ANTIBIOTIC RESISTANCE IN UTI: A BIG CHALLENGE FOR CLINICIAN

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ABSTRACT

Urinary tract infection (UTI) is a major problem worldwide. The resistance of bacteria causing UTI to commonly prescribed antibiotics is increasing both in developing as well as in developed countries. The risk of developing infection in diabetic patients is higher and urinary tract is the most common site for infection. Antibiotic resistance has emerged due to its frequent use. Resistance has emerged even to more potent antimicrobial agents. Resistance has emerged even to more potent antimicrobial agents. Resistance in Gram-negative bacteria has been increasing, particularly over the last 6 years. This is mainly due to the spread of strains producing extended-spectrum b-lactamases (ESBLs) such as CTX-M enzymes or AmpC b-lactamases. Many of the isolates producing these enzymes are also resistant to trimethoprim, quinolones and aminoglycosides, often due to plasmid co-expression of other resistance mechanisms. CTX-M-producing Escherichia coli often occurs in the community and as E. coli is one of the commonest organisms causing UTIs, the choice of agents to treat these infections is diminishing. Novel combinations of antibiotics are being used in the community and broad-spectrum agents such as carbapenems are being used increasingly as empirical treatment for severe infections. As resistance is becoming more widespread, prudent use of antimicrobials is imperative and, as asymptomatic bacteriuria is typically benign in the elderly, antibiotics should not be prescribed without clinical signs of UTI. The use of antibiotics as suppressive therapy or long-term prophylaxis may no longer be defensible. E.coli is found to be the commonest cause of UTI. However E. coli antibiotic resistance has escalated over the past many years. The present study provide an update of prevalence of multidrug resistant E.coli isolates and their antibiotic susceptibility pattern with special reference to northern region of Chandigarh.
INTRODUCTION
UTI is an infection that affects part of the urinary tract. When it affects the lower urinary tract, it is known as a simple cystitis and when it affects the upper urinary tract, it is known as pyelonephritis\[^1\]. UTI is one of the most common infectious diseases seen in the community. Empirical antibiotic therapy is usually applied here for treatment of infection. Treatment of UTI becomes even more challenging in the presence of various risk factors such as higher age, co morbidity, and immune suppression. Many times, physicians resort to prescribing broad-spectrum antibiotics over specific antibiotics in the view of resistance of the causative organism to the antibiotic. Poor patient compliance and incomplete course of antibiotic therapy have resulted in the evolution of resistance to many of these antibiotics. Various studies done worldwide have shown changing patterns in the etiology of UTIs. However, studies on UTI and the pattern of antibiotic resistance in India are few. The present trends of the uropathogens and their susceptibility to various antibiotics are essential to formulate guidelines for the empirical treatment of UTIs while awaiting the culture sensitivity \[^2\].

Urinary tract diseases (UTD) are generally differentiated into two prime categories, which are lower urinary tract diseases and upper UTD. Cystitis is as a form of UTI which is characterized by swelling in the linings of the urethra as well as the bladder in an individual's body. However, on the other hand, pyelonephritis is a form of UTI characterized with swelling in the linings of the kidneys in the individuals \[^3\]. The common symptoms are associated with pyelonephritis or lower urinary diseases include extreme unbearable pain in the lower portion of the back, nausea, pain in the lower abdominal region, high fever and frequent vomiting. However, in serious and rare cases, individuals might also suffer from chills and diarrhea due to the UTI \[^4\]. The symptoms are associated with upper urinary tract diseases or cystitis include dysuria, frequent feeling and urge for urination especially during the nights, mild fever and passing of foul smelling and black colored urine. However in certain serious cases, individuals pass urine having traces of blood in it, this condition is known as hematuria. For urinary tract infections, or UTIs, the first line of treatment is often oral antibiotic therapy. A wide range of antibiotics can be prescribed to treat UTIs, and more than one type may be prescribed when the infection does not respond to initial treatment. The drugs which are usually used for treating UTI are beta-lactam, cotrimoxazole, fluoroquinolones, tetracycline, amoxicillin like antibiotic line etc \[^5\]. The clinical manifestations of UTIs can vary significantly, especially in the extremes of age. UTIs in children can present with different symptoms. Symptoms in children younger than 2 years of
age tend to be nonspecific, and can include fever, vomiting, and failure to thrive. In contrast, the elderly patient who has a UTI may be asymptomatic. When symptoms are present, they can include abdominal pain or mental status changes. Some patients with acute pyelonephritis can present with sepsis. There are many different etiologies, both infectious and non-infectious, that can present with acute dysuria. The differential diagnosis of acute dysuria may include pyelonephritis, cystitis, urethritis, infectious vaginitis, atrophic vaginitis, and interstitial cystitis. A good history and physical examination usually gives the clinician enough information to make a correct diagnosis in most situations [6]. The present review article summarized the causes of UTI resistance due to irrational uses of antibiotics with their risk factors including its management.

**Antibiotic resistance** is the ability of bacteria to withstand the antimicrobial power of antibiotics. Antibiotic resistant bacteria are bacteria that cannot be fully inhibited or killed by an antibiotic. The antibiotic may have worked effectively before the resistance occurred. Bacteria become resistant to antibiotics by adapting their structure or function in some way that prevents them from being killed by the antibiotic. This mechanism might happen in several ways:

- Bacteria can neutralize the antibiotic before it has an effect
- Bacteria may be able to pump the antibiotic out
- Bacteria may be able to change the site (receptor) where the antibiotic normally works
- Bacteria can mutate and transfer genetic material that codes for resistance to other bacteria

Overusing powerful medications, in particular quinolone antibiotics like makes bacterial resistance to these drugs develop even faster, according to the study. Antibiotic resistance, a natural evolutionary process, is a form of drug resistance where a microorganism survives even after contact with an antibiotic because it is adjusting to the medication. When it survives, it can pass on its resistant traits. Although these concerns have gained worldwide importance with the harmful and potentially-fatal bacteria (methicillin-resistant Staphylococcus aureus), scientists have said that resistance is common in several other bacteria [7].

The aim of the present study has been designed to evaluate the present clinical scenario of antibiotic resistance in UTI with the discussion of local clinician. This study will show the enlist clinical applicable current approach in UTI treatment. Antibiotic is a chemical that is produced by micro-organism and that, in relatively high dilution, inhibits the growth or
reproduction of some other microorganisms. Antibiotics are required in very low concentration; these are also called as chemotherapeutic agents. However, it is important to note that all chemical substance produced by living cells cannot function as antibiotics [8].

**CAUSES OF UTI**

*Escherichia coli (E. coli)* is by far the commonest cause of uncomplicated community-acquired UTIs in both outpatient and inpatient settings. Other common uropathogens are *Enterococcus faecalis*, *Enterobacter* species, *Staphylococcusaprophyticus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and Pseudomonas species are involved in UTI [9]. Women are particularly at risk of developing UTIs because of their short urethra, and certain behavioural factors which include delay in micturition, sexual activity and the use of diaphragms and spermicides which promote colonization of the periurethral area with coliform bacteria. Infection in women most often results from perineal or periurethral bacteria that enter the urethra and ascend into the bladder, often in association with sexual activity, or due to mechanical instrumentation such as catheterization [10]. Gram negative organisms are those most commonly isolated from urine samples of children with uncomplicated UTI with *E. coli* accounting for 70 to 90% of infections [11].

**ANTIBIOTIC ASSOCIATED BACTERIAL RESISTANCE & MANAGEMENT**

The resistance problem can be seen simplistically as an equation with two main components: the antibiotic or antimicrobial drug, which inhibits susceptible organisms and selects the resistant ones; and the genetic resistance determinant in microorganisms selected by the antimicrobial drug [12]. The resistance emerges only when the two components come together in an environment or host, which can lead to a clinical problem. Selected resistance genes and their hosts spread and propagate under continued antimicrobial selection to amplify and extend the problem to other hosts and other geographic locations. There are more than 15 classes of antibiotics whose targets are involved in essential physiological or metabolic functions of the bacterial cell. No One has escaped a resistance mechanism. Millions of kilograms of antimicrobials are used each year in the prophylaxis and treatment of people, animals and agriculture globally, driving the resistance problem by killing susceptible strains and selecting those that are resistant. But how do bacteria acquire resistance? Drug resistance is mobile—the genes for resistance traits can be transferred among bacteria of different taxonomic and ecological groups by means of mobile genetic elements such as bacteriophages, plasmids, naked DNA. These genes are generally directed against a single family or type of antibiotic, although multiple genes, each bearing a single drug resistance
trait, can accumulate in the same organism. And, like the antibiotics themselves, resistance mechanisms are varied. In the absence of plasmids and transposons (which generally mediate high-level resistance), a step-wise progression from low-level to high-level resistance occurs in bacteria through sequential mutations in chromosomes. This process was responsible for the initial emergence of penicillin and tetracycline resistance in N. gonorrhoeae. The organism later acquired transposons bearing genes with high-level resistance to these drugs. Strains of E. coli and other Enterobacteriaceae have evolved increasing resistance to FQs, the result of mutations in the target enzymes (topoisomerases) and an increase in the expression of membrane proteins that pump the drugs out of the cell.

Antibiotic-resistant organisms that cause UTI include Gram-positive cocci such as Methicillin-resistant Staphylococcus aureus (MRSA), Methicillin-resistant coagulase-negative Staphylococci (MRCoNS), Vancomycin-resistant Enterococci (VRE) and Gram-negative organisms particularly those species that produce AmpC enzymes or extended-spectrum b-lactamases (ESBLs). Urea-splitting organisms such as Proteus spp., Morganella morganii and Providencia stuartii are often found in patients with indwelling devices. Pseudomonas spp. with their intrinsic resistance is also problematic. Other resistant urinary bacteria include Enterobacter cloacae that express a chromosomal AmpC b-lactamase. This enzyme is inducible on exposure to b-lactams such as Cephalosporins. Plasmid-mediated AmpC b-lactamase in bacteria such as Klebsiella spp. and E. coli can also confer a wide range of resistance to penicillins and most Cephalosporins apart from the fourth-generation agent’s Cefepime and Cefpirome. These enzymes are resistant to inhibition by clavulanic acid. Some of these bacteria remain susceptible to Trimethoprim and the Quinolones. The oral options available for the treatment of UTI caused by ESBL or AmpC-producing bacteria are limited, particularly if susceptibility testing indicates concurrent resistance to Trimethoprim and Quinolones. Most organisms remain susceptible to Nitrofurantoin. One alternative is an agent used more widely in the Europe is Fosfomycin. Fosfomycin is approved by the Food and Drug Administration in the United States for treatment of uncomplicated lower UTI and single-dose therapy (3 g oral powder) was found to be equivalent to a 7 day course of Norfloxacin in a randomized open label study. The dose regimens of 3 g every 2–3 days for up to 21 days have been used, but due to limited systemic absorption, Fosfomycin should not be used for pyelonephritis or severe urinary sepsis. However, there is evidence that the addition of Clavulanic Acid results in a decrease in MIC bringing it down from an intermediate/resistant range to within the susceptible range.
[19]. A combination of agents containing clavulanic acid with other readily available extended-spectrum oral antibiotics that resist hydrolysis by common β-lactamases, such as Pivmecillinam, Cefixime or Cefpodoxime, has been used to treat UTIs [20]. Carbapenems, such as Meropenem and Imipenem, are broad-spectrum agents that can be used as empirical therapy for severe sepsis that may be caused by ESBL- or AmpC-producing bacteria. Intravenous therapy with a Polymyxin (Colistin or Colistimethate Sodium) has been used to treat infections due to multi-resistant Gram-negative organisms [21].

Ciprofloxacin and Ofloxacin are the most extensively used Fluoroquinolones (FQs) for the treatment of UTIs. The emergence of resistance for FQs is multifactorial. Resistance to Ciprofloxacin has emerged in a variety of genera of the family Enterobacteriaceae. Apart from the notable resistance of E. coli to Ciprofloxacin, other organisms were also found to be resistant to Ciprofloxacin especially K. pneumoniae, Citrobacterspp, Pseudomonas spp, Acinetobacterspp, Proteus spp and Enterobacterspp, Staphylococcus spp, and E. faecalis. Also, FQs resistance in E. coli has emerged particularly in patients with urinary tract infections who have received FQs prophylaxis. An association between the increase in Quinolone prescriptions and an increase in bacterial resistance has been reported from several countries. Usually, the prevalence of FQs resistance is related to the intensity of antibiotic use. Resistance rates for Ciprofloxacin against uncomplicated UTI pathogens were reported as 2.5 per cent in the USA and 1.2 per cent in outpatients in Canada [22]. A total of 170 urine culture sensitivity reports were analyzed in the study between Aug 2009 and July 2010. The predominant growth of single bacteria was seen in 143 (84.12%) samples. The most common organisms isolated were Escherichia coli, klebsiella, pseudomonas, and Staphylococcus aureus. More than 80% of the isolates were sensitive to Amikacin and Nitrofurantoin, while more than 70% were sensitive to Norfloxacnin, Ciprofloxacin and Levofoxacin [23]. E. coli showed high sensitivity to Amikacin 98.91%, Nitrofurantoin 93.48% and Ceftazidime 80.43% with good susceptibility to FQs –{Levofoxacin 75%, Norfloxacnin 73.91%, Ciprofloxacin 69.56%} and Minocycline 75%. The Klebsiella showed highest sensitivity to Amikacin 89.65% and Nitrofurantoin 75.86%, while it was also susceptible to the Ceftazidime 68.96% and FQs- {Levofoxacin 72.41%, Norfloxacnin 72.41%, and Ciprofloxacin 68.96%} and Gentamicin 62.10%. Pseudomonas showed highest sensitivity to Ceftazidime 84.62% and FQs {Norfloxacnin 76.92%, Ciprofloxacin 69.32%} followed by Aminoglycosides {Amikacin 61.54%, Gentamicin 53.85%. The Staphylococcus aureus showed high sensitivity to Amoxiclav 88.9%, Amoxicillin 77.8%, Nitrofurantoin 88.9%,
Ciprofloxacin 77.8%, Gentamicin 55.5% [24]. Over the last decade, the treatment of choice for UTIs has changed from Cotrimoxazole to Quinolones owing to the rate of resistance to Cotrimoxazole and its high level of therapeutic failure. Antimicrobial resistance has been associated with an increased rate of clinical failure, and reports from Canada and the US indicate that the prevalence of Cotrimoxazole resistance exceeds 15% and can be as high as 25%. Use of FQs are recommended for uncomplicated UTIs in areas where the incidence of Cotrimoxazole resistance exceeds 10%, as well as for the treatment of complicated UTIs and acute pyelonephritis [25]. These data were collected from hospitalized patients. The overall rate of resistance to FQs (Norfloxacin, Ofloxacin, Pefloxacin, and Ciprofloxacin) was 5.3%. Reported studies, which primarily considered ciprofloxacin and then norfloxacin, showed that trends toward E. coli resistance to this class of antibiotic have steadily increased. However, rates differed widely from one study to another [14]. Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage and efficacy comparable to 3 days of Trimethoprim-Sulfamethoxazole [26]. Trimethoprim-Sulfamethoxazole (160/800 mg twice-daily for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modelling studies. In some countries and regions, Trimethoprim (100 mg twice daily for 3 days) is the preferred agent and is considered equivalent to Trimethoprim-Sulfamethoxazole on the basis of data presented in the original guideline. Fosfomycin trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with standard short-course regimens according to data submitted to the US Food and Drug Administration [27, 28]. Pivmecillinam (400 mg bid for 3–7 days) is an appropriate choice for therapy in regions where it is available (availability limited to some European countries; not licensed and/or available for use in North America), because of minimal resistance and propensity for collateral damage, but it may have inferior efficacy compared with other available therapies. β-Lactam agents, including Amoxicillin-Clavulanate, Cefdinir, Cefaclor, and Cefpodoxime-Proxetil, in 3–7-day regimens are appropriate choices for therapy when other recommended
agents cannot be used. Other β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings. The β-lactams generally have inferior efficacy and more adverse effects, compared with other UTI antimicrobials. For these reasons, β-lactams other than Pivmecillinam should be used with caution for uncomplicated cystitis. Amoxicillin or Ampicillin should not be used for empirical treatment given the relatively poor efficacy. In patients suspected of having pyelonephritis, a urine culture and susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen.

Susceptibility would help to communicate the current status of resistance in a location, facilitating more appropriate choices of treatment. Such surveillance would alert public health officials to new pathogens and would spur the implementation of control policies. In this regard, the Alliance for the Prudent Use of Antibiotics has established its Global Advisory on Antibiotic Resistance Data project to synthesize, evaluate and report the surveillance data from five large global surveillance systems. Commensal organisms are common reservoirs of antibiotic resistance plasmids, transposons and genes. E. coli and the enterococci of the gut serve as reservoirs from which several antibiotic resistance genes can spread. The commensal Haemophilus parainfluenzae has been shown to confer β-lactamase-specifying plasmids to H. influenzae. Similarly, Staphylococcus epidermidis serves as a reservoir for resistance genes and plasmids for the more pathogenic S. aureus. Vancomycin resistance determinants found initially among enterococci appeared in other commensal bacteria before emerging in S. Aureus. This concept has been recently formalized by an Alliance for the Prudent Use of Antibiotics–based Reservoirs of Antibiotic Resistance project that supports studies examining the link between resistance in commensal flora and resistance in clinical isolates.

Some are directed at the antibiotic itself: enzymes such as β-lactamas destroy penicillins and cephalosporins, and modifying enzymes inactivate chloramphenicol and aminoglycosides such as streptomycin and gentamicin. Others target how the drug is transported; for example, an active efflux of drug mediates resistance to the tetracyclines, chloramphenicol and the fluoroquinolones. A third type of mechanism alters the intracellular target of the drug—for example, the ribosome, metabolic enzymes or proteins involved in DNA replication or cell wall synthesis—making the drug unable to inhibit a vital function in the microbial cell. The same kind of drug resistance mechanism can be specified by many different genes. Although most FQs resistance stems from chromosomal mutations in the gyrase target or from drug efflux, a plasmid-mediated resistance to FQs has been recently described. Multidrug
resistance can be specified by chromosomal genes for regulatory proteins such as MarA and SoxS. These proteins promote drug resistance by controlling the expression of other chromosomal genes, such as those involved in drug efflux \[^{30}\].

Oral Ciprofloxacin (500 mg twice daily) for 7 days, with or without an initial 400-mg dose of intravenous Ciprofloxacin, is an appropriate choice for therapy in patients not requiring Hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10\%. If an initial one-time intravenous agent is used, a long-acting antimicrobial, such as 1 g of Ceftriaxone or a consolidated 24-h dose of an Aminoglycoside, could be used in lieu of an intravenous FQ. If the prevalence of FQ resistance is thought to exceed 10\%, an initial 1-time intravenous dose of a long-acting parenteral antimicrobial, such as 1g of Ceftriaxone or a consolidated 24-h dose of an Aminoglycoside, is recommended \[^{26}\].

**IRRATIONAL USE OF ANTIBIOTICS IN UTI**

The bacterial infections which contribute most to human mortality and morbidity are also those in which emerging antimicrobial resistance is most obvious: diarrhoeal diseases, respiratory infections. Development and spread of antimicrobial resistance (AMR) are commonly due to overuse, misuse, and indiscriminate use of antimicrobials by doctors, nurses and pharmacists, non-compliance and self medication by patients and use in animal husbandry and agriculture. It is estimated that 70-80\% of prescriptions for antimicrobials are probably advised unnecessarily by the health professionals. In spite of the fact that most common colds and diarrheal episodes are viral in origin, yet, antimicrobials are used indiscriminately. Reasons for over prescribing are often lack of confidence, peer pressure, patient pressure and pharmaceutical company pressure. Antimicrobial use is a key driver of the resistance. Poverty and inadequate access to antibiotics constitute a major factor in the development of resistance. Another common cause of developing resistance is improper diagnosis. In many instances the death of an adequately equipped diagnostic laboratory in the vicinity compels the physician to prescribe antibiotics empirically, thus, increasing the likelihood of the patient receiving a wrong antibiotic. Furthermore, ready availability of antibiotics over-the-counter and sales promotion schemes by the pharmaceutical manufacturers also leads to the promotion of indiscriminate use, thus, increasing the likelihood of development of resistance. Counterfeit drugs are also a problem contributing to development of resistance. These contain either the wrong ingredient, or lesser amount of the active ingredient. In some instances, the medication poisons are capable of causing disability.
or even death. The impact of the media has also contributed to the development of resistance. Patients often demand antibiotics for their ailment on the basis of advertisements read or seen. Unwitting use of more active drugs at sub therapeutic doses leads directly to the development of multi drug resistance. Irrational use of antimicrobials is widespread throughout the world. This is harmful in terms of increased cost of therapy, unnecessary adverse drug reactions, therapeutic failure, reduced quality of care and worst of it is AMR. There are some important examples of drug associated bacterial resistance include penicillin-resistant streptococcus pneumonia, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, multi-resistant Salmonella typhi, Shigella dysenteriae, Neisseria gonorrhoea, Pseudomonas aeruginosa and multi-resistant Mycobacterium tuberculosis. The development of resistance to drugs commonly used to treat P. falciparum malaria is of particular concern, as is the emerging resistance to antiretroviral drugs.

**NEW THERAPEUTIC APPROACHES IN UTI:** Confronted with a shortage new Antimicrobials, we must use our current drugs more prudently. Reducing and improving use can diminish resistance and permit a drug to resurface eventually as an effective therapy. The appropriate use of the antibiotics not only can help to reverse high resistance frequencies, but also can curb the appearance of resistance to newer agents. Decreasing antibiotic usage in the intensive care and other hospital units has shown that susceptible indigenous strains will repopulate the ecological niche in the absence of drug-selective pressure. But the process is slow and more difficult when addressing MDR strains, for which the use of many antibiotics must change to affect the presence of that strain. In addition, such efforts cannot succeed alone. They need to be complemented by other actions. For tuberculosis, better compliance after ‘directly observed therapy’ has clearly proved to be effective in treating the disease and in preventing the emergence of resistance continued use of the same drugs in areas where resistance is endemic should be halted From what we have learned, shorter-course therapies with highly active antibiotics will also reduce the pressure on multidrug resistance. A different approach focuses on preventing infection by inhibiting key gene products that are involved in the infection process itself. Because the inhibition of these targets does not affect growth, selection for resistance should be considerably reduced. The pipeline for new drugs is small, because the major pharmaceutical companies have largely abandoned the antibiotic discovery field. The availability of rapid diagnostics for the healthcare provider would greatly enhance the ability to prescribe more appropriately [31]. The testing of the microorganism responsible for UTI is a best method for the selection of best treatment to reduce the
resistance. It has reported that isolation of the multidrug resistance patients in one unit and analyse separately in the hospital resulting less resistance in other patients [32].

CONCLUSION
One can truly affirm that the choice of drugs in the treatment of UTI is quite narrow today due to the wide scale resistance that the common UTI pathogens showed to antibiotics. Antimicrobial resistant patterns are constantly evolving, it is a present global public health problem, and there is the mandatory for effective antibiotics sensitivity surveillance. This will help clinicians provide safe and effective therapeutics therapy for UTI. Our study has reviewed the various causes of antibiotics resistance may be due to irrational uses of drugs and theirs alternative way for treatment. It has been noted that various uropathogens like E. coli, as expected, the leading cause of UTI both in general and among other Gram negative bacteria. The study has indicated higher resistance rates to β-lactam antibiotics with Ampicillin being the least effective agent for treating UTIs whereas the Aminoglycoside antibiotics have been reported as the most effective agents with Gentamicin being the least resisted agent.

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