Commonly Use of Oral Antibiotic Resistance in Children Urinary Tract Infection an Increasing Global Problem

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A urinary tract infection (UTI) is an infection that affects part of the urinary tract.[1] When it affects the lower urinary tract it is known as a bladder infection (cystitis) and when it affects the upper urinary tract it is known as kidney infection (pyelonephritis).[2] Symptoms from a lower urinary tract include pain with urination, frequent urination, and feeling the need to urinate despite having an empty bladder.[1] Symptoms of a kidney infection include fever and flank pain usually in addition to the symptoms of a lower UTI.[2] Rarely the urine may appear bloody.[3] In the very old and the very young, symptoms may be vague or non-specific.[1] [4]

The most common cause of infection is Escherichia coli, though other bacteria or fungi may rarely be the cause. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history.[5] Although sexual intercourse is a risk factor, UTIs are not classified as sexually transmitted infections (STIs).[6] Kidney infection, if it occurs, usually follows a bladder infection but may also result from a blood-borne infection.[7] Diagnosis in young healthy women can be based on symptoms alone.[8] In those with vague symptoms, diagnosis can be difficult because bacteria may be present without there being an infection.[9] In complicated cases or if treatment fails, a urine culture may be useful.[10]

In uncomplicated cases, UTIs are treated with a short course of antibiotics such as nitrofurantoin or trimethoprim/sulfamethoxazole.[3] Resistance to many of the antibiotics used to treat this condition is increasing.[1] In complicated cases, a longer course or intravenous antibiotics may be needed.[2] If symptoms do not improve in two or three days, further diagnostic testing may be needed.[10] Phenazopyridine may help with symptoms.[1] In those who have bacteria or white blood cells in their urine but have no symptoms, antibiotics are generally not needed,[11] although during pregnancy is an exception.[12] In those with frequent infections, a short course of antibiotics may be taken as soon as symptoms begin or long-term antibiotics may be used as a preventative measure.[13]

About 150 million people developed a urinary tract infection each year.[5] They are more common in women than men.[3] In women, they are the most common form of bacterial infection.[14] Up to 10% of women have a urinary tract infection in a given year and half of women having at least one infection at some point in their lives.[3] [8] They occur most frequently between the ages of 16 and 35 years. [3] Recurrences are common.[3] Urinary tract infections have been described since ancient times with the first documented description in the Ebers Papyrus dated to c. 1550 BC.[15]

Patients with cystitis usually complain of dysuria, urinary frequency and urinary urgency. The presence of more than one of these symptoms increases the likelihood of UTI. Burning through out the course of micturition may help differentiate cystitis from urethritis where pain is classically at the beginning of urination (most patients however cannot explain this difference). Patients usually have no fever or constitutional symptoms and are comfortable except during micturition. There is no costovertebral angle tenderness. Mild suprapubic tenderness is elicited. Cystitis is very common in adult females. At least 30% of women experience at least one episode of cystitis in their lifetime. In contrast, cystitis is very rare in men. This is thought due to be secondary to the presence of a longer urethra making the ascension of bacteria more difficult and also due to the bacteriostatic nature of prostatic secretions. Male infants are however at a higher risk of urinary tract infections (UTI). Prostatic hypertrophy and prostatic carcinoma along with urethral obstruction, urinary retention and stasis contribute to the increased incidence of UTI in older men. Pregnant women (especially if they have sickle cell trait) have a higher incidence of UTI. Diabetes mellitus per se does

not increase the risk of UTI unless associated with a disorder of bladder emptying. UTIs in diabetics however may be more virulent.A recent categorization of UTIs is most helpful clinically because it divides patients into groups based on clinical factors and their impact on morbidity and treatment. These categories are as follows: acute uncomplicated cystitis in young women; recurrent cystitis in young women; acute uncomplicated pyelonephritis in young women; complicated UTI and its subcategories; UTI related to indwelling catheters; UTI in men; and asymptomatic bacteriuria.

Urinary tract infections are a fairly common problem in childhood and may have either a benign course responding to simple antibiotic therapy or be associated with significant disruption in either the anatomy or function of a child's urinary system. This editorial letter will focus on UTIs affecting children, with an emphasis on those less than 12 years of age. The principles discussed in introductory section, however, are applicable to that age group.

Urinary tract infections which are more often seen in girls than boys are among frequently seen bacterial infections during pediatric age. [16] Urinary tract infection in children is a significant source of morbidity. It is generally agreed that children with UTI require further investigation and continuing urinary surveillance to minimize future complications. Escherichia coli are the most common cause of urinary tract infection [17]. Other microorganisms include Klebsiella pneumoniae., Enterobacter aerogenes., Citrobacter spp., Proteus spp., Pseudomonas aerugenosa, Enterococcus faecalis [18-20]. Our findings are consistent with these reports. In our study confirmed Escherichia coli are major urinary pathogen and urinary tract infection was more common among females than male childrens.

A study by Bryce et al (2016) that reviewed studies investigating the prevalence of antibiotic resistance in UTI caused by Escherichia. coli in children found that the prevalence of resistance is high, particularly in countries outside the Organization for Economic Co-operation and Development (OECD). Resistance in countries outside the OECD was: 79.8% for ampicillin, 60.3% for co-amoxiclav, 26.8% for ciprofloxacin, and 17.0% for nitrofurantoin. [21]

In a study of 607 children with reflux diagnosed by VCUG after a first or second UTI, the subjects were randomized to antibiotic prophylaxis with TMP-SMX or placebo. The risk of recurrences was reduced by 50% in the treatment group (hazard ratio, 0.50; 95% CI, 0.34-0.74). The risk of renal scarring overall did not differ significantly between the groups over 2 years. Also, the occurrence of a subsequent UTI with a TMP-SMX — resistant organism was significantly increased in the treatment group. The children enrolled were aged 2-71 months, a wider age range than the AAP guidelines currently encompass. [22]

Antibiotic resistance is one of the world's most pressing public health problems. The antibiotic resistant organisms can quickly spread and so threaten communities with new strains of infectious disease that are more difficult to cure and more expensive to treat. Treatment failures may arise due to the resistance offered by pathogen against effective broad spectrum antibiotics. These treatment failures and hard to treat infections may results in high death rates. [23]

The antibiotics may not be saving us from UTIs for very much longer. Scientists tracking UTIs from 2000 to 2010 found a dramatic uptick in cases caused by Escherichia. coli that do not respond to the drugs that are our first line of defense. In examining more than 12 million urine analyses from that period, they found that cases caused by Escherichia. coli resistant to ciprofloxacin grew five-fold, from 3% to 17.1% of cases. And Escherichia. coli resistant to the drug trimethoprim-sulfame-thoxazole jumped from 17.9% to 24.2%. These are two of the most commonly prescribed antibiotics used to treat UTIs. When they are not effective, doctors must turn to more toxic drugs, and the more those drugs are used, the less effective they in turn become. When those drugs stop working, doctors will be left with a drastically reduced toolkit with which to fight infection.

Some of this growing resistance in Escherichia. coli and other bacteria is due to the fact that antibiotics are being overprescribed, handed out to patients who have no bacterial infections. There is also evidence that the genes that give bacteria resistance to drugs are being spread in livestock farming operations, where antibiotics are a common ingredient in animal feed. Ciprofloxacin is one of those antibiotics, and researchers have found that Escherichia. coli resistant to it are thriving in poultry farms. Very closely related strains of drug-resistant Escherichia. coli have been found in people, suggesting that the bugs spread from the birds to humans.

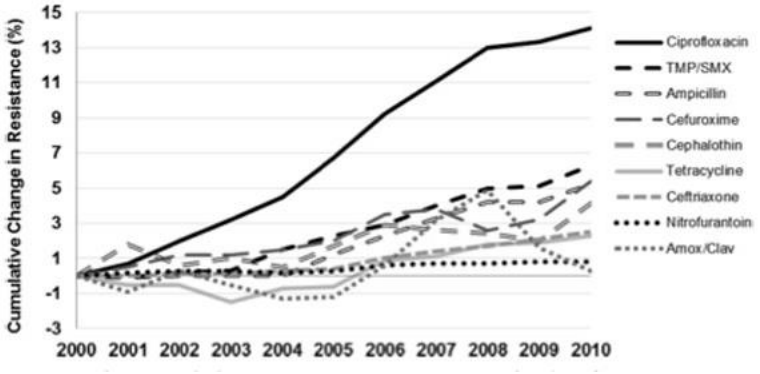

Fig. 7.1: The Trends in Antibiotics Resistance

People suffered from UTIs long before antibiotics were discovered in the early twentieth century, of course. Should these drugs cease to be effective, we'll have to go back to what we were doing before. The truth is, though, before antibiotics we had no real treatment. Sicknesses resembling UTIs have been described in medical texts for thousands of years, by everyone from the ancient Greeks and Chinese to the pioneers of evidence-based medicine in the early 1900s. Some of these doctors prescribed various tinctures, ointments, and special diets to deal with the symptoms, but in cases in which the infection spread to the bladder and kidneys and beyond, they were fairly helpless. As a last-ditch effort, they operated to drain puss from the infected kidneys and hoped the patient would survive. Treatment did not fundamentally change until antibiotics arrived on the scene.

In a world without antibiotics, many peoples' UTIs would doubtless subside under attack from the immune system. But some fraction of them would not, and those people would find themselves in dire straits. And about the common idea that cranberry juice can prevent or treat UTIs: evidence is pretty spotty. Better to try to reduce the irresponsible use of antibiotics than rely on juice.

Biswajit Batabyal et al., (2018) [24] study indicate a high incidence of microbial resistance to commonly used oral antibiotics such as Amoxicillin/clavulanic acid, Co-trimoxazole, Cefixime, Cefpodoxime, Cefprozil, Cefalexin in urinary tract infections among children and suggest that physicians should be cautious about treatment with these antibiotics. Knowledge of the local antibiotic resistance patterns will help in guiding antibiotic choice.

Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes. Community and hospital-acquired ESBL-producing Enterobacteriaceae are prevalent worldwide [25]. Reliable identification of ESBL-producing organisms in clinical laboratories can be challenging, so their prevalence is likely underestimated. Carbapenems are the best antimicrobial agent for infections caused by such organisms.

Beta-lactamases are enzymes that open the beta-lactam ring, inactivating the antibiotic. The first plasmid-mediated beta-lactamase in gram-negative bacteria was discovered in Greece in the 1960s. It was named TEM

after the patient from whom it was isolated (Temoniera) [26]. Subsequently, a closely related enzyme was discovered and named TEM-2. It was identical in biochemical properties to the more common TEM-1 but differed by a single amino acid with a resulting change in the isoelectric point of the enzyme.

Antibiotic resistance is an important issue affecting public health, and rapid detection in clinical laboratories is essential for the prompt recognition of antimicrobial-resistant organisms. Infection-control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria efficiently to minimize the spread of these bacteria and help to select more appropriate antibiotics. This is particularly true for ESBL-producing bacteria. The epidemiology of ESBL-producing bacteria is becoming more complex with increasingly blurred boundaries between hospitals and the community. Escherichia. coli that produce CTX-M βlactamases seem to be true community ESBL producers with different behaviors from Klebsiella spp, which produce TEM-derived and SHV-derived ESBLs. These bacteria have become widely prevalent in the community setting in certain areas of the world and they are most likely being imported into the hospital setting. A recent trend is the emergence of community-onset bloodstream infections caused by ESBL-producing bacteria, especially CTX-M-producing Escherichia. coli. These infections are currently rare, but it is possible that, in the near future, clinicians will be regularly confronted with hospital types of bacteria causing infections in patients from the community.β–lactums contribute a measure class of safer antibiotics. They are widely used as broad spectrum antibiotics for all the type of infections. New generation of antibiotics is predominantly preferred in clinical use. Many more new β- lactums are expected for the clinical use and many new β- lactums are expected in future. There is a better scope, prosperity for the discovery and development of new and safer β- lactums.The structure of β- lactams,their nature, classification, chemistry to be well studied. β-lactums, their mode of action, their bactericidal properties and their future growth is seen with new hopes.

Nursing-home patients may be an important reservoir of ESBL-producing multidrug-resistant Escherichia coli and Klebsiella pneumoniae [27-29]. In our study, resistance to more than one antibiotic was rather common and the spread of ESBL-producing isolates was quite alarming. The resistance rate to fluoroquinolones observed in this study was quite high, particularly in Escherichia. coli, and poses some concerns about their use in empirical treatment of UTIs. Resistance to fluoroquinolones is known to be associated with the previous use of antibiotics, particularly fluoroquinolones, and previous reports have demonstrated that underlying urinary tract diseases predispose patients to repeated UTIs and, in turn, to exposure to antibiotics such as fluoroquinolones [30--32].

Biswajit Batabyal et al., (2018) [24] study clearly demonstrates the development of resistance for commonly used of oral antibiotics in children UTI. Different factors are attributable for emergence of resistance of antibiotics mainly include; high consumption of antibiotics, irrational use, incomplete course of therapy, and self-medication by patients, leading to the emergence of resistance and even treatment failures. One major cause of self-medication is poverty. India is an under developed country, people are used to treating themselves without obtaining prescriptions from physicians. The present situation is alarming, an effective antibiotic would be failed to treat even simple or minor infections. Curtailed follow up of regimen also creates resistance. Generally patients stop their treatment when they feel slight improvement and the microorganisms start adapting the environment rather than get killed. Governments must initiate different educational programs, seminars, workshops in collaboration with the media to make people aware of the consequences of self-medication, especially with broad- spectrum antibiotics. In addition to this, routine antimicrobial susceptibility testing must be timely performed to determine the current status of resistance against antimicrobial agents (MIC, E test, Disk diffusion method). Otherwise therapy failures may occur which increase the cost of the therapy as well as recovery time from the underlying disease.

The problem of infection has been persistent in the surgical world even after the introduction of antibiotics. Ongoing researchers on antibiotic development signal the fact that numerous drug resistant organisms still continue to bother us and render the management of surgical wound infections a continue challenge. In spite of

proper application of the basic principles in surgical wound care, a number of patients develop infection needing proper identification of the organisms for appropriate management.

Although aerobic infections have been known to cause devastating postoperative complications, most anaerobicidal agents are very effective in neutralizing this problem. It is in the treatment of aerobic bacterial infections where variable antimicrobial responses exist. With the influx of voluminous number of antibiotics, the clinician often finds himself overwhelmed by the variety of options. Determination of the etiologic agent is vital in the final choice antibiotics. Most especially in a situation where empirical treatment has to be started without the benefit of a gram-stain or culture and sensitivity results, a working knowledge of the most likely causative organism and the prevailing antibiotic sensitivity/resistance pattern will be of great help.

The Indian Council of Medical Research has invited research proposals from scientists to generate scientific evidence on antimicrobial resistance. This move indicates that the apex medical research body has finally realized there is no place for jingoism in matters of science, and that the latest findings on antibiotic resistance must be taken seriously and verified scientifically. This exercise will prove to be useful only if the researchers are truly free to report the presence of the superbugs and the extent of their spread. The second important development has been the drafting of the much-needed national policy for the containment of antimicrobial resistance. The policy admits that the use of antibiotics is inappropriate in 20 per cent to 50 per cent of the cases. It targets the indiscriminate use of antibiotics in food animals and intends to curb the practice, since it ultimately causes drug resistance in humans. The Indian government should waste no time in creating a national surveillance system for measuring antibiotic resistance if it is serious about getting on top of the problem. By all parameters, our war against antibiotic-resistant bacteria is far from winning. The question is – are we serious? Will the Indian government do its role and save the hospitals and its public?

In summary of this editorials letter rising antibiotic resistance among urinary pathogens, and especially the emergence of multi-drug resistant clonal groups, has provided urgency to the development of novel preventative and therapeutic strategies. Some older drugs, such as fosfomycin, may prove to be very useful in treating antimicrobial-refractory UTIs, especially those due to ESBL-producers. Newer drugs, such as the recently approved doripenem, have proven highly effective in the clinic to treat complicated UTIs. Research into novel anti-virulence therapies, such as inhibiting the production of, or adherence by, urinary pathogenic Escherichia coli (UPEC) fimbriae is still an early stage but holds promise for future development. The use of probiotics to prevent vaginal urinary pathogenic Escherichia coli (UPEC) colonization and the use of an immuno-stimulatory urinary pathogen extract (SolcoUrovac) are currently in clinical trials to determine efficacy in preventing recurrent UTIs. Another preventative strategy is vaccination, and experimental vaccines have been developed that are effective in preventing UTIs in primates.

In conclusion of this editorials letter, it is important that each country should have its own epidemiological data, and physicians should know antimicrobial resistance rates in their regions so as to arrange treatment, and prophylaxis accordingly. Antimicrobial resistance rates are increasing steadily against antibiotics expected to exert clinical efficacy in the treatment of UTI as a result of their widespread, and erroneous use. We think that at certain intervals centers should identify urinary pathogens prevalent in their regions, and aware of antimicrobial susceptibilities of these pathogens which are very important for the economy of the country, and appropriate treatment.

Antimicrobial resistance is a globally ever increasing problem. The emergence and spread of antimicrobial resistance are complex and driven by numerous interconnected factors. The principle causes of microbial resistance are inappropriate, irrational, high consumption, and profligate use of antibiotics. The use of antimicrobials must be restricted and monitored in order to decline the resistance. The present results in increasing antibiotic resistance trends in UTI patients in children indicate that it is imperative to rationalize the use of antimicrobials and to use these conservatively. Considering the relatively increase rates of UTI and drug resistance observed in this study, continued local, regional, and national surveillance is warranted. Antibiotics should only be issued when prescribed by physicians.

Antibiotic resistance is a growing problem in pediatric urology as highlighted by the significantly increased urinary pathogen resistance to commonly use of oral antibiotics. Poor empiric prescribing practices, lack of urine testing, and nonselective use of prophylaxis exacerbate this problem. However, three small changes in practice patterns may curb the growing resistance rates: use of urine testing in order to only treat when indicated and tailor broad-spectrum therapy as able; selective application of antibiotic prophylaxis to patients; and use of local antiobiograms, particularly pediatric-specific antiobiograms, with inpatient versus outpatient data.

This editorial letter will provide novel, clinically important information on the diagnostic features of childhood UTI and the cost effectiveness of a validated prediction rule, to help primary care clinicians improve the efficiency of their diagnostic strategy for UTI in children. Regular monitoring is required to establish reliable information about resistance pattern of urinary pathogens for optimal empirical therapy of patients with UTIs. A combination of traditional and innovative prevention and treatment strategies is being deployed to combat the threat of emerging antibiotic resistance among urinary pathogens. Finally, I suggest that empirical antibiotic selection should be based on the knowledge of local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal guidelines.

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