Chapter 4

Urinary Tract Infection in Diabetics

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Additional information is available at the end of the chapter

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Abstract

Diabetes is a metabolic disease with increase blood sugar level. A large population of world is affected by diabetes. The patients suffering from diabetes have many other complications like cardiovascular disease, kidney disease, retinopathy, diabetic foot, diabetic neuropathy, urinary tract infection, etc. The patients with diabetes are more prone to get urinary tract infection due to frequent urination and high blood sugar level. The high sugar level gives favorable growth environment to the pathogens. Early diagnosis and proper medication are necessary for management of urinary tract infection in diabetic patients. The diagnosis of urinary tract infection is dependent on urine culture reports. The treatment should preferably be started after antimicrobial susceptibility reports. The misuse or overuse of antibiotics may lead to antimicrobial resistance. The antimicrobial resistance is another challenge in management of urinary tract infection.

Keywords: diabetes mellitus, urinary tract infection, Gram-negative bacilli, antibiotic, antimicrobial resistance

1. Introduction

Diabetes is a global threat that affects the quality of life, and it is estimated that it will affect 220 million people by the year 2020 worldwide. Morbidity and mortality in diabetic patients are caused by infections. Evidence suggests that, urinary tract infection (UTI) is the most common bacterial infections among diabetic patients. According to American Diabetes Association (ADA) report, patients suffering from type 2 diabetes are more likely to have a urinary tract infection (UTI) and repeat UTI than patients without diabetes. Symptomatic bacteriuria in patients with diabetes is serious and warrants proper clinical attention for diagnosis and treatment. High glucose concentration in the urine can provide a rich source of nutrients for

bacteria. Therefore, bacteria can multiply and make foundation for infection also. High glucose concentration in the urine can allow urinary colonization by microorganisms. Moreover, multiple mechanisms were involved in UTI patients with diabetes. Diabetic female, diabetic overweight, and diabetic obese patients are having the highest risk of UTI. In general diabetic population, other risk factors associated with urinary tract infection were found to be diabetic nephropathy, diabetes with hypertension, and insulin therapy. Emphysematous pyelonephritis, emphysematous cystitis, renal and perinephric abscesses, urosepsis, and bacteremia are the complications of diabetes-associated UTI. Longer hospitalization, recurrence of UTI, relapse and re-infection, bacteremia, azotemia, and septic shock are the outcomes of diabetes-associated UTI [1].

2. Diabetes

Diabetes is a persistent disease. This disease is characterized by increase of blood glucose level. The reasons of increase of blood glucose level may be either insufficient production of insulin, a hormone that regulates the blood glucose level, or the insulin produced cannot be used properly. Frequent urination, increased thirst, and increased hunger are the common symptoms of diabetes. Uncontrolled blood sugar level can cause many complications. These complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the eyes, diabetic ketoacidosis, etc. Diabetes mellitus can be described as group of metabolic disorders causing increase in blood sugar level due to defect in insulin secretion, insulin action, or both [2]. The digestive system breaks carbohydrates, sugars, and starches found in many foods into glucose, which is a type of sugar that enters the bloodstream [3]. By the action of the hormone insulin, cells throughout the body absorb glucose and use it for energy. Diabetes develops when the body does not produce enough insulin or is unable to use insulin effectively or both. Insulin is produced in the pancreas. Clusters of cells found in the pancreas are called islets. Pancreas having islets, which contain beta cells, produces insulin and releases it into the blood.

3. Types of diabetes

- Type 1 diabetes also called as insulin-dependent diabetes mellitus (type I diabetes occurs due to β-cell destruction, usually leading to absolute insulin deficiency).
- Type 2 diabetes also called as noninsulin-dependent diabetes mellitus (type II diabetes occurs due to a progressive loss of insulin secretion).
- Gestational diabetes mellitus (GDM) (diabetes detected in the second or third trimester of pregnancy that is not clearly overt diabetes).
- Specific types of diabetes due to other reasons, for example, monogenic diabetes syndromes (such as maturity-onset diabetes of the young [MODY] and neonatal diabetes),

diseases associated with exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as use of glucocorticoid, in the treatment of HIV/AIDS or after organ transplantation).

Type 1 diabetes occurs in childhood, mainly due to destruction of pancreatic β-cell islets through autoimmune-mediated, causing complete insulin deficiency. Type 2 is more associated with adults and elderly people, which are mainly due to insulin resistance or abnormal insulin production. The exact reason of pancreatic failure and insulin resistance is unknown, but they are associated with disease condition, food habit, and environmental impact. Diabetic patients are more susceptible to various type of infection such as skin diseases and carbuncles [4].

Gestational diabetes is other type of diabetes, which is mainly associated with pregnancy. It occurs in the 4% of pregnancies in US, usually during the third trimester. It causes increased perinatal morbidity and mortality unless properly diagnosed or managed. Genetic defects of β-cell function or insulin action is also a type of diabetes mellitus commonly called maturity onset diabetes. Neonatal diabetes mellitus is also a type of diabetes, in which first 3 months of life insulin is required for the maintenance of blood glucose level in. It may be caused by intrauterine growth retardation and defects of chromosome. The heart, blood vessels, eyes, kidneys, and nerves can be damaged by diabetes, leading to disability and premature death.

4. Urinary tract infection in diabetics

Infections are frequent causes of morbidity and mortality in diabetic patients. Evidence suggesting that urinary tract infection (UTI) is the most common bacterial infections among diabetic patients. High glucose concentration in the urine can provide a rich source of nutrients for bacteria [5, 6]. Therefore, bacteria can multiply and make foundation for infection; also, high glucose concentration in the urine can allow urinary colonization by microorganisms. Moreover, some of the immunological defects like impaired neutrophil function, reduced T cell-mediated immune response, low levels of prostaglandin E, thromboxane B2, and leukotriene B4 may contribute to the increased risk for infection. Other conditions such as bladder dysfunction (incomplete bladder emptying) caused by autonomic neuropathy also may contribute to the increased risk for infection [7, 8]. UTI in diabetes can lead to severe complications including bacteremia, renal abscess, and renal papillary necrosis. In some cases, diabetes modifies the genitourinary system and may cause damage to the organ, which leads to pyelonephritis. This type of UTI occurs 15 times more frequently in diabetic patients. Therefore, early diagnosis and correct treatment are very important for diabetes patients with UTI [9, 10]. Molecular reasons for an increased frequency of UTI in diabetic patients include depression in the function of polymorphonuclear leucocytes especially during acidosis, dysfunction of chemotaxis, and phagocytosis [10]. High blood glucose levels may cause nerve damage, affecting the ability of the bladder to sense the presence of urine and thus allowing urine to stay for a long time in the bladder and increasing probability of infection [11].

Various types of UTI in patients with diabetes include

- Asymptomatic bacteriuria
- Acute cystitis
- Complicated lower UTI (including catheter-associated UTI)
- Uncomplicated pyelonephritis
- Complicated pyelonephritis/urosepsis

5. Pathogenesis of UTI in diabetics

The chance of occurrence of UTIs in diabetic patients used to increase many folds due to several factors. Multiple potential mechanisms unique to diabetes may cause increased risk of UTI in diabetic patients. Elevated renal parenchymal glucose levels create a positive environment for the growth and multiplication of microorganisms, which is one of the precipitating factors of pyelonephritis and renal problem such as emphysematous pyelonephritis. Several problems in the immune system, including humoral, cellular, and innate immunity, may help in the pathogenesis of UTI in diabetic patients [12–14]. Lower urinary interleukin-6 and interleukin-8 levels were found in diabetic patients with UTI. An outline of process involved in pathogenesis of urinary tract infection in diabetic patients is mentioned in **Figure 1**.

Some suggested host related mechanisms include [15]:

i. Presence of glycosuria

ii. Increased adherence to uroepithelial cells

iii. Immune dysfunction

5.1. Presence of glycosuria

The presence of glycosuria is responsible for the growth of different microbial strains. Among all *E. coli* is the major cause for the condition of UTI [15]. The bacteria isolated from diabetic patients with a UTI are similar to the bacteria found in nondiabetic patients with a complicated UTI. As in uncomplicated UTIs, *E. coli* causes the majority of infections. For example, one study reported *E. coli* to be the causative uropathogen in 47% of the UTIs in diabetic patients and in 68% of the UTIs in nondiabetic patients. Non-*E. coli* uropathogens found in patients with diabetes, include *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., Group B *Streptococci,* and *Enterococcus faecalis* [16].

Geerlings et al. [17] in their study reported that urine samples with glucose concentrations between 100 and 1000 mg/dL, which comes in the range of moderate to severe glucosuria, were responsible for enhanced bacterial growth after 6 h, compared with normal urine.

E. coli gain access to the urinary tract by the mechanism which reflects an exceptional ability to adapt to an environment very different from the gut. They need to alter their metabolism [18],

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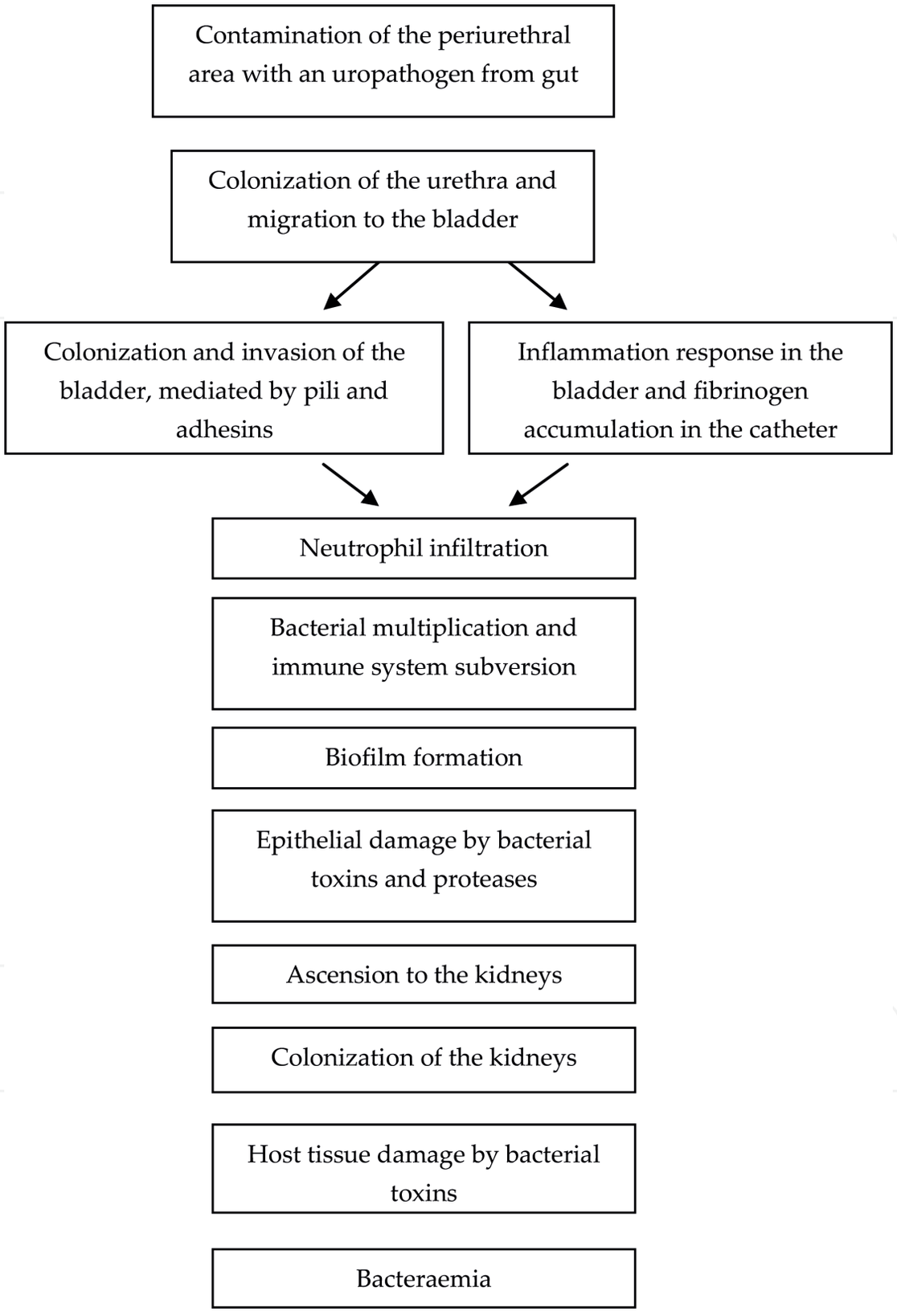

Figure 1. Process involved in pathogenesis of UTI in patients with diabetes.

ascend against the flow of urine, and adhere to the epithelial layer. *E. coli* that successfully invade the urinary tract harbor a specific factor that enables them to survive. These strains of *E. coli* are commonly named uropathogenic *E. coli* (UPEC). Flagellae are thread-like structures which provide *E. coli* with the ability to move. It has been found to bind to TLR5 [19] and is of importance for the immune response to *E. coli* in UTI in mice [20]. A critical step for UPEC is adhesion to avoid being washed out with the urine and the first step in a series of events leading to infection. The type-1 fimbriae are adhesion factors studied in great detail and are critical for adhesion and invasion of UPEC into bladder cells [21, 22]. They are equipped with a protein on the tip called FimH, which is responsible for the interaction with the host cell [23]. It binds to several structures on uroepithelial cells, the most important being uroplakin IA that coats the facet cells of the bladder [24]. They also bind to β-integrin, which triggers cytoskeleton rearrangement leading to bacterial internalization [25]. In renal epithelial cells, complement factor 3, which is secreted by epithelial cells during infection, can link with type 1 fimbriae to form a complex that interacts with CD46 to promote internalization. Other fimbriae like P fimbriae are connected with kidney infection, since they bind to glycosphingolipids on kidney epithelial cells [26].

Flagella provide the bacteria with mobility and may interact with the superficial bladder cell through TLR5. Further adhesion is provided by type 1 fimbriae binding to uroplakin 1A or β1-integrin, which also promote internalization into the cell. Complement secreted upon bacterial infection binds to the bacteria and promotes interaction with the bladder through CD46. In the kidney, P fimbriae of the bacteria bind to glycosphingolipids on the surface of renal epithelial cells. Bacterial invasion is further promoted by TLR4 and TLR5.

5.2. Increased adherence to uroepithelial cells

The uroepithelium is having a very important property of flexibility by which it will allow filling and emptying of the bladder and at the same time impermeable to fluid and able to cope with the varying pH, osmolality, and toxicity, for example, high ammonium concentration. It is composed of different layers of cells with the umbrella or facet cells lining the lumen are multinuclear, large cells with uroplakin facing the urine. Uroplakins are proteins contributing to the impermeability of the epithelium but can also act as a receptor for type 1 fimbriae on the uropathogenic *E. coli* [27].

The important step in the pathogenesis of UTIs is the adherence of uropathogens to the bladder mucosa. Therefore, adhesins (fimbriae) are important virulence factors. Although virulence factors have been distinguished best in *E. coli* (the most common uropathogen), many same principles may be applicable to other Gram-negative uropathogens, for example, Klebsiellae. Type 1 fimbriae mediate the adherence of glycoprotein receptors (uroplakins) on the uroepithelial cells to *E. coli*, whereas P fimbriae bind to glycolipid receptors in the kidney [25].

5.3. Immune dysfunction

It is observed that hyperglycemic environment alters immune function in patients with diabetes. Several aspects of immunity may be affected, including polymorphonuclear leukocyte function and adhesion, phagocytosis, and chemotaxis. This may play a part in the pathogenesis of urinary tract infections in patients with diabetes. Lower urinary concentrations of

interleukin-8 and interleukin-6 in women suffering from diabetes have been shown to correlate with a lower urinary WBCs count that may contribute to the increased incidence of UTIs in this patient group [28].

If UPEC comes in contact with the epithelium, within minutes, the antimicrobial peptide cathelicidin is secreted and acts on the bacteria. Within hours, cytokines and chemokines are produced and their signaling will start to fix professional immune cells to the site of infection. The bacteria on the other hand will try to circumvent the immune defense in different ways. One is to enter the cell cytoplasm and form intracellular bacterial communities (IBCs) in order to "hide" from the immune response [29]; another is to down regulate the immune response with different modes of signaling. Depending on the number of bacteria, the host status, and the virulence factors they carry, the bacteria will either survive in the urinary tract or be eliminated and washed out with the urine [29].

If this first line of defense against pathogens entering the urinary tract fails, an inflammatory response is initiated. Attachment to the bladder uroepithelial cells by bacterial fimbriae allows for close contact between host and pathogen. Trans-membrane signaling through TLRs leads to the production of inflammatory mediators such as chemokines with subsequent recruitment of professional immune cells to the infectious focus. Chemokine IL-8 is required for neutrophil recruitment and activation in the urinary tract [30].

When the inflammatory response subsides, bacteria may still be left in the bladder epithelium. Bacteria that form IBCs can escape the different steps in host defense and treatment with antibiotics will be less efficient because of poor antibiotic penetration into the IBCs. From the IBC, bacteria can be expelled from the cells by a TLR4 mediated mechanism or in mature IBCs, and bacteria form filamentous structures and then separate from the cell to colonize adjacent cells. The cells may also be exfoliated, allowing the underlying immature cells to be exposed to further UPEC invasion. Here, they can turn into quiescent intracellular reservoirs (QIRs) for weeks, only to re-emerge to cause recurrent infections. Pyelonephritis may develop if the bacteria ascend further in the urinary tract. In the kidney, bacteria may cause damage of tissue and reach the blood circulation, causing septicemia, commonly called urosepsis. This increases the mortality from 0.3% in pyelonephritis to 7.5–30% in urosepsis [31].

6. Classification of urinary tract infection

UTIs are classified based on laboratory data, clinical symptoms, and microbiological findings. Practically, UTIs have been divided into uncomplicated and complicated UTIs and sepsis. The present guidelines give an outline of a tentative improved system of classification of UTI based on various factors as follows: (Guidelines on Urological Infections by European Association of Urology)

i. Classification based on grade of severity of infections and symptoms

ii. Classification based on underlying risk factors

iii. Classification based on anatomical level of infection

iv. Classification based on microbiological findings

v. Classification based on complications

7. Diagnosis of urinary tract infection in diabetics

Upper and lower UTI can be suspected in diabetic patients with most common symptoms. Symptoms vary in upper and lower UTI. **Table 1** highlights the symptomatic difference between upper and lower UTI.

Diagnosis of urinary tract infection can be done by following methods.

- **Examination of midstream urine specimen:** After the symptomatic identification, a midstream urine sample should be examined for the presence of WBCs, as pyuria is present in almost all cases of UTI.
- **Pyuria detection:** Pyuria can be detected either by microscopic examination (defined as >10 leukocytes/mm^3) or by dipstick leukocyte esterase test (sensitivity of 75–96% and specificity of 94–98%).
- **Colonization:** An absence of pyuria on microscopic assessment can suggest colonization, instead of infection, when there is bacteriuria [32].
- **Microscopic examination:** Allows for visualizing bacteria in urine.
- **Dipstick:** Tests for the presence of urinary nitrite.
  - **Positive test:** Indicates the presence of bacteria in urine.
  - **Negative test:** is the product of low count bacteriuria or bacterial species that lack the ability to reduce nitrate to nitrite (mostly Gram-positive bacteria).
- **Urine culture:** Should be done in all cases of suspected UTI in diabetic patients, prior to initiation of treatment (preferred method of obtaining a urine sample for culture is from voided, clean-catch, and midstream urine) [33].

7.1. Diagnosis of UTI in women patients

All women with recurrent UTI should undergo a physical examination to evaluate urogenital anatomy and vaginal tissues estrogenization. Postvoid residual urine volume also should

Lower UTI	Upper UTI
• Frequency • Urgency • Dysuria • Suprapubic pain	Costovertebral angle pain/tenderness fever and chills, with or without lower urinary tract symptoms

Table 1. Symptomatic difference between upper and lower UTI.

be measured. Diabetes screening is indicated in patients with other risk factors like family history and obesity. Most women do not need extensive urologic investigations. However, women who suffer infection with organisms which is not common causes of UTI, such as *Proteus, Klebsiella, Enterobacter,* and *Pseudomonas,* may have structural abnormalities or renal calculi. They would benefit from imaging studies of the upper urinary tract and cystoscopy. Women who have persistent hematuria after recovery of their infection also require a complete urologic workup. Although empirical therapy based on symptoms is generally accurate and cost-effective, women who are thought to be in the early stages of a problem with recurrent UTI should have documented cultures. Urine culture serves as the gold standard for diagnostic accuracy. The standard definition of a UTI on culture is >100,000 colony forming units per HPF. This value has excellent specificity but a sensitivity of only 50% [34].

8. Complications of urinary tract infection in diabetics

Emphysematous pyelonephritis (EPN) is a severe and necrotizing form of multifocal bacterial nephritis along with gas formation within parenchyma of the kidney. So far, more than 200 cases have been reported in literature. Underlying poorly controlled diabetes mellitus is present in up to 90% of affected patients [28].

The commonest offending organisms are Klebsiella and *Escherichia coli* followed by Proteus. The clinical manifestations are nonspecific and not different from the classic triad of upper UTI (i.e., fever, flank pain and pyuria); due to this, the diagnosis of EPN is often delayed. Disseminated intravascular coagulopathy, acute respiratory distress syndrome, disturbance of consciousness, acute renal failure, and shock can reveal some severe forms. Diabetic ketoacidosis is a very uncommon presentation, and only few cases have been reported so far.

EPN needs a radiological diagnosis. Conventional radiography may indicate gas bubbles overlying the renal fossa. Ultrasonography (US) characteristically shows an enlarged kidney that contains high amplitude echoes within the renal parenchyma. Computed tomography (CT) is the imaging procedure of choice, which confirms the presence and extent of parenchymal gas.

9. Pathogens of UTI in diabetes

A descriptive, cross sectional study was conducted on UTI and antibiotic sensitivity pattern among diabetic patients in National Academy of Medical Sciences (NAMS), Mahabouddha, Kathmandu, Nepal. According to this study, *E. coli* is the most common organism followed by *Klebsiella, Proteus,* and *Pseudomonas*. Most of the urinary isolates were sensitive to Ceftriaxone, Ciprofloxacin, and Cotrimoxazole, whereas resistance was high for ampicillin [35].

A study was conducted to find out the prevalence of UTI in diabetic patients. A total of 1470 diabetic patients (847 women and 623 men) were included in the study, admitted to the Diabetes Clinic of the Emergency Clinical County Hospital Timişoara between January and December 2012. According to this study, 10.7% in overall population had positive urine

Gram-negative microorganisms	Frequency (%)	Gram-positive microorganisms	Frequency (%)
Escherichia coli	56.75	Alpha *Streptococci*	33.33
Klebsiella pneumonia	21.62	*Staphylococcus aureus*	66.66
Pseudomonas aeruginosa	9.54	*S. epidermidis*	0
Enterobacter aerogenes	4.05	—	—
Proteus mirabilis	4.05	—	—
Citrobacter freundii	4.05	—	—

Table 2. Pathogens of UTI in diabetes.

cultures. In this population, almost 78% of patients were having asymptomatic bacteriuria. The most frequent bacteria involved in UTI are *Escherichia coli* (68.9%) [9].

About 10.5% of type 2 and 12.8% of type 1 diabetic patients had UTI. There is no significant difference between type 1 and type 2 diabetes ($p = 0.45$); 4.5% of men and 15.3% of women developed UTI, an extremely significant difference ($p < 0.0001$)

Chiţă et al. concluded that urinary tract infections are more prevalent in diabetic patients. Because of the high proportion of asymptomatic forms among diabetic patients, the urine culture should be done in all hospitalized patients with diabetes.

The pathogens involved in causing urinary tract infection in diabetic patients and their frequency are mentioned in **Table 2**.

10. Management of urinary tract infections in diabetics

Generally, treatment of UTI is similar in both diabetic patients and nondiabetic patients [5]; however, the choice of antibiotics in UTI patients with diabetes is one of the important considerations in the therapeutic management. Possible drug interactions between antimicrobials and antidiabetics or certain antibiotics may lead to impaired glucose homeostasis.

UTI treatment in diabetes patients depends on various factors including [5];

- Presence of symptoms
- Presence of infection in the bladder (lower UTI) or also involves the kidney (upper UTI)
- Presence of urologic abnormalities
- Severity of systemic symptoms
- Occur with metabolic alterations and renal function

Moreover, UTI treatment varies based on patient's age, sex, infecting agent, underlying disease, and whether there is lower or upper urinary tract involvement. Several clinical trials revealed that increasing trends of resistance to many antimicrobials with the increasing trend

of antibiotic resistance in *E. coli*, with limited therapeutic options, the management of urinary tract infections is likely to become complicated.

10.1. Treatment recommendations for UTI in diabetes according to Infectious Diseases Society of America (IDSA)

10.1.1. Acute cystitis management in patients with type II diabetes

Acute cystitis treatment should be tailored according to culture results, if obtained. Apart from proper glucose control, one of the following UTI treatments is mandatory for acute cystitis management [36]. **First line treatment management**: Nitrofurantoin 100 mg three times daily for 5 days or fosfomycin trometamol 3 g single dose, or trimethoprim-sulfamethoxazole 960 mg twice daily for 3 days (can be used empirically only if resistance prevalence is known to be less than 20% and medication was not used in previous 3 months). **Second line management**: Quinolones and β-lactams.

10.1.2. Pyelonephritis management in patients with type II diabetes

Hospitalization should be done for the patients with severe symptoms for initial intravenous antibiotic therapy [5, 36]. Empiric antibiotics treatment: broad-spectrum cephalosporins, aminoglycosides, fluoroquinolones, piperacillin-tazobactam, or carbapenems should be started [37]. Severe sepsis presenting patients or those known to harbor-resistant uropathogens or the patients who have received multiple antibiotic courses should receive broad-spectrum coverage, guided by current urinary culture report. Treatment should be tailored when culture reports are available.

11. Antimicrobial agents

There are several types of antimicrobial agents such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics. Likewise, there are several types of microorganisms such as bacteria, fungi, viruses, and parasites. Microorganisms are responsible for various infectious diseases and sometimes leading to death. Antimicrobial agents play an essential role in decreasing morbidity and mortality associated with infections. Antimicrobial agents increased the life expectancy and quality of life. Different antimicrobial agents and their mechanism of action are mentioned in **Table 3**.

11.1. Benefits of antimicrobial agents

- Prevent and treat infection
- Increased the expected life spans of human being
- Prevent or treat infection after surgery (C section, organ transplants, joint replacements, etc.)
- Prevent or treat infection at the time of chemotherapy treatments
- Antimicrobial drugs decrease the morbidity and mortality caused by food-borne, waterborne, and other poverty-related infections

Antimicrobial agents	Effect on bacteria	Mechanism
Penicillins, cephalosporins, carbapenems, polypeptide antibiotics	Bactericidal	Inhibition of cell wall synthesis
Lincosamides, aminoglycosides, macrolides, tetracyclines, chloramphenicol	Bacteriostatic	Inhibition of protein synthesis
Quinolones, metronidazole	Bactericidal	Inhibits DNA synthesis
Rifamycins	Bactericidal	Inhibitions of RNA transcription
Sulfonamides	Bacteriostatic	Competitive inhibition

Table 3. Different antimicrobial agents and its mechanism of action.

12. Antimicrobial resistance

Resistance to antibiotics and other types of antimicrobial agents is growing and represents the single greatest challenge in the treatment of infectious diseases today. According to WHO, "AMR occurs when microorganisms change when they are exposed to antibiotic and antimicrobial drugs." Due to anti microbial resistance, antimicrobial agents turning ineffective and infections persist in the body, increasing the risk of spread to others. AMR affects the effective prevention, and treatment of infections caused by bacteria, parasites, viruses, and fungi. WHO says that AMR is a growing and alarming threat to global public health that requires lot of action from the government. Moreover, people should get a lot of awareness message regarding antimicrobial resistance. An antimicrobial resistance developing microorganisms are sometimes called as "superbugs" [38].

As per WHO cost analysis data, health care cost of resistant infections is higher than nonresistant infections because of

- Longer duration of illness
- Additional tests
- Use of more expensive drugs

Global WHO statistics says that a total of 480,000 people develop multidrug resistant TB each year, and drug resistance is starting complication in treatment of HIV and malaria as well.

12.1. Emergence of drug-resistant bacteria

Emergence of penicillinase-producing *Staphylococcus aureus* and emergence and spread of multidrug-resistant *S. aureus* in the early 1960s, emergence of MRSA in 1961, emergence of PISP in 1967, emergence of penicillinase-producing *H. influenzae* in 1974, emergence of PRSP in 1977, emergence of BLNAR *H. influenzae* in 1980, emergence of ESBL-producing

Gram-negative bacilli in 1983, emergence of VRE in 1986, increased infections with MRSA, PRSP, BLNAR, etc. and increase of resistant *gonococci* in 1990s, increase of MDRP, and increase of quinolone-resistant *E. coli* in 2000s are the emergence of drug resistance bacteria.

Major reasons for increasing antimicrobial resistance:

- Ineffective infection-control practices
- Noncompliance with infection-control practices
- Using sub-optimal dose of antibiotics for prophylaxis and treatment of infection
- Multiple comorbidities in hospitalized patients
- Prolonged hospitalization
- Increased number and duration of intensive care unit stays
- Colonized patients transfer from hospital to hospital
- Grouping of colonized patients in long-term-care facilities

Major mechanisms for acquired antimicrobial resistance:

- Enzyme that degrades the antimicrobial agent
- Enzyme that alters the antimicrobial agent
- Mutation in the antimicrobial agent's target which reduces the antimicrobial agent binding.
- Posttranslational or posttranscriptional modification of the antimicrobial agent's target, which reduces binding of the antimicrobial agent
- Reduced uptake of the antimicrobial agent
- Active efflux of the antimicrobial agent
- Antimicrobial agent target overproduction

13. Conclusion

Urinary tract infections are more common in the diabetic patients. Diabetic patients are severely affected with urinary tract infection. Treatment of UTI without proper diagnosis may lead to antimicrobial drug resistance. Treatment with antimicrobial agents should be started on the basis of culture reports. Only bacteriuria with symptoms of UTI should be treated with antibiotics to avoid the spread of drug resistant pathogens in the society. This practice can reduce the morbidity and mortality in diabetic patients suffering from urinary tract infection. The multidrug resistant pathogens are a challenge to society.

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