Peritoneal Dialysis–Related Peritonitis: Atypical and Resistant Organisms

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Summary: Peritoneal dialysis (PD)-related peritonitis remains to be one of the most frequent and serious complications of PD. In this study, existing literature has been reviewed on PD peritonitis caused by atypical organisms and antibiotic resistant organisms and their impact on patient outcomes. Although uncommon, delay in recognition of PD peritonitis caused by atypical organisms can lead to poor patient outcomes if there is a delay in diagnosis and implementation of appropriate treatment. There is also a large difference in prevalence of antibiotic-resistant infections across the world with variable impact on reported patient-level outcomes.
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Repeated exposures to conventional peritoneal dialysis (PD) solutions have been associated with an impairment in host cell defense,[1] reduction in peritoneal mesothelial cell viability,[2] and progressive peritoneal membrane injury.[3] In consequence, PD-related peritonitis is one of the most frequent and serious complications of PD, which directly contributes to approximately 20% of technique failures[4] and up to 6% of deaths.[5,6] Reported rates of PD peritonitis range widely from 0.06 to 1.66 episodes per patient-year across different centers and countries.[7] The first part of this article reviews the peritonitis caused by atypical organisms, with particular focus on risk factors, presence of any variation in clinical presentations, and diagnostic and treatment strategies. The second part reviews the development of antibiotic resistance over time and its impact on treatment outcomes.

PERITONITIS CAUSED BY ATYPICAL MICROORGANISMS

The most common micro-organisms responsible for peritonitis are aerobic bacteria, such as *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and *Pseudomonas aeruginosa*.[4] Culture-negative peritonitis accounts for up to 12% of all peritonitis episodes,[8] which may be owing to peritonitis caused by atypical organisms, including mycobacteria and fungi (other than the *Candida* species, which is a group of fungi that grows readily in routine cultures). Although they are rare, a delay in the diagnosis and implementation of appropriate treatment can result in adverse patient outcomes, including death.

PERITONITIS CAUSED BY MYCOBACTERIA

The genus *Mycobacterium* contains several species, many of which have caused human illnesses. *Mycobacterium tuberculosis* causes tuberculous disease and form *M tuberculosis* complex with three other closely related mycobacterial species (*Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*) (Table 1). Mycobacteria other than those that make up the *M tuberculosis* complex are called *nontuberculous* or *atypical mycobacteria*. Patients with end-stage renal disease have relative defects in cell-mediated immunity,[9] which may predispose them to develop infections from these organisms.

Tuberculous Peritonitis

The risk of active tuberculosis is increased dramatically by many factors that affect the innate and adaptive immune systems,[10] including older age, presence of diabetes mellitus, and human immunodeficiency virus (HIV) infection[11] (Table 2). Although the relative risk for developing active tuberculosis in patients with end-stage renal disease is 5 to 15 times greater than in the general population,[12-16] the reported incidence of tuberculous peritonitis is low (<3%),[11] with a higher prevalence in Asian countries.[17] The diagnosis is challenging and often delayed, with fewer than half of all cases diagnosed before 6 weeks after the initial presentation.[11,17] For reasons that are unclear, the classic finding of peritoneal fluid containing a predominance of lymphocytes with peritoneal tuberculosis (not specifically related to PD) is uncommon in PD-associated tuberculous peritonitis, in which neutrophils usually predominate (>60% of cases).[11,17,18] A case of eosinophilic peritonitis caused by *M tuberculosis* also has been observed.[19] Timely diagnosis is compromised further by extremely low sensitivity of a smear for acid-fast bacilli

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Table 1. List of Atypical Microorganisms Causing Peritoneal Dialysis–Related Peritonitis

Group	Species
Tuberculous peritonitis	*Mycobacterium tuberculosis*[19,*]
Atypical mycobacterial peritonitis	*Mycobacterium abscessus*[37]
	Mycobacterium avium complex[34]
	Mycobacterium chelonae[37]
	Mycobacterium fortuitum[37]
	Mycobacterium gastri[34]
	Mycobacterium gordonae[34]
	Mycobacterium heckeshornense[34]
	Mycobacterium kansasii[34]
	Mycobacterium phlei[102]
	Mycobacterium porcinum[34]
	Mycobacterium rhodesiae[34]
	Mycobacterium smegmatis[34]
	Mycobacterium trivale[34]
	Mycobacterium xenopi[34]
Fungal peritonitis (non-*Candida*)	*Aspergillus species (Aspergillus fumigatus, Aspergillus niger, Aspergillus thermomutatus)*[50,53,56]
	Bipolaris spicifera[50]
	Cryptococcosis (Cryptococcosis neoformans)[50,103]
	Fusarium[104]
	Histoplasma capsulatum[50]
	Hormonema dematiodes[50]
	Lecythophora mutabilis[50]
	Mucormycosis (Rhizopus, Absidia, Mucor, and other Zygomycetes)[50]
	Paecilomyces species (Paecilomyces variotii, Paecilomyces taitungiacus)[50]
	Penicillium species[50]
	Roseomonas gilardii[50]
	Trichosporon species[50]

*Forms a tuberculosis complex with *M bovis*, *M africanum*, or *M microti*.

Table 2. Risk Factors for Peritoneal Dialysis–Related Peritonitis From Atypical Microorganisms

Type of organism	Risk factors
Tuberculous peritonitis	*Compromise in innate and adaptive immune systems,*[10,11] *including*
	Older age
	Diabetes mellitus
	HIV infection
	End-stage renal disease
	Residence in Asia[17]
Atypical mycobacterial peritonitis	*Immunosuppression, including*[34-36]
	Autoimmune diseases (eg, systemic lupus erythematosus)
	Diabetes mellitus
	HIV infection
	Bone marrow transplantation
	History of frequent bacteria peritonitis[11,36]
	History of concomitant bacterial/fungal infections
	Unknown number. Use of prophylactic exit-site gentamicin cream[37,38]
Fungal peritonitis	*Recent history of antibiotic use*[47,50,51]
	Use of immunosuppressive therapy[56,57]
	Immunosuppressive condition (eg, HIV infection, multiple myeloma)[53,58]
	Low adherence to antifungal chemoprophylaxis[59-63]

(3% positive smear in culture-confirmed or pathologically confirmed cases), and relatively low yield (30%) from culture of peritoneal dialysate, which may take more than 4 weeks before results are known.[20] The gold standard for the diagnosis of tuberculous peritonitis is laparoscopy, which has the best diagnostic yield (sensitivity, 84%-100%), but is an invasive procedure that may not be readily available.[21] There are several newer, relatively noninvasive tests and more rapid investigations that can confirm *M tuberculosis*, including polymerase chain reaction (PCR) assay,[22] and measurement of adenosine deaminase (ADA) in the peritoneal dialysate.[23] ADA is a purine-degrading enzyme that catalyzes the deamination of adenosine in an irreversible manner, which results in the production of inosine. An increase in ADA activity has been reported to relate to the intensity of stimulation and the maturation state of the lymphocyte, owing to an immune cellular response against *M tuberculosis*.[24-26]

ADA levels in body fluids can be measured rapidly, and its level in ascitic fluid has been reported to be a sensitive (0.93; 95% confidence interval, 0.89-0.95) test for the diagnosis of tuberculous peritonitis based on a meta-analysis.[23] However, it is a nonspecific test and is considered at best a useful screening test in high-risk patients or in countries with a high incidence of tuberculosis.[27] In contrast, PCR is a specific test to detect *M tuberculosis*, which can be performed directly on the obtained tissue samples. Uzunkoy et al[22] also have reported reliable diagnoses by performing PCR analyses on ascitic fluid, with their outcomes similarly replicated by others.[28,29] Upon confirmation of diagnosis, timely initiation of antituberculous therapy is necessary. Before deciding on the regimen, the possibility of drug resistance should be considered. Risk factors for drug-resistant tuberculosis include a previous episode of tuberculosis, exposure to a person with drug-resistant tuberculosis, and residence in an area with a high prevalence of multidrug-resistant or extensively drug-resistant organisms. Once drug regimen is determined, its pharmacokinetics in relation to dialysis also needs to be evaluated (eg, pyrazinamide is cleared by dialysis and should be administered after hemodialysis). The International Society for Peritoneal Dialysis guideline recommends combination of four drugs: rifampicin, isoniazid, pyrazinamide, and ofloxacin.[30] Treatment with