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Uncomplicated Urinary Tract Infections in the Elderly

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Abstract

A healthy urinary tract is not a sterile environment, but is settled by various microorganisms that change according to the factors of the environment and the patient. Older patients are predisposed to urinary tract infections and asymptomatic bacteriuria. Hence, distinguishing these two conditions remain obscure. They are specific for a number of issues: pathogenesis of infection and causative agents, diagnostic procedures, applied therapy and preventive measures. Correct interpretation of symptoms, sampling of material for analysis and interpretation of results are of great importance. Correct procedures allow the patient to be saved from an inappropriate treatment and complications of antibiotic therapy, but also reduce the resistance of bacterial species.

Key words: urinary tract infections, elderly people, diagnostic, therapy, prevention

Introduction

Urinary tract infections (UTI) are responsible for about 15.5% of hospitalizations due to infectious diseases in people over 65 years of age (immediately after pneumonia), and are the cause of death in about 6% of patients [1]. UTI can be divided, as in younger people, based on several criteria: by location (cystitis, pyelonephritis), tendency to repeat (occasional, recurrent), symptomatology (asymptomatic, symptomatic) and based on the present complication (complicated and uncomplicated). In people with a normal genitourinary tract, these infections are called uncomplicated UTIs, while structural and functional abnormalities of the urinary tract lead to complicated UTIs. The gold standard for the diagnosis of UTI is the finding of pathogens in the urine in the presence of symptoms by the patient. However, the bacteriuria threshold value is not clearly defined or standardized by microbiological laboratories. Many laboratories define a value of 10^5 CFU/ml (Bacterial Colony Forming Units) as the cutoff, however, it is possible to miss some infections and a lower cutoff value (10^3 CFU/ml) is advised.

According to IDSA (Infectious Disease Society of America) criteria, asymptomatic bacteriuria (AB) is defined as if patients have in their urine $\geq 10^5$ CFU/ml or more than one bacterial species in two consecutive urine samples in women, and one sample in men in the absence of clinical signs and symptoms characteristic of UTI [2].

Epidemiology

The incidence of AB increases with age and reaches 20% in women over 80 years of age. In healthy men, AB is not typical before the age of 60, while the incidence is 5-10% in men older than 80 years [3]. Symptomatic infections are not directly correlated with AB, nor are incident renal failure and hypertension [2]. Older women have a higher frequency of UTI than men, but this difference is not so pronounced as in younger ones.

Compared to ambulatory elderly people, people who are placed in institutions for the care have a higher incidence of AB: 25-50% in women and 15–40% in men [2]. Bacteriuria is a dynamic phenomenon: one third of people diagnosed with AB will have a negative urine culture within 3 to 6 months, while a third of patients with an initially negative culture will develop bacteriuria. AB in institutionalized persons is not associated with poor survival, but is often the cause of unnecessary use of antibiotics, which leads to an increased incidence of infections caused by Clostridium difficile and other negative effects of antibiotic therapy.

Out of all infections, symptomatic UTI is the second most frequent infection in elderly with frequency of 0.5 per 1,000 hospital days [4]. In elderly individuals who are able to provide valid information about their symptoms, distinguishing UTI from AB is relatively easy. On the other hand, in those with cognitive impairment, AB is difficult to distinguish from UTI. Out of all bacteremia in institutionalized patients, 45–56% is explained by urinary origin, and this mostly refers to people with a permanent catheter.

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Mortality due to UTI is uncommon [5]. An analysis of 270 people with an average age of 83.7 years who were hospitalized due to UTI (of which 14% from nursing home), showed that hospital mortality was 8.9% and mortality risk factors were inadequate antimicrobial therapy, APACHE II at admission ≥15, dementia and solid neoplasms [6]. An Israeli study that included 191 people aged 75 to 105, who were hospitalized in a geriatric hospital, showed that in-hospital mortality was 33% and the risk factors were hospitallization for more than 20 days, dementia and comorbidity, but not gender and age [7]. Obviously, the mortality of patients with UTI depends on several factors.

Pathogenesis

In non-hospitalized elderly patient risk factors are similar for AB and UTI and include menopause in women, prostatic hypertrophy in men, diabetes mellitus, functional and cognitive impairment, incontinence.

In postmenopausal women, recurrent infections are associated with previous frequent infections at a young age and non-secretion of blood group antigens [8]. Women with diabetes aged 55-75 years have twice the frequency of UTI compared to women without diabetes [9]. Due to the lack of estrogen, colonization with Lactobacilli spp, which maintains the acidic pH of the vagina, decreases in the postmenopausal period. A higher pH allows colonization by uropathogens (E. Coli and Enterococcus spp), which in turns increases the incidence of UTI in postmenopausal women [10]. It is believed that estrogen replacement therapy can restore vaginal flora and pH, although the relationship between infections and estrogen is not fully understood.

Prostate hypertrophy has a special place in the pathogenesis of UTI in older men. It causes obstruction and turbulent flow of urine, that facilitates the penetration of bacteria into the bladder wall. Bacteria can remain in the prostate permanently due to the difficult penetration of antibiotics into the gland. Incontinence favors bacteriuria and can be the cause of infections in older men and women. Residual urine volume is a common finding in women between the ages of 62 and 90 [11]. In men, with a median age of 62 years, the average residual urine volume was 257 ml in case of positive bacteriuria and 133 ml without bacteriuria [12]. However, a prospective study did not confirm the correlation between UTI and residual urine volume in women aged 55-75 years, that indicates a complex relationship between these two clinical conditions [13].

Very old people, above 80 years, deserve a special review. A Swedish study confirmed that risk factors for bacteriuria in very old women are immobility and incontinence, and in men, prostate disease, stroke and dependence on someone else help [14]. Gender and place of residence were not risk factors for the occurrence of UTI [15].

In people who are institutionalized, AB is associated with urinary disorders due to neurological diseases (cerebrovascular diseases, Parkinson's disease, dementia), which are also the reason for institutionalization [16]. The volume of residual urine does not correlate with the occurrence of symptomatic or asymptomatic infection. Men who use an external urinary catheter in the form of a condom have a higher frequency of bacteriuria and symptomatic infections compared to the incontinent men who do not use them [17].

Causes of infection

In the case of symptomatic infections, E. coli but also Enterobacteriaceae, Enterococcus spp and Pseudomonas aeruginosa are most often isolated as causative agents and Coagulase-negative staphylococci can be isolated from asymptomatic infections in men. Candida can be detected in people who have additional risk factors such as diabetes, urological devices, and the use of broad-spectrum antibiotics. In the elderly, isolates are more often multi-resistant to antibiotics compared to younger people, which is related to the previous (mis)use of antibiotics and urological procedures. A Spanish study confirmed that in ambulatory patients with urinary infection, age was significantly associated with the isolation of E coli resistant to fluoroquinolones, and the independent risk factor of this resistance was the use of antibiotics during the previous month [18]. Similarly, data from an American study showed tigecycline-insensitive, carbapenam-resistant Klebsiella pneumoniae and the risk factor was hospitalization in nursing homes [19]. Also, E. coli is the most common cause of infection in nursing homes, but the presence of other enterobacteria is more common than in outpatients. Among people in institutions, polymicrobial infection is more common (10-25%), even without the presence of a permanent catheter. Also, resistance to antimicrobial therapy is more common, which makes treatment more difficult.

Diagnosis

Clinical diagnosis is based on a spectrum of symptoms starting from lower urinary tract irritation to septic shock. In ambulatory patients, frequent urination, dysuria, nocturia, suprapubic pain and sometimes hematuria occur most often. Symptoms of pyelonephritis include pain in the costovertebral region, fever and elevated temperature with or without dysuria. However, it is more difficult to make a clinical diagnosis in people who are Institutionalized due to their difficult communication and the presence of chronic symptoms. Clinical worsening of the underlying condition without localized genitourinary symptoms is most likely not a consequence of UTI in patients with bacteriuria [16]. However, atypical symptoms and changes in the patient's clinical status such as falls, decreased functionality, and change in mental status are often attributed to UTI in the elderly. Changes in the smell, color and turbidity of the urine correlate with bacteriuria, but are more often related to incontinence worsening or dehydration than symptomatic infection and are not sufficient to establish a diagnosis of UTI [19-21]. Recognizing symptoms is very important because they are the main criteria for starting therapy in suspected UTI: acute dysuria or high temperature, acute confusion and fever with worsening of one of the genitourinary symptoms (urgent urination, frequent urination, suprapubic pain, hematuria, pain in the costovertebral region, urinary incontinence) [22]. In this way, the use of antibiotics is significantly reduced compared to the standard approach. Where the diagnosis is unreliable, it is advised to monitor the patient and if local symptoms do not appear in the area of the genitourinary tract, treat the patient as a condition of sepsis of unknown cause rather than as a UTI [23].

Laboratory diagnosis is necessary both for a definitive diagnosis and for the treatment of UTI in the elderly, given the high percentage of microorganism resistance [16]. The exception is a healthy women with repeated acute cystitis in outpatient settings, in which usually short-term antibiotic administration is effective. However, they should also have a urine culture if the desired effect on empirical therapy is missing, if the symptoms are atypical or if there is a rapid return of symptoms after the therapy, which all points to a resistant causative agent.

One of the main obstacles in UTI diagnosis is the proper urine sampling for analysis and prevention of sample contamination. In women who are unable to follow the instructions, a one-time catheterization is performed, and in men, a clean condom-catheter is advisable. The diagnostic criterion implies the finding of more than 10^5 CFU/ml of a single microorganism in the urine sample. When a small number of germs or multiple microorganisms are isolated, the urine culture findings are interpreted according to the clinical symptoms. A smaller number of colonies is found in about 10% of healthy postmenopausal women with acute uncomplicated UTI [13]. Also, in UTI, a smaller number of colonies can be isolated if frequent urination interferes with the incubation time of bacteria in the bladder due to the frequent voiding. Therefore, for men, the diagnosis of UTI is doubtful if pathogens are isolated in the number of 10^3 CFU/ml or more in a properly taken urine sample (except in the case of an indwelling urinary catheter when the criterion is 10^5 CFU/ml) [16]. If pyelonephritis is suspected, the finding of a single microorganism in the number of 10^4 CFU/ml or above is the recommended diagnostic criterion. The finding of microorganisms in the number of 10^2 CFU/ml or more is indicative of infection if the sample is obtained by a single catheterization of the urinary bladder [24].

Pyuria is a non-specific laboratory finding in the elderly [16]. It is often positive even without bacteriuria, and in people with bacteriuria, it does not distinguish symptomatic from AB. On the other hand, the absence of pyuria has a high negative predictive value for the exclusion of UTI [25]. When UTI is suspected in people in nursing homes, first examine the presence of pyuria, and if the finding is negative, urine culture is unnecessary [25]. In women older than 80 years, an elevated value of leukocyte esterase, IL-8 and IL-6 can distinguish between AB and acute cystitis. However, the use of these biomarkers has no major clinical significance [26].

Antimicrobial therapy

In the elderly, treatment of AB is not recommended, considering that the treatment does not reduce the occurrence and frequency of subsequent UTI, nor does it improve the symptoms, and it may lead to the appearance of side effects of the therapy [2]. Therefore, screening of elderly people for AB is not indicated.

Table 1. Antimicrobial treatment of UTI in elderly people with normal kidney function (daily doses of drugs)

	Peroral therapy	Parenteral Therapy
First line	Trimetoprim/Sulfametoksazol 2x160/800mg Nitrofurantoin 2x100 mg Ciprofloksacin 2x250-500 mg Norfloksacin 2x400 mg Levofloksacin 1x250-500 mg	Ampicilin 4x500 mg±gentamicin or tobramicin 5-7 mg/kg /24 h Ceftriakson 1-2 g/24 h Cefotaksim 3x1 g Ciprofloksacin 2x400 mg Levofloksacin 500-750 mg/24 h
Second line	Amoksicilin 3x500 mg Amoksicilin/klavulonska kiselina 2x875 mg or 3x500 mg Cefaleksin 4x500 mg Cefuroksim 2x500 mg Cefiksim 1x400 mg Doksiciklin 2x100 mg Fosfomicin 3 g Trimetoprim 2x100 mg	Amikacin 2x7,5 mg/kg or 1x15 mg/kg Cefazolin 3x1 g Ceftazidim 3x1 g Ceftazidim/avibaktam 3x2,5 g Doripenem 4x500 mg Ertapenem 1x1 g Meropenem 4x500 mg ili 3x1 g Piperacilin/Tazobaktam 3x3,375 g Vancomycin (for Gram+) 2x1 g

The selection of antimicrobial therapy should be guided by the effectiveness of the drug, tolerability by the patient, clinical presentation of the disease, renal function, the need for parenteral therapy and the cost of treatment. If the clinical presentation allows it, it is advisable to wait for the results of the urine culture. Although creatinine clearance decreases with age, it is not advisable to reduce the dose of drugs based only on the patient's age.
The first line of oral therapy for acute cystitis is trimethoprim/sulfametoxazole and nitrofurantoin (Table 1), with the fact that nitrofurantoin is not effective for prostate and kidney infections, but only in lower urinary tract infections.
As for the causative agents of infection, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa are resistant to nitrofurantoin, while beta-lactamase-producing E. coli and Vancomycin-resistant Enterococci are sensitive to it. Although fluoroquinolones (norfloxacin, ciprofloxacin and levofloxacin) are effective for the treatment of UTI, their use is often limited by resistance of bacterial species and side effects [27]. The use of fluoroquinolones should be reserved for empirical therapy of patients with pyelonephritis, when there is resistance to other medications or when patients do not tolerate other therapy. Oral therapy with cephalosporins, fosfomycin, doxycycline, amoxicillin and amoxicillin/clavulonic acid is the second line of therapy according to the patient's antimicrobial sensitivity and tolerance.
Parenteral therapy is indicated if the patient has hemodynamic instability, if they do not tolerate oral therapy and/or have uncertain absorption from the gastrointestinal tract, or if it is an infection that is insensitive to the spectrum of oral therapy. Parenteral therapy is given during the first 48-72 hours when the patient's condition is re-evaluated and therapy is eventually continued with oral therapy. If aminoglycosides are administered for longer than 7 days, it is necessary to monitor the drug level in the blood and kidney function.
It has been shown that in women with an average age of 78.5 years, the treatment results are the same if ciprofloxacin is administered for three and five days [27]. Also, administration of trimethoprim/sulfamethoxazole for three days and nitrofurantoin for five days has favorable results.

Prevention

Long-term antimicrobial prophylaxis can prevent acute uncomplicated infections in elderly ambulatory women. The first line of therapy is nitrofurantoin 50 or 100 mg daily or trimethoprim/sulfamethoxazole half a tablet daily or every other day. The initial duration of prophylaxis is 6 to 12 months. Although there are data that topical estrogen can reduce the incidence of UTI in women, this prevention has had less success than nitrofurantoin prophylaxis [28].
A prospective cohort study did not confirm the positive effect of cranberry-based preparations in women aged 55-75 years [13]. Administration of cranberry juice was less effective than trimethoprim and compared to placebo. Lactobacillus was also significantly less effective than trimethoprim/sulfamethoxazole in the prevention of UTI in postmenopausal women with uncomplicated UTI despite the finding of microorganisms resistant to this drug [29].
Prevention of UTI institutionalized patients has not been described. Systemic administration of estrogen and cranberry preparations has not been shown to be an effective preventive strategy. Prophylactic use of antimicrobial therapy did not protect against subsequent episodes of complicated UTI. In patients with AB who are preparing for genitourinary procedures that are accompanied by bleeding, there is an increased risk of bacteremia and sepsis after the procedure, and prophylactic antimicrobial therapy is advised immediately before the intervention [2].
Adequate fluid intake is very important in the prevention and treatment of UTI in the elderly. The elderly avoids liquids in order to urinate less often, and the consequences of such a habit should be explained to them. Other preventive measures that apply to younger people also apply to the elderly, and above all, including urgent urination immediately after the urge.

Specifics of urinary tract infection related to elderly with indwelling catheter

Data from the literature indicate a high frequency of permanent urinary catheters in institutionalized elderly patients [30]. According to data from US, about 13% of people admitted to nursing homes have a permanent catheter, and an analysis of 67 Swedish nursing homes showed that 16% of men and 3% of women have catheters [31]. These patients always have bacteriuria and symptomatic UTI occurs 2.2 times more often and bacteremia up to 39 times more often than in people without a catheter [32-34]. Also, the autopsy finding of acute pyelonephritis is eight times more common in catheterized persons. However, the increased mortality of people in nursing homes is a consequence of functional impairment and comorbidity rather than from urinary infection.
The most important pathogenetic mechanism in the occurrence of bacteriuria and UTI in people with a catheter is the formation of a biofilm soon after the placement of the catheter [24]. Microorganisms immediately adhere to the surface of the catheter and multiply on the outside and inside, creating polysaccharides. Urine components (Tamm-Horsfall protein, calcium and magnesium ions) that are incorporated into the biofilm also contribute to the formation of biofilm.

Micro-colonies are protected in a biofilm, where antibiotics and local defense factors (leukocytes and immunoglobulins) hardly penetrate. Urine alkalization by urease-producing bacteria promotes the deposition of calcium and magnesium salts, which results in the formation of a crystalline biofilm. Also, crystalline biofilm can form encrustation and obstruction of the catheter.

People with catheters have the most common E. coli, Enterococcus faecalis and Proteus mirabilis. Also, urease-producing bacteria-Proteus mirabilis, Morganella morganii, Klebsiella pneumonia and Providencia stuartii [35] are frequently found. Proteus mirabilis is particularly active in the formation of biofilm and crystalline biofilm and in about 80% of cases is responsible for all catheter obstructions [36].

The clinical presentation of symptomatic infection in people with a catheter is most often characterized by a high temperature but without local genitourinary symptoms [24]. Some patients may experience pain and tension in the costovertebral region, catheter obstructtion or hematuria. The consensus regarding starting empiric antibiotic therapy implies the presence of one of the following symptoms: high temperature, new tightness of the costovertebral angle, new delirium and absence of an alternative source of infection [37,38].

In case of infection, it is advised to take a urine with a new catheter. Thus, bacteria is exclusively from urine and not from biofilm, and a number higher than 10 CFU/ml is considered relevant for the definition of bacteriuria. Also, it is advised to start the therapy only after replacing the catheter if it was placed more than two weeks ago.

Treatment of AB in patients with catheter is not recommended because it does not reduce the frequency of UTI and leads to reinfections with resistant germs [2]. The optimal choice of therapy does not differ compared to patients without a catheter (Table 1). It is preferable that the treatment lasts seven days, if there is a quick response to the therapy. Longer treatment leads to more frequent side effects of therapy. The benefit of removing the catheter before starting therapy is reflected in reduced relapses with germs remaining in the biofilm.

Prevention of infections associated with indwelling catheters finds its place in existing recommendations [39,40]. The most important issue is to reduce the use of catheters if possible or to leave them for as short a period as possible. Also, some authors advise external, condom-catheters, which carry a lower risk of infections [41]. Special attention should be paid to non-traumatic placement of the catheter to avoid bleeding that favors infection. It is important to recognize the obstruction in time and replace the catheter. Special catheters impregnated with antimicrobial agents or drainage bags with antiseptics do not seem to have met expectations in terms of reducing the frequency of infections [42]. During catheter replacement, transit bacteremia may occur, which does not have serious consequences, and antimicrobial prophylaxis is not advised during catheter replacement.

Conclusion

In elderly, there is a high frequency of asymptomatic bacteriuria and urinary infections. Asymptomatic bacteriuria does not require treatment except before urological surgical procedures. The diagnosis of symptommatic infections is overestimated and is a source of antibiotic abuse and reinfection with resistant microorganisms. In institutionalized patients, distinguishing between AB and UTI is not easy considering the unreliability and non-specificity of the symptoms. Patients with indwelling catheters represent a special population with different diagnostic, therapeutic and preventive strategies.

Conflict of interest statement. None declared.

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