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Peritoneal dialysis – associated peritonitis during treatment with continuous ambulatory peritoneal dialysis

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Abstract. *Infections associated with peritoneal dialysis (infection of the catheter, tunnel infection and peritonitis) are the most common complications of this method. Despite significant progress in the methodological approaches to the prevention, diagnosis and treatment of PD associated infections, peritonitis remains the main risk factor for mortality in PD patients (up to 6%) and plays a significant role in more than 1/6 of the deaths associated with non-infectious complications such as cardiovascular and / or cerebrovascular disease. Besides, PD-associated infections are the most common cause of loss of peritoneal function and the patients' transition to hemodialysis treatment. About 5% of PD patients are converted to hemodialysis treatment in the first year after postponed peritonitis.*

Keywords: *кenal substitution therapy, permanent outpatient peritoneal dialysis, complication, recurrent peritonitis.*

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Перитоніти, асоційовані з постійним амбулаторним перитонеальним діалізом

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Резюме. *Інфекції, асоційовані з перитонеальним діалізом (ПД): інфекція місця виходу катетера, тунельна інфекція та перитоніт, є найбільш поширеними ускладненнями ПД. Незважаючи на значні досягнення у методичних підходах до профілактики, діагностики та лікування ПД-асоційованих інфекцій, перитоніт залишається основним фактором ризику смертності ПД-пацієнтів (до 6%) та відіграє значну роль у більш ніж 1/6 частині смертельних випадків, пов'язаних з неінфекційними ускладненнями, як то серцево-судинні та/або цереброваскулярні захворювання. Крім того, ПД-асоційовані інфекції є найпоширенішою причиною втрати перитонеальної функції та переведення хворих на лікування гемодіалізом. Близько 5% ПД-пацієнтів переводяться на лікування гемодіалізом у перший рік після перенесеного перитоніту.*

Ключові слова: *ниркова замісна терапія, постійний амбулаторний перитонеальний діаліз, ускладнення ПД, рецидивуючий перитоніт.*

Chronic kidney disease (CKD) is one of the socio-economic problem all over the world. This issue becomes especially important in view of the stable increase (up to 7% annually) in the patients` number with CKD treated with renal replacement therapy (RRT), including continuous ambulatory peritoneal dialysis (CAPD). The increase in patients` rate with CKD exceeds five times the rate of the world population growth [1]. On the date of January 1, 2017, according to the National Register of patients with CKD, the method of CAPD is used in the treatment of 886 patients, which is 9.6% in the structure of RRT in Ukraine [1]. According to Sakaci T., the survival rate among the patients treated with this method in almost half of the patients is limited to only 5 years and, accordingly, requires a change in the modality of RRT [2]. These facts are indicating the urgency of the problem and necessity of improving the survival of the peritoneal dialysis (PD) method – which means maintaining its adequacy and safety for a longer time after initiation.

PD is a method of substitution renal therapy used in the treatment of patients with CKD stage V along with hemodialysis and kidney transplantation. The basis of the method lies in the ability of the peritoneum as a semipermeable membrane to separate the products of nitrogen exchange and endotoxin [3]. The large surface of the peritoneum, a thin mesothelial covering, powerful blood, and lymph flow create an opportunity for significant transperitoneal movement of substances with different molecular masses, including water, electrolytes, and protein catabolism products [4]. The method has several advantages, such as a low mortality rate in the first years of treatment, more convenience for the patient (the possibility of having a PD patient staying at home), flexibility, fewer visits to hospital, longer preservation of residual renal function, etc [5].

However, as with any other method, CAPD has a number of disadvantages and the main one is high risks of infectious complications, which can cause loss of the peritoneum transport function. Therefore, there is technique's usage terms limitation [6].

Nowadays, the world's practice is experiencing and defining complications associated with the insertion of the catheter for peritoneal dialysis (Tenkhoff catheter), early and late, infectious and non-infectious. Early complications include those that occurred within 30 days after surgical intervention, and late - after 30 days, respectively [7].

The biggest part of the general complication list has an infectious nature, namely PD-associated dialysis peritonitis (DP). This complication constitutes about 7-12% of all deaths in PD patients [8, 9]. In this case, there are a lot of diverse infection ways (Table 1).

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Table 1

Infection pathway Promoting factor Microorganism Frequency

Infection pathway	Lead factor	Microorganism	Frequency
Intracatheteral	Disruption of aseptic connection and separation of highways, dialysate containers and peritoneal catheter	*Staphylococcus epidermidis, Acinetobacter*	30-40%
Pericatheteral	Disorders of the insertion catheter technique, infection of the catheter exit site or catheter tunnel	*Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas, Fungis*	20-30%
Transmural	Violation of the abdominal cavity's permeability and the microorganisms transposition through the intestinal wall	*Intestinal microflora, anaerobes*	25-30%
Hematogenic	Transfer of bacteria with blood from an extra-oculomotoric hearth	*Streptococci saprophyticus, Mycobacterium tuberculosis*	5-10%
Transvaginal	Transvaginal	*Fungus, Lactic acid bacteria*	2-5%

Usually DPs have infective etiology. According to various data, there are bacteria as pathogens (~ 80% of cases) [**10**]. Frequently 70-75% episodes of peritonitis occur due to contamination of the microflora in the abdominal cavity during the procedure of PD (the so-called intraluminal pathway of infection). In this case, the most common etiologic agent is a gram-positive autoflora. The inflammatory process in the abdominal cavity, often triggered by the pathogens of Staphylococcus and is generally well cured by antibiotic therapy, and the fatal outcome in such cases does not happen in more than 1% of patients [**11**].

Prognostically unfavorable DPs caused by gram-negative microorganisms lead to death in 4-10% [**12, 13**]. Fungal infections are not as common as bacterial infections (only 3-6% of cases), however they may be after the usage of antibacterial drugs [**14**]. Infection in such cases usually occurs via transmural (in inflammatory diseases of the abdominal cavity), hematogenous (in extra-abdominal infectious processes) or ascending (in gynecological diseases) paths. Sometimes DPs are caused by subcutaneous catheter tunnel's infections (peri-laminar contusion of the abdominal cavity), and in these situations bacteriological studies reveal both gram-positive and gram-negative or fungal flora [**15**], that was shown by the experience of Hsin-Hui Wang, Chung-Hao Huang and co-authors. Using the adequate antibacterial regimens and compliance with developed protocols, most episodes of the GP rapidly regress, allowing successful dialysis. However, repeated episodes of DP, associated with the lack of rehabilitation of infectious cells (usually nasal) or permanent re-infection of the abdominal cavity due to violations of the technique of the procedure, can cause the termination of CAPD [**16**]. In circumstance of persistent infection, it's necessary to eliminate peritonitis, remove the catheter and switch to the HD, with the continuation of antibacterial therapy until the signs of the infectious and inflammatory process completely disappear [**17**].

Also the relative imperfection of the connective systems and catheters for the PD that undoubtedly creates a known risk of contamination of the abdominal cavity should be taken into consideration. At the same time, in the pathogenesis of recurrent peritonitis, a special role is given to the so-called "biofilm", that is, the composite formation from the cells of microorganisms and fibrin, which over time covers the walls of the peritoneal catheter [**18**].

Nowadays, disputes over the schemes of antibiotic therapy continue. Despite the recommendations of the ISPD, there are few data that can justify for the antibacterial drugs dosing for ADF patients. There are various recommendations regarding care of the site of catheter for infections prevention, the use of various local products containing antibacterial drugs and antiseptics, the use of bandages [**19, 20**]. For example, in the latest ISPD guidelines the daily local usage of antiseptics is indicated for the treatment of the catheter exit site [**21**].

But still, there is a controversial issue regarding the timing of the peritoneal catheter's removal and the possibility of its re-insertion which is caused by lack of a single view to the conservative treatment terms of peritonitis and absolute indications for the restocking of the Tenkhoff catheter [**22**].

The risk of death is significantly increased in case of dialysis peritonitis due to inflammatory bowel disease. For example, with established active diverticulitis with violation of the intestinal wall integrity, mortality reaches 50% [23]. Untimely initiation of treatment, as well as inadequate antibacterial therapy or delayed surgical treatment in cases where it is necessary, may also be the cause of death in some cases [24].

DP is one of the serious complications both in the therapeutic and in the surgical plans [25]. It can occur in any period of treatment when an infection enters with dialyzing solutions directly into the abdominal cavity. Continuous improvement of the peritoneal dialysis technique has significantly reduced the frequency of peritonitis (from 1 episode in 5-10 months to 1 episode in 18-24 months), but DP remains the most important infectious iatrogenic comorbidity, and has an adverse effect on the properties of the peritoneum and causes the large extent determined not only the possibility of using the method, but also the patients survival [26]. The frequency of peritonitis, according to the latest recommendations of the members of the Advisory Committee (International Society of Peritoneal Dialysis), for peritoneal dialysis infections, should not exceed 0.67 per year [27].

According to ISPD data, DPs are differentiated as follows (Table 2).

Table 2

Types of DP in patients treated with CAPD

Simple peritonitis	rapid reduction of symptoms after the start of therapy and their complete disappearance within 2-3 days. Any prolongation of symptoms is an indicator of a complicated course or inadequate selection of antibacterial therapy
Refractory peritonitis	PD-associated peritonitis, which can not be treated (lack of clinical improvement) within 3-5 days
Recurrent peritonitis	the reappearance of peritonitis symptoms with the same agent defining after confirmation of its eradication or increase in the number of polymorphonuclear leukocytes in dialyzate after their reduction. Relapse reflects either inadequate treatment or abscess formation in the abdominal cavity
Reverse peritonitis	the repeated appearance of peritonitis symptoms in 4 weeks with the same pathogen defining after the completion of therapy and confirmation of its eradication. Evidence of inappropriate therapy or the presence of an infection (inflammation of the catheter, tunnel infection). In majority of cases is caused by Staphylococcus epidermidis or gram-negative microorganisms
Reverse infection	a new episode of peritonitis, which occurs in more than 4 weeks after recovery with the same or another microorganism. Determining the same pathogen indicates the presence of an internal focus of the infection

Also the literature considers the importance of other infection risk factors complications in CKD. One of these factors may be the deterioration of the systematic antibacterial response caused by uremia itself and described by Kakuta T, Tanaka R., who studied reduced phagocytic activity and functional inferiority of polymorphonuclear leukocytes in patients with CKD and improved peritoneal membrane functional activity [28]. Recent studies have shown apoptosis activation in CKD stage V, as well as pronounced monocytic and macrophageal dysfunction with uremia. At the same time Wu, J. and co-authors gave the special role to TGF-b1 (transforming growth factor, beta-1 (TRFbeta-1)) [29]. According to some data, the risk of peritonitis in CAPD is also associated with a decrease in peritoneal capacity to local antibiotic response due to the constant adverse effect of dialysis solutions (DS) on it. In particular, Simon F, Tapia P. in their study showed that high glucose concentration in DS also affects the production of peritoneal leukocytes by some anti-inflammatory factors and leads to death of peritoneal mesothelium cells [30].

In peritoneum's protective properties violation, the key role is played by glucose degradation products (GDP), which accumulate after the sterilization of DS [31]. It is assumed that at least some of the GDPs, such as glyoxal, 1.2-dicarbonyl, and 5-hydroxymethylfurfural are capable of suppressing the reparative properties of mesothelium [32].

The oxidative stress plays not the last role in chronic inflammation. It accompanies patients with PD. Even during the first year after the initiation of the method, mainly due to the chronic accumulation of end-products by glycosylation, oxidative stress and inflammation processes, as well as chronic structural and functional deterioration of the peritoneal membrane due to high concentration of glucose in DS, lead to loss of ultrafiltration and further transfer of the patient to hemodialysis [33].

During PD-associated peritonitis, protein loss is increased to 15-20 g / day. Also, the prognostic signifi-

cance of the initial level of albumin to the long-term outcomes of this method is shown in many studies. In particular, Guest S noted that traditionally, serum albumin was an indicator of chronic inflammation and intrathecal status, and studies of high level were therefore included in the monthly blood test in most centers. Progressive hypoalbuminemia in patients with PD was one of the mortality predictors [**34**]. The important role of serum albumin in PD is also emphasized by Jiang J. [**35**]. They found a correlation between the level of serum albumin and mortality and the risk of infectious complications. A total of 149 patients with CAPD were enrolled in this study. By serum albumin level, patients were divided into two groups: a low albumin level group (<35 g / l) and a high albumin rate (≥35 g / l).

According to the results of the study, the group with hypoalbuminemia showed a higher incidence of cardiovascular mortality and a higher incidence of DP. Also, it should be noted that in this study hypoalbuminemia was associated with poor survival of the PD methodology, with a decrease in the initial level of albumin per 1 g / l resulted in a 20% reduction in the survival rate of the technique. Thus, DP is a cause of worse survival and death, not only because of its inflammatory effect but also as a cause of hypoalbuminemia. There is a so-called "vicious circle", the essence of which is that the DP and hypoalbuminemia are factors that provoke the emergence of each other [**35**].

Thus, the review of actual studies allows us to establish that DP is the most characteristic infectious complication of CAPD and is a frequent cause of death in this category of patients which occurs not only as a result of bacterial infection of the abdominal cavity but also as an outcome of these factors combination with the weakening of the systemic and local antibacterial responses to the morpho-functional reorganization of the peritoneal membrane due to contact with the dialyzing solution. However, for today, a lot of data on the stability of antibacterial drugs needs to be reviewed including the increased duration of the research in order to find out whether it is an acceptable prophylactic approach to their prescription. If intraperitoneal antibacterial drug concentrations are effective, if there is any frequent necessity of antibacterial drugs combination use, and how the activity of antibacterial drugs changes in the peritoneal environment?

So as a conclusion, we can state that there is high demand for further clarification of surgical tactics in the DP issue, namely, the results of rapid and delayed removal of the catheter and safe intervals for rearrangement of the catheter. Other important areas where more data are needed are the effect of peritonitis and treatment strategies on the residual renal function and the long-term results of CAPD treatment. More questions should be defined on modifying risk factors for peritonitis. Previous data suggests that low levels of albumin and depressive symptoms are risk factors for subsequent peritonitis, but it is not known whether the risk of DP is reduced by the correction of these problems. Still, there remain concerns of chronic inflammation and oxidative stress as consequences of glucose metabolism products in dialysis solution on the one hand and specific proteins that may induce an inflammatory reaction on the other hand. Taking into consideration all these data, the DP problem is so far relevant and requires close attention and continuation of research to reduce the risk of their occurrence and prolong the duration of the method of DP.

Author contributions.

M. Malasaie: searching and information analysis, article writtening control and article redaction;

I. Dudar: control and article redaction;

A. Shymova: preparation for printing.

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