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AN OVERVIEW OF CIPROFLOXACIN TREATMENT IN URINARY TRACT INFECTIONS

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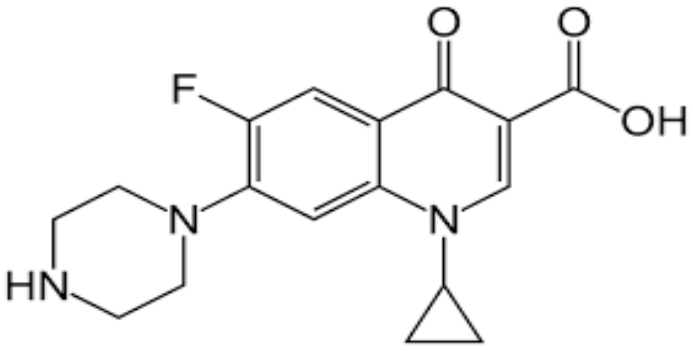
ABSTRACT

Symptomatic urinary tract infections (UTIs) constitute a major health problem throughout the Western world, Urinary tract infections (UTIs) account for approximately 4 million ambulatory care visits each year. 2-7 Fluoroquinolones, including ciprofloxacin, are suggested as alternatives in communities in which trimethoprim/sulfamethoxazole (TMP/SMX) resistance associated with uropathies is ≥10% to 20%. This study systematically reviewed the literature and where appropriate, systematically overviewed studies investigating ciprofloxacin resistance in community- and hospital-acquired bacteria causing UTIs. Complicated urinary tract infections occur in patients with structural abnormalities or comorbidities such as diabetes, old age, pregnancy, or immunocompromised status. Ciprofloxacin is an FDA approved antibiotic agent in the fluoroquinolone class used to treat bacterial infections such as urinary tract infections. In this review represents the clinical data of ciprofloxacin causes, symptoms of urinary tract infections

I. INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infectious diseases worldwide. Approximately >50% of women at least once in their lifetime have suffered from UTI and received antibiotic treatment. Serious UTIs are difficult to treat as it involves a wide array of Gram-positive as well as Gram-negative bacteria. Escherichia coli (E. coli) is the primary causative agent implicated in >80% of UTI cases

Structure of ciprofloxacin



Background

Among all the infectious diseases, UTIs are the second most common after respiratory tract infections. Approximately, 150 million people worldwide are diagnosed with UTI per annum. It is more prevalent in females than in males, with estimates of prevalence suggesting that 40 to 50% of females have at least one clinical episode during their lifetime. The majority of UTIs develop in the normal urinary tract and are therefore termed "uncomplicated" and can affect the lower or upper urinary tract. Urinary tract infections (UTI) are one of the most frequent bacterial infections affecting people both in the community and in hospitals. It is estimated that about 150 million people per annum are diagnosed with UTI worldwide

Organism causing UTI

Ur pathogenic E. coli (UPEC) causes >80% of community acquired UTIs, while Staphylococcus saprophyticus, Klebsiella pneumonia, Proteus mirabilis, and Enterococcus faecalis are responsible for other infections.3 A cohort study by Das et al. checking antimicrobial count in urine samples from nursing residents have found that E.coli (53.6%) was the major organism followed by Enterobacteriaceae (34.8%), Proteus (14.6%), Klebsiella (13.9%), Providential (3.7%) and some cases of Gram-positive bacteria such as Enterococcus (4.5%) and

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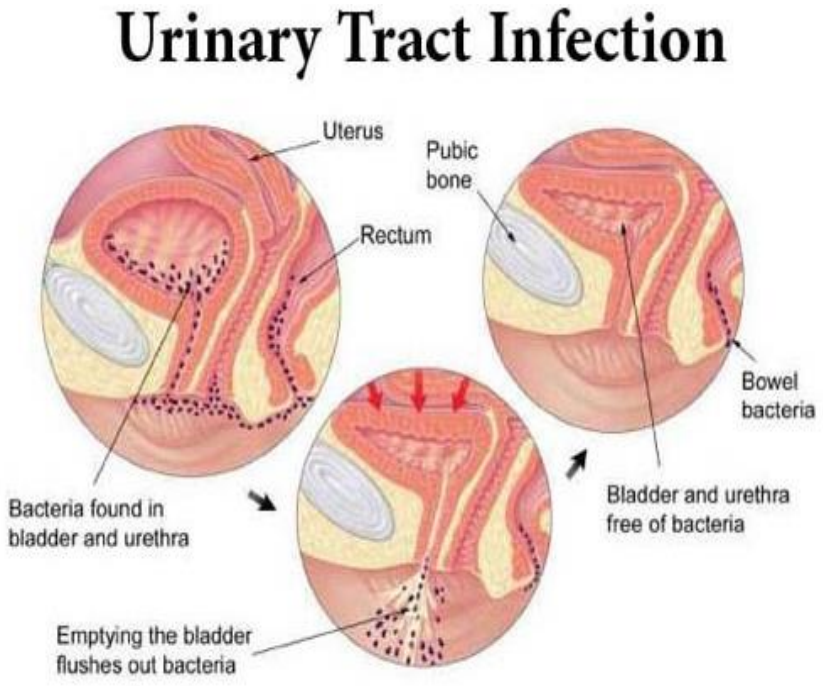
Staphylococcus (4.1%).Furthermore, the cross-sectional study examined urine sample of 32 nursing care facility reported that E. coli were the most common organism causing UTI accounting for 69% of positive cases. Other organisms Klebsiellas and Enterobacteriaceae were found in 12 and 8% cases respectively



TREATMENT OF UTI

UTI TREATMENT		
Asymptomatic	Positive urinalysis or culture in a patient without signs of symptoms of UTI - only treat in pregnant patients	If pregnant, treat for 3-7 days: **Amoxicillin** Or **Cephalexin** Or **Nitrofurantoin** (before late 3rd trimester) Or **TMP-SMX** (before the 3rd trimester)
Uncomplicated	UTI in a healthy, non pregnant female with a normal GU tract	**Nitrofurantoin 100 mg BID x 5 days** **Back up:** **TMP-SMX 160/800 mg BID x 3 days (if resistance rates <20%)** Or **Fosfomycin 3 g x 1** Or **Ciprofloxacin 500 mg BID x 3 days if no other option** Or **can consider cephalosporins x 3-7 days** **Do NOT use: amoxicillin empirically**
Complicated	UTI in patient with structural/functional abnormalities of the GU tract/kidney, relevant co-morbidities, or GU tract instrumentation, or men.	**Oral therapy if mild/moderate illness, tolerating PO:** **Ciprofloxacin 500 mg PO BID x 5-14 days** Or **TMP-SMX 160/800 mg PO BID x 5-14 days** **IV treatment** (pregnant, severe illness) **Ceftriaxone 1 g IV qDay** Or **Levofloxacin IV qDay** (not in pregnancy) Or **Gentamicin** Or **TMP-SMX** (before the 3rd trimester)
Uncomplicated Pyelonephritis	Positive urinalysis + flank and costovertebral angle pain, chills and fever, urinary frequency, urgency, and dysuria	
Complicated Pyelonephritis	Signs of pyelonephritis + systemic toxicity, late pregnancy, immunocompromised, significant co-morbidities	**Hospitalizaiton and IV ABX** **Ceftriaxone 1 g IV qDay** Or **Levofloxacin IV qDay (not in pregnancy)** Or **Gentamicin** Or **TMP-SMX (before 3rd trimester)**

Treatment of UTI with proper antimicrobial therapy can reduce morbidity and mortality due to complications. Choosing the appropriate antimicrobial agent may at times present a therapeutic challenge, but development in

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the understanding of the pathophysiology of UTI, the introduction of new diagnostic tests, and the availability of new antibacterial agents have allowed physicians to wisely select precise treatment for each patient. Current guidelines followed for treatment of UTI are: for acute uncomplicated cystitis, nitrofurantoin, cotrimoxazole or fluoroquinolones (ciprofloxacin, levofloxacin) are the first-choice drug and cefuroxime is an alternative drug. For acute uncomplicated pyelonephritis, aminoglycosides (amikacin or gentamicin) are first-line therapy, and piperacillin-tazobactam or etoperidone or ertapenem are administered parenterally as second line drug therapy. For the treatment of complicated pyelonephritis, Piperacillin-tazobactam or amikacin or etoperidone are first-line drugs followed by parenteral carbapenems as alternative drugs.

Fluoroquinolones are the group of drugs having a quinolone ring structure with fluorine or more fluorine substitutions in the ring structure. These act by inhibiting deoxyribonucleic acid (DNA) synthesis in the bacteria by inhibiting DNA gyrase enzyme in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. Ciprofloxacin, one of the fluoroquinolones, frequently prescribed medication for treatment of UTIs as it has good safety profile, marketed as both oral and intravenous formulations, gets easily absorbed after oral administration, has a higher urinary excretion rate and exhibits broad-spectrum activity against gram-negative organisms. Other than UTIs, it is also used for joints, bones and respiratory tract infections and chronic infections such as diarrhoea, anthrax, and intra-abdominal infections.

There are some of home remedies for the relief of urinarary track infection at home are follows

CIPROFLOXACIN PHARMACOLOGY

Absorption

Ciprofloxacin is readily absorbed, but it is complete absorption oral administration. The absolute bioavailability of oral ciprofloxacin is within a range of 70-80% with no substantial loss by first pass metabolism. An intravenous infusion of 400 mg ciprofloxacin given over 60 min every 12 hr. has been shown to produce an area under the serum centime curve (AVC) equivalent to that produced by a 500 mg oral dose given every 12 hr

Distribution: -

Ciprofloxacin distribution in the tissues is superior to that of many other drugs of its class because there is little binding to plasm protein. It has good penetration in various fluid & tissues of the body, except the central nervous system (CNS) after oral administration. Penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. The urinary drug conc. Is higher than the minimum inhibitory conc. So, it is mainly used in urinary tract infection.

Metabolism & elimination: -

Ciprofloxacin differs widely in the degree to which it is metabolised & eliminated in the liver by renal excretion. The metabolism is inactivating & is primarily by glucoronate conjugation at the 3- carboxylic group. The

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piperazine ring is readily metabolised and this result in decreased antimicrobial activity. Elimination occurs by both renal and non-renal routes, but the primary route by glomerular filtration and tubular secretion

Toxicology of ciprofloxacin: -

Toxicity is mild at therapeutic does, and generally limited to gastrointestinal disturbances such as nausea, vomiting and diarrhoea. Although resistance to this class of antibiotics in pneumococci is rare, nevertheless some reports indicate that resistance to ciprofloxacin is increasing. Ciprofloxacin has been reported to be an effective therapeutic for anthrax, A large does is needed due to the blood- brains barrier and heavy use of ciprofloxacin in such cases had been suspected to induce aseptic meningitis.

Genotoxicity of ciprofloxacin: -

All in vivo genotoxicity revealed no genotoxic effect for ciprofloxacin. In addition, ciprofloxacin was found to be non-carcinogenic in two rodent long- term bioassays. Ciprofloxacin is considered to be safe for therapeutic use.

#Safety pharmacology: -

Ciprofloxacin is a bactericidal antibiotic of the fluoroquinolone drug class. It inhibits DNA replication by inhibiting bacterial DNA poisoners and DNA – gyrase

#Efficacy of drug: -

Ciprofloxacin is effective in complicated and sever lower respiratory tract infection, including those in patient with infection exacerbation of chronic bronchitis and cystic fibrosis, and pseudomonal infection. #Reproductive toxicology: -Nephrotoxic reaction to ciprofloxacin appears to be unusual but potentially serious. It has previously been reported that fluoroquinolones could cause acute renal failure (ARF) after the ingestion of large quantities, but is now recognised that therapeutic doses of fluoroquinolones can also cause renal injury.

#Brand name: -

Ciprofloxacin (tablets and liquids),

Cytoxan (eyedrops and eye ointment)

central (eardrops)

#Approved

- The oral tablet form of ciprofloxacin was approved in October 1987; the intravenous form of ciprofloxacin is approved in 1991

#Originated: -

Ciprofloxacin was patented in 1980 and introduced in 1987. It is on the world health organization list of essential medicines. The world health organization classifies ciprofloxacin as critical important for human medicine. Cipro is available in 500 mg and 1000mg (ciprofloxacin equivalent tablet strength

CIPROFLOXACIN RESISTANCE

Due to wide usage of ciprofloxacin for treatment of UTIs, its resistance against uropathies has increased to a great extent. Blatter et al. reported increased resistance to ciprofloxacin from 1.8 to 15.9% from 1997 to 2007.

A Brazilian study documented that E. coli (10%) and K. pneumoniae (19%) were resistant to ciprofloxacin. Furthermore, another study from Brazil reported that 35% of E. coli were resistant to ciprofloxacin. A retrospective study conducted for five years 2010-2014 in Brazil reported that 36% of E. coli strains were resistant to ciprofloxacin.

Recently, a systematic review and meta-analysis compared ciprofloxacin resistance in hospital acquired and community acquired UTI and found that there was significantly Resistance to Ciprofloxacin in Urinary Tract Infection that resistant pattern of various fluoroquinolones as norfloxacin (60.6%), ofloxacin (60.6%), nalidixic acid (56.4%) and ciprofloxacin (55.5%).15 Furthermore, Kandel et al. reported fluoroquinolone resistant as ciprofloxacin (59%), levofloxacin (60%), ofloxacin (62%), Gemifloxacin (58%) and Nalidixic acid (67%) in UTI pathogens Increased number of prescriptions also plays an important role in the development of antimicrobial resistance

The previous study analysed 72 general practice prescriptions and reported increased resistance of 5.5% with 10 prescriptions over a month in comparison to resistance levels of 3% in practices with one prescription per

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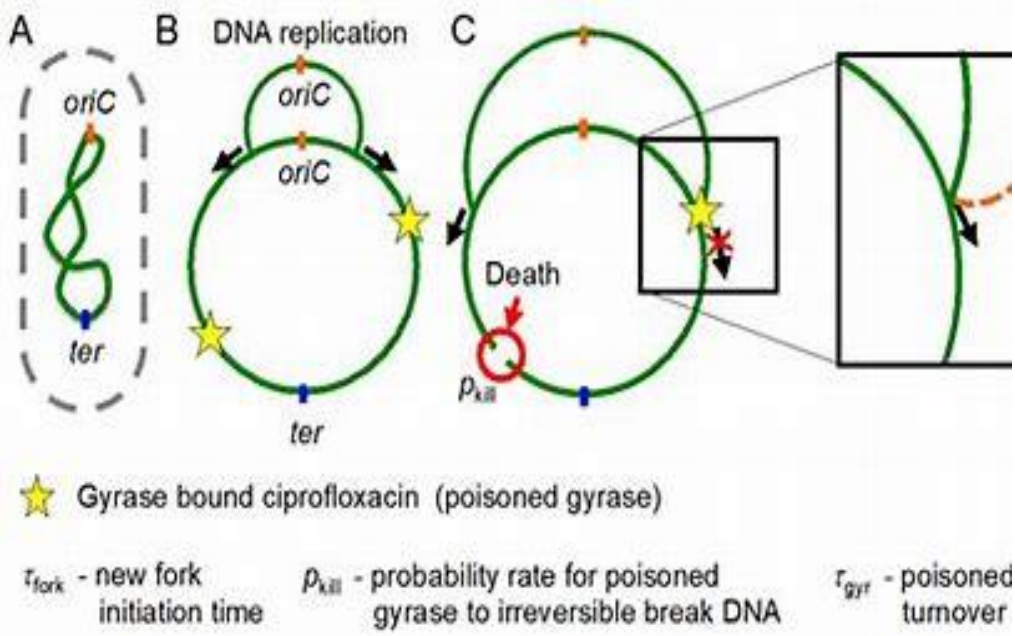
month. A systematic review documented that frequent non-prescription use of antimicrobials in some countries such as in Africa (100%), Asia (58%) and Middle East (39%) can lead to the development of resistance.

MACHANISM OF ANTIMICROBIAL RESISTANCE

There are various mechanisms by which bacteria develop resistance to an antimicrobial agent such as enzymatic degradation of the antibiotic, changes in the site of the action leading to loss of permeability, increase the activity of efflux pump and alterations of the cell permeability. The mechanism for fluoroquinolones resistance includes the reduction in affinity of antibiotic to target site by alteration in chromosomally encoded target gene ,encoding subunits A and B of topoisomerase II/IV.



The patient to know or influence on patient allocation), unclear (not sufficient information available to reach a judgement) or inadequate (description of randomization methods as non-opaque envelopes or presence of information allowing for a biased assignment of the study subject to some group in particular). Statistical analysis of the results was conducted using the STATA 11.0 statistical package for Mac, considering the sub-routines for the development of meta-analyses. For dichotomous (e.g., bacteriological eradication vs. no eradication), the results were expressed as the RR with a 95% confidence interval (95% CI), whereas for continuous measuring scales, data were expressed through the weighted mean difference (WMD). In the cases where primary exploration allowed for a heterogeneity value (I2) higher than 60% to be identified, the decision was made to analyse the results using a random effects model (inverse of the variance). Statistical heterogeneity was explored using Egger's graphs, and publication bias was assessed using a funnel plot.

CLINICAL OVERVIEW

During 2001, 40 patients presented to UCSF's emergency department or outpatient clinics with E. coli isolates (≥105 cuff) and ciprofloxacin resistance in whom outpatient medical records were available. In the same time period, ciprofloxacin resistance was observed in 10% of UCSF outpatient E. coli isolates and in 21% of inpatient isolates.

To obtain a 1:2 ratio of case to controls, we randomly selected 80 patients with ciprofloxacin-susceptible E. coli, presenting during the same time period, as the study group.

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Author	Year	Treatment 1	Treatment 2	n1	n2	Multi-center	Blinding	Randomized
Naber et al.[38]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 400 mg SD	360	371	Yes	Double	Yes
Naber et al.[38]	2004	Ciprofloxacin 500 mg BID x 5 days	Gatifloxacin 300 mg BID x 3 days	360	371	Yes	Double	Yes
Auqer et al.[50]	2002	Ciprofloxacin 500 mg SD	Norfloxacin 400 mg BID x 3 days	164	161	Yes	Double	Yes
Gomolin et al.[52]	2001	Ciprofloxacin 250 mg BID x 10 days	TMP 160/800 mg BID x 10 days	86	86	Yes	Oben label	Yes
Iravani et al.[61]	1999	Ciprofloxacin 100 mg BID x 3 days	TMP 160/800 mg BID x 7 days	168	174	Yes	Double	Yes
Iravani et al.[61]	1999	Ciprofloxacin 100 mg BID x 3 days	Nitrofurantoin 100 mg BID x 7 days	168	179	Yes	Double	Yes
Henry et al.[59]	1999	Ciprofloxacin 250 mg BID x 7 days	Sparflox 400 mg SD	386	395	Yes	Double	Yes
Henry et al.[59]	1999	Ciprofloxacin 250 mg BID x 7 days	Sparflox 200 mg OD x 3 days	386	394	Yes	Double	Yes
McCarty et al.[62]	1999	Ciprofloxacin 100 mg BID x 3 days	Ofloxa 200 mg BID x 3 days	229	228	Yes	Double	Yes
McCarty et al.[62]	1999	Ciprofloxacin 100 mg BID x 3 days	TMP 160/800 mg BID x 3 days	229	231	Yes	Double	Yes
Iravani et al.[80]	1996	Ciprofloxacin 500 mg BID x 5 days	Norfloxacin 400 mg BID x 5 days	249	227	Yes	Double	Yes
Iravani et al.[86]	1993	Ciprofloxacin 250 mg BID x 7 days	Fleroxacin 200 mg OD x 7 days	204	180	Yes	Double	Yes
Pfau et al.[92]	1993	Ciprofloxacin 500 mg SD	Ofloxacin 400 mg SD	59	59	No	Double	Yes
Pfau et al.[92]	1993	Ciprofloxacin 500 mg SD	Norfloxacin 800 mg SD	58	57	No	Double	Yes
Henry et al.[128]	1986	Ciprofloxacin 250 mg BID x 10 days	TMP/SMX 160/800 mg TID x 10 days	31	34	No	Double	Yes

(Table 1). The only variables that remained significant in the logistic regression analysis were previous use of any fluoroquinolone and re current UTI. Figure 1 describes susceptibility patterns from ciprofloxacin-resistant isolates. Among the 40 cipro floxacrine-resistant isolates, 38 remained susceptible to nitrofurantoin and 31 were susceptible to cefazolin; only 3 were susceptible to TMP/SMX. The susceptibilities to all other antibiotics were not recorded.

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II. CONCLUSION

Ciprofloxacin is one of the most prescribed fluoroquinolones for the treatment of uncomplicated UTI. However, the incidence of resistance to ciprofloxacin has increased steadily during the past few years. Thus, the empirical use of fluoroquinolones for treatment of UTI should be reconsidered and the drug used only when there are clear laboratory tests confirming sensitivity to the drug.

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