

A Review on Clinical Manifestation and Treatment Regimens of UTI in Diabetic Patients

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ABSTRACT

The pervasiveness of urinary tract infections (UTIs) with their clinical manifestations in patients with diabetes mellitus has escalated amidst the past decade or so, as myriad predisposing factors contribute to its occurrence. Although the causative agent of UTI is *Escherichia coli*, the etiopathogenesis can be traced back to glycosuria in the renal parenchymal region. This has precipitated pyelonephritis and renal complications, including cytopathic and altered metabolism. Furthermore, impaired immunity with scarce IL-6, 8 in urine, urinary retention, and dysfunctional voiding raise susceptibility towards uropathogens, mainly *E. coli*. Treatment for UTI with diabetes is based on symptoms and severity, urologic abnormalities, renal function, bladder infections, and metabolic alteration. The treatment process or regimens for patients with type 2 diabetes with asymptomatic bacteriuria are very low or negligible. Adequate management with antibiotic regimens in symptomatic patients after critical diagnosis is crucial for prophylaxis and effective treatment.

Keywords: Diabetes Mellitus, Glycosuria, Therapeutics, Urinary Tract Infection, Uropathogens

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1 Introduction

Diabetes mellitus is a heterogenic disorder altering metabolic abilities of the body, primarily characterized by persistently high glucose levels attenuating every bodily function. Recent epidemiological studies and analytical experimentation of patients with pre-existing diabetes mellitus have authenticated their plausibility of developing urinary tract infections (UTIs) that are potentially perilous with fatal manifestations. Integrated data of various studies indicate that a total of 40.2% of patients develop UTI concurrently suffering from DM, with females holding 63.16% and males 36.84% prevalence (1). However, most recurrent recorded infections are ASB (Asymptomatic Bacteriuria), fungal cystitis, emphysematous cystitis, pyelonephritis, perinephric abscess, and renal papillary necrosis. Taking account of uropathogens most typically isolated ones are *Escherichia coli*, *Enterobacteriaceae*, resistant strains of beta-lacta-

mase *Enterobacter*, and Fungus species *Candida* (2). Assorted etiopathogenesis includes glycosuria, high HbA1c levels, neutrophil dysfunction, increased adherence to renal parenchymal cells, insufficient voiding, and impaired immunity that all provide a preferable environment for microbial growth (2). Critical treatment for prophylaxis and symptomatic infection is vital to avoid recurrence and complications. All aspects mentioned above will be schematically considered in this review article.

1.1. Methodology

This retrospective observational study is aimed at schematically reviewing critically acclaimed articles regarding the susceptibility of diabetic patients to developing complicated UTIs. The data collected from numerous renowned journals was compiled to obtain a brief overview of epidemiology, etiopathogenesis,

prevalence, complications, treatment, and critical management of severely affected patients.

1.2. Epidemiology

Innumerable epidemiological studies have concluded the incidence, distribution, and control factors contributing to UTIs occurrence in diabetic patients. In one study, 429 mid-stream urine samples were analyzed to isolate various urinary tract pathogens, out of which the majority were bacterial microorganisms (97.2%). The remaining infections were caused by fungi (2.8%). The most prevalent causative organism was *Escherichia coli* (39.3%), followed by *Staphylococcus* species (20.2%). Thirdly, *Leuconostoc* species (11.4%), *Klebsiella* spp. (8.4%), *Salmonella typhimurium* (6.3%), *Demacoccus nishinomiyaensis* strain (6.3%), *Citrobacter freundii* (5.2%), and for the fungal ones, *Candida krusei* (2.7%) was the most common among the infected victims. While considering the gender, the majority of the infected subjects were female (71.7%). Observational studies point out the increased susceptibility of females to suffer from this ailment with concurrent risk factors and underlying conditions mentioned in the article, absent in the male population (3). In another urological study, 248 consecutive patients, all of them with diabetes, were observed and carefully monitored. Out of the given number of diabetic patients, 177 (71.4%) individuals didn't have any specified symptoms pointing towards the type of uropathogens involved, and 78 patients (28.6%) showed a clinical presentation of UTIs. The majority of patients were females (54.8%) out of the enrolled group, and the rest were males. The age group taken under consideration were adults, including geriatric patients ranging from (20 to 83 years). Two types of diabetes patients were diagnosed with type I diabetes mellitus (49.6%), and the remaining (50.4%) had the differential diagnosis of type II diabetes mellitus. Around 90 people out of the total group had a history of diabetes for a decade. In regards to the uropathogenic strains isolated from grown cultures, *E. coli* was most prevalent (35.1%), followed by coagulase-negative *Staphylococci* (CONS) (18.9%), *Enterococcus* spp. (16.2%), and *Staphylococcus aureus* (10.8%). Taking account of fungal causative organisms, more than half of the infections were caused by *Candida* (52.6%), and the rest (47.4%) were non-albicans. Infection was severe in symptomatic type (49.3%) rather than in asymptomatic people (11.9%) (4). UTIs are one of the epidemic infections in the United States, with annual complaints of 4 million women seeking treatment and being hospitalized. Around \$2 billion are predicted as a liability to meet the expenditure of diagnosis and treatment of UTIs (5). With increased instances of antibiotic resistance among organisms globally, it's becoming a clinical catastrophe.

2. Etiopathogenesis of the Infection

Taking account of multitudinous risk factors and etiological agents solely responsible for the development of this condition along with the pathogenesis is crucial to trace back the infection and make the correct differential diagnosis. While enumerating the etiopathogenesis of UTIs, innumerable host mechanisms amalgamate simultaneously in generating a vital response against the infiltrating pathogen and make collaborative efforts for its demise. Significant underlying mechanisms include the presence of glycosuria, the ineffective immune response generally regarded as neutrophil dysfunction, amplified adherence of uropathogens to epithelial cells, compromised innate, and acquired immunity alongside bowel bladder syndrome (6). Insulin is required in our body for the proper use of sugar by the cells. In the case of diabetic patients, elevation in sugar level in blood also results in an increase of sugar level in the patient's urine. Diabetic patients also have increased size of the pancreas or bowel bladder syndrome because urine retention in the bladder is more prone to have UTIs. Sugar in urine acts as a substrate for the bacteria causing urinary tract infection in a diabetic patient. Uropathogens further invade the urethra, and the bladder colonizes with the help of adhesins and pili on superficial umbrella cells generating immune response by deploying immunological cells, i.e., macrophages, neutrophils, phagocytes, and neutrophil infiltration (6). Supervised inflammatory responses are mediated by cytokines for further damage control. But some resistant strains of bacteria and toxins escape and multiply further by hijacking the immune system primarily by "Bio-film Formation," leading to epithelial cell damage by potent proteases and toxic enzymes induced by bacteria (7). Finally, they bridge the upper urinary tract and ascend to the kidneys entering the blood circulation, causing bacteremia (7). It is buttoned up with TLR5 and is of eminent significance about mounting an immune response against *E. coli* as depicted in lab rats (8). They variably adhere to the epithelial walls and access their mobility via fimbriae and pili as they possess a protein at the far end termed FimH (9) that facilitates host cell interaction and binds to pivotal enzyme uroplakin (UP) IA that skims the constituent cells of the bladder, which is decisive for colonization of Uropathogenic *E. coli* (UPEC) (10). They also selectively attach to β -integrin, which initiates cytoskeleton rearrangement, which results in the invasion of infection to tissues (6). Secondly, the significant underlying fact to be considered in pathophysiology is enhanced adherence of causative agents with uroepithelial cells. The uroepithelium works as an interface between tissue space and inner lining and acts as a selective barrier against osmotic flux by ions, water, and solute. It further influences

urine formation by acting as a sensory web with constant to and for information of external milieu. This adjacent system alongside governs a dynamic control over endocytosis as well as exocytosis across the urinary tract, both upper and lower regions, including prostate ducts (11). The bladder epithelium is also known as "transitional epithelium," having 3 consecutive layers, each serving a vital role in defense. These are named as innermost basal layer (measures up to 10 µm in diameter), middle cell layer (covers up to 20 µm), and the outermost surfaced apical layer constituting of major hexagonal shaped cells with a diameter ranging from 25–250 µm approximately, officially known as "umbrella cells" (12). UPEC has lethal virulence factors, including adhesions, toxins, surface polysaccharides, flagella, iron acquisition system, which facilitates peri-urethral areas forming colonies residing as quiescent intracellular reservoirs (QIRs) that increase septicemia. They attach to the inner layers by damaging structural components and are themselves resistant to the scrutiny of immune attacks. They possess Lipopolysaccharide (LPS) and FIM operons encode for type 1 pili and pap operons. These are responsible for putative virulence determinants having FimH and PapG domains on the distal end, allowing copolymerization with the mucous layer. While the chaperon usher (CU) pathway assembles pili, the type 1 Pilus rod has FimH, FimG, FimF adaptor subunits that augment bacterial compliance (13). The immune system fends off to uropathogenic *E. coli* patterns via pathogen-associated molecular patterns; PAMPs or molecular fragments from infected or lysed cells danger-/damage-associated molecular patterns; DAMPs. Pattern recognition receptors (PRRs) identify these specific sequences with assistance from differentiated immunological cells, epithelium associated cells, and subsequent tissues and mount an immunological response (14).

The alpha-hemolysin is closely linked with end-stage kidney failure and necrosis by inducing calcium influx in the proximal and distal tubule, therefore facilitating adhesion in the ureter wall and renal parenchymal cells amplifying colonization, causing urinary flow obstruction. Recently it was found to generate pro-inflammatory caspase1/caspase-4-induced apoptosis in epithelial origin cells of the urinary bladder, which develop consequent hyperplasia (15). The most circumstantial and crucial step to establishing recurrent infection and progression is achieved by overpowering the immune system, which can be regarded as due to altered poly-morphonuclear leukocyte function and facilitated adhesion, inefficient phagocytosis, and chemotaxis. The interaction between bacteria and a vast array of host defense has the goal of symbiosis, removal, or clearance of the pathogen either by biochemical (e.g., Oxidation),

cytological (e.g., Phagocytes and macrophages), or biomechanical tactics comprising of exfoliation. PMNs, i.e., polymorphonuclear cells and phagocytes represent the first line of protection and are primarily recruited at invasion sites that neutralize the microbe with reactive oxygen species, degrading enzymes, or apoptosis (16). The bladder epithelium produces cytokines via TLR4 (Toll-like receptor 4) stimulation. Still, UPEC and *Staphylococcus* species have enhanced resistant mechanisms which can trick these cells as they suppress cytokine production by blocking stimulus and escape into the bloodstream either alive or in spores carrying the infection. The same was demonstrated by the observational study that reported similar confirmations that UPEC dampened the serum IL-6,8 levels while there was only a slight rise in IL-6 concentration in urine which is vital for exponential immune response as neutrophil production and IL-6,8 levels are closely co-related (17). The generated QIRs are not detected by immune cells and are not engulfed by phagocytic cells resulting in recurrent infection. The same was suggested by a study conducted for the role of the Sula mediated cell division pathogenic cycle of UPEC that implied filamentation is rate-limiting for bacterial arsenal against innate response and evasion of the immunological cascade (19). The fusiform vesicles (FVs) are specialized organelles equipped with readymade crystalline arrays of protein origin present in the umbrella cells delivered to the apical layer of umbrella cells. To gain access to epithelial cells, UPEC coordinates with superficial cells and exploits the volume regulating mechanism by initiating exocytosis phenomenon in vesicles right and facilitates bacteria's attachment.

Replication followed by internalization is rapid, leading to IBCs evolution and bio-film generated for extended resistance. Therefore, Lysosomal neutralization interferes as encapsulated bacteria that were internalized protectively enclosed in Rab27b+ formed compartment-like structures that act as a barrier (20). Toll receptors quickly recognize intrusion and activate response tactics; furthermore, TLR4 enhances the inward movement of secondary messenger (cAMP) that sets off the expulsion procedure of RAB27b+ vesicles shielding *E. coli* and forces the bacteria to be expelled out intracellularly towards the bladder. Despite this phenomenon, some strains still escape the encapsulated vacuole and are decamped from urinary expulsion; these leftover pathogenic fragments are further tackled by self-consumption and are carried to suicidal bags. The lysosomal transient receptor mucolipin 3 Ca²⁺ channel (TRPML3) is predominantly opted out, causing rapid calcium influx, which induces spontaneous expulsion of potent lysosomal enzymes. Intruder sensitive TLR4 receptors triggers the formation of specialized resolvable

antimicrobial chemicals (AMP, sub-categorized into cathelicidin and β -defensin), antibacterial amino acid chains [such as pentraxin3 (PTX3)] (21), and chemokine signals [such as CXC-chemokine ligand 1 (CXCL1) and CC-chemokine ligand 5 (CCR5)]. Moreover, a mannose glycoprotein uromodulin strives a shielding effect against the infection by competitive inhibition when UPEC FimH binds to uroplakin.

The data presented in the critically acclaimed study provided convincing numbers in favor of filamentation, assisted by Sula, an imperative part of the immunological cascade against *E. coli* which is predominantly immune-competent with the host. The UPEC transition from the primary to the second generation of IBC is assisted by Sula-mediated inhibitory action on cell division and restoring cell competence. The given observation is primarily relevant to the fact that a steep decrease in CFU post one day of infection is seen. The recorded duration is required for secondary IBC formation (22). After mass destruction by defense mechanisms, equilibrium maintenance is critical, and to do the same, progenitor mast cells are appointed to restore superficial bladder epithelial cells (23). Eventually, exfoliation is triggered by caspase bound infected cells with subtypes involved, caspase 3 and 8 for apoptosis and consecutive shedding of bladder lumen. However, this process only eliminates bacteria's superficial proportion, neglecting deeper tissue bacterial dissemination. Strategically UPEC induces death of the uppermost bladder layer via potent virulent strains to gain access to underneath tissues to implant QIRs in sub-epithelium, which is multiple drug-resistant and further facilitates re-infection and prolonged host

susceptibility (23). To defend tissue's integrity, direct phagocytosis is induced by neutrophils through intricate and for cross signaling within LY6C- and LY6C+ macrophages, ensuring precise action. These native LY6C cells release CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 1 (CXCL1), and macrophage migration inhibitory factor (MIF) to attract more polymorphonuclear from nearby arterial and vascular circulation (23). Tumor necrosis factor (TNF) further commands immune cells to initiate CXCL2 manufacturing, which is accountable for spontaneous assembly of matrix metalloproteinase 9 (MMP9) by neutrophils and commences transport to trans-epithelial (24). The resident LY6C- macrophages act as primary pro-inflammatory cells, in contrast to the recruited LY6C+ macrophages that maintain pathogen proximity (25).

2.1. Uropathogens Table Representing Different Microbial Isolation from UTI Patients

A wide spectrum of pathogens invades the genitourinary tract to develop a pathological ailment, causing a diversified set of infections commonly termed UTIs. According to a cross-sectional study conducted in St. Paul specialized hospital millennium college, Ethiopia, April-July 2015, 248 diabetic patients with the present complaint of either symptomatic or asymptomatic UTIs were critically examined and observed to get a detailed insight of spectra of uropathogens and their share in fostering UTIs. Clean-catch midstream urine samples were collected from each subject. The pathogen was identified using standardized laboratory techniques, and the data was recorded (Table 1).

Table 1. Different bacterial and fungal isolates from diabetic men and women having urinary tract infection.

Uropathogen Isolated	Species	Asymptomatic		UTI		Total	
		Male %	Female %	Male%	Female%		
Bacterial	<i>E. coli</i>	7.7	23.1	15.4	53.8	35.1	
	CNS	28.6	14.2	28.6	28.6	18.9	
	<i>Enterococcus</i>	16.7	16.7	33.3	33.3	16.2	
	<i>S. aureus</i>	25	25	50	0	10.8	
	<i>K. pneumoniae</i>	0	0	50	50	5.4	
	<i>P. mirabilis</i>	50	0	50	0	5.4	
	<i>Enterobacter</i> spp.	0	0	100	0	5.4	
	<i>Citrobacter</i> spp.	100	0	0	0	2.7	
	Total		18.9	16.2	32.4	32.4	100
	Fungus	<i>C. albicans</i>	0	20	20	60	52.6
Non albicans <i>Candida</i>		11.1	55.6	0	33.3	47.4	
TOTAL		5.3	36.8	1.50	47.4	100	

The occurrence of microorganisms' fungal infection amongst diabetic patients has been recorded at 22.6%. The infection rate was considerably higher in symptomatic UTI patients (49.3%) than in asymptomatic UTI patients 11%. An overall percentage of diabetic patients (22.6%) had bacterial growth in their urine samples, and 7.7% were candiduric. Eight bacterial species were selectively isolated from positive urine cultures (Table 2). *E. coli* amount (35.1%) was found to be predominantly higher, followed by Coagulase-negative *Staphylococci* (CONS) (18.9%), afterward *Enterococcus spp.* (16.2%), *S. aureus* (10.8%) and others were found in trace amounts. Out of 7.7% Candiduric positive samples, a large portion was accounted by (52.6%) *Candida albicans* and the remaining (47.4%) were non-albicans *Candida spp.* A significantly higher amount was seen

in females compared to males due to earlier discussed pathological approaches (26).

Another authenticated study was carried out with similar results where UPEC shared the majority cascade in community-acquired UTIs and was found in 80–90% specimens. In-vitro investigations concluded four major UPEC phylogroups (A, B1, B2, and D) based on the occurrence of Genomic Pathogenicity Islands (PAI) and the expression of causative virulent mainly being concluded as adhesive molecules, toxins, surface polysaccharides, flagella, and iron-acquisition systems. Besides that, *Klebsiella pneumoniae* contributed about 7%, *Proteus mirabilis* (5%) and *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Streptococcus bovis*, and the fungus *Candida albicans* were found in variable quantities (27).

Table 2. Frequency of occurrence of urinary tract infection in different age groups

Socio-demographic characteristics	Classification of variables	Frequency
AGE	20-35	51
	36-45	45
	46-55	52
	>56	100
SEX	Male	112
	Female	136
Type of diabetes	Type1	123
	Type2	125
Duration of Diabetes	<5 yrs	65
	5-10 yrs	93
	>10 yrs	90
Glucose level	<126 mg/dL	99
	>126 mg/dL	149
History of urinary infection	Yes	73
	No	175
History of antimicrobial therapy	Yes	106
	No	142

Table 2 examines numerous risk factors associated with UTI in people with diabetes, i.e., age, sex, type of diabetes, duration, glucose level, history of UTI, and antibiotic used for therapeutic outcomes. It's clearly stated that geriatric patients are the most affected due to acknowledged factors {100} furthermore, females {136} take a larger proportion of susceptibility as compared to masculine beings. Type 2 {125} and type 1 {123} patients are approximately at the equalized tendency of developing the infection in context to the duration of the same, prolonged suffering related to recurrent infections. Hyperglyc-

emia {149} is predominant in UTIs and re-infection {73} as given in Table 2 (25).

3. Diagnosis and Pathogen Identification

Patients present with variable, potentially differential symptoms, while the case is associated with upper or lower genitourinary tract involvement. Typically, lower UTI is associated with frequent urination, a sense of urgency, dysuria, acute suprapubic pain, while costovertebral angle pain alongside tenderness, recurring fever, and chills occur in upper UTI. Clinical symptoms differ with the type of compromised organ as well as in case of complications, e.g.,

peripheral or autonomic neuropathy, cystitis, pyelonephritis (26).

3.1. Diagnosis

3.1.1. Clinical

Includes accurate patient history regarding symptoms, onset, severity, diabetic profile, and severity at the time of presentation. Female patients require a proper physical assessment to evaluate urogenital anatomy and vaginal tissue estrogenization (27). Incidence of hypo or hyperglycemia is common with hyperosmolar dehydration or ketoacidosis in severe patients.

3.1.2. Laboratory Findings-

1. Midstream urine sample test:

Symptomatic patients' urine specimen is analyzed to get an insight into WBC's presence and the pathogen involved.

2. Pyuria detection:

It's a universal indicator of symptomatic infection evaluated with microscopy and is defined as >10 leukocytes/ mm^3 or by dipstick leukocyte esterase test (sensitivity of 75–96% and specificity of 94–98%) but doesn't differentiate with the type of bacteremia.

3. Colonization:

Negative pyuria in microscopical findings after assessment indicates bacterial colonization when a patient has bacteriuria and no typical findings (4).

4. Microscopic examination:

Allows bacterial visualization in urine and identification of the strain present.

5. Dipstick:

A nitrite test is performed on a urine sample. The tests are positive when nitrite metabolizing bacteria are present in contrast to negative tests suggesting bacteriuria or bacterial species (mostly Gram-positive bacteria) incapable of nitrite conversion.

6. Urine culture: Crucial for correct treatment and therapeutic regimen, which involves obtaining a urine sample from clean-catch, and midstream urine followed by isolation and incubation. UTI is confirmed when culture is $>10^5$ colony forming units per mL. This value shows high-grade sensitivity present in 50% (12).

7. Bacteriuria is declared if $> 10^5$ CFU/mL of a particular pathogen is isolated from a given voided

urine sample. In the case of females with diabetes mellitus without long-term complications with known acute uncomplicated cystitis, quantitative counts $< 10^5$ CFU/mL are isolated from 20 to 250 Å of premenopausal women and 100 Å from postmenopausal women (28).

8. Diagnostic imaging- The amplified frequency of life-threatening complications of UTIs for obtaining diagnostic imaging along with accuracy and pathogen specificity (28). These patients present with systemic manifestations of the disease, marked with severe bacteremia or septic shock. Resistant or critical patients who developed tolerance to appropriate antimicrobial therapy within the crucial 48-72 hours' time frame, or the person experiencing a reoccurrence of infection along with symptoms just after abolishing the therapeutic regimen must be subjected to diagnostic imaging mandatorily to identify underlying abnormalities for selective and compliant interventions (29).

3.1.3. Ultrasound and Intravenous Urography

Ultrasound and intravenous urography are previously considered because they are safe, economical, and easy to perform with detection ability of calculi, obstruction, or an anatomical abnormality. Computerized tomography (CT) is regarded as the precise imaging model with high-grade recognition ability alongside modality for prognosis and follow-up of abnormalities. An enhanced CT is recommended, but contrast media should be selected cautiously in case of renal disease. Standard procedure indicates metformin should be discontinued on the test day with a close evaluation of GFR (30). Magnetic resonance imaging (MRI) has a limited but important role in renal diagnosis, applied for allergic and hypersensitive patients. Diabetic screening is utilized for females with cystoscopy or vaginal atrophy. People accompanied by risk factors are more susceptible, so the early prognosis is mandatory for prophylaxis (31). In patients with prolonged catheterization, preferred sample collection is done by freshly placed catheters instead of the previous one due to biofilm formation (32).

Differential diagnosis can recommend cervicitis, vaginitis, interstitial cystitis, prostatitis, hemorrhagic cystitis, and secondary ailment according to episodes of UTI symptoms, and precisely urine analysis is negative. Figure 1 illustrates the prognosis approach commonly employed for identification.

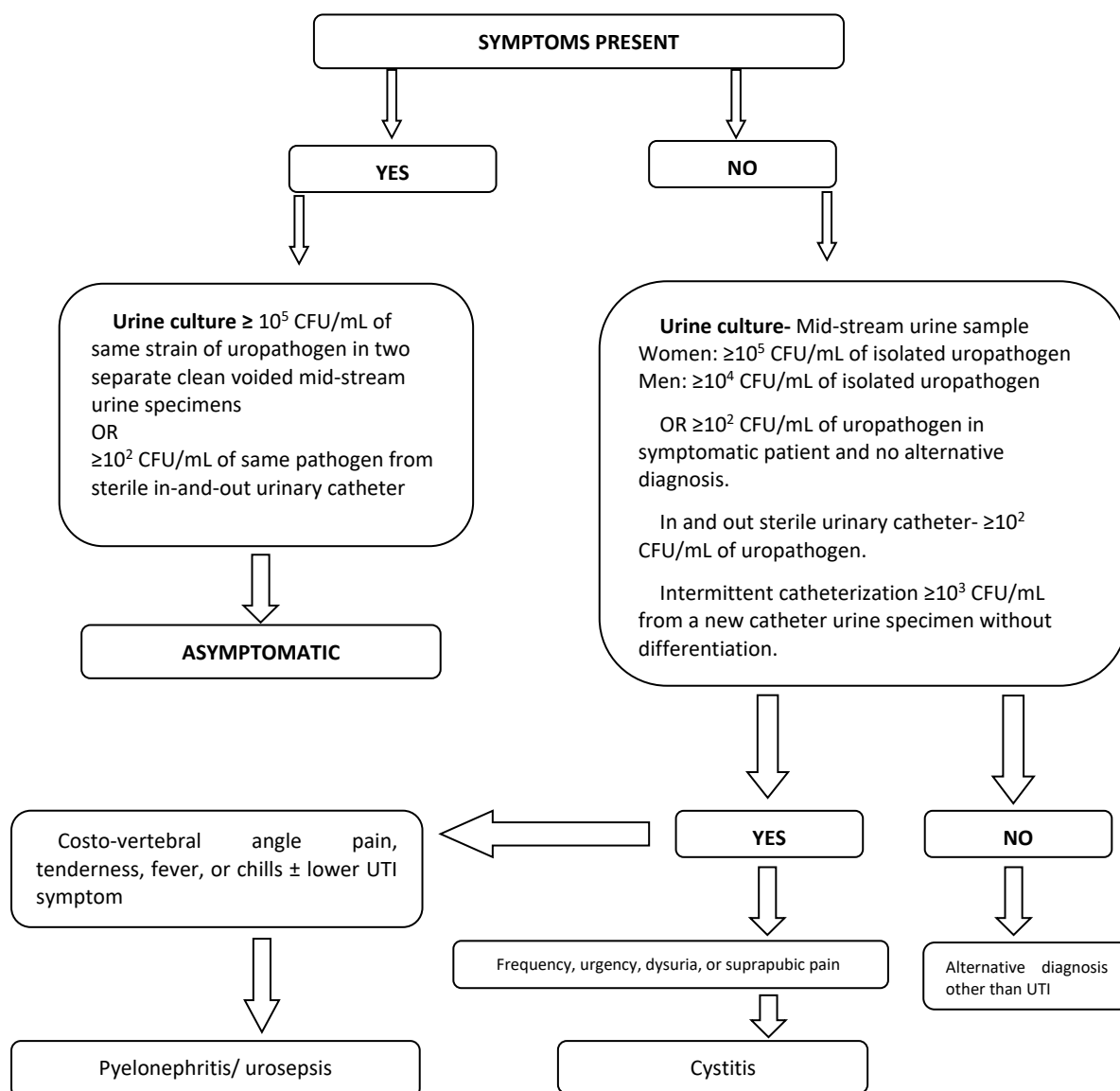


Figure 1. Depicts Flow chart for stepwise diagnosis of urinary tract infection in patients with type 2 diabetes mellitus (33)

3.2. Clinically Complicated Urinary Tract Infections

While considering clinically complicated UTIs' medical approach, disease characteristics and presentation are severe in terms of symptoms. A complex therapeutic regimen is employed for adequate management. The list given below covers the spectra of complicated UTIs-

1. Emphysematous pyelonephritis
2. Emphysematous pyelitis
3. Emphysematous cystitis
4. Xanthogranulomatous pyelonephritis
5. Renal/ perirenal abscess
6. Renal papillary necrosis

3.2.1 Emphysematous Pyelonephritis

It's a rare inflammatory condition of the kidneys accompanied by chronic necrosis of bacterial origin forming gas in parenchymal surroundings due to uncontrolled diabetic UTIs infections confirmed in 90% of the diseased (34) found in diabetic patients. The condition is predominantly culminated in females as compared to males in ratio 6:1 concluded in an authenticated experimental study (35). Symptomatic patients present with the classical triad of fever, abdomen pain, and nausea. Complications are characterized by perinephric abscess extension, severe hydronephrosis, and rest with bilateral kidney impairment (36). Diagnostically, gas analysis is done for confirmation, and pathological findings indicate defective tissue perfusion, vascular thrombosis, glomerulosclerosis, hemorrhage of interstitial origin,

atherosclerosis (hyaline type), microinfarction, severe diabetic nephropathy with lesions from inflammatory reactions (37). Management is preceded by antibiotics; if the therapy doesn't generate desirable outcomes, PCD (Percutaneous catheter drainage) is performed alone or combined with antimicrobial therapy. The last possible treatment approach is direct nephrectomy (36).

3.2.2 Emphysematous Pyelitis

It's a disease characterized by severe tissue necrosis involving the parenchymal regions of the kidney with higher mortality rates in females than males. Its isolated gas production is confined to the collecting part of the excretory system and acts as a benign entity rather than a parenchymal region characterized by emphysematous pyelonephritis. It belongs to the first class of EPN (also known as acute pyelonephritis) with poor glycemic control alongside urinary tract obstruction with low mortality (37). *E. coli* is the most prevalent causative agent, and differential diagnosis is made by computed tomography or radiological examinations. Clinical presentation is like EPN, i.e., fever, chills, dysuria, suprapubic pain, and tenderness (36). Radiological features highlight the presence of gas in the outer layers of ureters and pelvicalyceal, while posterior shadowing of high intensity is seen in obstructed spaces (38). Treatment options are quite like EPN already mentioned above.

3.2.3 Emphysematous cystitis

It's a distinct form of complicated UTI with exaggerated air production and entrapment of air pockets within the bladder wall and lumen. Predisposing factors include catheters, obstruction, or neurogenic bladders. Demographical data concludes that women are more dwelled towards the disease than men, i.e. (64% and 36%) (39). Patient complaints are summarized as hypochondrial pain, fever, vomiting, septic shock, and abdomen discomfort. Differential diagnosis is made with abdomen x-ray (84%), CT studies (40%), cystourethroscopy (39%) and ultrasonography (7%). More than half the percentage of the diseased were *E. coli* infected (40). Treatment is suggested with complex antibiotic combinations, strict glycemic control, and bladder drainage.

3.2.4 Xanthogranulomatous Pyelonephritis

It's a chronic form of pyelonephritis portrayed by granulomatous abscess formation possessing a close resemblance with renal cell carcinoma with recurrent occurrences of pain and urosepsis. Microscopically these granulomas are lipid-derived entities; hence the Greek word "Xantho" means yellow (41). Diversified effects portfolio is mimicked with perinephric abscess, renal carbuncle, renal tuberculosis, sarcomatoid renal cell carcinoma, leiomyosarcoma, megalocytic interstitial nephritis. All symptomatic patients have a fever,

flank pain, weight loss, hematuria, malaise, and anorexia (42). Urinary analysis reveals classic culprit *E. coli* and staghorn grossly defined hypertrophied mass in the renal region. Imaging studies and histological examinations via computed tomography demonstrate the form present either localized or diffused (43). Nephrectomy is usually the preferred treatment opted out by physicians. Patients with contraindicated surgical provisions are employed with broad-spectrum antibiotics and symptomatic management (44).

3.2.5 Renal/ Perirenal Abscess

It's a collection of suppurative material (pus-forming) in renal or perinephric space with insidious histology. It's probably a secondary manifestation of severe UTI infection and hematogenous spread. It proposes a diagnostic challenge as the condition is asymptomatic with generalized complaints of fever, chills, malaise, flank pain, intensifying the risk of mortality and morbidity (45). Intrarenal reflux at tips of open ducts of papillae demonstrates voiding alongside vesicoureteral reflux susceptible to scar formation, and further complexity leads to papillary necrosis and pyonephrosis. The histological description shows inflammation, edema, tubular necrosis with neutrophil infiltration caused by gram-negative species *E. coli*, *Klebsiella*, *Proteus* (46). Diagnosis is established by tomographical imaging and is classified accordingly. Therapeutic management is carried out by nephrectomy and antibiotic treatment. Other approaches employ abscess aspiration and percutaneous drainage (47).

3.2.6 The Renal Papillary Necrosis

This form is marked with necrosis of renal papilla and lesions due to continuous ischemia progressed via pyelonephritis and synergy of numerous diseases, e.g., Analgesic nephropathy or diabetes mellitus, which hinders collecting ducts of kidneys and induces obstruction (48). Diminished circulation and obstruction cause ischemia, followed by activation of an immunological cascade cultivating a series of responses activating necrosis. Even chronic condition remains deceptive symptomatically and causes death due to renal failure and high-grade septicemia. Symptoms range from fever, cloudy urine, painful and dysfunctional voiding.

Diagnosis is made by cystoscopy, histological specimens, and ureteroscopy (49). Supportive treatment is employed via stenting, careful observation of the patient's hemodynamic status with aggressive glycemic control, and treatment of the consecutive underlying complication (50).

4 Treatment Strategies

The desired patient-derived goals of treatment, as well as management, are crucial for mortality and morbidity. Expected outcomes include:

1. To eradicate the causative pathogen;
2. Prophylaxis as well as treatment of systemic consequences of the infection;
3. Prevent relapse or reoccurrence of infection;
4. Decrease the potential of collateral organ damage;
5. Rational drug therapy to minimize the consequence of resistance (51).

4.1 Stepwise Evaluation of the Patient includes:

- 1.. Selecting an appropriate antimicrobial agent concerning the severity of symptoms
2. Site of infection
3. Whether the presentation is complicated or uncomplicated
4. Antibiotic susceptibility
5. Side effect potential
6. Accurate medical history
7. Current antimicrobial exposure and susceptibility
8. Previous occurrences of UTI

9. Diabetic profile (with duration, medications, glycemic control)

10. Pharmacokinetic and pharmacodynamics profile of the drug (52).

Considerations for rational therapy are essential for efficacy, and all the points mentioned above should be of utmost priority while formulating an individualized regimen. For standardized treatment, categorization of the type of infection into – acute uncomplicated cystitis, symptomatic abacteriuria, asymptomatic bacteriuria, systemic complications, recurrent occurrence, or relapse of infection is of primary concern. Secondly, pathogen identification via laboratory techniques (urine analysis, gram staining, microscopical differentiation) should be obtained (Table 3). Thirdly, resistance and susceptibility of the pathogen against the given antimicrobial agent should be ruled out by following a rationalized approach. Based on established 2015 guidelines of the European Association of Urology, for efficient prophylaxis and relapse prevention, non-pharmacological and non-antibiotic measures should be predominantly employed to prevent ADRs {adverse drug reactions} and delay resistance patterns to manage prolonged disease conditions (51, 52).

Table 3. Antimicrobial therapy for lower UTI in adults

	Antibiotic	Dose	Interval	Duration
Uncomplicated	Trimethoprim – sulphamethoxazole	1 DS	BD	3 days
	Nitrofurantoin monohydrate	100mg	BD	5 days
	Fosfomycin	3g	OD	1 day
	Ciprofloxacin	250mg	BD	3 days
	Levofloxacin	250mg	OD	3 days
	Amoxicillin clavunate	500mg	TDS	7 days
Complicated	Trimethoprim-sulfamethoxazole	1 DS	BD	7-10 days
	Ciprofloxacin	500mg	BD	10 days
	Levofloxacin	250-750 mg	OD	5-10 days
	Amoxicillin clavunate	500 mg	TDS	7-10 days
Recurrent infection	Trimethoprim-sulfamethoxazole	½ SS	OD	6 Months
	Nitrofurantoin monohydrate	50 mg	OD	6 Months
Acute pyelonephritis	Trimethoprim-sulfamethoxazole	1 DS	BD	14 days
	Ciprofloxacin	500-1000 mg	BD	14 days
	Levofloxacin	250-750 mg	OD	10 days
	Amoxicillin clavulanate	500 mg	TDS	14 days

DS- Double strength, SS- Single strength (53)

This dose-related antibiotic regimen is most prevalently employed to treat Lower tract urinary infections as *E. coli* remains susceptible to trimethoprim-sulfamethoxazole, and the emergence of resistance is yet to be observed. Some drugs of fluoroquinolone class are also in practical usage, but significant exposure leads to resistance or therapy

failure in case of prolonged use. In addition to these broad-spectrum cephalosporins are used, but they cause collateral destruction of the vital GI flora. Both Fosfomycin and nitrofurantoin have a less lethal effect on the gut flora, so they are somewhat safer alternates currently in use (54).

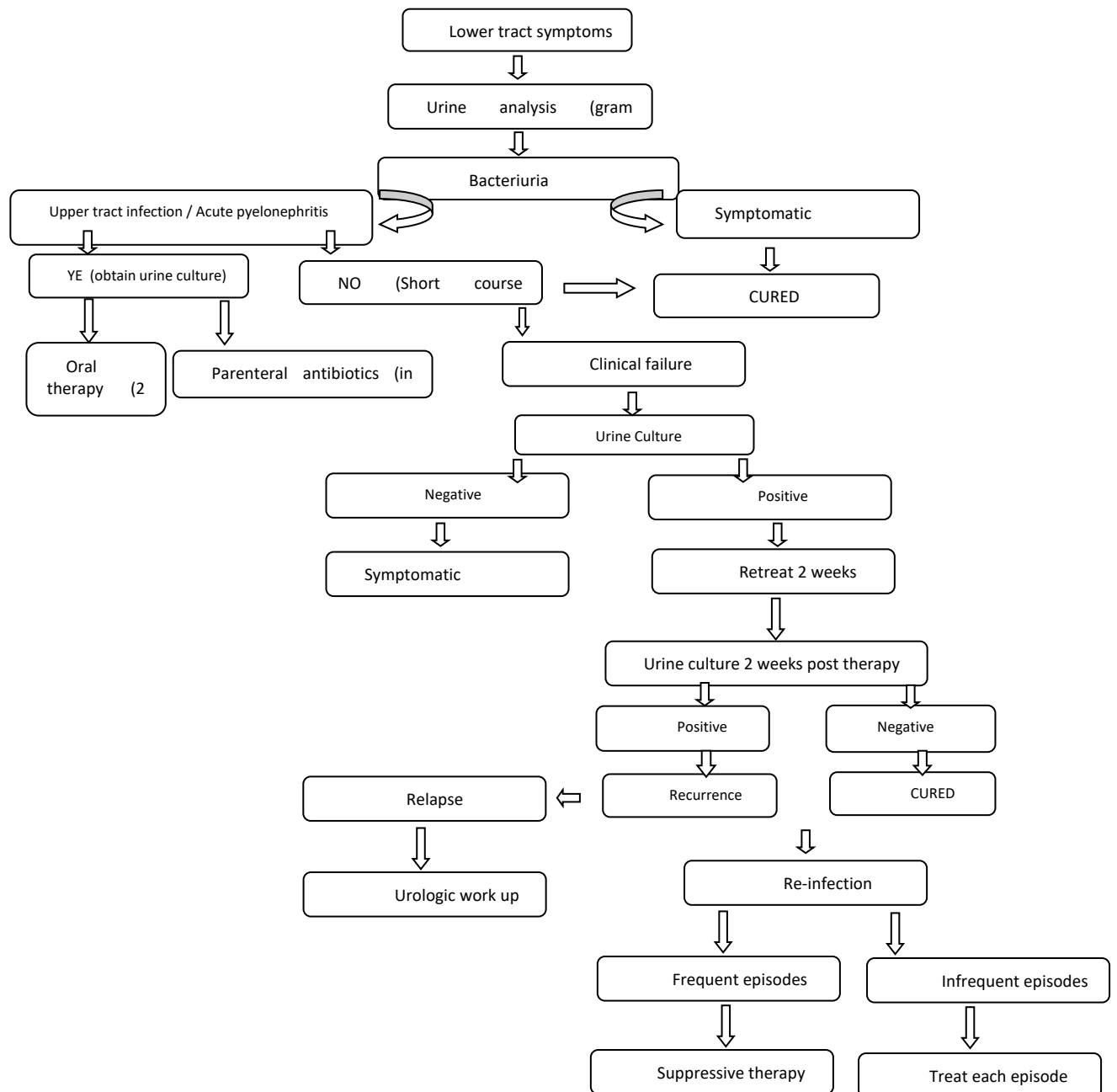


Figure 2. Flow chart explaining different complications and treatment of Urinary tract infection

Figure 2 enlists the strategic flowchart and specimen collection options for a more efficient and sensitive way of documenting the diseased female under different clinical circumstances and serves as a reference criterion recommended for the standar-

dized setting (54). UTI management in the male population is a little complex concerning females as the infections are of endogenous origin, disrupting urinary tract functions and requiring prolonged therapy if the urinary system is compromised further

with catheterization, renal and urinary stones, or systemic complications are involved. Present patient history should be precisely recorded, followed by a urine culture. Antimicrobial agent employment should be based on the bacterial strain, and initial treatment

should be for 2 weeks, i.e., a short course of therapy if no complications are foreseen. In case of structural abnormalities or obstruction is suspicious, parenteral antibiotics and the patient's hospitalization should be considered (Figure 3) (55).

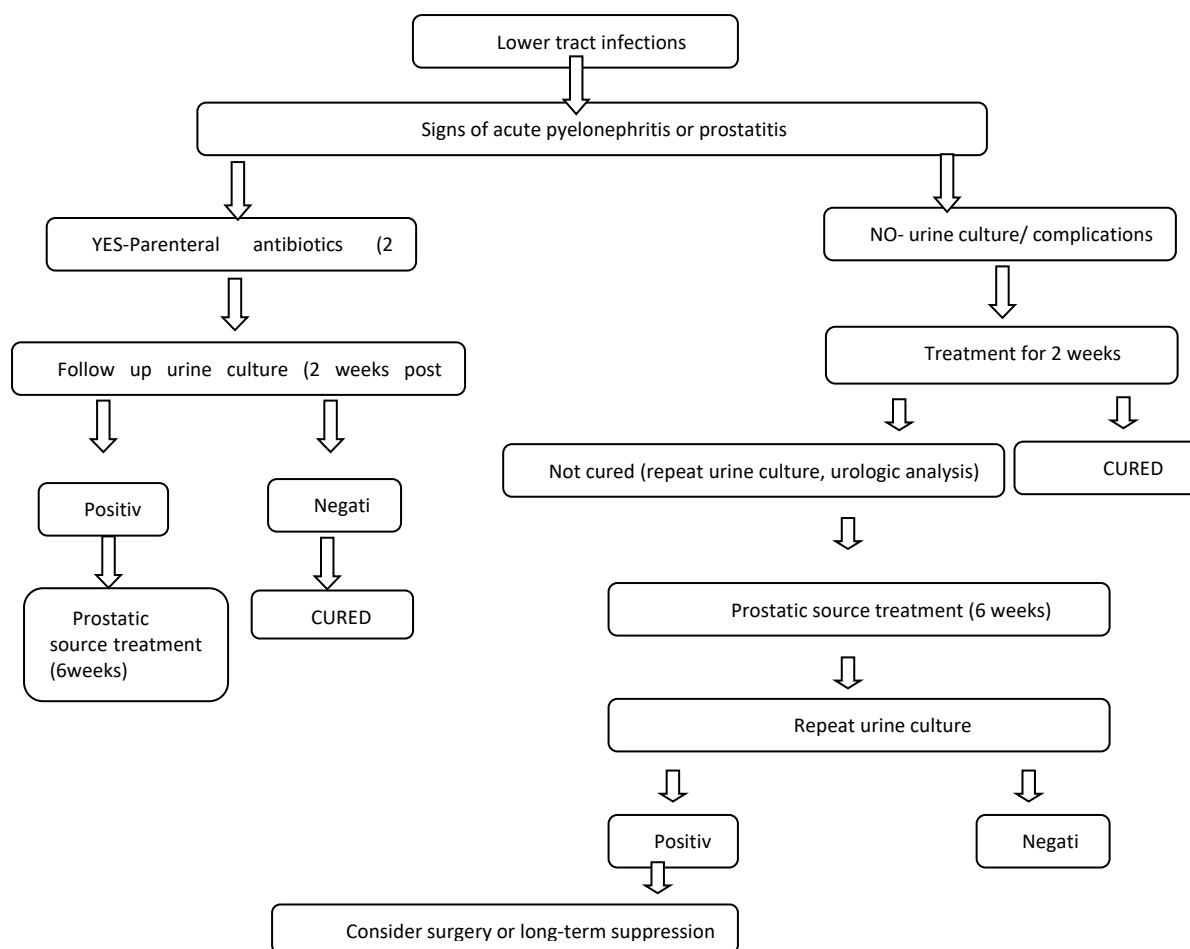


Figure 3. Flowchart showing timeline from occurrence of disease to the follow-up diagnosis and treatment

4.2 Treatment

For the treatment of acute uncomplicated cystitis, which perceives through both the upper and lower urinary tract, a fair proportion of the condition is aided by *E. coli* and *Staphylococcus*, so relapse and prevention of inoculation in GI and the genital region is the goal. Monotherapy makes the use of Trimethoprim sulfamethoxazole and Fluoroquinolone class drugs

continued for three days. Recent studies suggest casualties in Fluoroquinolone usage; instead, it's replaced with nitrofurantoin for five days or Fosfomycin single dose as first-line therapy. In case of resistance or failure of a treatment switch to beta-lactams every week (56).

Table 4. Recommended strength and quality based on evidence generated trials Category/grade

Diagnosis	Pathogen	Treatment	Duration	Comments
Acute uncomplicated cystitis	<i>E. coli</i>	Nitrofurantoin Trimethoprim sulfamethoxazole	5 days [A, I] 3 days [A, I] OD	Short course therapy is more efficient. Beta lactams and fluoroquinolones should be used in severe cases as an alternative.
	<i>Staphylococcus saprophyticus</i>	Fosfomycin Fluoroquinolone Beta-lactam	3 days [A, I] 3-7 days [A, I]	
Pregnancy	<i>E. coli</i>	Amoxicillin clavulanate Cephalosporin	7 days	Avoid these drugs in the third trimester.
	<i>Staphylococcus saprophyticus</i>	Trimethoprim-sulfamethoxazole	7 days 7 days	
Acute pyelonephritis	The most common is <i>E. coli</i> , while others are <i>Proteus</i> , <i>Klebsiella</i> , and <i>Enterobacter</i>	Nonsteroidal anti-inflammatory drugs (NSAIDs)	7-10 days	Management is crucial, and rationalized therapy can prevent resistance.
		For uncomplicated cases: oral cephalosporins or TMP-SMX Complicated cases: intravenous (IV) antibiotics (piperacillin-tazobactam, fluoroquinolones, meropenem, and cefepime)	14 days 7-14 days	
Uncomplicated	<i>E. coli</i> Gram-positive bacteria	Quinolone Trimethoprim sulfamethoxazole Amoxicillin	7 days [A, I] 2 weeks [A, I] 2 weeks [A, I]	
Complicated	<i>E. coli</i> <i>P. mirabilis</i> <i>K. pneumoniae</i> <i>Enterococcus faecalis</i>	Quinolone Penicillin+ aminoglycoside	2 weeks	Oral therapy should be for 2 weeks and then switch to parenteral depending on the severity and urine analysis.
Prostatitis	<i>E. coli</i> <i>K. pneumoniae</i> <i>Proteus</i> spp. <i>P. aeruginosa</i>	Quinolone Trimethoprim sulfamethoxazole	4-6 weeks both	If treatment is failed, switch to i/v.

Strength of Recommendation

A- Sufficient evidence to support prescription for or against;

B- Moderate safety data to support for or against the use;

C- Unsatisfactory evidence to support the use.

4.3 Quality of Evidence

I - Safety and efficacy data from more than one controlled trial;

II – Safety and efficacy data from a controlled trial via a case-control analytical approach from multiple centers;

III – Safety and efficacy data from authorities, clinically experienced opinions, and descriptive collaborative reports from experts.

Further symptomatic bacteriuria primarily seen in women can be treated with concomitant use of the antibiotics mentioned in [Table 4](#) and case of acute

pyelonephritis oral therapy ciprofloxacin (500 mg BD) for a week is suitable, loading dose or at the time of initiating the therapy, 400 mg dose of ciprofloxacin via I/V can be given to increase the probability of curing the patient to avoid hospitalization. The occurrence of resistance for community-acquired uropathogens can be overcome with the use of fluoroquinolones (A-I). If the resistant microbe further prevails, surpassing the fluoroquinolone regimen prolongs intravenous therapy of long-acting antimicrobials such as ceftriaxone (B-III) or an alternate 24-h dose of an aminoglycoside, is endorsed (B-III). To avoid complications and hospitalization, oral fluoroquinolone (OD), with ciprofloxacin (1000 mg) for at least a week or levofloxacin (750 mg) or oral Trimethoprim sulfamethoxazole with double strength should be prescribed for 2 weeks. Oral beta-lactam antibiotics are incompetent in pyelonephritis. As 75-95% of the fatalities are due to *E. coli*, individualized susceptibility and resistance patterns should be recorded before the initiation of therapy and antimicrobial selection concerning the recorded patterns (53).

4.4 Treatment of Re-infection

The instance of reoccurrence of the infection is often detected in female patients with complaints of cystitis, and numerous risk factors contribute to the ailment, e.g., self-administered therapy, resistant diabetes, post-coital therapy, irrational prophylaxis, so long-term therapy is administered with symptomatic management. Nitrofurantoin (50-100mg), Trimethoprim-sulfamethoxazole (SS), Fluoroquinolone (500 mg daily) all are well tolerated and produce the desired effect (57).

4.5 Resistance Patterns

We can accurately trace back the emergence of resistance to many risk factors with epidemiological characteristics and the type of antimicrobial agent a given population is simultaneously indulged towards via direct or empirical therapy. Standardized literature and clinical trial data should be prioritized above clinical opinions and expert advice. Still, the above can be employed in case of scarcity of particular information concerning active medicament.

Table 5. Susceptibility pattern of gram-negative bacteria isolated from diabetic patients after urine analysis

Bacterial isolates	Type	APM	AMC	SXT	GEN	CPR	CTX	CPZ	CRO	NIT	TOB	AMK
<i>E. coli</i> (n=13)	S	1	5	10	10	10	11	11	11	13	12	12
	R	12	8	3	3	3	2	2	2	0	1	1
<i>K. pneumonia</i> n=2	S	0	1	1	2	1	2	1	2	1	2	2
	R	2	1	1	0	1	0	1	0	1	0	0
<i>P. mirabilis</i>	S	1	1	1	1	2	2	2	2	2	2	2
	R	1	1	1	1	0	0	0	0	0	0	0
<i>Enterobacter</i>	S	0	1	1	1	2	2	2	2	2	2	2
	R	2	1	1	1	0	0	0	0	0	0	0
<i>Citrobacter</i> spp	S	1	1	1	1	1	1	1	1	1	1	1
	R	0	0	0	0	0	0	0	0	0	0	0
Total	S	3	9	15	15	16	18	17	18	19	19	19
	R	1	1	5	5	4	2	3	2	1	1	1

Abbreviations used above:

R – Resistant

S – Sensitive

AMC – Amoxicillin

SXT – Trimethoprim/Sulfamethoxazole

GEN – Gentamicin

CPR – Ciprofloxacin

CTX – Cefotaxime

CPZ – Ceftazidime

NIT – Nitrofurantoin

APM – Amphetamine

CRO – Ceftriaxone

TOB – Tobramycin

AMK – Amikacin

[Table 5](#) disputes the susceptibility patterns of the mentioned gram-negative strains of bacteria against drugs.

Despite advancements in the treatment and having a rainbow platter in terms of antibiotic selection, multiple drug resistance and therapy failure is the highest level of concern in the emerging infections as bacterial strains rapidly adapt and mount an over-enthusiastic response against human defense strategies. UPEC is resistible to approximately 11.8% of third-generation cephalosporins in European countries, and a double percentage of fluoroquinolones are rendered useless (58). In the United States of America, 31.3% of UPEC isolated from hospitalized patients are fluoroquinolone-resistant (59). Moreover, worldwide UPEC strains are resistant to TMP, and its use with a sulfonamide has proven to be an effective prophylactic agent (60). High circulating values of levofloxacin are insufficient to cure UTIs, while the combination of ceftolozane with tazobactam was more efficient as an alternate in fluoroquinolone resistant subjects (61). Variable resistant strains of UPEC against ampicillin (97%), tetracycline (86%), amikacin (72%), ciprofloxacin (68.5%), and gentamycin (59.1%) were isolated in pregnant women with a compiled history of recurrent UTIs (62). Bacterial interference, both active and passive is a more revolutionized treatment that recently came under consideration in which less virulent strains of bacteria antagonize the bacterial pathogen during surface colonization and wrangle for limited nutritional supply Newly developed antibiotics, such as colistin, finafloxacin, and cefiderocol (S-649266), which are yet in the trial phase and are proceeding towards clinical development, might become a breakthrough in the treatment of UTIs (52). Despite continuous efforts to eradicate this ailment and provide everlasting immunity for prophylactic and therapeutic use, no potential vaccine is yet approved, with numerous target ones still competing in trials

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based on genome, transcription, and proteomic strategies employed (63). Currently, urovac, urovaxom, urvakol, and urostim are the names making the charts and have generated optimistic results in animal models, yet to progress in further trials (64). One study generated clinical data for target genes crucial for developing an efficient vaccine and also unraveled the four antigens, namely IreA, Hma, lutA, and FyuA that are to be targeted for a revolutionary formulation and also the need of the hour states the importance of research on adjuvants, route of administration and rationalized dose for an undefeated vaccine. Scientists are needed to develop a working combination of all these factors to generate a ray of hope for millions in disaster management of the infection called UTI (65).

5. Conclusion

The occurrence of UTI and high prevalence rate of ASB (Asymptomatic Bacteriuria) is very much common among type-I and II Diabetes Mellitus (DM) patients. However, the severity is seen more in patients without DM than in type II patients. Due to complex signs and symptoms, the treatment regimes should be offered more to such patients. The antibiotic treatment provided to diabetic patients should be thoroughly planned with proper dosage based on the severity. Further research or treatment should be focused on UTI analysis in type II DM patients.

Acknowledgment

Not applicable.

Ethical Statements

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

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Abbreviations

UTI	Urinary Tract Infection
IL	Interleukins
DM	Diabetes Mellitus
ASB	Asymptomatic Intracellular
HbA1c	Hemoglobin A1c
TLR5	Toll Like Receptor 5
UPEC	Uropathogenic <i>Escherichia coli</i>
QIR	Quiescent intracellular Reservoir
CU	Chaperon Usher
PAMPs	Pathogen-Associated Molecular Patterns
PRRs	Pattern Recognition Receptors
PMN	Poly Morphonuclear neutrophil
FVs	Fusiform Vesicles
IBCs	Intracellular Bacterial Communities
cAMP	Cyclic Adenosine Monophosphate
TRML3	Transient Receptor Mucolipin 3
AMP	Ampicillin
CFU	Colony Forming Unit
MIF	Minimum Inhibitory Factor
TNF	Tumor Necrosis Factor
CNS	Central Nervous System
CONS	Coagulase Negative Staphylococci
PAI	Pathogenic Islands
CT	Computerized Tomography
MRI	Magnetic Resonance Imaging
EPN	Emphysematous pyelitis
ADR	Adverse Drug Reaction
GI	Gastro-Intestinal
GEN	Gentamycin
CPR	Ciprofloxacin
CTX	Cefotaxime
CPZ	Ceftazidime
NIT	Nitrofurantoin
VAN	Vancomycin
APM	Amphetamine
AMK	Amikacin
TOB	Tobramycin
CRO	Ceftriaxone