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Rewiev

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 pa-

tient'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	Ampicilin 4x500 mg±gentamicin
	Nitrofurantoin 2x100 mg	or tobramicin 5-7 mg/kg /24 h
	Ciprofloksacin 2x250-500 mg	Ceftriakson 1-2 g/24 h
	Norfloksacin 2x400 mg	Cefotaksim 3x1 g
	Levofloksacin 1x250-500 mg	Ciprofloksacin 2x400 mg
		Levofloksacin 500-750 mg/24 h
Second line	Amoksicilin 3x500 mg	Amikacin 2x7,5 mg/kg or 1x15 mg/kg
	Amoksicilin/klavulonska kiselina 2x875 mg or 3x500 mg	Cefazolin 3x1 g
	Cefaleksin 4x500 mg	Ceftazidim 3x1 g
	Cefuroksim 2x500 mg	Ceftazidim/avibaktam 3x2,5 g
	Cefiksim 1x400 mg	Doripenem 4x500 mg
	Doksiciklin 2x100 mg	Ertapenem 1x1 g
	Fosfomicin 3 g	Meropenem 4x500 mg ili 3x1 g
	Trimetoprim 2x100 mg	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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Original article

Renal Function Improvement after Transurethral Prostate Vaporesection with Thulium YAG Laser and Resection with High-Frequency Electrical Current

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Abstract

Introduction. Benign prostatic hyperplasia/Benign prostatic obstruction (BPH/BPO) and chronic kidney disease (CKD) are two important public health problems in elderly men, with a huge medical and social impact on rapidly aging population globally. Clinical studies have proven obstruction of the lower urinary tract, secondary to BPO as a cause of a decreased renal function and CKD development. Conversely, the reverse process of the lower urinary tract obstruction relieve should be improving the renal function. The aim of this study is to evaluate the possibility of simultaneous improvement in renal function with transurethral prostate surgery for treatment of BPO.

Methods. A randomized, study (1:1) initiated in July 2022 at the University clinic for urology in Skopje, Republic of N Macedonia, was conducted on 40 patients with BPO to compare the efficacy and safety of the two endourological transurethral surgical methods for BPO treatment: in our country the recently introduced Tm:YAG laser transurethral vaporesection of the prostate (ThuVARP) and the traditional and well-established method of transurethral resection of the prostate (TURP) by using high-frequency electric current (TURP). For evaluation two types of indicators were used, BPO related and renal function (RF) related indicators. The BPO related indicators (International Prostate Symptom Score-IPSS, maximum flow rate-Qmax, prostate volume-V, and post-void residual urine volume-PVR) were assessed preoperatively and reassessed at 6 months postoperatively. RF related indicators (serum potassium, serum creatinine, and estimated glomerular filtration rate (eGFR) evaluated with the 2021 Creatinine equation (CKD-EPI) were also assessed preoperatively and reassessed after 7-10 days, postoperatively. By comparing the pre and postoperative values within each surgical group, conclusions were drawn about the possible effect of BPO surgery on renal function improvement. Other risk factors for CKD like diabetes, hypertension, smoking, obesity, dyslipidemia and metabolic syndrome were not considered in this study.

Results. Significant improvements were observed postoperatively in all BPO related indicators in both surgical groups. In the ThuVARP group, Qmax increased from 6.06±2.1 to 16.59±6.2ml/s (p=0.00) and IPSS, prostate V and PVR decreased from 25±1.9 to 3.56±5 (p=0.00); 61.4±33.4 to 26.2±11.9 ml (p=0.00); and 142.8±79.1 to 7.97±11 ml (p=0.00), respectively. In the TURP group, Qmax increased from 7.96±3.5 to 18.14±6.6 ml/s (p=0.00); and IPSS, prostate V and PVR decreased from 22.89±4.4 to 6.68±5 (p=0.00); 61.5±16.2 to 21.13±14.4 ml (p=0.00); and 128.9±86.1 to 23.45±47.2 ml (p=0.00), respectively.

RF related indicators also presented significant improvements postoperatively. In the ThuVARP group, serum potassium and serum creatinine decreased from 4.44±0.5 to 4.17±0.4mmol/L (p=0.019) and 86.77±23.2 to 78.84±19.3 (p=0.029), respectively and eGFR increased from 83.26±18.3 to 88.63±15mL/min/1,73m² (p=0.049). In the TURP group, serum potassium and serum creatinine decreased from 4.32±0.3 to 4.13±0.5 mmol/L (p=0.041); and 78.59±12.3 to 73.44±12.0 ηmol/L (p=0.004), respectively and eGFR, increased from 89.05±11.8 to 93.65±10.70 mL/m in/1,73m² (p=0.0028).

Conclusion. Our findings suggest that prostate surgery

with consecutive relief of the lower urinary tract obstruction, regardless of the chosen method (ThuVARP or TURP) may improve the renal function and be potentially benefitial in CKD patients.

Key words: BPO, Renal function, CKD, serum creatinine, eGFR, Thulium laser, ThuVARP, TURP

Introduction

Benign prostatic hyperplasia (BPH) is the most common urologic condition in male population over the age of 50 [1]. It is a histologic term for a condition which is age dependent and has prevalence in autopsy studies increasing from around 20% in men aged 41–50 years to 50% in men aged 51-60 years and >90% in men over 80 years old. At the age of 55, about 25% of patients experience obstructive symptoms, typically with complain of a decreased strength and caliber of urinary flow, which rate increases to 50% by the age of 75 [2]. Its high prevalence presents this condition as very important medical and social issue requiring vast resources for management, especially after decades of progressive ageing in population worldwide. Its significance is clearly presented in the United Nations World Population Prospects from 2019 where by 2050, one in six people in the world will be over age 65, up from one in eleven in 2019. Often, but not necessarily, BPH leads to a certain level of urinary obstruction referred to as benign prostatic obstruction (BPO), and presents with symptoms termed as lower urinary tract symptoms (LUTS) of variable intensity. Therefore, the term BPH has been replaced with the more appropriate term BPO. LUTS in men mainly come from BPO, even though other entities like urethral stricture, prostate cancer and urinary incontinence may present with LUTS [3]. If untreated or when therapy fails, BPO could lead to serious complications such as acute or chronic urinary retention, urinary tract infection (UTI), calculosis, urine stasis, and acute or progression to chronic kidney disease (CKD). Consequently, it is very important, to promptly and properly diagnose, evaluate, follow up and if needed treat BPO [3].

CKD is another very important public health problem. It is also more prevalent in the elderly population, with approximately 50% in patients older than 70 years. It develops over months to years, with early stages often being asymptomatic [4]. BPO as the main reason for distal urinary tract obstruction, depending on its severity and length of exposure, may cause urinary stasis initially in the bladder and later in the proximal urinary tract. Urinary stasis leads to a decline in the glomerular filtration rate (GFR), and an inevitable destructive effect on nephrons in both kidneys with a consecutive decrease in renal function and development of certain level of post-renal CKD [5]. On average, 13.6% of the patients with BPO presenting to urological clinics for treatment have any stage of CKD [6]. There is a continuous controversy in the urology guidelines on whether to implement a routine screening on serum creatinine levels among men presenting with LUTS secondary to BPO for identifying patients with CKD. As of 2003, the guidelines of the American Urological Association (AUA) no longer recommend men with LUTS regularly to be screened for serum creatinine. As opposed to that, the European Association of Urology (EAU) guidelines recommend renal function evaluation if an abnormal renal function is suspected, based on the patient's medical history and clinical examination, suggesting a possible correlation between renal function and LUTS.

With BPO as one of possible reasons for renal function impairment, it is of a great importance to evaluate whether and to what extent the reverse process of treating BPO and relieving the obstruction in the distal urinary tract with transurethral prostate surgery would improve the renal function as potential treatment of CKD.

Material and methods

A randomized (1:1) study was conducted in July 2022 at the University clinic for urology in Skopje, on 40 patients with BPO and prostate volume between 30-80ml, to compare the efficacy and safety of the two transurethral surgical methods in treating BPO. Namely, one is in our country a recently introduced method of Tm:YAG laser transurethral vaporesection of the prostate (ThuVARP), and the other is the traditional and well-established method of transurethral resection of the prostate by using high-frequency electric current (TURP). The primary endpoint was detection of renal function improvement after surgical treatment for BPO with either of the two transurethral surgical methods.

The ThuVARP method, as an energy source uses the latest and most powerful 200W Thulium YAG, 2013 nm, continuous wave laser (ROCAMED Hemera). An 800 micrometer end-firing optical core laser fiber is introduced through a 26F continuous-flow laser resectoscope (Richard Wolf, Knittlingen, Germany) with normal saline as irrigation. With precise hand movements the excessive prostate tissue at the level of the prostatic urethra is vaporesected under direct vision. The term vaporesection describes the simultaneous process of vaporization and resection of the prostate tissue and is closely related to the exclusively high vaporization capacity of the thulium laser. The resection process is controlled by the surgeon's hand movement of the laser fiber through the prostatic tissue. The TURP method uses the similar transurethral approach, but a metal loop mounted on a resectoscope

is used to resect excessive prostate tissue with an alternating high frequency electric current as an energy source (ERBE VI0 3 electrosurgical unit).

Study inclusion criteria were: bothersome lower urinary tract symptoms or chronic urinary retention, secondary to BPO. Exclusion criteria were neurogenic lower urinary tract symptoms, prostate cancer, previous prostate or urethral surgery and prostate specific antigen (PSA) level outside the normal age-related range without prostate cancer excluded by biopsy. Patients with indwelling catheter due to an acute urinary retention were excluded from the study since considered relieved from the obstruction.

Patients were evaluated with two types of indicators: BPO related and renal function (RF) related. BPO related indicators included: 1. International Prostate Symptom Score (IPSS), provided with an IPSS questionnaire; 2. Maximum flow rate (Qmax), provided with uroflowmetry; 3. Prostate volume, (V); and 4. Post void residual urine volume (PVR), provided with transabdominal ultrasonography. The RF related indicators included: 1. serum levels of potassium; 2. serum levels of creatinine, provided by biochemistry, and 3. estimated glomerular filtration rate (eGFR) calculated with a Chronic Kidney Disease Epidemiology Collaboration equation (2021 CKD-EPI Creatinine equation) from patients' sex, age, and serum creatinine values.

The RF and BPO related indicators were assessed preoperatively and reassessed at postoperative 7-10th day and at 6 months, respectively. The eGFR was provided pre and 7-10 days postoperatively.

The preoperative and the postoperative values of the BPO and RF related indicators were compared within each surgical group. Statistical analyses were performed using Microsoft Excel t-test with paired analysis at one-tailed distribution. Indicators were expressed as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

Results

Study patients were randomized (1:1) in two groups, consisted of 20 participants, labeled as ThuVARP and TURP group, based on the surgical method used. The preoperative and postoperative values of BPO and RF related indicators were compared within each group and presented in Table 1 and Table 2.

Table-1. Patients surgically treated with ThuVARP technique. BPO related indicators at baseline and 6-months after surgery. RF related indicators at baseline and 7-10 days after surgery

ThuVARP		**Mean ± SD (range)**		
No. of pts.		**20**		
Age		**69.37±5.1 (58-80)**		
		Baseline values	***6 months***	***P- value***
BPO related indicators	IPSS	25±1.9 (21-29)	3.56±5 (0-22)	0.000
	Qmax (ml/s)	6.06±2.1 (3.5-10.6)	16.59±6.2 (5.1-34.8)	0.000
	Prostate V (ml)	61.4±33.4 (4-150)	26.2±11.9 (5.6-61)	0.000
	PVR (ml)	142.8±79.1 (10-330)	7.97±11 (0-35)	0.000
		Baseline values	***7-10 days***	***P- value***
Renal function related indicators	Potassium (mmol/L)	4.44±0.5 (3.34-5.05)	4.17±0.4 (3.06-4.7)	0.019
	Creatinine (μmol/L)	86.77±23.2 (56-141.3)	78.84±19.3 (58-124)	0.029
	eGFR (mL/min/1,73m²)	83.26±18.3 (46-106)	88.63±15 (53-102)	0.049

Data are mean ± SD (range). IPSS, international prostatic symptom scores; Qmax, maximum urinary flow rate; PVR, post-voiding residual volume; prostate V, volume with transabdominal ultrasonography; eGFR, estimated glomerular filtration rate - 2021 CKD-EPI Creatinine equation

Table-2. Patients surgically treated with the TUR P technique. BPO related indicators at baseline and 6-months after surgery. RF related indicators at baseline and 7-10 days after the surgery

TURP		**Mean ± SD (range)**		
No. of pts.		**20**		
Age		**66.55±5.7 (59-79)**		
		Baseline values	***6 months***	***P- value***
BPO related indicators	IPSS	22.89±4.4 (10-29)	6.68±5 (1-17)	0.000
	Qmax (ml/s)	7.96±3.5 (3-13.5)	18.14±6.6 (8.6-27.8)	0.000
	Prostate V (ml)	61.5±16.2 (21-80)	21.13±14.4 (7.1-67)	0.000
	PVR (ml)	128.9±86.1 (28-300)	23.45±47.2 (0-200)	0.000
		Baseline values	***7-10 days***	***P- value***
Renal function related indicators	Potassium (mmol/L)	4.32±0.3 (3.88-5)	4.13±0.5 (3.3-5.39)	0.041
	Creatinine (μmol/L)	78.59±12.3 (65-108)	73.44±12.0 (50.95-104)	0.0004
	eGFR (mL/min/1,73m²)	89.05±11.8 (68-104)	93.65±10.70 (69-106)	0.0028

Data are mean ± SD (range). IPSS, international prostatic symptom scores; Qmax, maximum urinary flow rate; PVR, post-voiding residual volume; prostate V, volume with transabdominal ultrasonography; eGFR, estimated glomerular filtration rate - 2021 CKD-EPI Creatinine equation

In the ThuVARP group (Table-1.), the mean values of all BPO related indicators improved significantly at 6 months postoperatively. A significant increase in Qmax and decrease in IPSS, prostate V, and PVR were estimated postoperatively. There was also a significant postoperative improvement in all RF indicators. The serum levels of potassium and creatinine significantly decreased, and eGFR increased at 10 days postoperatively, when compared with baseline values.
In the TURP group (Table-2.), a significant improvement in all BPO related indicators could also be noted at 6 months postoperatively. RF related indicators also improved significantly at 7-10 days after surgery, with a significant decrease in the serum levels of potassium and creatinine, and an increase in eGFR, when compared with the baseline values.

Discussion

In CKD, the loss of renal function is gradual and often progressive, resulting from the damage of the kidneys (intra-renal), the vessels supplying them (pre-renal) or any obstructive pathology within the distal urinary tract (post-renal).
Urologist's focus are the post-renal reasons for kidney impairment with BPO as the most common cause of distal urinary tract obstruction and CKD development by impacting both kidneys chronically [1]. Thus the other risk factors for CKD as diabetes, hypertension, smoking, obesity, dyslipidemia and metabolic syndrome were not considered in this study. As early as in 1957, Olbrich and associates observed that men with urinary obstruction due to prostatic enlargement had 33% reduction in GFR compared to men of similar age with no obstruction [7]. Additionally, the obstructed patients who presented with infected urine had even greater decrease in the GFR to 50 % of normal values for men of similar age [7-9]. For the literature search on the effect of BPO on the renal function, we used data from the three high volume clinical studies. In all three the decreased Qmax (<15 ml/s) was found as significantly positive predictive factor for renal impairment and CKD development. [5,6,10] In the first one, a large South Korean study from 2009, on a group of 2741 men with LUTS of varying severity the potential association of various BPO related indicators and those of CKD (RF related indicators) was analyzed and besides the decreased Qmax (<15 ml/s), a history of hypertension and DM were found as risk factors for RF worsening and development of CKD. Other indicators, e.g. age, BMI including other BPO related indictors as PSA level (>1.4 ng/ml), IPSS (>7), quality-of-life score, prostate volume (>30 ml), and PVR, were not significantly associated neither with elevated serum creatinine nor with decreased eGFR [6]. In the same line are also the results from a latter South Korean study (2013), on a large group of 1400 middle-aged men, aged 40-59, with moderate to severe LUTS in which BPO and RF related indicators were also evaluated for a possible association and found the decrease in Qmax as only indicator that significantly correlated with eGFR reduction and RF impairment. [10] In contrast to the previous two, the third study from Mayo Clinic College of Medicine from 2005 by Rule and all, on a sample of 2115 white men (in a subgroup of 476) found that besides decreased Qmax (<15 ml/s), an increased IPSS (>7), PVR(>100ml) and history of hypertension were significant predictors of RF worsening and CKD occurrence. [5] Similar results were presented in another study were men over age of 50 with a bladder outlet obstruction and decreased Qmax, had significantly lower eGFR compared to men with normal Qmax. (65±25 vs 81±17 mL/min/1.73 m2 p<0,005) [11].
Multiple mechanisms have been proposed to explain the association between BPO and a decrease in RF. This includes: 1. Chronic urinary retention, 2.Acute urinary retention and 3.Urinary tract infection (UTI) [6]. The chronic urinary retention is thought to be the dominant mechanism of renal function impairment. Knowing this mechanism is very important in order to estimate the possibility of RF reversal by the surgical treatment of BPO [12-14].
The results in our study proved both surgical techniques safe and effective in achieving relieve from BPO. The transurethral prostate surgery, irrespective of the chosen method, as expected, has sufficiently relieved the urinary tract obstruction (BPO), presented with a significant improvement in all BPO related indicators but our primary aim was to determine the effect of surgery on the RF. The outcome of all RF related indicators, measured 7-10 days postoperatively, showed simultaneous significant improvement, supporting the possibility of RF improvement and recovery after surgical treatment of BPO as the underlying cause. It is important to emphasize that our patients were selected solely in relation to BPO, with urinary retention and the need of a surgical treatment. The RF was not considered, thus patients in both groups were estimated having initial to moderate CKD, predominantly in Stadium I and II (only 2 patients in Stadium III), according to 2021 CKD-EPI equation. Even at this level of CKD, a significant renal function improvement was achieved after surgery.
We found our results in line with those in other clinical studies. Speakman *et al.*, presented chronic urinary retention to be the major mechanism for CKD development in patients with LUTSs/BPH with a confirmed association of BPO with decreased GFR. Upper urinary tract dilatation or increased serum creatinine was diagnosed in half of all patients with chronic urinary retention secondary to BPH/BPO. The surgical treatment of BPO with TURP improved renal function post-surgery [15]. Another study from 2019

by Zamzami on 88 patients with obstructive uropathy due to BPH, showed decrease in the mean serum creatinine levels to normal limits 14 days after TURP [2,4mg/dL (212,2μmol/L) to 1,1mg/dL (97,2μmol/L) p<0,001], with improvement of the kidney function [16]. In accordance with this finding was the study from 2018 by Sarier *et al*., on a group of 98 patients with renal transplant who underwent TURP due to BPH, in which 1 month after surgery a significantly decreased mean serum creatinine level was observed [1.99±0.83 mg/dL (175,9 μmol/L) to 1.67±0.9 mg/dL (147,6 μmol/L) p<0,001] [17].

Conclusion

The simultaneous and significant postoperative improvement in all BPO and RF related indicators in both surgical groups, suggest that transurethral prostate surgery with a consecutive relief of the lower urinary tract obstruction, regardless of the chosen method (Thu VARP or TURP) may improve the renal function being potentially benefitial in CKD patients.

Conflict of interest statement. None declared.

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Case report

Post-Transplant Paradoxes: A Complex Case of Kidney Transplantation and Insights on Managing Chronic Kidney Disease

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Abstract

Introduction. Diabetes, hypertension, or genetic predispositions often cause chronic kidney disease (CKD), which is characterized by a persistent decline in renal function. As CKD develops through five stages, i.e. from a moderate impairment to an end-stage renal failure, a prompt treatment becomes critical. Kidney transplantation is frequently the recommended treatment for individuals with end-stage renal disease, since it provides a better long-term survival and quality of life compared to dialysis. Despite breakthroughs in transplantation and immunology, complications continue to pose substantial hurdles.

Case report. This case report details the clinical progression of a 55-year-old male patient who underwent a living donor kidney transplant. Serious complications with the kidney graft, such as renal vein rupture and hematoma, necessitated rapid revision and a graft implantation during surgery. The patient had hemodynamic instability, requiring hemodialysis and inotropic support. Despite many challenges, we explanted the graft and the routine monitoring revealed no cytotoxic HLA antibodies. Unexpectedly, the patient restored his kidney function, which ultimately led to his release into a stable condition.

The discussion underscores the critical importance of a holistic and multidisciplinary approach in kidney transplantation. Preoperative optimization and careful intraoperative management are key factors for risks reduction, while regional anesthesia plays a significant role in enhancing patient comfort and outcomes. The paper further highlights the complex, multifactorial nature of post-transplant complications.

Conclusion. This paper reinforces the need for a comprehensive, multidisciplinary approach to kidney transplantation, with particular attention to the unique importance of living donor grafts, ultimately leading to enhanced patient survival and quality of life.

Key words: chronic kidney disease, complications, end-stage renal disease, kidney transplantation

Introduction

The kidneys become damaged and unable to filter blood properly when you have chronic kidney disease (CKD). Diabetes, high blood pressure, heart disease, and a family history of renal failure are the leading causes of kidney disease [1].

CKD, commonly known as chronic kidney failure, causes a progressive decrease in kidney function. Advanced CKD can cause harmful levels of fluid, electrolytes, and waste products to accumulate in your body. In the early stages of CKD, we may have only minimal signs or symptoms [2].

This condition is commonly associated with aging. It can affect anybody; however, it is more frequent in those who are black or of South Asian descent. CKD can worsen with time, and the kidneys may finally quit functioning completely, but this is unusual. Many people with CKD can live their long life [3].

CKD progresses in five phases. The phases are dependent on kidneys' ability to filter waste products from the blood. Blood and urine testing is essential to establish the current stage of CKD. The phases progress from a very mild (stage 1) to renal failure (stage 5). Healthcare practitioners use the glomerular filtration rate (GFR) to estimate the stage of the kidney function [4].

CKD affects approximately 34% of people aged 65 and over, compared to 12% of those aged 45 to 64 years, and 6% of people aged 18 to 44 years. Furthermore, females are somewhat more likely than males to develop CKD (14% vs. 12%) [5].

Routinely the GFR is measured to assess kidney function, and urine albumin measured to detect protein leakage, while serum creatinine levels were used to determine waste products filtering efficiency. Recognizing the

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cause, symptoms, and diagnostic procedures is critical for treating and minimizing the effects of CKD [6].
Kidney transplantation is considered as best treatment option for those with end-stage renal disease (ESRD). Placing patients with ESRD on a waiting list and subsequently receiving kidney transplantation has a higher long-term survival rate than keeping them on dialysis. Moreover, kidney transplant recipients often have a higher quality of life and a 10-year longevity advantage over dialysis patients. There is a definite survival advantage for kidney transplant patients over those who continue on dialysis [7].
A kidney transplant is frequently regarded as the best treatment for renal failure in people who are found suitable for the operation. The benefits of a successful kidney transplant are significant: most patients have improved lifespan and a higher quality of life since they no longer need dialysis. Many people report increased energy, greater ease of work and travel, less food limitations, and better sexual health and fertility. However, the process is not without risks. A kidney transplant is a complex medical surgery with inherent risks, including bleeding. Infections are also prevalent after transplant, necessitating balanced administration of powerful immunosuppressive drugs to avoid organ rejection, with the use of potent antibiotics for their treatment. Patients may need further procedures to treat problems, and while rare, there is a danger that the transplanted kidney may not work well or that renal disease will reappear in the new organ [8].
This paper presents a comprehensive overview of CKD and transplantation throughout our case presentation. However, it also identifies some significant research gaps that require additional investigation. Finally, our report could benefit from a greater emphasis on patient-centered treatment, including the psychological effects and quality of life for transplant patients, as well as the management of a delayed graft function, which currently lacks established guidelines. Addressing these gaps might help us better understand and treat CKD and its consequences.

Case Presentation

Hospitalization for left kidney transplantation was necessary for a 55-year-old male patient with CKD who had reached ESRD. Because kidney transplantation is a specific surgical procedure for both the donor and recipient, careful anesthesia preparation is required to ensure patient safety and good graft function. Preoperative optimization is the process of identifying and managing risks in order to reduce perioperative problems.
The living donor was his mother 78 years old in a good clinical condition and without any known medical history. Independent HLA antibody testing revealed that there were no cytotoxic HLA antibodies against the donor antigens. The recipient on the other hand had DM type I and hemoglobin levels between 9-10 g/dl, and erythropoiesis-stimulating medications were used to address the anemia. The primary goals of intraoperative management were hemodynamic monitorring, intravascular volume maintenance, and judicious anesthetic method selection. Furthermore, we kept the mean arterial pressure between 80 and 110 mmHg. Additionally, we carefully monitored perioperative glucose control due to the administration of high-dose (500 mg) metilprednisolon as an imunosupressant and Manitol 25% for osmotic diuresis. We administered short-acting opioid remifentanil in dose of 0.025 mcg/kg/min and propofol 0.5mg/kg/min intravenously to manage anesthesia together with a single shot erector spine block ultrasound guided. The avoidance of postoperative delirium was helping patients to fully recover.
Collaboration between surgical teams, anesthesiologists, and healthcare providers is critical for effective kidney transplantation results. Our case was very specific, since during the surgery, substantial complications occurred, including bleeding and spontaneous renal vein rupture outside the place of anastomosis. The patient underwent immediate revision of the graft, resecting the renal vein and placing a prosthetic graft. After the surgery, the patient was fully awaken and prepared for transfer outside the operating room. We noticed abrupt bleeding, hemorrhagic shock, and complete deteriorization of the patient when we placed the drain on the bed.
The patient had hypotension (blood pressure of 60/40 mmHg), bradycardia (heart rate of 42 bpm), and steady oxygen saturation (SaO2 of 98%). Upon his unresponsiveness, we initiated immediate treatment with reintubation, inotropic support, and blood products transfusion (with depleted erythrocytes and fresh frozen plasma). Reopening the surgical wound revealed a new vein rupture unrelated to the previous one. New graft was placed but unfortunately, it appeared without sufficient perfusion of the new kidney. Patient stayed in operation theater for 8 hours, but unfortunately the treatment was not successful; the graft was not saved, and explantation was performed.
Following surgery, he had hemodialysis via femoral venous catheter, effectively eliminating 3 liters of fluid. During his stay at the hospital corticosteroid therapy was continued to avoid rebound effect due to high doses used pre- and intraoperatively. Furthermore, we noticed he improved his diuresis. We followed up with complete laboratory tests every day after the surgery, shown in Table 1.

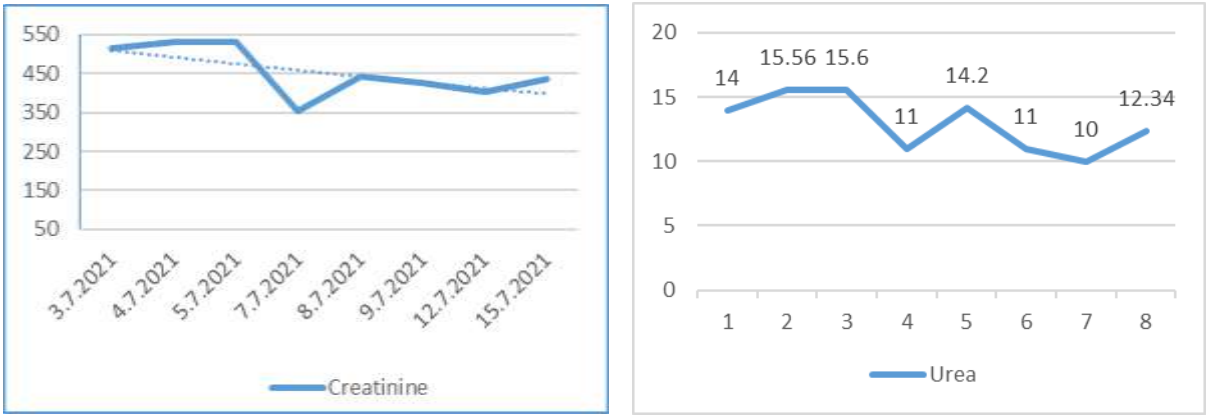

Fig. 1. Creatinine and Urea Levels

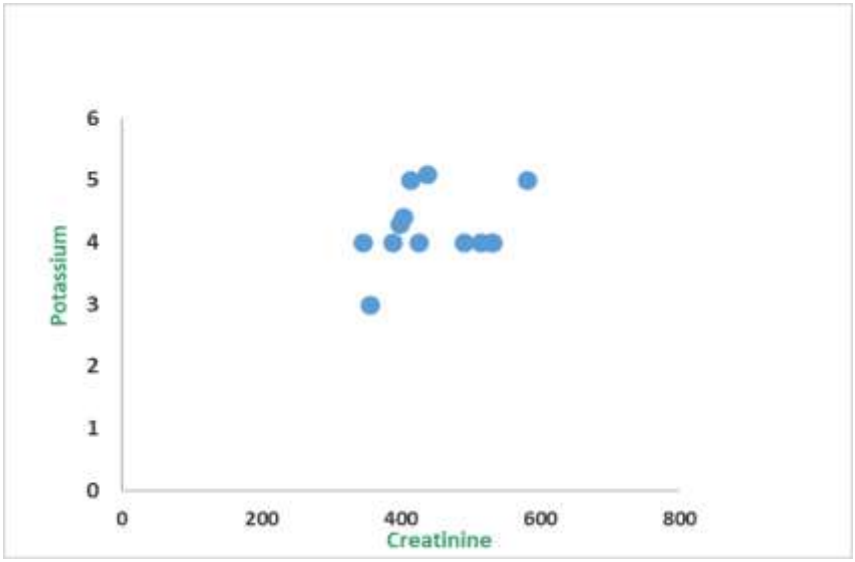

Fig. 2. Relationship Between Creatinine and Potassium Levels in Patient Observations

Our patient's test results showed insufficient but still present renal function. Creatinine levels (514, 531, 530, 355, 444, 425, 403, 436) are substantially higher than normal (Figure 1), which ranges between 45-109 µmol/L depending on age, gender, and muscle mass. The elevation shows that the kidneys are not filtering adequately, which might indicate renal failure or injury. In contrast, the urea levels (14, 15.56, 15.6, 11, 14.2, 11, 10, 12.34) are often within or slightly over the normal range of 4-9 mmol/L. While higher urea (Figure 1) might indicate dehydration, excessive protein consumption, or compromised kidney function, these values are less alarming than creatinine. As additional assessments, urin analyses were done, which were required to further assess kidney function and discover any underlying problems (Table 1).

Table 1. Lab reports during hospitalizations

	03.7	**04.7**	**05.7**	**06.7**	**07.7**	**08.7**	**09.7**	**10.7**	**12.7**	**13.7**	**15.7**
RBC	3.01	3.20	3.16	3.04	2.59	3.29	3.08	3.45	3.21	3.17	3.28
HBG	94	101	98	96	81	98	97	105	98	98	93
MCV	86.4	87.6	88.9	86.2	87.1	88	87.4	90	90	87.1	89.6
Albumins	29.12	33.3	29	30	23.6	28	29	31.5	28	29	35
Total Proteins	44.99	51.5	50	50	38.1	51	49	54	53	56	60.4
CRP	59.63	71.33	81.0	63.1	36.1	44.6	27	21	14.3	15.7	75.9
LDH	190.48	219.48	196	237	210	236	231	226	204	210	223
AP	53.14	67.84	62	72	78	104	111	120	97	98	112
Glucose	6.4	7.14	6.69	7.16	5.48	6.78	5.28	x	4.31	4.72	6.3

*(RBC-red blood cells normal ranges 4,20-5,50 10*12\L, HGB-hemoglobin 120-180 g\L, MCV- mean corpuscular volume 82.9-98.0 fL, Albumines 35-50 g\L, Total Proteines – 63-83 g\L, CRP - 0-6 mg\L, LDH-lactate dehydrogenase borderline 248 U\L, AP-alkaline phosphatases 36-126 U\L, Glucose 3.5-6.1 mmol\l)

Based on the creatinine values, we created a scatter plot to see if the changes in creatinine levels affected potassium levels. The data revealed variable creatinine levels, beginning with 580 on June 28, 2021, and varying between 388 and 437 in the following weeks. Potassium levels were very consistent, primarily around 4, with slight variations up to 5 and a drop to 3 on July 7. The scatter plot revealed no clear correlation (Figure 2) between creatinine and potassium levels, indicating that fluctuations in creatinine did not significantly impact potassium levels. The patient's general health gradually improved, resulting in his hospital discharge in stable condition and receiving appropriate follow-up treatment.

Discussion

To the best of our knowledge, this case represents the first reported instance of its kind. General anesthesia (GA) with total intravenous drugs metabolized through the liver, rather than the kidneys, was employed in our case, along with an erector spinae block under ultrasound guidance using bupivacaine. This approach was chosen due to the surgeons' use of heparin, making spinal anesthesia unsuitable for our patient. While local anesthetics are widely used across medical specialties-including catheter insertions, fistula and graft operations, and kidney transplants-their application in patients with renal impairment is less documented. However, studies demonstrate minimal toxicity and excellent outcomes when local anesthetics like bupivacaine are used during kidney transplantation [9].

Due to a lack of resources and personnel in our resource-constrained centers, prolonged mechanical ventilation after surgery is not an option for patients. The ICU is the only place where this is possible, and it poses a significant risk to immunocompromised patients. Our surgical team prefers intraoperative heparin use over neuroaxial anesthesia for our patients. However, despite the long-standing preference for an epidural catheter, several patients have experienced prolonged bleeding at the catheter site, leading us to avoid its use. That's why the new regional plexus blocks under ultrasound are an excellent option for patients undergoing transplantation and provide long lasting analgesia for up to 12 hours [10-12].

Kidney transplant recipients are at significant risk of requiring dialysis and experiencing increased mortality. While advances in immunosuppression have improved certain outcomes, the slow progress of new treatments emphasizes the necessity of addressing modifiable non-allogeneic risk factors for better long-term outcomes. The quality of the allograft and the immune response of the recipient are controlled by HLA matching and donor-specific antibodies, respectively. In general, these factors determine how long the graft may last. Donor and recipient ages, glomerular disease recurrence, dialysis duration, and pre-existing cardiovascular problems are all influencing outcomes. Despite their importance for patient health, traditional risk factors like hypertension, proteinuria, anemia, dyslipidemia, diabetes, and bone mineral abnormalities often receive less attention than immunity [13]. Regretfully, in our instance, the cause was most likely a poor-quality graft and blood vessels rather than an acute rejection. Even more importantly, it was a pathological defect outside of the anastomosis site.

In a year-long study conducted on 40 kidney transplant patients indicators of post-transplant problems were evaluated. The researchers discovered that recipients had a substantially lower mean age than their donors, who were mostly females. Majority of patients had been on dialysis for an average of 18.1 months before transplantation. Common problems were hypertension, proteinuria, and chronic rejection, with a high mortality rate of six patients dying, mostly from surgical complications. A history of diabetes mellitus, higher pre-transplant blood urea nitrogen (BUN) and createnine levels, recipient age, and higher low-density lipoprotein (LDL) values have all significantly predicted complications. Surprisingly, increased pre-transplant parathyroid hormone (PTH) levels were associated with a minor protective benefit against problems. These data highlight the crucial role of addressing modifiable risk factors in the post-transplant period in improving patient outcomes and reducing complications. The study emphasized the need for more research to develop comprehensive strategies for enhancing care in kidney transplant recipients [14]. Our patient was on dialysis before surgery for only 8 months.

Acute tubular necrosis (ATN) can develop following kidney transplantation, resulting in delayed graft function, in which the transplanted kidney does not generate urine right away. This condition can result from a variety of circumstances, including donor-related concerns such as a low blood pressure during CPR or prolonged kidney storage following removal. As there is no particular therapy for ATN, individuals may require dialysis for a few weeks up to three months whereas most often their kidney function recovers. If creatinine levels remain high with no meaningful decrease, a biopsy may be required to rule out rejection. In rare circumstances, primary non-function occurs when the transplanted kidney never starts working, necessitating its removal and urgent dialysis following surgery. We assume that the patient recovered his kidney function due to an immunological underlying condition and high doses of metilprednisolon administered the day before and on the day of surgery.

Despite this, patients may still be considered for re-transplantation. Furthermore, infections are a persistent concern to transplant recipients due to immunosuppressive medicines, necessitating preventive antibiotics during the first several months. Dehydration is

another issue; whereas dialysis patients previously limited fluid consumption, working kidneys require appropriate water to keep creatinine levels from increasing, especially during a warmer weather. Urine leaks can also occur if the ureter, which drains urine from the kidney to the bladder, becomes disconnected owing to high bladder fullness before healing. This disease usually necessitates surgery to reattach the ureter. After transplantation, monitoring fluid intake and urine frequency is critical for avoiding bladder function issues [15].

Researchers have linked surgical site problems to lower transplant survival and recipient mortality. Furthermore, surgical site infections cause 2.5% of post-transplant rehospitalizations, and patients with these infections are more likely to require a second surgery than those without [16].

Researchers at Qilu Hospital in China looked into the wound-related issues in 118 kidney transplant recipients. The study discovered many significant risk variables, including age over 50, comorbidities, and living donor transplants. The most prevalent complications were delayed wound healing (21.2%) and infections (16.9%), with medications successfully treating infections. There were no significant relationships between problems, gender, BMI, or previous transplants. The findings highlight the need for personalized post-operative treatment in reducing complications and improving patient outcomes [17]. Although guidelines recommend broad spectrum antimicrobial therapy single dose peri-operative still in our country therapy continues during whole hospitalization [18].

According to the current literature and European guidelines, Hand-Assisted Laparoscopic Live Donor Nephrectomy (HALDN) is the preferred method for donor kidney explantation. At our hospital, we began performing HALDN in 2018 and published our initial findings, comparing HALDN with standard open nephrectomy. Our findings confirm that HALDN is a safe and effective minimally invasive procedure, yielding optimal outcomes for both donors and recipients, while emphasizing donor safety and the altruistic nature of live kidney donation. In the example we are presenting, the patient's mother, the donor, underwent HALDN. The graft had warm ischemia time of 1 minute and 25 seconds and a cold ischemia time of 120 minutes. She recovered completely and was released from the hospital five days after the procedure [19].

Conclusion

This case study sheds light on the difficulties and consequences that come with kidney transplantation for people with CKD. Even with significant advancements in immunosuppressive and transplantation techniques, issues and complications sometimes arise. Improving patient outcomes depends on treating these issues effectively, which includes meticulous preoperative optimization and specialized postoperative care. The graft function and general quality of life of transplant patients can be enhanced by highlighting the importance of interdisciplinary approaches. The long-term success of kidney transplantation depends on ongoing assessment and control of modifiable risk factors, particularly as the prevalence of CKD rises.

Conflict of interest statement. None declared.

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Case report

A Neurosurgical Patient with Acute Renal Failure

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Abstract

Rhabdomyolysis is a common cause of acute renal failure. It represents a peripheral muscle damage with myoglobinuria and electrolyte disturbances with or without volume changes and renal injury. We present a 47-years-old male patient with traumatic subdural hematoma who developed acute renal failure after two grand mal seizures. After alkalization, hydration and diuretic treatment renal failure subsided and the patient underwent successful evacuation of hematoma. We discuss the pathogenic mechanisms of development of acute renal injury in rhabdomyolysis.

Keywords: acute renal failure, rhabdomyolysis, epileptic seizure, traumatic brain injury, traumatic subdural hematoma

Introduction

Rhabdomyolysis (RM) is striate muscle-cell damage with a release of intracellular constituents to the circulation, myoglobinuria, electrolyte abnormalities, with or without subsequent kidney injury [1]. The main intracellular constituents that are released in circulation after myocyte damage are myoglobin, creatin phosphokinase (creatin kinase) and lactate dehydrogenase, along with potassium and phosphates [1]. Myoglobin is a muscular cell oxygen-binding protein with molecular weight of 18.8 kDa that binds plasma proteins and small amounts reach urine. In massive striate muscle damage, plasma proteins cannot bind the excessive amount of myoglobin and the latter reaches the urine. In acidic environment, urinary myoglobin can precipitate and cause tubular obstruction and toxicity leading to an acute kidney injury (AKI) [1]. The injured muscle fibers can sequestrate large amount of fluid in the form of muscle cell oedema that leads to a decreased effective circulating volume and renal hypoperfusion that can further exacerbate the kidney injury [2]. Moreover, the efflux of fluid to the injured muscular fibers may lead to a severe hypokalaemia with an additional impact on renal tubules. The striate muscle damage can also cause severe hyperkalaemia, hypercalcemia and hyperphosphatemia with hyperuricemia that can have additional harmful effects on the renal tissue [3,4]. Another characteristic laboratory sign of rhabdomyolysis is the development of metabolic acidosis with increased anionic gap (due to release of organic acids from the disintegrated muscle cells) [3,4]. RM is one of the leading causes of AKI, associated with up to 10% of the cases every year [3]. The true prevalence of RM worldwide is unknown and is probably significantly underestimated [3], because in the majority of cases it undergoes spontaneous resolution. Approximately 26 000 cases of RM are reported in the US every year [3]. Moreover, the incidence of AKI in RM patients remains unclear. The estimated incidence of this complication is 4-33% of all RM patients [1,3].

RM can be classified in two main subtypes: traumatic (muscle trauma) and non-traumatic (associated with seizures or strenuous physical activity, muscle compression, alcohol and/or drug abuse, dehydration, and inborn metabolic defects). No matter the cause, up to one third of RM patients can develop AKI, presenting with the following clinical signs and symptoms: pain, oedema and muscle weakness of the injured sites, myoglobinuria (pinkish to reddish discoloration of the urine), and decrease in the urine volume to anuria [1-4].

We present a patient with acute renal failure due to rhabdomyolysis, associated with seizures at the background of traumatic acute subdural haemorrhage.

Case presentation

A forty-seven years old male patient was admitted to the Clinic of Neurosurgery for evacuation of traumatic fronto-parietal subdural hematoma that developed after blunt head trauma. At the admission the patient was brady-psychic but adequate contact and showed no neurological deficit. Vital signs were within the normal limits. The physical examination showed no ab-

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normalities, except for hematoma on the left side of his forehead. He reported hitting his head after he fell down in the afternoon of the day before the admission. No loss of consciousness after the trauma was reported. Approximately 6 hours after the trauma he had a grand mal seizure and was taken to another hospital where he had a second seizure and underwent computed tomography of the head that detected small subdural hematoma in the left fronto-parietal area. The patient was referred to the Clinic of Neurosurgery in our hospital for evacuation of the hematoma and on the way to Neurosurgery he developed a third grand mal seizure. The patient reported pinkish discoloration of the urine the morning at the admission.

The initial laboratory investigations revealed increased white blood cell count of 14.5 G/l, serum creatinine of 155 mcmol/l, urea of 16 mmol/l, uric acid 540 mcmol/l, potassium 6.8 mmol/l, sodium 139 mmol/l, chlorides 96 mmol/l, calcium 2.92 mmol/l, phosphates 2.6 mmol/l, AST 240 U/l, ALT 63 U/l, creatin kinase 10 008 U/l. Urinalysis revealed positive protein and blood in the urine with no red blood cells in the sediment. Alkaline base balance revealed mild metabolic acidosis (pH of 7.28, base excess of (-10), standard bicarbonate of 16 mmol/l) with increased anion gap of 33.8 mmol/l. Serological markers for viral hepatitis (HAV, HBV and HCV) were negative.

Abdominal ultrasound revealed increased kidney size with widened and slightly hyperechogenic parenchyma with marked hypoechogenic pyramids (Figure 1).

Fig. 1. Abdominal ultrasound – enlarged kidneys with thickened slightly hyperechogenic parenchyma and visible pyramids

The patient was diagnosed with RM-associated AKI, caused by symptomatic epileptic seizures due to acute subdural hematoma. He was initiated on intravenous infusions with saline and alkalization with intravenous sodium bicarbonate 60 ml, intravenous furosemide 40 mg and underwent an emergency evacuation of the hematoma. After the operation, at the background of saline infusions, intravenous alkalization and diuretic administration, renal function improved and creatinine, urea and uric acid levels returned to normal limits within 4 days. The hyperkalaemia, hypercalcemia, hyperphosphatemia and the acid-base balance also normalized. Cytolytic enzymes and urine investigations normalized within 7 days, while the renal parenchymal echogenicity returned back to normal within 14 days.

The postoperative CT revealed no residual collection, the patient was put on prophylactic anti-epileptic treatment with carbamazepine. One year after the surgery the patient remains seizure-free, with normal renal function and urinary dip-stick tests and normal cytolytic enzymes. The control CTs revealed no residual collections.

Discussion

Rhabdomyolysis is among the most common causes of AKI, especially in neurological and neurosurgical patients. The key mechanisms of renal injury in these cases include [1-4] an oxidative stress due to iron overload of the tubular cells in myoglobinuria, inflammation and apoptosis of tubular cells due to the oxidative injury, acute tubular obstruction in myoglobinuria and increased uricosuria, renal hypoperfusion due to decreased circulating volume (developing due to oedema of the necrotic muscle fibres), vasoconstriction due rennin-angiotensin-aldosterone system activetion in hypovolemic state, and dyselectrolitemia-hypokalaemia due to efflux of potassium in the necrotic muscle fibres, or hyperkalemia, hyperphosphatemia and hypercalcemia due to liberation of ion from the necrotic muscle cells.

If treated properly, renal damage in RM can be reversible. The recommended therapeutic strategies in RM include [1-3,5] general supportive measures, renal replacement therapy, anti-inflammatory medications (corticosteroids), iron chelators, antioxidants and N-acetyl cysteine, recombinant human erythropoietin and mesenchymal stem cells in particular cases of mice models, but no studies have been performed in humans.
The mortality in RM is between 2% and 46% [1,3], depending on the aetiology, timely treatment and comorbidity. The renal recovery depends on the timely treatment and the severity of RM, determining the extent of subsequent development of tubule-interstitial and glomerular fibrosis. At present, yet, no studies on the long-term outcome of RM in humans have been performed [1,3].
In our patient, we observed mild AKI with predominantly extrarenal uraemia (more marked increase in urea and uric acid levels than of creatinine levels), hyperkalemia, hypercalciemia and hyperphosphatemia, metabolic acidosis with increased anion gap (calculated according to the following formula: $[Na^+ + K^+] - [Cl^- + HCO3^-]$, normal levels 4-12 mmol/l [6]) due to the liberation of intracellular constituents in the circulation, increased cytolytic enzymes (AST>ALT, creatin kinase), false positive blood on urine dipstick test (due to the presence of myoglobin in the urine). The abdominal ultrasound scan revealed the typical renal image of rhabdomyolysis-associated renal injury-enlarged kidneys with thickened parenchymal zone and increased parenchymal echogenicity-due to precipitation of myoglobin within the tubular lumens [7]. The RM was caused by three grand mal seizures associated with head trauma with subdural hematoma. The timely diagnosis and the proper and timely treatment of both, neurosurgical and nephrological emergencies lead to fast and complete recovery. As the prevalence of post-traumatic seizures can be as high as 24% in acute and 11% in chronic [8] subdural hematomas, RM should be considered as an important cause of AKI in such patients and prophylactic anti-convulsant treatment should be initiated in all cases of acute subdural hematomas [9].
Multiple cases of seizure-associated traumatic RM with ARF have been described in the literature. Mishra et al. reported a patient with acute renal failure (ARF) after epileptic seizure [10]. L. Wang *et al*., present a case of rhabdomyolysis and hyperuricemia leading to ARF in a patient with status epilepticus [11]. In both cases the patients required acute temporary dialysis due to conservatively not manageable oligoanuria. Kara *et al*., also report a young patient with AKI following seizure-induced RM that required temporary dialysis [12]. The extracorporeal blood purification and conservative treatment (rehydration, alkalization and forced diuresis) lead to the restoration of kidney function. The first and the second case underline the role of hyperuricemia for the development of renal injury in RM and the third patients revealed the importance of an early diagnosis and timely treatment for the prognosis of ARF. Singh *et al*., also report a young patient with RM-induced ARF [13] on the day after developing two short lasting tonic-clonic seizures. Aggressive rehydration lead to a fast restoration of renal function and decrease in both cytolytic enzymes and creatinine levels without the need of extracorporeal blood purifycation. Our patient also developed ARF with hyperuricemia due to seizure-associated RM. The early diagnosis and initiation of the conservative treatment, including forced alkaline diuresis (saline infusions, alkalization and stimulation of diuresis with furosemide), lead to a rapid restoration of renal functional capacity without the need for acute dialysis.

Conclusion

In conclusion, in patients with ARF at the backgound of seizures and trauma, the timely and adequate diagnosis and treatment (including rehydration and forced alkaline diuresis) are of crucial importance for preservation of the renal function and patient's life and require the team efforts of neurologists, neurosurgeons, anaesthesiologists and nephrologist.

Conflict of interest statement. None declared.

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Case Report

Uncommon Pathogen, Common Complication: *Rhizobium radiobacter*-Induced Peritonitis in Peritoneal Dialysis

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Abstract

Rhizobium radiobacter is an uncommon opportunistic pathogen commonly found in soil. To date, only a few cases have reported R. radiobacter as a cause of PD-related peritonitis. Our patient developed R. radiobacter peritonitis after gardening, presenting with cloudy dialysate without pain or febrility. The infection was successfully treated with cefepime. However, it relapsed one month later, ultimately leading to catheter removal.
Physicians must remain vigilant for this rare pathogen despite the much more common causes of peritonitis. Education of patients about the connection between Rhizobium radiobacter, soil exposure, and non-sterile conditions is crucial for prevention of relapses and avoiding the need for catheter removal.

Key words: acute peritonitis, Rhizobium radiobacter, catheter removal, soil

Introduction

Peritonitis is a serious non-mechanical complication of peritoneal dialysis (PD) [1]. Gram-positive organisms have been recognized as the leading cause of PD-related peritonitis [2]. To date, only few cases reported *Rhizobium radiobacter* as a cause of PD-related peritonitis. It is an aerobic Gram-negative rod present in the soil, known mainly for causing opportunistic infections [3].
Herein we present a case of *Rhisobium radiobacter*-induced acute peritonitis, leading to the removal of the peritoneal dialysis catheter.

Case Report

A 58-year-old female patient with end-stage renal disease (ESRD) was under hemodialysis treatment for three years. The primary underlying cause of ESRD was autosomal dominant polycystic kidney disease. She underwent two kidney transplantations, both times followed by allograft failure due to an acute rejection. After the second allograft failure, the patient resumed hemodialysis. However, due to the lack of vascular access caused by thrombotic and stenotic changes, a forced PD was introduced. A year after initiating PD, she developed her first episode of acute peritonitis caused by *Staphylococcus epidermidis* and the treatment was carried out according to the antibiogram.
Only a month later, the patient was re-hospitalized for suspected acute peritonitis. She came to the emergency room after noticing cloudiness of the dialysis fluid. Additionally, a decrease in ultrafiltration and an increase in leukocyte count in the dialysis fluid ($5.2*10^9$/L) were noted. The patient remained afebrile throughout, denied any pain, and vitals were stable. Microbiological analysis had shown the presence of *Rhizobium radiobacter*. An intraperitoneal cefepime therapy was initiated and continued for a total of 6 weeks. Follow-up microbiological findings remained sterile for 6 days after finishing cefepime therapy. Unfortunately, two months after the second relapse- a third one occurred. The clinical presentation was identical- afebrile, no pain, stable vitals as well as cloudy dialysis fluid. Once again, *Rhizobium radiobacter* was isolated. The catheter removal was indicated along with intravenous cefepime (1g/ day) for 14 days in total.

Discussion

Rhizobium radiobacter is an uncommon opportunistic pathogen [4,5]. A 6- year study found only 13 patients with Rhizobium radiobacter infections, 10 of which had an underlying haematological malignancy or solid-organ cancer [4]. Besides PD- related peritonitis, other reported infections include pulmonary infections, liver dysfunction, spondylodiscitis, cerebral abscesses, and *R. radiobacter* endocarditis.
R. radiobacter is commonly found in soil. Zhang HP et al. reported that 5 out of 6 patients had been closely exposed to soil prior to the infection [5]. Similarly, our

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patient reported some gardening activities. There were 15 cases of *Radiobacter* induced peritonitis reported since the first case in 1990 [6]. Out of the 6 publicly available case reports, 4 patients had abdominal pain, fever, and cloudy dialysis fluid, while 2 patients were afebrile [3,6-10]. In contrast, our patient exhibited no symptoms other than cloudy dialysis fluid. In 4 cases patients were treated with intraperitoneal cephalosporins (cefazolin, ceftazidime, cefepime). Other reported regimens included intraperitoneal vancomycin with oral ciprofloxacin [9], or combinations of meropenem, ciprofloxacin, and amoxicillin/clavulanic acid [7]. Catheters were removed in 2 cases, one of these patients had a relapse [8] while the other had Moraxella C. superinfection and no signs of improvement despite the antibiotic treatments [7].

Conclusion

It is essential for physicians to remain vigilant for this rare pathogen, despite the much more common causes of peritonitis. Educating patients about the connection between *Rhizobium radiobacter*, soil exposure, and non-sterile conditions is crucial for prevention of relapses, thus avoiding the need for catheter removal.

Conflict of interest statement. None declared.

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Letter to the Editor

Acinetobacter Pittii Acute Peritonitis Succesfully Treated with Prolonged Ciprofloxacin Usage

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Dear Editor,

Acute peritonitis is a common complication in patients treated with peritoneal dialysis (PD). The outcome of PD-related peritonitis strongly depends on the infecting micro-organism. Acinetobacter species are seldom cause of PD-related peritonitis but are associated with severe infection and increased possibility of a dropout or even lethal outcome. Acinetobacter pittii belongs to the Acinetobacter calcoaceticus-baumannii family of aerobic, gram-negative coccobacilli [1]. Only one PD peritonitis caused by A. pittii has been reported in the literature, resulting in recurrent PD peritonitis with the same organism, presumably from biofilm formation [2]. We present a case of a 58-year-old male treated with automated PD since May 2023 who presented with severe colicky abdominal pain and cloudy dialysis fluid. PD effluent demonstrated a peritoneal fluid total white blood cell count of 14850×10^6/L; culture revealed A. pitti. Initial C-reactive protein was 246.2 ml/L. He was treated with gentamycin and ciprofloxacin intraperitoneally for ten days, followed by peroral ciprofloxacin for an additional two weeks, without signs of recurrent peritoneal infection.

This case demonstrates the importance of rapid diagnostics and aggressive and prolonged treatment of Acinetobacter pitti PD-associated acute peritonitis in order to avoid dropout and lethal outcomes.

Conflict of interest statement. None declared.

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