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PERITONITIS IN PERITONEAL DIALYSIS PATIENTS – A DIAGNOSTIC AND THERAPEUTICAL CHALLENGE

SUMMARY

Continuous or chronic ambulatory peritoneal dialysis (CAPD) has been widely accepted as safe and cost-effective treatment for end-stage chronic renal failure. It is well-known that peritonitis is the most common complication of CAPD. The majority of these cases of peritonitis have catheter-related etiology. Its clinical importance regarding the differential diagnosis of secondary peritonitis often make CAPD peritonitis a diagnostic and therapeutical challenge and significant medical issue. Due to its specific etiopathogenesis and management, peritoneal infection in CAPD patients should be considered as a separate entity and additional category in group of peritonitis. We review and present available information on etiopathogenesis, clinical presentation, diagnosis, treatment and prevention of this challenging condition. Prevention of peritonitis in patients undergoing CAPD requires intensive education regarding aseptic technique and catheter care.

Keywords: **CAPD, peritonitis**

INTRODUCTION

Over the past three decades, since its emergence in the late 1970s, continuous or chronic ambulatory peritoneal dialysis (CAPD) has been widely accepted as safe and cost-effective treatment for end-stage chronic renal failure. However, this technique is often abandoned in significant number of patients because of its most common complication, peritonitis (1). The majority of these cases of peritonitis have catheter-related etiology. Although a single microorganism usually causes these peritoneal infections, 6-9% of cases have polymicrobial origin. The incidence of peritonitis complicating CAPD varies considerably between individual patients and centers. In fact, its incidence reflects the experience of the center, the quality of technology used and the general health condition of patients, that is their susceptibility to infection and ability to comply with procedure (2). In most developed countries, that is USA, the average incidence of CAPD peritonitis is 1,3-1,4 episodes per patient per year (3). In addition to increasing costs of treatment, its clinical importance regarding the differential diagnosis of secondary peritonitis often makes CAPD peritonitis a diagnostic and therapeutical challenge and significant medical issue. Due to its specific etiopathogenesis and management, peritoneal infection in CAPD patients should be considered as separate entity and additional category in group of peritonitis.

Etiology and pathogenesis

Microbiology of CAPD peritonitis. CAPD peritonitis is usually caused by a single pathogen that originates from the normal skin or upper respiratory tract flora. In 60-70% of cases these infections are

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caused by gram-positive cocci, in 20-30% by gram-negative bacilli and in rest of the cases by various other bacteria, fungi and mycobacteria (4). Coagulase-negative Staphylococcus is far the most common pathogen, followed by Staphylococcus aureus and Streptococcus. Among the gram-negative microorganisms, the most frequent pathogens associated with CAPD peritonitis are Enterobacteriaceae species, without single species predomination. Pseudomonas aeruginosa causes CAPD peritonitis in 5-10% of cases and is associated with significant morbidity and late complications (5). Also, in recent years fungi are becoming more important cause of CAPD peritonitis because of their increasing frequency and difficult management. Candida albicans accounts for 80-90% of cases and the rest are caused by many different species, including Rhizopus, Mucor, Aspergillus, Alternaria, Penicillium, Fusarium, Drechslera etc. (4,5). Risk factors for the development of fungal peritonitis are existing prolonged bacterial peritonitis, recent hospitalization, presence of extraperitoneal infection, use of immunosuppressive agents and concomitant HIV infection. Mycobacteria have been reported as cause of CAPD peritonitis in less than 3% of cases, but they may also account for group of cases labeled as „culture-negative" (6). The most frequent mycobacterial isolates are of group IV (rapid growers)(86%), such as M.fortuitum and M.chelonae. Other rare causes of peritonitis in patients undergoing CAPD are viruses, algae and Mycobacterium tuberculosis.

Pathogenesis of CAPD peritonitis. There are several mechanisms of peritonitis development in CAPD patients. The two most important routes are: *transluminal*, resulting from an unsterile technique of dialysate exchange and *contiguous spread*, in which microorganisms access the peritoneum along the dialysis catheter. Less common portal of entry is hematogenous spread from a distant site of infection. Once microorganisms reach the peritoneal cavity their further growth depends on their survival in the presence of dialysis fluid. Their ability to grow in dialysis fluid and to produce extracellular slime (biofilm) contribute to pathogenesis of peritonitis. For example, fresh dialysate solutions are capable of supporting growth of Escherichia coli, but not of staphylococci. However, after instillation and time spent in peritoneal cavity, dialysis effluent supports growth of both microorganisms (3). Also, the presence of peritonitis enhances 1000-fold the growth of Pseudomonas aeruginosa and Escherichia coli in dialysis fluid in comparison to the growth of these microorganisms in such fluid in uninfected peritoneal cavity (7). Both staphylococci and Candida albicans grow as microcolonies on polymeric surfaces (8) and produce biofilm that surrounds these microorganisms and protect them from host defenses and antibiotic activity (9). The host defense factors seem to have an important role in the pathogenesis of peritoneal infection (10). It was observed that some patients most probably with strong peritoneal host defense mechanisms remain free of CAPD-related peritonitis for years. Microbial pathogens that reach the dialyzed peritoneal cavity are removed by three major lines of defense: 1) efficient fibrin trapping and sequestration of microorganisms in the dialyzed peritoneum (despite the dilution of fibrinogen and coagulation proteins), 2) the inoculum of contaminating microorganisms decreases with the removal of dialysate and 3) a complex interaction of opsonization, phagocytosis and intracellular killing by peritoneal macrophages, mesothelial cells and neutrophils combat bacterial invasion and prevent infection. Unfortunately, these cellular and immunologic defense mechanisms are weakened in CAPD peritonitis because of low pH (5,5-6,0), high osmolarity (300-400 mOsmol/kg) and decreased levels of IgG and complement (1% of their normal levels) in the dialyzed peritoneal cavity.

Clinical presentation and diagnosis

The diagnosis of CAPD-related peritonitis is based on positive two of the following three criteria:

1. signs and symptoms of peritoneal irritation,
2. cloudy dialysate effluent and leukocyte count of >100/mm³ and
3. positive culture of dialysate fluid.

Clinical manifestations of CAPD peritonitis vary from mild to severe, depending largely on the virulence of the pathogen, the stage of infection and general health condition of patient (1). Due to its frequent unspecific clinical presentation, peritonitis in patients undergoing CAPD is as a rule diagnostic challenge, frequently misleading to diagnosis of secondary peritonitis-related acute abdomen.

Pain is usually the predominant presenting feature of CAPD peritonitis. Pain in catheter-related peritonitis is usually gradually increasing over time, diffuse and steady. It is often accompanied with nausea, vomiting and fever. However, the location of maximum pain, mode of onset and progression and character of pain is most frequently difficult to determine because of the „spread and lavage" effect of the dialysis fluid that transfer very quickly the pain from one point to another over abdomen. CAPD peritonitis may successfuly mimic many acute abdominal conditions and lead to unnecessary operative treatment. Pain is always accompanied with variously intense palpatory tenderness of the abdomen and very often with dehidratation, hypotension, tachycardia and prostration.

Turbid dialysate is usually the first and most common symptom of CAPD peritonitis to appear. Laboratory examination of cloudy peritoneal fluid is mandatory and crucial to establish the diagnosis. Leukocyte count of >100/mm³ in the dialysate effluent is traditional, but not specific diagnostic criteria. The differential cell count of dialysate may have a better predictive value. For example, the predomination of polymorphonuclear leukocytes in dialisate effluent of the patient (>50% of the total cell count, mean 85%) strongly supports the diagnosis of peritoneal infection considering that these cells account for <40% (mean 12%) of total cell count in peritoneal fluid of uninfected CAPD patients (11). Also, in the self-limited condition named „eosinophilic peritonitis“ which often follows the placement of Tenckhoff catheter and may represent allergy to the tube, a predomination of the eosinophils in the dialysate effluent can be found (12). Peritoneal eosinophilia also occurs in fungal peritonitis or after recent intraperitoneal administration of antibiotics.

Gram staining of dialysis fluid detects only 20-30% of peritonitis episodes and gram-positive microorganisms (especially Staphylococcus aureus) are more likely to be detected than gram –negative ones. Microbiological cultures of dialysate effluent offer a considerably higher accuracy and are of greater diagnostic value than gram staining, but require concentration of the dialysate by centrifugation, filtration or lysis-centrifugation (13). Culture of peritoneal fluid usually reveals a single microorganism or less commonly, a polymicrobial infection. In any case, several days are required to obtain microbiological diagnosis. Even with these specialized methods, 3-30% of CAPD peritonitis episodes are culture-negative. These episodes are most probably caused by fastidious, low-virulence microorganisms or coagulase-negative staphylococci that survive less well in peritoneal dialysis fluid (7). In these cases of culture-negative peritonitis that do not respond to empirical antibiotic treatment, further dialysate fluid cultures for mycobacteria and fungi should be performed.

Abdominal ultrasound and computed tomography scans are useful in evaluating abdominal pain and establishing early differential diagnosis between CAPD peritonitis and acute abdomen due to secondary peritonitis. However, these studies are commonly unrevealing in the early acute abdomen because of the presence of free peritoneal fluid in patients undergoing CAPD which may mislead the physician to diagnosis of hollow abominal organ perforation. In addition, clinical presentation and course of common gastrointestinal acute conditions (such as acute appendicitis, peptic ulcer perforation etc.) is very often atypical in CAPD patients and, therefore, early isolation of those patients with polymicrobial peritonitis from gastrointestinal source may be very difficult. Also, initial intraperitoneal antibiotic treatment of CAPD patients with peritonitis invariably adds to the delay in diagnosis and definitive treatment of eventually present gastrointestinal source of infection. Such delay in diagnosis and definitive therapy of acute abdomen in patients undergoing CAPD is related to an extremly high mortality rate (>50%). Thus, the management of these patients with CAPD peritonitis remains a challenging experience for both surgeons and nephrologists.

Treatment

The first line of CAPD peritonitis management is antibiotic therapy. Intraperitoneal administration of antibiotics is the preferred method for drug delivery in patients with CAPD peritonitis because it achieves high local concentrations and permits self-treatment by the patient (14). The increased use of intraperitoneal antibiotics as therapy for peritonitis has allowed most patients to be treated on an ambulatory basis. Numerous antimicrobial agents have been used successfully including penicillins, cephalosporins, aminoglycosides, fluoroquinolones, imipenem, aztreonam and macrolide and glycopeptide antibiotics. Initial empirical treatment usually consists of cephalosporin or vancomycin and further therapy should be guided by the results of the dailysis fluid gram staining or culture and susceptibility tests, if positive. In mild to moderate episodes of peritonitis, a single agent with antistaphylococcal activity may also be suitable. A single specific agent is adequate treatment in the majority of cases of bacterial CAPD peritonitis. The exception is Pseudomonas aeruginosa peritonitis which is associated with high rate of therapeutic failure and frequent relapses (5). A sinergistic combination of antibiotics, such as an antipseudomonal β-lactam drug plus an aminoglycoside, has been recommended in addition to removal of the dialysis catheter. Therapy usually continues for 10-14 days and occasionally may need to be extended in cases of extraordinary severe, slow-to-respond or resistant infections. Hospitalization is indicated only for severely ill patients or those unable to manage intraperitoneal administration of antibiotics at home.

In not so rare cases of existing acute abdomen of gastrointestinal origin (secondary peritonitis) in patients undergoing CAPD, the effect of the intraperitoneal antibiotic lavage on a primary inflammatory focus is unclear and it is likely that it allows partial treatment of, for example, appendicitis, cholecystitis, diverticulitis etc. Nevertheless,

the misdiagnosis of secondary peritonitis and inadequate intraperitoneal administration of antibiotics in such patients may be fatal. Surgical exploration is a challenging decision because of two reasons: preoperative diagnosis and isolation of patients who would benefit from surgery are as a rule very difficult and postoperative adhesions may preclude further CAPD. On the other hand, delay in diagnosis and treatment of acute abdomen of gastrointestinal origin in high-risk patients increases morbidity and mortality rates and, thus, the earliest surgical approach that offers the best chance of success is preferred. So, patients that worsen or fail to resolve with correct intraperitoneal and systemic antibiotic therapy and those with suspicious imaging tests can benefit of a more aggressive approach, and surgical exploration should be performed.

Laparotomy or laparoscopy? The laparoscopic approach is feasible and safe if performed by experienced surgeon. It is the only minimally invasive approach that provides diagnostic accuracy as well as therapeutic capabilities. Laparoscopy reduces postoperative intraperitoneal adhesions, pain, hospitalization and care costs and improves recovery of gastrointestinal function, general health condition and cosmetic results. It is associated with minimal morbidity rate (wound infection) with no clinical significance compared to the prognosis of acute abdomen treated with delay. Therefore, early laparoscopic exploration is strongly advisable in patients with peritonitis/acute abdomen undergoing CAPD.

Management of very rare fungal peritonitis in CAPD patients is controversial. Treatment with intraperitoneal and/or systemic antifungal agents may be successful and the removal of peritoneal catheter is mandatory to prevent relapse (2,15). After catheter removal, which may be curative alone in selected patients, most often a short course of systemic amphotericin B (250-500mg) is given. Mycobacterial peritonitis in CAPD patients also requires potentially curative catheter removal. Most of these microorganisms are resistant to conventional antituberculous agents and susceptibilities vary greatly among the species. Therefore, in vitro susceptibility tests or published recommendations are needed for the appropriate choice of antibiotic therapy (6,16).

Prevention

Prevention of peritonitis in patients undergoing CAPD requires intensive education regarding aseptic technique and catheter care. The most significant advances in prevention include instrumentation changes such as devices that facilitate connection of tubing (eg titanium adapters), devices that help maintain field sterility during exchanges (ultraviolet light systems and in-line filters) and devices that protect intraluminal sterility during exchanges (connector systems with disinfectant – Y-connector, O-set). Most of these devices favorably impact the incidence of peritonitis, but appreciably increase the overall cost of CAPD. Prophylactic oral or intraperitoneal use of antibiotics to prevent occurrence of clinical CAPD peritonitis have been mostly unsuccessful so far.

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PERITONITIS KOD BOLESNIKA NA PERITONEALNOJ DIJALIZI – DIJAGNOSTIČKI I TERAPEUTSKI IZAZOV

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Kontinuirana ili hronična ambulantna peritonealna dijaliza (CAPD) široko je prihvaćena kao bezbedan, jeftin i efikasan način lečenja bolesnika u završnoj fazi hronične bubrežne insuficijencije. Poznato je da je peritonitis najčešća komplikacija CAPD. Većina slučajeva peritonitisa uzrokovana je infekcijom preko katetera. Klinički značaj CAPD peritonitisa u pogledu diferencijalne dijagnoze sekundarnog peritonitisa čini ovo oboljenje dijagnostičkim i terapijskim izazovom i značajnim medicinskim problemom. Zbog svoje specifične etiopatogeneze i lečenja, infekcija peritoneuma kod bolesnika podvrgnutih CAPD predstavlja zaseban entitet i dodatnu kategoriju među peritonitisima. Prezentujemo dostupne informacije o etiopatogenezi, simptomatologiji, dijagnozi, lečenju i prevenciji ovog ozbiljnog stanja. Prevencija peritonitisa kod CAPD zahteva intenzivnu edukaciju u polju aseptične tehnike instalacije, zamene i nege katetera.

Ključne reči: **CAPD, peritonitis**