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Research Article

Urinary Tract Infection and Its Treatment Options

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ABSTRACT:
UTIs (Urinary tract infections) are the most overall infection in various age circulations. UTIs can infect any part of your body that is incorporating into urinary tract. Causative agents generally bacteria but it may be infected by viruses as well. UTIs can be complicated or uncomplicated. Early infection isn't so much complicated but infection with no treatment it might be dangerous or complicated (i.e. cystitis, pyelonephritis). Diabetes, hypertension or immunocompromised individuals have more chances to infect from UTI. UTIs are more common in ladies than men. One of the two women experiences UTI once in her life, especially the elderwomen and sexually active have seen. Urinalysis, diagnostic imaging and molecular techniques are used as a diagnostic tool for UTIs. Symptoms of UTIs include itching during urination, milky or dark color of urine, and abdominal pain. Mostly UTIs are treated by antibiotics but with a passage of time microbes become multiple drug resistant, so other therapies or treatment needed. The most common uropathogen is E. coli, Uropathogen E.coli (UPEC) also has been in the list of superbugs issued from WHO. multidrug In last fifteen years, by the drastic increase of antibiotic resistant UPEC, we need to better understand the virulence mechanism, an interaction between host-pathogen during infection and the strategies adapted by the microbe to become multidrug resistant, it will help us to cure the infection. Here, we discuss all the recent efforts and knowledge in medicinal therapies to cure multidrug resistant UTI and how the nanotechnology positively revolutionized the medicine.

Keywords: Urinary tract infection, Uropathogen, Nanotechnology, Multidrug-resistant uropathogens.

[1] INTRODUCTION

Urinary tract infections are involving around the kidneys, bladder, urethra or ureters, any part of the body that is include in renal system can be infected by bacteria or any other microorganism (i.e. fungus, parasite, viruses) [1]. Microbes cause an invasion and inflammation in urinary tract and multiply their self, they can extend their self towards medulla and cortex and causes upper UTI [2]. An uncommon uropathogen,
viruses also causes UTI, but in immunocompromised person lower UTIs have been seen by viruses, mostly the people who have renal transplant or stem cell transplant hemorrhagic cystitis have seen by *BK virus*, *Adenovirus*. *E. coli* is the most common uropathogen and also became resistant towards antibiotics day by day [3].

1.1. Types of UTIs:

Pyelonephritis

A kind of kidney infection commonly called upper UTI. UTI first infected bladder and then moves upward, may be affected one or both of the

kidneys. It can be life threatening. Another term Pyelitis related to an inflammation of pelvis and calyces, collectively both these terms nephritis and Pyelitisalso called as pyelonephritis. Bacteria cause inflammation in kidneys tissues and renal pelvis. It is present in body with symptoms like fever, nausea, abdominal pain and itching during urination [4].

Cystitis

Cystitis is a term related to an inflammation of the bladder, inflammation caused by an uropathogen i.e. bacteria or fungi. Bacteria enter in a urinary tract through urethra, reside there and cause inflammation in the walls of bladder. *E.coli* is the mostcommon causative agent of cystitis. [5].

Urethritis

Urethritis is an inflammation of urethra, mostly caused by bacteria. It is usually sexually transmitted infection. Symptoms include painful urination and burning sensation. Causative agents include *Neisseria gonorrhoeae* (gonococcal urethritis), *Chlamydia trachomatis* (non gonococcal urethritis). Viruses are also a causative agent (i.e. *Adenoviridae*&*Cytomegalovirus*) [6].

1.2. Uropathogen:

Table: 1. Types of Uropathogen and Normal flora of Urinary tract.

Common Uropathogen	Uncommon Uropathogen	Normal Flora
Enterobactersp p	*Streptococcus Group B*	*Streptococci (viridians)*
Escherichia coli	*Neisseria gonorrhoeae*	*Lactobacillus spp*
Klebsiellaspp	*Garnderellavaginal is*	*Bacillus spp*
Pseudomonas aeruginosa	*Corynebacteriumjei keum*	*Diptheroids*
Serratiamarces cens	*Corynebacterium group D-2*	*Mycoplasma*
Proteus spp	*H.influenzae*	*Candidaspp*
Yeasts	*M.tuberculosis*	*Enterococcus spp*

1.3. Complications of UTI:

UTIs occur in all population but females particularly affected in all ages instead of males, males affected at their extremes of life, person who has structurally abnormalities, neurological disorder regarding urinary tract and kidney transplant patients are more likely to suffer from UTIs. Not only an individual affected from UTI, it produces more complication like acute pyelonephritis, cystitis to sepsis, chronic infection can cause paraurethral abscesses, renal abscesses and it can be worst bone and joint infection, septic shock or even death. It's important to classify the infections into more subdivision according to its presence, morphology and complication; it's easy for physician for clinical procedure [7].

1.4. Pathogenesis:

The most common uropathogen is *E.coli*, there are distinctive strains of *E.coli* as compared to other bacterial strains, these have special bacterial structural properties, virulence factors and genome, virulence factors help them to invade in a host urinary tract and play a host defense mechanism. Virulence factors play an important role in their pathogenesis in urinary tract infection. They have factors for adhesion (P fimbriae, mono-resistant adhesions) to the walls of host urinary tract, K capsule hemolysin and serum killing resistance. The more virulence factor expresses the more severe chances of infections [8].

[II] EPIDEMOLOGY AND PREVALENCE

One of the most worldwide infections is UTI in all populations from neonate to geriatric. According to WHO (World Health Organization), in children about 1% of boys and 8% of girls, in infants, boys have more chances (rate of 2.7% of boys compared with 0.7% of girls) to prevail an infection [9].A study showed that more than 50 children experience yellow marrow (bone marrow) transplants have hemorrhagic cystitis and *Adenoviruses* are identified by molecular detection. The prevalentof UTIs are more in pregnancy and chemotherapy. The resistance of *E.coli* against common antibiotics is much depends on geographical location. The drug resistance has more seen in low sources or under developing countries. Globally it's very challenging to determine the exact prevalence rate

but from the recent findings and through literature we can conclude [10].

2.1. Epidemic in Pakistan:

According to the study carried out at District Health Quarter (Gilgit, Pakistan) 300 patients were enrolled in 2012, identification procedures were according to WHO guidelines, *E.coli* were isolated from 143 out of 300 patients,32 samples shown *Klebsiella pneumonia*, 41 were *Enterococci spp*. *E.coli* was highly antimicrobial resistant reported in females [11]. Another study was conducted by KTH (Khyber Teaching Hospital. Pakistan), this study was conducted by enrolled 115 pregnant women and 60 non-pregnant women, 34 out of 115 (29.57%) pregnant women suffers from UTI, from control group of 60 women 14 (23.33%) were affected . Uropathogens were isolated: *E.coli, Pseudomonas sp, Klebsiellaspp, Proteus spp, Staphylococcus epidermidis, Staphylococcus spp and Citrobacterspp*[12].

[III] DIAGNOSIS & SYMPTOMS

Lower UTIs symptoms include dysuria, small volume urination, itching in a urinary tract during urination, abnormal color (Milky color, green or blue), frequent urination, strong smell during urination, abdominal pain, burning sensation during urination. People with catheters also experience fever [13].

3.1. General criteria:

1. Analysis of urine sample under microscope, analyses to check the presence of blood cells (white or red blood cells), crystals, in case of kidney injury, kidney debris in the form of tube like structure called casts [14].
2. For cultural examination, Urine sample is send by physician for microbial culture examination, urine is streak on artificial media (CLED) Cystine lactose electrolyte deficient agar, incubate for 24-48 hrs, check the microbial growth by physically and microscopically [15].
3. By Molecular and serology techniques, detection of uropathogen can be by immunofluorescence, molecular techniques and genomic amplification. By using polymerase chain reaction (PCR) technique, primers are selected of desired gene and then amplification of desired gene is carried out [16].
4. By Diagnostic imaging, Radiological evaluation is used in complicated infections, to check structural abnormalities in urinary tract or bladder and inflammation of kidney [17].
5. By using of cystoscopy, a lens with a large tube doctor checks inner part of patient's urethra, bladder or kidneys to check the structural abnormalities and also displayed images on the screen with the help of camera [18].

3.2. Complicated UTI:

Diagnosis of UTI in pregnancy

Pregnancy causes many changes, hormonal imbalance and urinary stasis at risk (shortening of urethra). Diagnosis is based on the type of infection (i.e. lower UTI or upper UTI), for lower UTI vaginal swabs, microscopy or cystoscopy are suggested and for upper UTI doctors go for diagnostic imaging. Infections in pregnancy include: Cervicitis, Chlamydial Genitourinary Infections, Cystitis, Nonbacterial, Ectopic Pregnancy, Nephrolithiasis, Trichomoniasis, Trigonitis and Urethritis. *Chlamydia trachomatis* or *Neisseria gonorrhoeae* may be causative agent [19].

Diagnosis of acute pyelonephritis

Pyuria is present in all acute pyelonephritis patients, rapid diagnosis by leukocyte esterase test, nitrite test and dipstick hematuria, other test also include urinalysis and urine centrifugation to check the presence of WBCs and pathogen in urine. Specimen is collected by a midstream clean catch techniques [20].

Diagnosis in Postmenopausal women

Physician check the history of recurrent UTI, old symptoms, hospital visits, metabolic disorder and fever, go for microbial examination (resistance pattern of microorganism) and previous treatment and response of microorganism. Physical

examination, diagnostic imaging, urinalysis and cystoscopy are suggested [21].

Diagnosis of Catheterized patients

Patients who are catheterized have chances of asymptomatic bacteriuria, challenging for the physician to diagnosis of UTI because of long term catheter cause fever, worse conditions included systemic problem, mental illness, lethargy and acute hematuria. Only send urine sample for urinalysis do not use dipstick testing [22].

Diagnosis of UTI in Diabetic patients

In diabetes mellitus, there are several factors include: severity of diabetes with a time period, hyperglycemia causes immune disorder in host, abnormal function of neutrophil causes increase level of calcium in a body, apparently vaginal candidiasis, cystopathy and nephropathy are one of the main drawbacks of diabetes and play an important role in the development of UTI. Patients who have complicated UTI associated with diabetes also have chances to develop emphysematous pyelonephritis/cystitis, papillary necrosis and xanthogranulomatous pyelonephritis. Physician identifies UTI by these associated diseases, medical history, specimen sends for urine culture examination and also diagnostic imaging is used [23].

3.3. Uncomplicated UTI:

Uncomplicated UTI is most common in sexually active men and women. Mostly women are more affected. In US, approximately 8.3 million physician's visits are related to an uncomplicated UTI. The diagnosis and treatment costs exceed 1 billion dollars. Uncomplicated UTIs patients have normal genitourinary tract, no complicated medical history, no metabolic disorder. Symptoms include fever, dysuria, urgency, frequent urination and itching during urination. Dipstick urinalysis, nitrite testing and microscopic hematuria are used as diagnostic tools. Midstream urine is collected under sterile conditions [24].

[IV] MULTIDRUG RESISTANCE (MDR)

The term multidrug resistance is referring to those microbes that are resistant towards multiple classes of antibiotics [25]. Microorganisms change itself when they are introduced to antimicrobial substances, such as antibiotics, they develop antimicrobial resistance sometimes referred as "superbugs". The ESBL producing strain of *E.coli* is also included in superbugs that are listed by WHO in 2017. *E. coli* is listed in a most critical superbugs and it is resistant towards 2 major classes of antibiotics (i.e. cephalosporins and carbapenems). They adapt their self by these following mechanisms [26].

1. Develop mutation and alteration in target protein.
2. Inactivation of an enzyme in drug.
3. Prevent the drug to access its target.

[V] OLD TRADITIONAL THERAPIESFOR UTI

5.1. 1991- RCP guidelines:

In 1991, Royal College of Physicians (RCP) demonstrated the management of UTI; they described the guidelines regarding diagnosis and treatment therapies .Children of 7 years recommended for prophylactic antibiotics until the investigations not completed. If the ultrasound reports are abnormal so long term low dose of prophylaxis are recommended. Prophylaxis dose of trimethoprim or nitrofurantoin is given in night [27].

5.2. Chinese Traditional Herb Medicine:

Herb medicine is given by Chinese tradition to treat burning sensation and night sweats due to UTI. This medicine composed of Chinese Anemarrhena with Rehmannia Pills; it is specially suggested for postmenopausal women. In Chinese this medicine called as ZhiBai Di Huang Wan (jih bye deehwahngwahn), ChihPai Ti Huang Wan. Mostly patients were recovered very soon within a few days [28].

5.3. 2011-WHO guidelines:

According to WHO guidelines about the treatment and duration of therapy, for CA-UTI patients seven day treatment of antibiotic (e.g. nitrofurantoin) given but in case of delay response 10-14 days treatment is recommended. 5 days

regimen levofloxin is recommended for those who are not severely ill [27].

5.4. 1920's – Vaccines for UTI:

Vaccines for UTIs were used more than a century, these are used as a therapeutic rather than prophylactic, but in 1920's these vaccines were seen ineffective. By the large survey of physician they suggested for no use of vaccine therapy for cystitis and acute pyelonephritis [28].

[VI] RECURRENT MEDICINES FOR UTI

6.1. Anti-folates:

Trimethoprim and co-trimoxozole are included in this group. Trimethoprim is recommended for uncomplicated UTIs. Long term use of Trimethoprim does not induce resistance in an organism and it is inexpensive. Co-trimoxozole is used mostly in children to treat UTIs; Side effects included skin reaction and gastrointestinal problems, not recommended during pregnancy. Co-trimoxozole is no longer recommended because of its toxicity with sulphonamide.

6.2. Nitrofurantoin

It is mostly used for prophylaxis and lactation because it is suitable to use and didn't induced resistance in an organism. It is inexpensive. Side effects included nausea, rare pulmonary problems and hepatitis by prolong use, during pregnancy it can be used but should be avoided by the risk of neonatal hemolysis.

6.3. Penicillin:

It is safe to use during pregnancy and lactation. It is less expensive but should not be used until the sensitivity of an infection because of its resistance problem. Side effects included diarrhea, vaginal problem and genital itching. Amoxicillin has less spectrum of action than Co-amoxiclav and it is relatively less expensive. It can be used in pregnancy.

6.4. Quinolones:

Nalidixic acid is effectively used against uropathogen but it is expensive and has a low gastrointestinal tolerance and can't be used during pregnancy. Ciprofloxacin and ofloxacin is used in resistant cases, effective in complicated UTI .They also avoided to use during pregnancy, lactation because it has a risk of arthropathy[30].

[VII] RESISTANCE TO ANTIMICROIALS

Globally it becomes a new challenge for the economy and health. Resistance mechanism causes a prolong illness even death. This resistance may be naturally occurring by genetic changes or by the misuse of antimicrobial agents. There are some of the factors that enhancing resistance towards drugs discuss below:

7.1. ESBL's:

*Enterobacteriaceae*family (*E.coli* and *Klebsiella pneumonia*) is ESBL-Extended Spectrum Beta-Lactamase producing, they have genes on transferable element that coding ESBL. ESBLs have a broad activity against penicillin and cephalosporin [31].

7.2. CTX-Ms:

These enzymes are active against penicillin, cephalosporins and monobactams [32]. These genes also present in a plasmid that encoding ESBLs CTX-Ms but different from other beta lactamase encoded plasmid. It efficiently hydrolyses the beta lactamase ring and in result inactive open ring product is formed [33].

7.3. OXAs:

OXAs are encoded by a plasmid and are highly resistant towards ampicillin, cephalothin, oxacillin and cloxacillin. Similarly to CTX-Ms, hydrolyses of beta ring and also resist to beta lactamase inhibitor. Pseudomonas aeruginosa has OXAs [34].

[VIII] APPLIED MEDICINES

8.1. Bacterial adhesion mechanism targeted by vaccine:

This vaccine targets the adhesion mechanism of bacteria; Adhesion is a key point of microbial pathogenesis. These vaccines have anti FimH-C antibodies that block the adhesion of FimH-C, PapD-E adhesion complexes. These vaccines are under clinical trials [35].

8.2. Proteases, bacterial toxins and siderophores targeted by vaccines: Vaccine were made to reduce HylA (bacterial toxin) but in

clinical trials was not successful, similarly vaccine with hemolysin and hpmA did not show positive result against bacterial colonization. Positive results with a protection against bacterial colonization were shown by a vaccine with Pta (alkaline protease), protection against upper UTI [36].

[IX] NOVEL APPROACH TO TREAT UTI

9.1. *C*-mannosides:

Small molecules develop by a group of scientist called *C*-mannosides, these molecules have affinity to prevent the bacteria to adhere with bladder walls without disturb beneficial community of bacteria. These molecules don't kill bacteria they attack the virulence factor FimH of UPEC that is multidrug resistant bacteria, FimH mediate invasion and bacterial colonization in bladder walls and this compound prevent them to adhere, bacteria remove from the body by urination without any disturbance in microbiome and this compound shows successful result in clinical trials on mice orally. First this compound introduced as O-mannosides but it has a metabolic instability of O-glycosidic bond, replaced by *C*-linkages and it is more efficient and stable. Positive results were shown in mouse for acute and chronic UTI [37].

9.2. Immunization with FyuA (Yersiniabactin receptors)

Previous study showed that copper has bactericidal activity against UTI but UPEC-bound Yersiniabactin have ability to bind with copper, cobalt and other metals, it bind with metals and avoid metal to reach its toxic level. An experiment is carried out by immunization with six UPEC iron receptors for evaluation to use these metals as vaccine agent. Intranasal immunization of vaccine in mouse model of UTI is carried out by genetically engineered different strains of *E.coli* with FyuA, c0294, ChuA and other receptors (vaccine antigens), cholera toxins CT used as an adjuvant in UTI models. Results shows that vaccine antigens were lysed by bacterial culture and UTI is reduced more efficiently by FyuA as compared to other vaccines antigens. Moreover, IgA has been seen in urine of mouse and long lived plasma cells also seen by ELISA. These results interestingly show a novel approach for the development of vaccine against UTI [38].

9.3. Antibacterial activity of Silver nanoparticles:

Nanoparticles are very small in size; silver nanoparticles have more antibacterial activity as compare to copper against uropathogen has been seen. Most of the uropathogen are become multidrug resistant, treatment of UTI by nanotechnology is a novel approach and it is harmless and successful against many multidrug resistant pathogens i.e. *E.coli*, methicillin-resistant *Staphylococcus aureus* etc. Nanotechnology based medicine is a novel approach to treat UTI, bactericidal mechanism of silver nanoparticles depend upon its size and shape, AgNPs adhere with microbial cell wall and penetrate to the cell , they increase the permeability of membrane, they bind to thiol group of respiratory enzymes and deactivate the enzymes. They generate oxidative stress by reactive oxygen species in return apoptosis occur and inhibition of DNA replication. AgNPs slowly oxidizes a free radicals Ag^{+}, that inhibit protein synthesis. AgNPs alone and along with antibiotics have been used. Antibacterial activity against MDR uropathogen has been successfully evaluated in *E.coli*, *S.aureus*, *K.pneumonia*, *Neisseria* and more. Synergistic activity of AgNPs has been seen along with antibiotics like penicillin, ampicillin, erythromycin, clindamycin, and vancomycin to treat UPEC. Adverse effect of prolong use of AgNPs included Argyria (blue grey appearance of skin because of long deposition of silver) [39].

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