
Community acquired urinary tract infection

Abstract

Urinary tract infection (UTI) is one of the most common infectious diseases, which causes huge economic losses all over the world every year. The term ITU includes the pathology of different anatomical regions: urethritis, cystitis, pyelonephritis and prostatitis; Cystitis is the most common, usually manifested as dysuria, frequent urination and urgency. ITU includes a wide range of clinical manifestations, from simple colonization to septic shock. Intestinal bacteria are the main pathogens causing UTI, among which *Escherichia coli* is the main pathogen. It is the second largest cause of bacterial infection in the community after respiratory tract infection; The incidence increases with age and gender. For other healthy, sexually active, non pregnant female patients, these forms can be divided into non complex forms; Complications occur in patients with certain risk factors, such as structural or functional urinary tract abnormalities, basic diseases or special populations, such as pregnant women and children. The diagnosis is mainly based on clinic and urine examination is carried out as needed. In most cases, treatment is empirical and outpatient antibiotic treatment.

Key words: Urinary tract infection cystitis; *Pyelonephritis*; *E. Coli*.

Introduction

Urinary tract infection (UTI) usually occurs when urogenital pathogenic bacteria enter the bladder through the ascending channel and defeat the host's innate immunity. There are two main terms that need to be distinguished.

First, asymptomatic bacterial urine (BA) or urinary colonization refers to that the patient's urine carries $\geq 10^5$ colony forming units (CFU) / ml, but there is no clinical manifestation, which is usually found by accident; And urinary tract infection, that is, bacterial urine with clinical manifestations. Including cystitis, urethritis, pyelonephritis and prostatitis; Different classifications will be discussed later (1).

It is important to understand the pathogenesis of UTI and its related major pathogens, as well as how to interpret the symptoms in combination with the laboratory results of each patient. This review will discuss these aspects, the salient characteristics of different populations, and the management and prevention of the disease.

Method

Articles used for this literature review include Spanish and English publications no more than five years old provided by the University of Medical Sciences Library (ucimed), MEDLINE and update. The most important issues were selected under this topic in order to present their different aspects in an appropriate and up-to-date manner.

Epidemiology

It is one of the most common bacterial infections, although it may be caused by other pathogens. This condition is more common in women because of the short distance between the distal urethra and anus in female perineal anatomy (2-4). They affect 40-50% of women, accounting for 25% of the elderly, which means high social and health costs. In the United States, annual expenditures exceed \$1.5 trillion (1.5.6).

The prevalence of UTI in young men is less than 0.1% and increases with age. Risk factors for this group of patients were lack of circumcision, anal sex, and prostate pathology (7).

Women have a higher risk of UTI within 48 hours of sexual intercourse, using spermicide or diaphragm, postmenopausal (due to changes in vaginal flora) and previous history of cystitis (7).

Genetic factors associated with increased risk of UTI have also been reported; However, there is little evidence (1).

In addition to women, there are other factors that increase the risk of recurrent UTI, such as recent use of antibiotics, daily sexual activities, recent changes in sexual partners, sexual activity before the age of 15, possible post anal vaginal intercourse and post menopause, which are caused by related factors such as cystocele, urinary incontinence, urinary residue and reduced vaginal estrogen levels. One in four women with UTI relapsed in the first year (3.4) after the initial attack.

Etiology

They may be caused by BK virus, especially in transplant patients; Parasitological

Schistosomiasis, common in endemic areas, with increased risk of malignant tumors; Or fungal, most common in *diabetic* patients or *Candida albicans* with abnormal urinary tract anatomy; But the most common is bacteria. This is usually caused by pathogens in the intestinal flora. The most common is *E. Coli*, accounting for about 70-95% of cases (2). Other bacteria causing UTI include *saprophytic* *Staphylococcus*, *Enterococcus faecalis*, *kiwi protein* and *Pseudomonas aeruginosa* (1) (Table 1). More than 95% of ITU are single microorganisms (7).

Normally, the urethra is sterile except for one-third of the distal end of the urethra. Pathology occurs when microorganisms move upward to the bladder or kidney. However, a "urinary microbiota", a group of symbiotic organisms in the bladder, is currently being discussed, which may affect different urinary diseases and conditions, including UTI (8). These may interfere with host protection and susceptibility to urinary pathogens.

Bacteria are usually cleared by urination, unidirectional urine flow, and complete bladder emptying (1,3), although there are other factors that prevent bacteria from adhering to tissues, such as cytokines, urine osmolality, bladder mucus, and Tamm-Horsfall glycoprotein. If it cannot be excreted, the tissue will invade through the filamentous structure produced by bacteria to adhere to the epithelium and produce toxins to cause infection.

Less commonly, invasion can occur through blood or lymphatic pathways, which usually leads to substantial (high) urinary tract infections (5.7).

Classification

I Anatomic

- i High: the solid organs of the urinary tract (prostate, renal pelvis, kidney) are affected and present as an infectious syndrome.
- i Lower: urethral mucosa and bladder are involved respectively, that is, urethritis and cystitis. Clinically, it is usually manifested as micturition syndrome (2).

I Clinic

- i Complex: associated with UTI events in patients with increased risk factors (Table 2). Due to urinary tract diseases, lower virulence factors are a necessary condition for UTI, which makes the host more vulnerable to a wider range of pathogens.
- i Uncomplicated: it refers to acute cystitis or pyelonephritis (PNA) in other healthy women without the above risk factors (1).

I Introduce

- i New or simple
- i Recurrence: Cases with 2 or more ITU attacks within 6 months, or 3 or more ITU attacks last year. The incidence is 30 times higher in women than in men (3,4,7).
- i Recurrence: UTI attack occurred 2-3 weeks after the end of antibiotic treatment, which may be due to the persistence or recurrence of the original strain. The possible causes of these diseases are: potential urological pathology or improper treatment. They occur earlier than relapses (3).

Table 1. The common causes of UTI (uncomplicated and complex) are ranked in descending order of prevalence.

ITU is not complex	Complex ITU
1. Escherichia coli	1. Escherichia coli
2. Klebsiella pneumoniae	2. Types of
3. Staphylococcus saprophyticus	3. Enterococcus
4. Enterococcus faecalis	4. Klebsiella pneumoniae
5. Streptococcus agalactiae (group B streptococcus)	5. Candida species
6. Proteus mirabilis	6. Staphylococcus aureus
	7. Proteus mirabilis
	8. Pseudomonas

7. Pseudomonas aeruginosa	aeruginosa
8. Staphylococcus aureus	Streptococcus agalactiae (group B streptococcus)

Source. Walsh C, colyns T. Pathophysiology of urinary tract infection. 2020.

Table 2. Complex ITU standard

I Basic pathology
i Renal failure
i Diabetes
i Immunosuppression
i Multiple sclerosis
i Renal calculus
i Prostatic hypertrophy
I Abnormal urinary tract
i Functional
n Neurogenic bladder
n Backflow
i Anatomic
n Congenital urethral flap
n Bladder diverticulum
I Special population
i Pregnant woman
i Children
i Aged
i Male

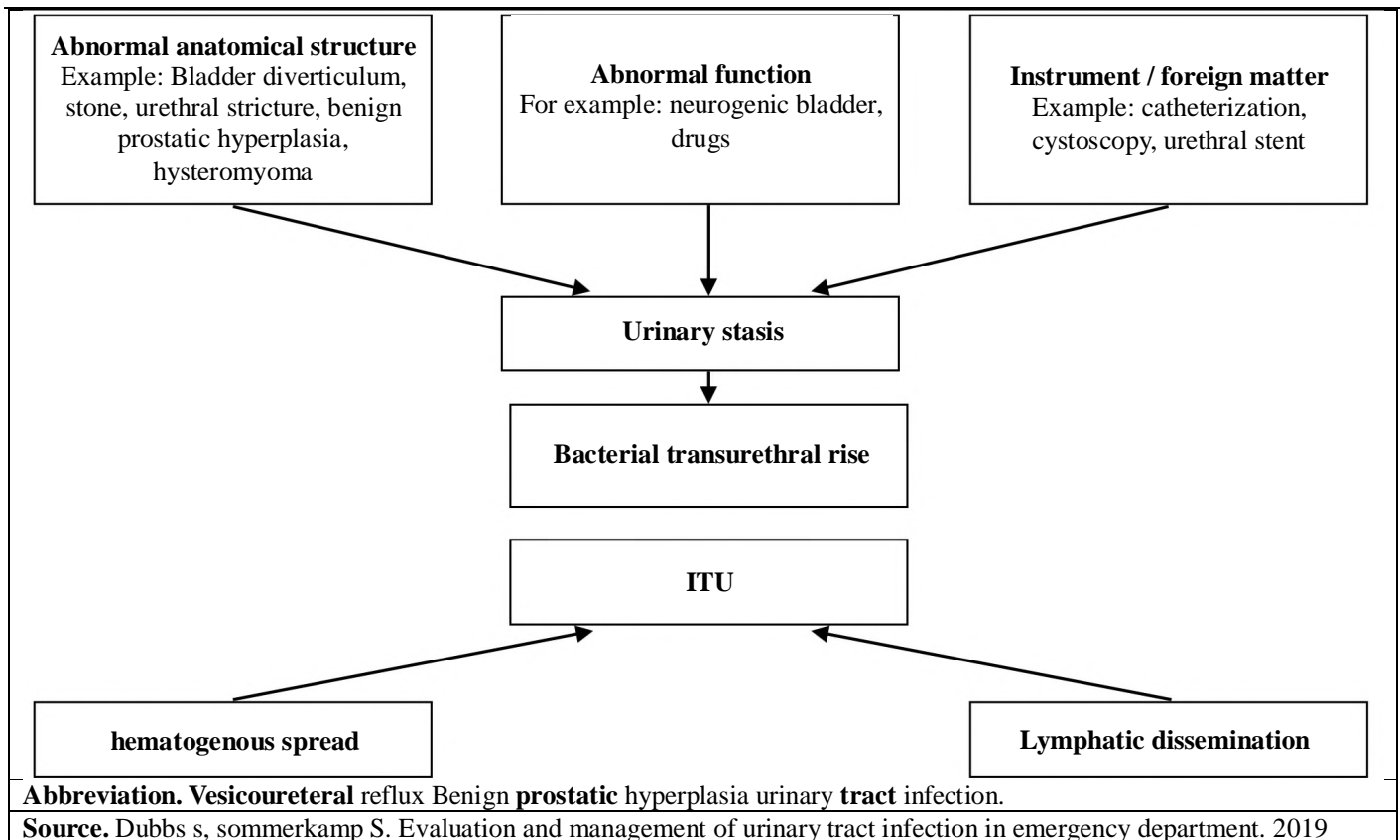
Source. Urinary tract infection 2019

Pathophysiology

E. Coli is a gram-negative anaerobic bacterium, which exists in the human gastrointestinal tract as part of the normal flora. This is the main reason for ITU events in non complex and complex tables. This bacterium has different strains, including uropathogenic *Escherichia coli* (*UPEC*). They have some virulence factors different from other strains, which give them greater ability to invade the urinary tract. The production of pili or pili, toxin and the ability to inhibit neutrophil movement are some factors in favor of these strains (4).

Abnormalities in the function or anatomy of the urinary tract impair the normal flow of urine and lead to blood stasis, making the urine vulnerable to bacterial invasion (**Fig. 1**). When the protective mechanism cannot inhibit colonization, this process begins. The pathogen uses its pili adhesion to move from the urethra to the bladder or kidney, and changes the host's immune response to achieve invasion and infection.

Figure 1. Pathophysiology of urinary tract infection



Clinical table

Symptoms depend on the anatomy of the infection. The micturition syndrome of low urinary tract syndrome is usually characterized by local symptoms and signs, including dysuria, urinary tract changes, urgent micturition, micturition and urinary retention. High UTI is usually accompanied by systemic symptoms, i.e. Infectious syndrome, accompanied by fever, low back pain and sometimes vomiting (4,7). However, few of these symptoms may also occur in low urinary tract infections (1).

Cystitis is an acute micturition syndrome, often accompanied by suprapubic pain and hematuria. In addition, urinary incontinence is common in women and elderly patients (7). The presence of symptoms such as vaginal secretion or pruritus should guide the differential diagnosis, such as vaginitis or cervicitis (9,10).

Urethritis is usually not included in ITU terminology. This is usually due to infection with sexually acquired pathogens, such as *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, resulting in symptoms similar to cystitis (4).

PNA table is characterized by micturition syndrome,

accompanied by fever, chills and renal fossa pain, and an active percussion fist that can radiate to the external genitalia. In most cases, it has a self limiting process, but in 20-30% of cases, bacteremia occurs. If the severity of the infection progresses, the patient may develop hypotension, dizziness and mental state changes (5). The hospitalization rate was 7%. Some causes of noninfectious renal inflammation, such as kidney stones, may have similar clinical manifestations (4).

Patients with bacterial prostatitis will develop micturition syndrome, accompanied by general discomfort, fever, waist or suprapubic pain and scrotal pain. In addition, physical examination found enlarged prostate and pain (2).

Diagnostics

For uncomplicated cystitis, it can be presumed to be diagnosed according to medical history and physical examination. Patients with one typical uncomplicated ITU symptom have a 68% probability of having ITU, while if they have two typical symptoms, the probability increases to more than 90%. In this case, treatment is usually based on experience and does not need to be studied (1,7).

Urinalysis is particularly helpful when the diagnosis is uncertain. In patients with UTI confirmed by culture, the positive rates of leukocyte esterase, nitrite and microscopic hematuria were 90%, 76% and 75% (1). It should be noted that the presence of diabetes or proteinuria may lead to false negative leukocytes in urine. In addition, because nitrite is the product of nitrate transformed by Enterobacter, it reaches the maximum when the urine stays in the bladder for a period of time (about 4 hours), so it is recommended to test the first urine (2) of the day. False negative results may occur when the infection is in an early stage (5).

In cases where acute cystitis is highly suspected, systematic urine culture is not recommended because the range of pathogens that may produce acute cystitis is small (7).

The gold standard for the diagnosis of UTI is microbiological analysis of urine samples and bacterial CFU count. Bacterial counts > 105 CFU / ml (1) are usually classified as significant.

In PNA, erythrocyte sedimentation rate and C-reactive protein tests are usually increased. In 20% of cases, blood culture results are positive, but they are not carried out systematically (1).

Imaging examinations are reserved for serious cases with severe symptoms or risk of complications. Ultrasound examination showed suspicious stones and CT examination showed suspicious abscess (2).

Treatment

BA patients are mostly self limiting, without treatment, with high recurrence rate and no change of renal function. Antibiotic treatment is usually unnecessary unless the patient is undergoing high-risk urological surgery, such as prostate biopsy or resection, or pregnant patients, in which case they must be treated due to the increased risk of pyelonephritis, preterm birth and low birth weight (1,4,7,9). For patients with a history of renal transplantation less than 1 month, BA (4) can be considered.

The natural history of uncomplicated cystitis is symptom relief for 4-7 days, and the remission rate of symptomatic treatment with ibuprofen alone is as high as 75%. However, according to some studies, it is recommended to use antibiotics based on experience. The 3-day treatment regimen has a remission rate of 85-90%. For patients without risk factors, the start of treatment may be delayed by 48 hours to reduce the use of antibiotics and start the symptom relief process. However, in clinical practice, standardized 5-

7-day plans (1.9 days) are usually used more frequently.

The main drugs recommended by uncomplicated ITU are furantoin, trimethoprim, trimethoprim sulfamethoxazole (TMP-SMX) and fosfomycin ambuterol, together with acetaminophen or ibuprofen and appropriate infusion (1,5,6,11). The second line is fluoroquinolones and β - lactams (9). In PNA, fluoroquinolones can also be selected in areas with drug resistance < 10% (5).

There are criteria for selecting inpatient treatment rather than outpatient treatment (Table 3). If there is a standard of hospitalization, the treatment is carried out through parenteral route.

For ITU with basic pathology or abnormalities, in addition to treating the acute table, these changes should also be treated or stabilized, such as urinary tract drainage or abscess drainage due to urinary tract obstruction (2).

For patients who reappear symptoms within a short time after treatment or do not respond adequately to these symptoms, urine culture should be carried out at least one week after the end of antibiotic treatment, as it may be a drug-resistant pathogen (7).

Table 3. Indications of shunt for acute pyelonephritis	
	Severe clinical symptoms: fever > 39-39.5 ° C, severe sidewall pain, continuous vomiting
	Suspected sepsis (hypotension, disturbance of consciousness)
	Comorbidity and weakness (such as renal failure, urinary system disease, diabetes, etc.)
	Immunosuppression
	Social conditions that impede treatment and monitoring
	Pregnant
	The condition worsened after 72 hours of treatment
Source. Marin kanada J, Redondo Sanchez J. Female urinary tract infection 2019.	

Complication

Although PNA infections are usually focal, they may develop into severe and diffuse infections, especially in diabetic patients, who may develop acute focal nephritis, papillary necrosis or emphysema pyelonephritis; Or form renal abscess (caused by the same urinary pathogen) or perirenal abscess (hematogenous). In some cases, septic shock is the initial manifestation of table (1,7).

Prevention

Different preventive measures were taken for the occurrence

and recurrence of ITU; However, most have not been tested. Nevertheless, it is recognized that prevention is based on adequate, frequent, one-way and thorough diuresis. Preventive measures are particularly important for patients with recurrent UTI and should last for 6 months; If the ITU is resubmitted, the duration of the selected preventive measures will be extended (3,7,10).

Measures proposed include: dietary hygiene measures, blueberries, vitamin C, use of local vaginal estrogen, probiotics, vaccines, D-mannose and antibiotic prevention, whether continuous or after sexual intercourse (3,7).

In terms of hygienic dietary measures, the efficacy of ITU recurrence has not been observed, but they may contribute to isolated cystitis. These measures include proper hygiene after defecation, proper fluid intake and urination after sexual intercourse (3).

Cochrane's review of blueberries for prevention concluded that the use of blueberries was ineffective (1,11). This is because it cannot fully acidify urine and is not an antibacterial agent (3,7).

Taking vitamin C daily for urine acidification is ineffective because it is excreted quickly. The best option is to give the drug every 2-4 hours, but the patient's compliance is very low (3).

Vaginal estrogen can reduce recurrence, especially in patients with postmenopausal vaginal atrophy, because it can restore vaginal flora and improve pelvic muscle function. Oral estrogen does not reduce the risk of ITU recurrence and increases the risk of cardiovascular and breast pathology (3,7).

The results of probiotic studies vary widely, so they are reserved for patients with normal immune function who fail other preventive measures (3).

Oral, intranasal and vaginal vaccines are available, but they are temporary and need further research to verify their effectiveness (3). Vaccines against certain virulence factors of *E. Coli*, such as pili and toxin, are currently being studied (8).

D-mannose inhibited bacterial adhesion, and the daily preventive effect of 2G / day was similar to that of 50mg furantoin (3,7).

Studies have shown that antibiotics are effective in the prevention of vaginal pathogens, but also in the prevention of vaginal candidiasis. Trimethoprim, furantoin and

cephalexin are the most commonly used drugs, which are used in different administration schemes (3).

The preferred measure is vaginal estrogen and antibiotic prevention (4,6). For each patient, the possible causes of recurrence, risk factors, allergies, intolerance and side effects associated with long-term preventive measures should be studied in order to correctly select preventive measures.

Special population

Children

At least 2% of children under the age of 10 have ITU attacks. It affects 2 per cent of boys and 7 per cent of girls under the age of 7 (1.12 per cent).

This table can show isolated fever or gastrointestinal symptoms. In the absence of fever, the possibility of UTI is very low. The younger the patient is, the less specific the symptoms are (2,13).

In children under 2 years of age, the positive predictive value (VPP) of urine analysis with leukocyte, nitrite and hematuria was 97%, and in the absence of these three cases, the negative predictive value (VPN) was 97% (2).

According to the clinical practice guidelines of the American Academy of Pediatrics (AAP), UTI is defined according to urinary incontinence (10 or more leukocytes / mm³) and positive urine culture (suprapubic puncture or catheterization > 50000 CFU / ml; or collection > 105 CFU / ml) (12).

Recurrence has different definitions in this group. It is considered to have two or more high ITU episodes, one high ITU episode and one low ITU episode, or three or more low ITU episodes within a year (13).

Urogenital ultrasonography should be performed to exclude any child's genitourinary malformations within 24 months after the first febrile urinary tract infection (2,12).

All patients with fever and suspected ITU under 3 months are recommended to be hospitalized (2).

According to the PPA guidelines, antibiotic treatment should last for 7-14 days, and the treatment regimen is similar to that of adults, taking into account the drug resistance pattern in the region (12).

Pregnant woman

It is the most common infection in these patients. They are

at greater risk due to hormonal changes (promoting urinary reflux, urinary stasis and high fever in the bladder triangle), elevated urinary pH and physiological diabetes, and uterine, bladder and ureteral compression (2,14).

In these patients, the risk of colonization or infection is usually increased because of a previous history of urinary tract infection, frequent activity, low socio-economic levels, and preseasonal diabetes. Risk factors for PNA include young women, nulliparous women, smoking during pregnancy, late start of prenatal examination, chronic diabetes or sickle cell disease (14).

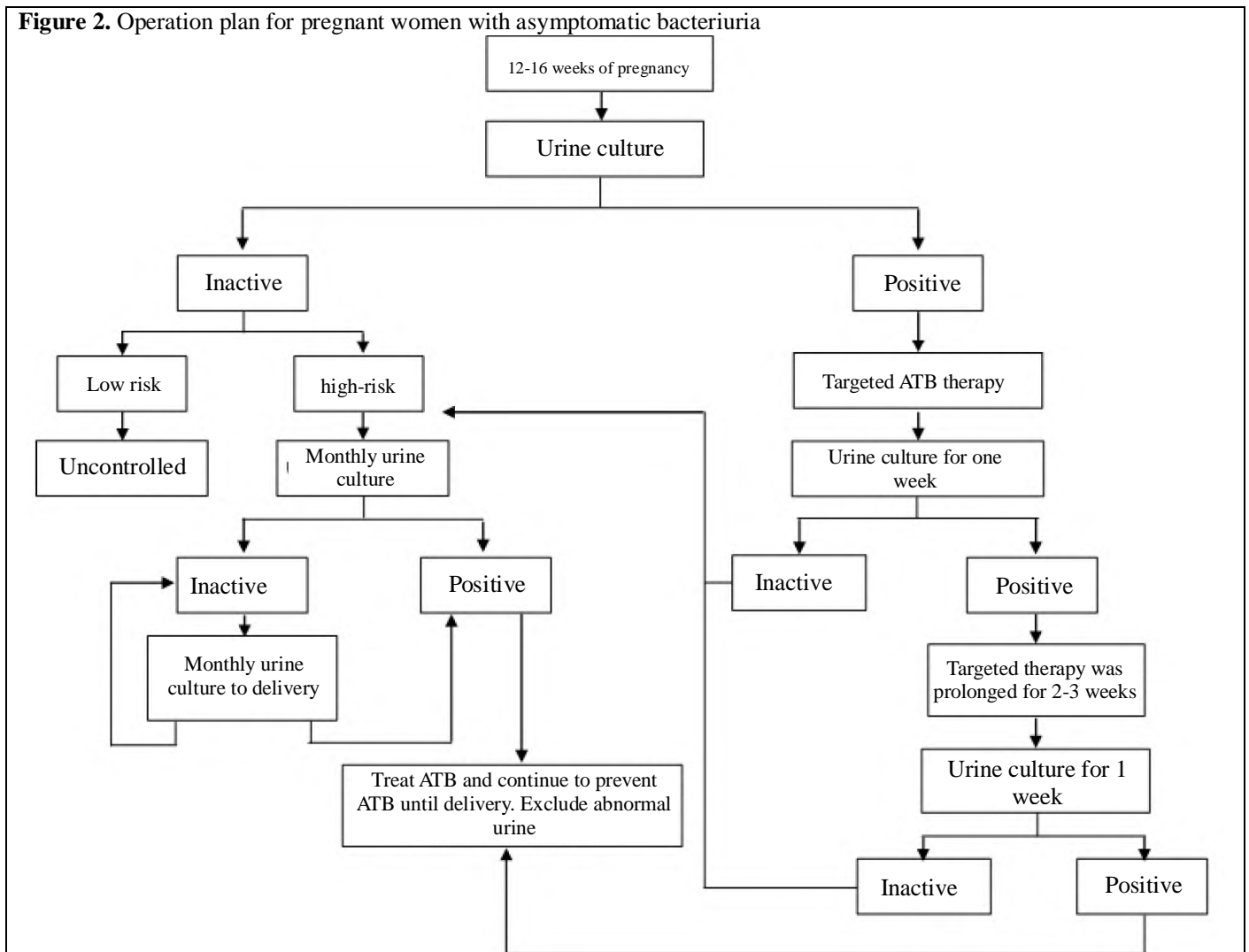
It is recommended that screening be performed at the first prenatal examination, followed by urine and urine culture every month from the 12th to 16th weeks of pregnancy (2,10,14). However, the presence of leukocytes and nitrite had lower VPP, between 46-100%, while the VPP without them was 90-99% and 82-98%, respectively (2).

Up to 30% of pregnant women develop PNA without treatment because of urethral dilatation caused by elevated progesterone levels (5,6). Antibiotic treatment of BA is a routine regimen for 4-7 days (10). (Figure 2). Amoxicillin or amoxicillin clavulanic acid is safe at any stage of pregnancy (14).

Patients with cystitis attack and mild PNA can be treated with cephalexin for 7-10 days because cephalosporins are safe and effective for these patients (1,5).

Nitrofurantoin is also effective, but should be avoided in early pregnancy only when no other drugs are available (5). TMP-SMX is not recommended for the first two months of pregnancy (14). Unlike non complex UTI or BA in non pregnant healthy patients, pregnant patients should be monitored by urine culture after treatment to check the eradication of bacterial urine (11).

Figure 2. Operation plan for pregnant women with asymptomatic bacteriuria



Abbreviation. Antibiotic
Source. About the authors: Wang Jianmin, Wang Jianmin, Wang Jianmin, et al. Empirical treatment of urinary tract infection. 2018

Male

In addition to the longer urethra, a protective factor for men is the presence of bactericidal substances in prostate secretions (15).

Men have a higher incidence of UTI in both age groups, and their morbidity and mortality are higher than women when there is high urinary tract infection (8). The most common recurrent UTI in this population is prostatitis (1).

A symptomatic male patient had a positive leukocyte or nitrite urine analysis with a VPP of 90% and a poor VPN in his absence (2). All male patients with suspected UTI should undergo urine culture before starting antibiotic treatment (1,15).

Patients with prostatitis may have elevated reactants and prostate-specific antigen in the acute phase; However, such studies are not systematically required and the level is usually normalized 4 weeks after treatment (15).

Since they have a higher risk of complications, a treatment regimen of at least 7 days is recommended. Like non complex ITU, the first-line drugs are trimethoprim and furantoin. Patients with prostatitis can consider using the third-generation quinolones or cephalosporins for 14 days (1).

Complications of prostatitis include urinary retention, prostatic abscess and orchitis (2,7).

The recurrence of ITU in these patients mainly leads to prostate hypertrophy (7).

Aged

In this population, diagnosis is often a challenge because symptoms are usually less specific, such as delirium, and typical symptoms may be missing or incorrectly reported. Another reason why older people are more difficult to recognize ITU is that many people exhibit one or more accompanying diseases that can simulate or hide ITU images (5).

Due to the high false positive rate, the use of urine reaction strips for the diagnosis of UTI in these patients is not recommended. If infection is suspected, a culture test is recommended. In terms of treatment, the use of

nitrofurantoin in patients with some degree of renal impairment (mainly creatinine clearance < 40 ml / min) should be avoided (5).

Conclusion

UTI is a common pathology, but its diagnosis and treatment may be challenging. Although most cases are usually benign, there are also cases that may endanger the patient's life.

Each patient should be evaluated separately because its complexity depends on many factors. For example, if there is evidence that bacterial urine in patients without risk factors is usually ignored or not treated, on the contrary, pregnant women should be treated according to the risk they face.

Lack of proper diagnosis and treatment leads to increased resistance to certain antibiotics, which is a health and economic problem.

Although research is currently under way to expand treatment options and case prevention (e.g. Treatment based on bacterial virulence factors and vaccines, respectively), more evidence is still needed and therefore takes time to use. Therefore, it is essential for doctors to have an appropriate understanding of this topic, because diagnosis can be difficult according to the type of patient, and understanding diagnosis and management can avoid overtreatment and reduce antibiotic resistance.

The authors declare that they have no conflict of interest.

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