice today with approximately150 million patients suffering from it per annum all over the world. These are infections of the urinary tract caused by microorganisms that cannot be accounted for by contamination, usually producing an inflammatory response. The infection may progress from the faecal flora and spread by an ascending process to the urinary tract or from another primary source by the haematogenous route following a descending path[1]. UTI is usually bacterial in aetiology, although other infectious agents can also cause UTI. These include viruses, fungi, and chlamydia. Frequent urinary tract infections can result in chronic kidney disease and hypertension, especially in childhood[2]. It may be either acute or chronic, and may affect any part of the upper or lower urinary system. It usually results in painful burning sensation during urination (dysuria), increased frequency or urgency to urinate with or without blood /pus in urine and a host of other symptoms.

UTI is characterised by its high recurrence rate. Recurrent UTI may be caused by either relapse due to treatment failure or reinfection. Patients who never improve or who immediately relapse following completion of treatment may be said to have persistent infection[3]. Generally, UTIs are treated with various antibiotics and fluid supplementation.

Pharmacological Therapy

Antimicrobial therapy for UTI may follow either the prophylactic or the therapeutic approach depending on the recurrence of infection in the patient. The therapeutic approach attempts to relieve the existing symptoms and prevent the development of further complications[4]. Selection of antibiotics for treatment of relapsed UTI should be done based on results of culture and susceptibility testing, and the duration of antibiotic therapy could be as long as 2 weeks. Recurrent UTI which occurs more than 2 weeks after the original infection is treated as a new infection and managed with therapeutic considerations similar to those for the initial infection. Those with frequent infections (3 or more/year) may be considered for chronic prophylactic therapy.

Consensus clinical guidelines recommend Nitrofurantoin monohydrate/macrocrystals 100 mg bid for 5 days or Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid for 3 days or

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

46

Fosfomycin trometamol 3 gm single dose or Pivmecillinam 400 mg bid for 5 days as preferred first-line antibiotics for treatment of uncomplicated UTI. Fluoroquinolones or β-lactams are to be used only when the first-line drugs cannot be used[5]. For many years, trimethoprim-sulfamethoxazole (TMP-SMX) was the preferred antibiotic for the treatment of UTI, given its efficacy and low cost[6]. However, development of a high prevalence of TMP-SMX resistance among uropathogens[7,8,9] has discouraged use of this drug in many communities. An effective alternative for many clinicians has been the fluoroquinolone class of antibiotics, which achieve high concentrations in the urine and have excellent activity against most uropathogens[6] . Of note, the 2011 Infectious Diseases Society of America (IDSA) guidelines for the treatment of UTIs discourage use of fluoroquinolones for acute, uncomplicated UTI as experts are concerned about overuse of fluoroquinolones leading to increased prevalence of fluoroquinolone-resistant pathogens[5]. The fluoroquinolones are more expensive, broader in the spectrum, and therefore, should be reserved for communities with high rates of resistance (greater than 10% to 20%) to trimethoprim or in patients who either cannot tolerate trimethoprim-sulfamethoxazole or have recurrent urinary tract infections. The use of first-generation cephalosporins or aminopenicillins is generally not recommended because of high levels of resistance and recurrence. Although resistance to the third-generation cephalosporins is lower than to the first generation, these agents are considered -third-line agents because of their high cost and lower efficacy. Most cases of Urinary Tract Infections are uncomplicated and can be treated on an outpatient basis with oral antibiotics

This study reviews 14 related articles in order to compare existing health care interventions to determine which strategy works best. The goal of Comparative Effectiveness Research is to discriminate among clinical interventions on the basis of clinical effectiveness, cost-effectiveness, adverse effects, or other distinguishing factors. Comparative effectiveness may either be analyzed by means of multisite randomized controlled trials or observational studies involving either primary or secondary data collection[10], of which the second method of CER is embraced to achieve a final conclusion.

Many trials that compare two treatment strategies include a quality of life assessment. It is either included as part of the main trial or classed as a separate quality of life study (sometimes called a substudy). QOL studies are usually done by asking participants to fill in a standardized and

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

47

validated questionnaire which tries to link an individual's health with tiredness, weakness, anxiety or depression experienced in everyday activities such as work and its management, home life, exercise and other interactions with the society. Improving a patients' quality of life is often a very important aim of treatment as patients are also more likely to follow a treatment if it has fewer side effects or if they don't have to go to the hospital so often.

REVIEW OF LITERATURE

Abdollah Iravani[11] et al (1999)

In women with acute, uncomplicated Urinary tract infection, oral ciprofloxacin (100mg bid) administered for 3 days was compared with co-trimoxazole (160/800 mg bid) or nitrofurantoin (100 mg bid) given for 7 days. Bacteriological and clinical evaluations were performed at the beginning of the study, during therapy and after the completion of therapy (4–10 days and 4–6 weeks later). *Escherichia coli* (83%) was the most frequently isolated pathogen in all treatment groups. Bacteriological eradication was reported in 88% of ciprofloxacin patients, 93% of co-trimoxazole patients and 86% of nitrofurantoin patients. At the 4–6weeks follow-up, ciprofloxacin had higher eradication rates than co-trimoxazole and nitrofurantoin. Clinical resolution results obtained 4–10 days after therapy and at the 4–6weeks follow-up was similar among the three groups. Low dose, short course Ciprofloxacin therapy was found to be equivalent to 7-day Nitrofurantoin therapy and better tolerated in the study population, as fewer side effects developed.

R. Raz and S. Boger[12] (1991)

They studied long-term prophylactic therapy with Norfloxacin versus Nitrofurantoin in women suffering from recurrent Urinary Tract Infection. 102 women with recurrent urinary tract infections were included in this study; 55 of whom were administered 200 mg of norfloxacin daily and 47 were given 50 mg of nitrofurantoin daily for a period of 6 months. 44 of the norfloxacin-treated patients and 27 of the nitrofurantoin- treated patients remained free of symptoms, while urine samples from 49 and 29 of the patients, respectively, were sterile. Side effects occurred with similar frequencies in both groups (15 and 17%) but were found to be of greater severity in women who received nitrofurantoin. Thus, it was concluded that norfloxacin

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

48

was a better prophylactic agent than Nitrofurantoin, the only drawback being the increased cost of the former.

Brumfitt W[13] and Hamilton-Miller JM (1998)

The efficacy and safety profile of long-term nitrofurantoin in urinary tract infections over a period of 18 years was studied from case files of 219 women. The population studied was divided into three groups, each being given a different form/ dose of Nitrofurantoin. Group A (43 patients) were given microcrystalline nitrofurantoin 50mg bid, Group B (110 patients) were given macrocrystalline nitrofurantoin 100mg od, and Group C (66 patients) were given macrocrystalline nitrofurantoin 50mg od. In 16% of the patients, prophylaxis was not helpful and no obvious differences in efficacy were noted between these 3 groups. Nausea was found to be the most common adverse event and it, along with all other adverse events was found to be most common in Group A patients. It was concluded that a dose of 50mg macrocrystalline nitrofurantoin was a better option than the microcrystalline form for long-term prophylaxis against recurrent UTI due to its comparatively favourable efficacy, safety and tolerability profiles.

Arul Prakasam K.C[14] et al. (2012)

A Cross-Sectional Study was done to assess the distribution of Urinary Tract Infection and their antibiotic utilisation pattern in Kerala. The objective was to determine the distribution, clinical, laboratory profile, and antibiotic utilization pattern by means of a cross-sectional study conducted on 200 outpatients over a period of 6 months. This study showed that young married females (65%) were more prone to the risk of UTI. Complicated UTI was found to be more common in males. *E. coli*, the predominant organism isolated showed maximum susceptibility to Meropenem and Amikacin antibiotics. Diabetes mellitus was found to be the predominant risk factor to UTI in this study. Ciprofloxacin was the most commonly prescribed antibiotic for general population and amoxicillin was more commonly prescribed to pregnant females. The diagnosis was mainly based on clinical presentation and rarely confirmed by culture and sensitivity. The isolated organism showed resistance towards commonly used antibiotics (fluoroquinolones and cephalosporins) which were concluded to be due to indiscriminate prescription and lack of patient compliance.

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

49

Smita Sood[15] and Ravi Gupta (2011)

They studied the antibiotic resistance pattern of community-acquired uropathogens at a tertiary care hospital in Jaipur, Rajasthan by analysing the urinary pathogenic flora and its antimicrobial susceptibility profile among patients of the outpatient clinics. 2012 consecutive urine specimens from symptomatic UTI cases were processed in a microbiology lab, bacterial isolates identified and antimicrobial susceptibility testing performed using the Kirby-Bauer disk diffusion method. Extended spectrum beta-lactamase (ESBL) production was also determined. Pathogens were isolated from 346 of the 2012 patients who submitted a urine sample and *E.coli* was the most frequently isolated community-acquired uropathogen which accounted for 61.84% of the total isolates. ESBL production was observed in 23.83% of E. coli strains and 8.69% of Klebsiella strains. With the exception of Nitrofurantoin, resistance to agents commonly used as empiric oral treatments for UTI was found to be quite high. Overall, women of reproductive age group were the major demographic in the study population but in the elderly, the predominance of males was found to be far higher than that of females. An increasing trend in the production of ESBLs among UTI pathogens in the community was noted. It was suggested by the researchers that Nitrofurantoin should be used as empirical therapy for primary, uncomplicated UTIs.

James A. McKinnell[16] et al. (2011)

Nitrofurantoin compared favorably to recommended agents as an empirical treatment of uncomplicated Urinary Tract Infections in a Decision and Cost Analysis conducted. The objective was to analyze the cost of nitrofurantoin therapy as compared to that of other antibiotics recommended for treatment of uncomplicated urinary tract infection by employing a decision analysis model to perform cost-minimization and sensitivity analyses as well as to determine the level of trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolone resistance that would favour the use of nitrofurantoin as a first-line empirical treatment of option. It was determined that nitrofurantoin became a cost-minimizing alternative when the fluoroquinolone resistance exceeded 12% or the prevalence of TMP-SMX resistance exceeded 17%. On the basis of efficacy, cost, and low impact on promoting antimicrobial resistance, the researchers suggested that clinicians should consider nitrofurantoin as a reasonable alternative to TMP-SMX and fluoroquinolones for first-line therapy for uncomplicated UTIs.

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

50

Seim A[17] et al (2005)

Lower urinary tract symptoms and quality of life in Norwegian men were assessed by what came to be referred to as 'the hunt study'. The aim of this study was to investigate the prevalence of LUTS and their impact on disease-specific QoL in men. Between 1995 and 1997 cross-sectional LUTS data were collected from 21694 male residents aged below 20 years in Norway, using the International Prostate Symptom Score (IPSS) and the IPSS bother questions (IPSS BQ). LUTS of each participant were then categorized into no symptoms (IPSS=0), mild symptoms (IPSS<7), moderate symptoms (IPSS=8-19), or severe symptoms (IPSS=20-35). The IPSS BQ also had standardised scores for each possible response and was then interpreted as poor QoL (IPSS BQ >3) and good QoL (IPSS BQ <3). The prevalence of each symptom was found to increase with increasing age. The strong association between severity of LUTS and poor QoL was found to be notable, as was the difference between the seven symptoms and the degree to which they affect QoL.

Anne K. Ellis[18] et al (2000)

Conducted a study on 'Quality of Life in Women with Urinary Tract Infections: Is Benign Disease a Misnomer?' by administering the RAND 36-Item Health Survey 1.0 (SF-36) to 47 women with a diagnosed urinary tract infection and a control population of 71 women from the female members of an undergraduate geography class, a community basketball league, and a local women's choir. All subsections of the SF-36 quality-of-life indices were found to be significantly decreased in the subject population compared to the control population.

Erika J Ernst[19] et al (2005)

Women's quality of life was analyzed when affected by acute cystitis and describe the relationship between QoL, clinical outcome and adverse events of each of the interventions used in the study. This was a randomized, open-label, multicenter treatment study involving patients from two family medicine outpatient clinics in Iowa. 157 women with signs and symptoms of acute uncomplicated cystitis participated, of whom 52 patients received trimethoprim/sulfamethoxazole (1 double-strength tablet) twice daily for 3 days, 54 patients received ciprofloxacin 250 mg twice daily for 3 days and 51 patients received nitrofurantoin 100 mg twice daily for 7 days. About 37% of the study population were identified to have had a

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

51

previous UTI in the 6 month period prior to the study. QoL was assessed at the time of enrolment and at 3, 7, 14 and 28 days after the initial visit using a modified and validated Quality of Well-Being scale. Clinical outcome was assessed by telephone interview on days 3, 7, 14 and 28 using a standardized questionnaire to assess resolution of symptoms, compliance with the prescribed regimen, and occurrence of adverse events. Patients experiencing a clinical cure had significantly better QoL at days 3, 7, and 14 compared to patients who failed treatment. While there was no difference in QoL by treatment assignment, patients experiencing an adverse event had lower QoL throughout the study period. Patients treated with ciprofloxacin appeared to experience adverse events at a higher rate (62%) compared to those treated with TMP/SMX (45%) and nitrofurantoin (49%). It was concluded that patients experiencing cystitis have an increase in their QoL with treatment. It was also observed that those reporting adverse events have lower overall QoL compared to those who do not experience adverse events. This study is significant in that it suggests that both cystitis and antibiotic treatment can affect QoL in a measurable way.

Lawrence C. Vogel[20] et al (2011)

The objective of the study was to identify outcomes of participation, life satisfaction, and medical complications as a function of impairment in adults with paediatric-onset spinal cord injury (SCI). Study participants were adults who sustained SCI at age 18 years or younger and were interviewed when at age 24 years or older. The telephonic interview conducted involved the use of an SF-12 questionnaire and several standardized measures. This study showed the drastic fall in quality of life in patients suffering from UTI, as it was identified as one of the major complications seen in patients with spinal cord injury.

Hande Arslan[21] et al (2005)

Identification of the Risk factors for Ciprofloxacin resistance among *Escherichia coli* strains isolated from Turkey was the aim of this study. It was performed with samples collected from community-acquired UTI patients treated at 15 centres that represented six different geographic regions of Turkey. All microbiological tests were carried out in a central laboratory and multivariate analysis was performed for detection of risk factors for resistance. The risk factors for resistance used as variables in the study were the use of quinolones more than once within the last year, living in a rural area, having a urinary catheter, age >50 and complicated infections. *E.*

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

52

coli was the pathogen responsible for 90% of the uncomplicated UTIs and in 78% of the complicated UTIs. 17% of *E. coli* strains isolated from uncomplicated cases and 38% of *E. coli* strains isolated from complicated UTI were found to be resistant to ciprofloxacin. *E. coli* producing extended-spectrum b-lactamase (ESBL) enzymes were two times more common in the patients who received Ciprofloxacin than those who did not (15% versus 7.4%).This led to the conclusion that the increasing prevalence of infections caused by antibiotic-resistant bacteria makes the empirical treatment of UTIs more difficult. Culture and sensitivity testing were suggested for all patients who have undergone Ciprofloxacin therapy previously, along with an evaluation of alternate strategies such as nitrofurantoin and fosfomycin in place of fluoroquinolones by means of efficacy and safety studies.

Syed Mustaq Ahmed[22] et al. (2012)

They conducted a study titled 'Urinary Tract Infections – An overview on the Prevalence and the Antibiogram of Gram Negative Uropathogens in A Tertiary Care Centre in North Kerala, India' in which 2540 urine samples collected from the patients at a medical college hospital were processed according to standard protocol over a period of one year. The antimicrobial susceptibility was tested by the modified Kirby-Bauer's disc diffusion method and 511(20.12%) were found to be positive for microbial isolates, of which 343 samples (67.12%) were from females and 168 samples (32.36%) were males. The highest rate of isolation was detected in the geriatric age group i.e., 61-80 years (39.53 %) and the most commonly isolated organism was *Escherichia coli* (81.80%). The isolation rates were highest in the surgical departments (38.34%). Piperacillin/Tazobactam, Cefoperazone/Sulbactam, Imipenem and Amikacin were found to be the most effective drugs in the treatment of isolated samples.

M. Eshwarappa[23] et al (2008)

Clinico-microbiological profile of urinary tract infection in south India was studied in 510 patients from various departments in M. S. Ramaiah Hospital, Bangalore to determine the presentation and risk factors associated with community-acquired urinary tract infection. It was observed that 57% of the study population belonged to the elderly age group (50–79 years). Fever and dysuria were identified as the most common clinical presentation. *E. coli* (66.9%) was the most common organism causing Catheter Associated-Urinary Tract Infections with extended

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

53

spectrum beta-lactamase (ESBL) resistance seen in nearly two-thirds of these cases (42.2%). The organisms recorded least resistance against carbapenem group of drugs and high resistance rate for fluoroquinolones (74.1%).

Debasis Biswas[24] et al. (2006)

They conducted a study on 'Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance' to identify the most appropriate antibiotic for the empirical treatment of community-acquired acute cystitis in Dehradun, India. It was a prospective clinico-microbiological study including all clinically diagnosed patients in a tertiary care teaching hospital over a period of three years. A survey was also conducted on 30 randomly selected local practitioners, in order to identify the prevalent prescribing habits in that area. 67.5% specimens yielded significant growth of *E. coli* and it was clear that more than 35% of the urinary *E.coli* isolates were resistant to fluoroquinolones. Resistance was found to be least against nitrofurantoin (9.3%) and Amikacin (11.0%). About 80% of the fluoroquinolone-resistant strains were found to be sensitive to nitrofurantoin. As such, it was suggested that the best *in vitro* susceptibility profile was shown by nitrofurantoin.

CONCLUSION

Uncomplicated Urinary tract Infection is very common in women, especially post-menopausal women. Nitrofurantoin seems to be very much effective and less prone to resistance by uropathogens. Fluoroquinolones seem to be very effective in tackling Urinary tract infections, but seem to be plagued by their greater susceptibility to uropathogenic resistance.As such, studies seem to suggest that Nitrofurantoin is a good alternative to Fluroquiolones.

The quality of Life assessment showed a decrease according to all researchers, although Urinary Tract infection is often considered as a mild condition. The fact that proper therapy could correct the fall in Quality of Life scores points to the need to undertake proper pharmacological management strategies by all afflicted individuals. Urinary tract infection is not to be treated lightly or left to be treated solely with home remedies and such

Most common causative organism isolated remains E.coli over the years. This can be considered as a factor responsible for increased resistance to the commonly used antimicrobial therapy as well.

Citation: Mary Kurian et al. Ijppr.Human, 2016; Vol. 6 (2): 45-56.

54

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56