



CURRENT THERAPIES OF URINARY TRACT INFECTIONS AND PREVENTION OF MULTI DRUG RESISTANCE

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Abstract

Urinary Tract Infections are very severe public health problem and are caused by Escherichia coli, Klebsiella, Proteus, Enterococcus, Pseudomonas, Acinetobacter, Citrobacter and Staphylococcus etc. Recurrent UTIs and multi drug resistance causes increasing in the economic burden. In this review article we discuss about the pathogens causing UTI, prevalence, current treatment options, multi drug resistance and its prevention. For prophylactic management in recurrent UTIs, there are no standard and uniform guidelines. Over use and misuse of the antibiotics leads to drug resistance in the patients. Mostly clinician's use empirical or targeted anti infective agents in the prevention and treatment of UTI along with long term low dose prophylactic antibiotics. However against the growing drug resistance within the uropatogens, alternative non antibiotic strategies like immuno prophylaxis, estrogen replacement in women are becoming an extremely attractive and reasonable solution in reducing the resistance.

Keywords: Urinary Tract Infections, resistance, prevention, current antibiotic therapy, susceptibility pattern, culture sensitivity report, causative organism.

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Introduction

Urinary tract infections are infections of the urethra, bladder, ureters, or the kidneys, which comprise the urinary tract. Females have a higher risk for UTIs than most males, probably because of their anatomy. A urinary tract infection (UTI) is an infection caused by pathogenic organisms (for example, bacteria, fungi, or parasites) in any of the structures that comprise the urinary tract. Normally urine is sterile. It is usually free of bacteria, viruses and fungi but does contain fluids, salts and waste products. An infection occurs when tiny organisms, usually bacteria from the digestive tract, cling to the opening of the urethra and begin to multiply. The organisms most commonly responsible for UTIs are E.coli, Proteus mirabilis, P.aeruginosa, and Streptococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycobacterium tuberculosis, Actinomycetes, Nocardia, Candida etc can cause UTI [3]. Urinary tract infections (UTIs) are some of the most common bacterial infections, affecting 150 million people each year worldwide [1]. Common symptoms of UTI are urinary urgency, urinary frequency, burning micturition, foul smell of urine, fever with chills, loin pain, nocturia, haematuria. The caregiver should obtain a detailed history from the patient, and if a UTI is suspected, a midstream urine sample is usually obtained for urine analysis [5]. A positive urinalysis is usually detection of about two to five leukocytes (white blood cells), about 15 bacteria per high-power microscopic field, and a positive nitrite test and/or positive leukocyte esterase test.

Current treatment options

Treatment of Lower UTI

Acute uncomplicated cystitis-urethritis: the first attack in a young, healthy women is treated by 3-day antibiotic therapy which reduces the rectal carriage of Gram-negative bacteria and is not associated with recurrence rate in UTI. Suggested oral antimicrobial regimens for acute uncomplicated cystitis include cotrimoxazole 2 tablets (b.i.d), trimethoprim 100mg (b.i.d), nitrofurantoin 100mg (b.i.d) and ampicillin 250-500mg (q.i.d). Cotrimoxazole is the best initial choice for empirical therapy in a non pregnant women. It is cost-effective and relatively safe. When low resistance to E.coli is known, nitrofurantoin 100 mg b.i.d

for 5-7 days is equally effective. More expensive alternative is fosfomycin 3g as single dose. Fluoroquinolones are not recommended as first line empirical treatment of uncomplicated cystitis [23].

Three-day therapy provides complete symptomatic relief but may not achieve 100% bacteriological cure. Hence, therapy for 7-14 days which achieves both clinical and bacteriological cure is preferred in following conditions:

- Failure of the 3 day regimen
- Symptomatic men
- Recurrences in both men and women
- Elderly (age more than 65 years)
- Symptoms persisting more than 7 days
- Pregnant women
- Children
- Patients with underlying renal disease, urinary tract obstruction/abnormalities and diabetes mellitus

Although a single dose cotrimoxazole, ampicillin/amoxicillin or fosfomycin has been used to treat first attack of UTI; such therapy gives low cure rate and leads to frequent recurrences. It fails to eradicate Gram negative bacteria from the rectum, the major reservoir for recruitment of ascending uropathogens, and hence, should not be recommended.

In pregnant women cystitis, amoxicillin (with or without clavulonic acid), cephalexin, cefodoxime, cefibuten and nitrofurantoin are treatment options. Single-dose therapy with fosfomycin tromethamine (3g) has been advocated for uncomplicated, first attack of infection in a pregnant women. Follow up urine culture is done 1-2 weeks after treatment and then monthly until delivery. Cotrimoxazole and fluoroquinolones should be avoided in pregnancy [12].

Recurrent infection, manifested by repeated bacteriuria usually within 2 weeks of apparently successful treatment, is caused by the same organism which caused the first infection. Recurrence should be documented by a culture at least once before starting therapy. Such women should receive treatment for at least 4-6 weeks with either cotrimoxazole or a fluoroquinolone. Other expensive alternatives are; amoxicillin+clavulonic acid; a third generation cephalosporin such as cefixime or cefpodoxime proxetil. It is important to eliminate the vaginal colonisation by E-coli. Also, hidden source of infection or a urological abnormality should be looked for.

In patients with suspected prostatic focus of infection, drugs like trimethoprim, erythromycin (for gram-positive bacteria), fluoroquinolones, doxycycline and aminoglycosides are recommended. Despite prolonged (6-12 weeks), the failure rate in chronic bacterial prostatitis is usually 30-40%. It should be remembered that non-bacterial prostatitis is far commoner than proven bacterial prostatitis (17). Where bacteriuria cannot be eradicated, chronic suppressive therapy with 1 tablet of cotrimoxazole or 50-100 mg of nitrofurantoin once daily can suppress symptomatic infection. Trimethoprim should alone be avoided for suppression for fear of development of drug resistance.

Treatment of upper UTI

Acute pyelonephritis is commonly associated with a predisposing factor such as obstructive Uropathy or diabetes mellitus (complicated UTI). The patient may be septicaemic and severely ill. Urine and blood cultures are mandatory before starting therapy; the results are helpful in modifying the initial therapy which is started without waiting for the culture report.

The drugs used in mild cases are ciprofloxacin 500mg b.i.d.; cotrimoxazole 2 tablets b.i.d.; amoxicillin-clavulonate 500 mg b.i.d. or ampicillin 1-2 g orally or i.v. (especially infection due to enterobacter) or a cephalosporin (19). Follow up urine culture is recommended after 2 weeks of therapy. In pregnant women, a parenteral cephalosporin and/or extended spectrum penicillin are indicated.

In severely ill patients and in those with recurrent, complicated UTI, empirical i.v. treatment should be started with:

1. A fluoroquinolone
2. A carbapenam
3. Piperacillin-tazobactem
4. Cefotaxime/ceftriaxone 1g i.v. followed by oral therapy with a fluoroquinolone.

The definitive treatment and its duration are guided by urine culture and are usually longer than 21 days.

Chronic pyelonephritis: This serious condition can lead to chronic renal failure and secondary hypertension. An underlying cause such as obstruction must be carefully searched for. The antibacterial treatment is prolonged and the choice of drug is governed by the identity of the organisms and their drug sensitivity, and by the extent of renal impairment [23].

It is difficult to treat. It is important to detect drug failure early so that an ineffective drug is discontinued. In such cases, it may be better to use antimicrobials only during acute episodes. Suppressive therapy is rarely effective.

Renal impairment: Tetracyclines, except Doxycycline, are avoided in chronic renal failure. The dose of aminoglycosides and cephalosporins must be scaled down. Nitrofurantoin and Nalidixic acid do not achieve adequate urinary concentration in patients with renal failure.

Follow up: successful treatment of an acute attack with an antibacterial agent leads to disappearance of bacteriuria within 24 h; but pyuria and symptoms take longer to disappear. Patients should be followed up for at least 6 months after treatment and urine cultures should be repeated at 1-2 months intervals. Cases with recurrent acute infection or with chronic infection need prolonged suppressive drug therapy (6-12 months) after the initial treatment. In such cases, follow up should be done for about 2 years.

Multidrug resistance & its prevention

The ability of the micro organisms to resist the drug which would normally kill them or inhibit the growth is called as Anti microbial resistance. The increased population of resistant micro organisms is due to using the anti microbial therapy against the small fraction of naturally resistant bacteria to the susceptible bacteria which giving the chance to increase the resistant organisms by exerting pressure on the susceptible organisms [22].

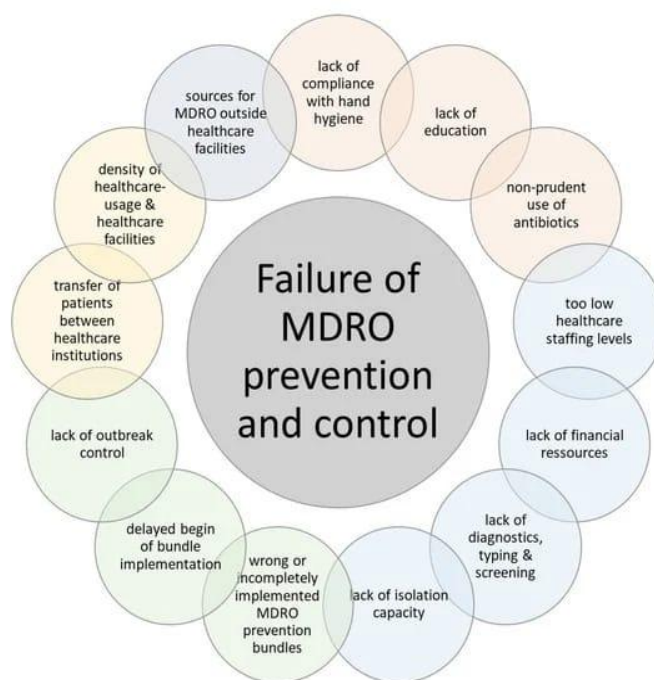
Mechanism of action of common antimicrobials and drug resistance

S.no	Drug or drug Class	Mechanism of action	Mechanism of Drug Resistance
1.	Beta - lactamases (penicillins, cephalosporins, aztreonam)	Inhibition of bacterial cell wall synthesis	Production of beta-lactamase Alteration in binding site of penicillin-binding protein Changes in cell wall porin size (decreased penetration)
2.	Aminoglycosides	Inhibition of ribosomal protein synthesis	Downregulation of drug uptake into bacteria Bacterial production of aminoglycoside-modifying enzymes
3.	Quinolones	Inhibition of bacterial DNA gyrase	Mutation in DNA gyrase-binding site Changes in cell wall porin size (decreased penetration) Active efflux
4.	Fosfomycin	Inhibition of bacterial cell wall synthesis	Novel amino acid substitutions or the loss of function of transporters
5.	Nirofurantoin	Inhibition of several bacterial enzyme systems	Not fully elucidated - develops slowly with prolonged exposure
6.	Trimethoprim-sulphamethoxazole	Antagonism of bacterial folate mechanism	Draws folate from environment (enterococci)
7.	vancomycin	Inhibition of bacterial cell wall synthesis	Enzymatic alteration of peptidoglycon at different point then target

Increasing multidrug resistance in bacterial uropathogens is an important and emerging public health problem. The Infectious Disease Society of America (IDSA) identified some microorganisms for new effective therapies. Those microorganisms were called “ESKAPE pathogens” which include *Enterococcus faecium*, *S. aureus*, *Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas* spp., and *Enterobacter* spp. Increasing drug resistance in UTI needs regular monitoring of the antibiotic susceptibility of uropathogens in a particular area. Generally, the antimicrobial treatment is initiated before the laboratories results which may lead to the frequent misuse of antibiotics. Before initiating the therapy culture sensitivity report is very important to know the resistance and sensitivity of the antibiotics to the particular organism. Using of antibiotics in an inappropriate way leads to increase in the no. of resistant micro organisms [22].

The various types of interventions used to control or eradicate MDROs are grouped into seven categories which include administrative support, judicious use of anti microbials, surveillance (routine and enhanced), standard and contact precautions, environmental measures, education and decolonization.

The attainment of balance between efficacy and ecology is the greatest challenge in the prevention of MDR. The selection of antimicrobials is mainly based on patient specific characteristics, risk factors for infections with specific pathogens and severity of illness. Untreated illness leads to severity which diminishes the efficacy of the initial anti microbial therapy increases the importance of study of antibiotic susceptible pattern. Most of the studies suggested that the use of combination therapy is the best choice over the mono therapy to decrease the mortality rate [21].



Methods to decrease resistance

- Early diagnosis
- Avoid the over usage of higher broad spectrum antibiotics without the evidence of culture sensitivity report.
- The results of culture sensitivity report should be rapid and accurate to detect the particular pathogen and susceptible pattern.
- Don't go for higher antibiotics even though the organism is susceptible for lower antibiotics.
- If the infection is not controlled by the oral antibiotics then only we should go for IV antibiotics (not in the sepsis conditions).
- Avoid the repeated usage of same antibiotic which increases the rate of resistance to that particular drug. So one should go for heterogeneity of antibiotics.
- Don't use the antibiotics without the doctor's prescription.
- Maintenance of hygienic conditions which is more crucial for inpatients.

Conclusion

The emerging urinary tract infections have greater resistance to the most antibiotics than ever before which leaves a challenge for the human world. We conclude that urinary tract infections should be treated and diagnosed early. The result of culture sensitivity test should be taken into considerations before prescribing the antibiotics. We can prevent MDR by reducing unnecessary antibiotic both qualitatively and quantitatively.

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Author Contribution

All authors are contributed equally

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