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General review

Aspergillus peritonitis in peritoneal dialysis patients: A systematic review

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ABSTRACT

Fungal peritonitis in patients undergoing peritoneal dialysis (PD) is very difficult to treat and is associated with significant morbidity and mortality. Among fungal pathogens, *Aspergillus* peritonitis presents a higher mortality rate when compared to *Candida* peritonitis and its identification as well as appropriate treatment remains a challenge for the physicians. We critical reviewed all published cases in literature of *Aspergillus* peritonitis in PD patients. The results showed that a total of 55 cases (51% males) of *Aspergillus* peritonitis in PD patients were reported from 1968 to 2019. Mean patient age was 49.54 ± 19.63 years and mean PD duration prior to fungal infection was 33.31 ± 32.45 months. *Aspergillus fumigatus* was isolated in 17/55 patients, *Aspergillus niger* in 15, *Aspergillus terreus* in 9, unidentified *Aspergillus* spp. in 6, *Aspergillus flavus* in 4, whereas sporadic cases of other *Aspergillus* spp. were reported. As far as predisposing factors are concerned, 75% of patients suffered from prior bacterial peritonitis receiving antimicrobial therapy. Initial antifungal treatment was intravenous and/or intraperitoneal administration of amphotericin B formulations monotherapy in 47.2% of patients or in combination with fluconazole in 13.2%, or with itraconazole in 13.2%, or with caspofungin in 3.8%, or with ketoconazole or with 5-FC in 1.9%, each. Peritoneal catheter removal was performed in 85.5% of cases. Mortality rate was 38.2%, while 81.8% of the survived patients switched to hemodialysis. Conclusively, *Aspergillus* peritonitis diagnosis can be difficult, due to unspecific symptoms. Early treatment with appropriate antifungal agents can be determinant for patient prognosis. Despite appropriate treatment, reported mortality remains high.

Introduction

Fungal peritonitis (FP) in patients undergoing peritoneal dialysis (PD) remains an uncommon complication but is considered to be difficult to treat and is associated with significant mortality and morbidity in patients with PD [1]. In addition, the inflammatory process of FP usually causes irreversible damage to the peritoneal membrane with subsequent dropout from PD therapy, followed switch to hemodialysis in about two third of patients.

The incidence of FP is 4–10% in children and 1–23% in adults, representing a total of 4–6% of peritonitis cases [2]. Among FP causes, *Candida* spp. constitutes the predominant genus isolated, especially, *Candida albicans* and *Candida parapsilosis* being the most often involved species, and refers to 70–90% of cases in adults and 80–100% in children [2]. Commonly referred to filamentous fungi include *Aspergillus* spp., *Penicillium* spp. and *Curvularia* spp. Other fungal pathogens are extremely rare as causes of peritonitis. Fungal peritonitis due to *Aspergillus* spp. is relatively uncommon reaching about 2% to 5% of FP cases, has a high mortality rate ranging from 15% to 50% as compared to *Candida* spp. with a mortality rate ranging from 10% to 35% and is known to be very difficult to treat [3,4]. Although the prevalence of FP is low, successful treatment is a challenge for the infectious disease physician.

For these reasons, data from case reports or case series, despite inherent limitations, may be useful for better understanding of *Aspergillus* peritonitis in PD patients. Based on this, we reviewed published cases including several parameters of *Aspergillus* in such patients with the aim to describe the clinical and microbiological features and the treatment of *Aspergillus* peritonitis in a context of PD.

Subjects and methods

General Information and literature search strategy

This review conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement [5,6].

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Eligibility criteria

In this review were include case reports and case series of patients followed definitions of FP. On the one hand, diagnosis of peritonitis was based on clinical manifestations such as abdominal pain, nausea, and fever combined with a cloudy peritoneal effluent count of 100 WBC/μL or greater, consisting of at least 50% polymorphonuclear (PMN) cells. On the other hand, primary FP was defined as a case presenting with a positive culture for fungi from peritoneal fluid with no past medical history of peritonitis in a context of PD. Secondary FP, need also a positive culture for fungi from peritoneal fluid, defined as a case in which FP developed within 30 days exposure to antimicrobial agents due to bacterial peritonitis or episode of FP concomitantly with bacterial peritonitis [7].

Definition of a proven fungal mold infection includes recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process. In addition, blood culture that yields a mold in the context of a compatible infectious disease process and/or amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue, constitute also criteria for proven fungal infections. Specifically, a positive culture for fungi from peritoneal fluid or a positive result with fungal DNA by PCR combined with DNA sequencing in peritoneal fluid, constitutes a proven fungal mold peritonitis. Probable invasive fungal diseases requires the presence of a host factor, a clinical feature, and mycologic evidence. Cases that meet the criteria for a host factor and a clinical feature but for which mycological evidence has not been found are considered possible invasive fungal diseases [8]. Early-onset peritonitis was defined as the first episode of peritonitis occurring within 6 months after the initiation of PD. In contrast, late-onset peritonitis occurring after 6 months.

An exit-site infection (ESI) was defined as the presence of purulent drainage, with or without erythema of the skin at the catheter-skin interface. Pericatheter erythema without purulent discharge is sometimes an early indication of infection. However, diagnosis of proven fungal ESI includes demonstration of fungal elements in diseased tissue obtained by a biopsy sample of the lesion. In addition, tunnel infection may present as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult. Tunnel infection usually occurs in the presence of an ESI but rarely occurs alone [7].

Information sources and search strategy

We searched the literature, the MEDLINE and Google Scholar databases and individual references for publications of single cases or case series with the following keywords: "*Aspergillus* peritonitis" and "PD patients".

Study selection

All potentially relevant articles were screened in two stages for eligibility by selected authors. In the first stage of assessment, the titles and abstracts of potentially relevant articles were screened independently by three authors (JD, AK, EK). In addition, the reference list of each article was searched by hand to verify that all published cases were collected for this review. For those abstracts which met the inclusion criteria, the full text was retrieved and independent reviewed by two authors in the second stage of assessment (JD, EK). Disagreements and technical uncertainties were discussed and resolved by all authors (JD, AK, EK, VK, AP, CG, NP).

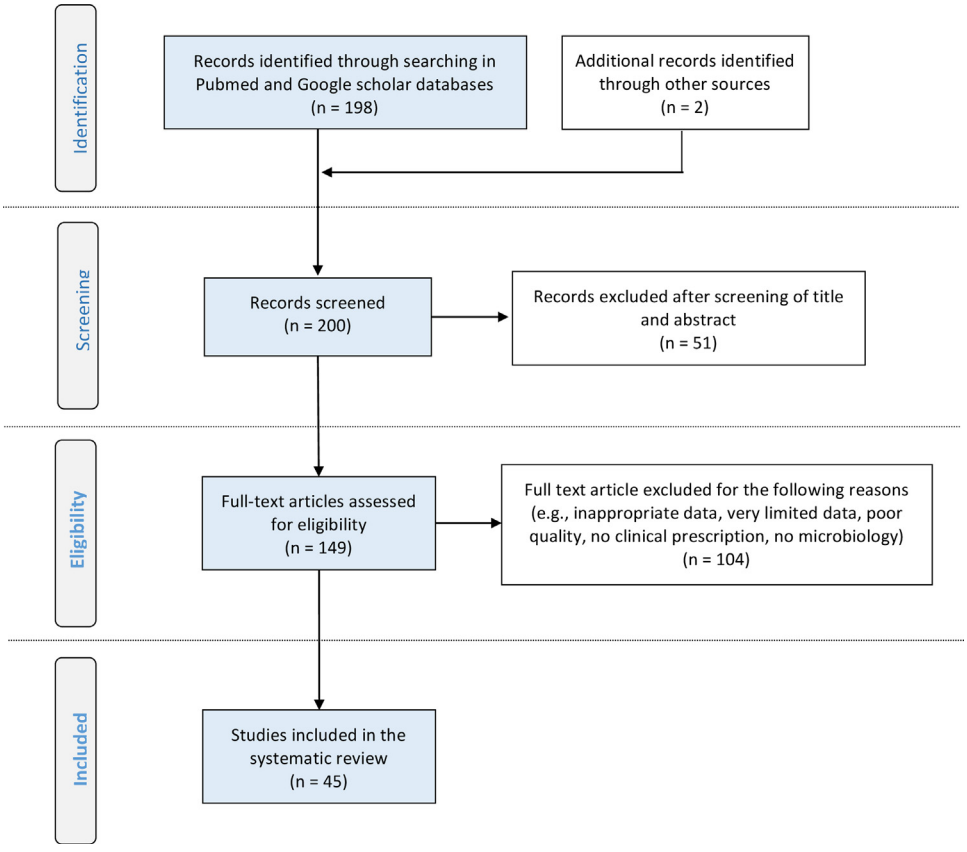

Fig. 1. PRISMA flow diagram of literature search, eligibility and inclusion process.

Table 1
Cases of *Aspergillus* peritonitis in peritoneal dialysis patients.

Patient	Reference	Year of publication	Age (years)	Gender	Peritoneal dialysis method (years)	Underlying disease	Predisposing factors	Prior peritonitis
1	Cicek et al. [9]	2017	15	M	CAPD (7 m)	Global sclerosis	Pulmonary aspergillosis	
2	Kurultak et al. [10]	2016	55	M	CAPD (8)	Chronic glomerulonephritis	Previous antibiotics (4 episodes of peritonitis)	*Staphylococcus epidermidis* peritonitis (1y before)
3	Vellanki et al. [11]	2014	19	F	CCPD (4)	aHUS	Eculizimab	
4	Yilmaz et al. [12]	2013	49	M	CAPD (4)	Diabetes mellitus		Y (2y before)
5	Yilmaz et al. [12]	2013	77	M	APD (2)	Hypertension, chronic obstructive pulmonary disease	Accidental cut of Tenckhoff catheter	
6	Kalawat et al. [13]	2013	70	F	CAPD (3)	Hypertension, Diabetes mellitus, hypothyroidism	Ureteric stent	*Pseudomonas aeruginosa* peritonitis
7	Roberts et al. [14]	2013	49	M	CAPD		No	
8	Ates et al. [15]	2013	42	F	CAPD (13)	Nephrolithiasis	No	
9	Indramohan et al. [16]	2013	52	M	CAPD (11)	Diabetes mellitus and hypertension		Y (1 m before)
10	Tsai et al. [17]	2012	20	F	PD (1)	SLE	Pulmonary tuberculosis (2004), 4 episodes of peritonitis (2007, 2010, 2011)	
11	Ulusoy et al. [18]	2011	25	F	CAPD (4.5)			
12	Varughese et al. [19]	2011	61	M	CAPD (4 m)	Hypertension		
13	Liu et al. [20]	2009	26	F	CAPD (2)	SLE		
14	Schwetz et al. [21]	2007	65	M	CAPD (4)	Diabetes mellitus	Antibiotic treatment for pneumonia (6 m before)	*Staphylococcus aureus* peritonitis (3y before), catheter exit-site infection (2y before), culture negative peritonitis (1 m before)
15	Verghese et al. [22]	2008	55	F	CAPD (1,5)	Diabetes mellitus, hypertension		
16	Annigeri RA [23]	2007	44	F	CAPD (9 m)	Diabetic nephropathy		
17	e Silva et al. [24]	2006	64	F	CCPD (2)	Diabetic nephropathy, vascular hypertensive disease		
18	Schatther et al. [25]	2006	45	F	CAPD (3)	SLE	Left nephrectomy and short antibiotic treatment	
19	Bonfante et al. [26]	2005	68	F	APD (3) => CAPD	Autosomal dominant polycystic kidney disease		
20	Chiu et al. [27]	2005	53	F	CAPD (11)	IgA nephropathy		
21	Ide et al. [28]	2005	82	M	CAPD	Diabetes mellitus, corticodependent chronic obstructive pulmonary disease		Polymicrobial bacterial peritonitis
22	Scotter et al. [29]	2004	60	M	CAPD (3 m)	Multiple myeloma	Immunosuppressive treatment	
23	Yilmaz et al. [12]	2004	NA	F				
24	Yilmaz et al. [12]	2004	NA	M				
25	Kalishian et al. [30]	2004	52	F	CAPD (5)	SLE		
26	Nannini et al. [31]	2003	41	M	CAPD (2)			
27	Yilmaz et al. [12]	2003	NA	M				
28	Matsumoto [32]	2002	8	F	CAPD (3.3)	FSGS		N
29	Nannini et al. [31]	2000	NA	NA				
30	Basok et al. [33]	2000	69	F	CAPD	Autosomic polycystic kidney disease		
31	Nannini et al. [31]	2000	NA	NA				
32	Tsoufakis et al. [34]	1999	61	M	CAPD	Chronic recurrent pyelonephritis		Gram-positive cocci peritonitis (8 m before)
33	Tsoufakis et al. [34]	1999	30	F	CAPD	Chronic glomerulonephritis		
34	Baer et al. [35]	1998 (2013)	48	M	CAPD	Diabetic nephropathy		
35	Baer et al. [35]	1998 (2013)	42	F	CAPD	Diabetic nephropathy		
36	Bren et al. [36]	1998	NA	NA				Y
37	Bren et al. [36]	1998	NA	NA				Y
38	Bren et al. [36]	1998	NA	NA				Y
39	Kitiyakara et al. [37]	1996	37	M	CAPD (1)		Previous antibiotics	Gram-positive cocci peritonitis (13d before)
40	Miles & Barth [38]	1995	56	M	CAPD (3)	Diabetic nephropathy		3 episodes of peritonitis
41	Tanis et al. [39]	1995	68	M				Y
42	Tsoufakis et al. [40]	1995	61	M	CAPD (4)			*Enterococcus* spp. peritonitis
43	Nguyen & Muder [41]	1994	68	M	CAPD (3)	Diabetic nephropathy		(3 m before)
44	Bibashi et al. [42]	1993	35	F	CAPD (1w)	Mesangiocapillary glomerulonephritis	Immunosuppression	N

Table 1 (*Continued*)

Patient	Reference	Year of publication	Age (years)	Gender	Peritoneal dialysis method (years)	Underlying disease	Predisposing factors	Prior peritonitis
45	Stein et al. [43]	1991	68	F	CAPD (1)	Nephroangiosclerosis		3 episodes of peritonitis during last year
46	Perez-Fontan et al. [44]	1991	69	M	CAPD (2)	Coronary heart disease and nephroangiosclerosis		Y
47	Tsai et al. [45]	1991	52	M	CAPD (1 m)	Henoch Schonlein purpura nephritis		N
48	Swartz at al [46]	1991	NA	NA				Y
49	Shridhar et al. [47]	1990	49	F	CAPD (44 m)			N
50	Prewitt et al. [48]	1989	66	M	CAPD (1)			N
51	Rodriguez-Tudela [49]	1988	40	M	CAPD (4)	Diabetic nephropathy		Multiple episodes of *Staphylococcus aureus* peritonitis
52	Kravitz & Berry [50]	1986	16	M	CAPD (2)	FSGS		Y
53	Carpenter et al. [51]	1982	64	F		hypertension, pericarditis		N
54	Arfania et al. [52]	1981	61	F	CAPD	Glomerulonephritis	Antibiotic therapy (*Escerichia coli* sepsis)	N
55	Ross [53]	1968	22	F	APD	Eclampsia, acute tubular necrosis	*Aspergillus* meningitis	N

M: Male; F: Female; PD: Peritoneal Dialysis; CCPD: Continuous Cycling PD; CAPD: Continuous Ambulatory PD; APD: Automated PD; SLE: Systemic Lupus Erythematosus; aHUS: atypical Hemolytic Uremic Syndrome; FSGS: Focal Segmental Glomerulosclerosis; w: week; m: month; y: year; NA: Not available; Y: Yes; N: No.

Data extraction

The primary citations obtained during database survey were recorded in a text file according to their topics and abstracts. None of the case reports found was excluded from enrolment in the analysis due to inadequacy of data reported or quality of data. Variables included in the database were year of publication, underlying disease, predisposing factors, demographic information about the patients (gender and age), PD method, switch to hemodialysis procedure and microbiology aspects such as fungus species and isolation method. In addition, data on treatment choice, duration and route of treatment, catheter removal procedure and outcome were recorded.

Statistical analysis

All the articles found by this means were systematically reviewed and a master database was constructed. Microsoft Excel (XP Professional) software (Redmond, WA, USA) was used to develop this database of categorical and continuous variables. The statistical program Graphpad Prism 8 (Graphpad Inc, San Diego, CA, USA) was used. A two-sided P value of < 0.05 indicated statistical significance.

Results

The systematic search, as illustrated in Fig. 1, resulted in an initial number of 200 potentially relevant articles. After screening the remaining 45 publications fulfilled the eligibility criteria and were included in this review. Of these, 40 were case reports and 5 were case series.

A total of 55 cases, including 51% males, of *Aspergillus* peritonitis in PD patients were reported from 1968 to 2019 [9–53]. All such cases are presented in Table 1 and Table 2. Early-onset peritonitis was found in only 4 cases with available data. In most cases, late-onset peritonitis was observed. The mean patient age was 49.54 ± 19.63 years and the mean PD duration prior to fungal infection was 33.31 ± 32.45 months. The most common specie isolated from peritoneal fluid cultures was *Aspergillus fumigatus* in 17/55 patients, followed by other *Aspergillus* spp. as presented in Table 3.

The number of proven cases of Aspergillus peritonitis were 38, probable were 2, while no possible cases were included. Although the data about the isolation method were not available in the rest 15 cases, they were included in the study based on the adequacy of the remaining data. In 35 patients, peritoneal fluid *Aspergillus* isolation was performed in Sabouraud dextrose agar (SDA) and established the diagnosis. A positive galactomannan test was present in 5 patients. However, only in 4 patients, *Aspergillus* spp. were isolated from biopsy specimens of peritoneum. In a few patients, diagnosis was established by more than one method. As far as predisposing factors are concerned, 75% of patients suffered from prior bacterial peritonitis receiving antimicrobial therapy. The most common underlying disease was diabetes mellitus/diabetic nephropathy in 34% of patients with available data.

Initial antifungal treatment was intravenous and/or intraperitoneal administration of amphotericin B formulations either as monotherapy in 47.2% of patients or as combination in 79.2% of patients. Monotherapy with other antifungal agents was given in 17% of them. In two patients (3.8%) no therapy was given and treatment consisted in peritoneal catheter removal without adjuvant antifungal administration. In detail, amphotericin B formulations combined with itraconazole was used in 18.9% of patients or with fluconazole in 17% or with caspofungin 7.5% or with ketoconazole or with 5-FC in 1.9%, each. As monotherapy, voriconazole was used in 9.4% of patients, fluconazole in 3.8%, itraconazole and ketoconazole in 1.9%, each. In addition, peritoneal catheter removal was performed in 85.5% of cases indicating an important therapeutic intervention for the treatment of *Aspergillus* peritonitis.

Mortality rate was 38.2%, however, when we take certain time points between years 1968–1988, $>$ 1988-2008 and $>$ 2008–2019, we found that mortality rate was 80%, 34.2% and 30.8%, respectively. The relationship between *Aspergillus* species, therapeutic intervention and outcome are shown in Table 3 and Table 4. In survived

Table 2
Microbiological findings and management of 55 cases of Aspergillus peritonitis.

Patient No	*Aspergillus* spp. isolate	Catheter tunnel	Isolation method	Catheter removal	Antifungal therapy (duration)	Duration of therapy (d)
1	*Fumigatus*		lung biopsy histological examination-GM	Y	AB + Caspo	4d
2	*Niger*		SDA + GM antigen test positive in the blood and PF	Y	AB	10w
3	*Niger*	ESI	SDA	Y	IV AB => Vor	NA
4	*Flavus*	ESI	SDA	Y	IV L-AB	26d
5	*Niger*		SDA	N	No treatment (catheter colonization)	
6	*Niger*		SDA	Y	IV Vor	NA
7	*Flavus*		SDA	Y	IP Vor	NA
8	*Niger*	ESI	GM and β-d-Glucan detection	Y	IV AB	NA
9	*Niger*		Peritoneal biopsy	Y	NA	NA
10	*Fumigatus*	ESI	SDA	Y	IV AB(4w) => oral Itra (6 m)	7 m
11	*Nidulans*	ESI	SDA	Y	IV L-AB (21d) => Vor	1y
12	*Terreus*		SDA	Y	IV AB (2w) => oral Flu (2 w) => oral 5-FC (4 w)	8w
13	NI		NA	Y	Vor (1 m) => Caspo + AB	NA
14	*Oryzae*		SDA and sequence analysis of the rDNA genes	Y	AB + Caspo (28d) => Itra (6 m)	28d
15	*Terreus*	ESI	Blood agar, chocolate agar, thioglycollate broth, SDA	Y	Vor	1w
16	NI	ESI	SDA	Y	Vor	3w (+24d)
17	*Terreus*	ESI	Cultures of fragments removed from the outer distal portion of the catheter, Positive for periodic acid-Schiff reaction	Y	oral Itra (catheter colonization)	4w
18	*Fumigatus*		SDA	Y	IV AB	19d
19	*Fumigatus*	ESI	SDA	Y	IV AB-d + oral Itra	3 m (AB)
20	*Sydowii*		SDA + sequence analysis of rRNA genes	Y	No	
21	*Fumigatus*	ESI	PF: SDA, Blood: GM, Catheter: SDA containing chloramphenicol	Y	oral Vor	1d
22	*Fumigatus*		Blood and PF: SDA, PCR and GM	N	IP AB + oral Itra	37d
23	*Terreus*		NA	Y	AB + Itra	NA
24	*Fumigatus*		NA	N	AB + oral Itra	NA
25	*Terreus*		SDA	Y	IV AB => Itra	38d
26	*Terreus*	ESI	SDA	Y	IV AB-d (28d) => L-AB (5d) => iv Caspo (3d)	36d
27	*Terreus*		NA	Y	AB	NA
28	*Thermomutatus*		Blood agar and SDA	Y	IV AB-d (170d) => L-AB (60d) => oral Itra	230d
29	*Niger*		NA	Y	IV L-AB + Flu	NA
30	*Niger*		NA	Y	IV L-AB (5d) + Flu (21d)	5d
31	*Niger*		NA	Y	IV AB-d (7d) + Flu (28d)	7d
32	*Fumigatus*		SDA	Y	IV AB + Flu	1 m
33	*Fumigatus*		SDA	N	IV AB(4w) + IP Flu (6w)	6w
34	*Flavus*		NA	Y	Flu (4w)	4w
35	*Terreus*	ESI	NA	Y	Flu (3w)	3w
36	*Fumigatus*		NA	Y	Ket	10d
37	*Fumigatus*		NA	Y	IV AB-d	7d
38	NI		NA	Y	IV AB-d + 5-FC	9d
39	*Niger*		SDA	Y	IV AB (65d) + oral Itra	65d AB
40	*Niger*	ESI	SDA	Y	IV AB-d	28d
41	*Fumigatus*		NA	Y	IV AB-d + Itra	35d
42	*Fumigatus*		PF and blood: SDA	Y	IV AB & Flu	3d
43	*Fumigatus*	ESI	SDA	Y	IV AB-d (21d) + Itra (14d)	21d
44	*Niger*	ESI	SDA	Y	IV AB-d (20d) + Flu	20d
45	*Fumigatus*		NA	Y	IV AB-d	40d
46	NI		SDA	Y	IP AB-d + Ket (10d) => IV AB-d (3d)	13d
47	NI		SDA	N	IV + IP AB-d	49d
48	NI		NA	Y	AB	11d
49	*Niger*		SDA	Y	IV AB	15d
50	*Niger*	ESI	SDA	Y	IV AB-d	42d
51	*Niger*		SDA	Y	IV AB-d	14d
52	*Terreus*		SDA	Y	IP AB(13d) => IV AB	NA
53	*Flavus*		SDA, biopsy	N	IV AB-d	4d
54	*Fumigatus*	ESI	NA	N	IV + IP AB-d	5d
55	*Fumigatus*		Autopsy–SDA	N	NA	NA

NA: Not available; NI: Non identified *Aspergillus* spp.; Vor: Voriconazole; AB: Amphotericin B; LAB: Lipid formulation of Amphotericin B; AB-d: Deoxycholate Amphotericin B; Flu: Fluconazole; Itra: Itraconazole; 5-FC: Flucytosine; IV: Intravenous; IP: Intraperitoneal; PF: Peritoneal Fluid; ESI: Exit Site Infection; SDA: Sabouraud Dextrose Agar; GM: Galactomannan test.

Table 3
Relationship between *Aspergillus* species and outcome.

Aspergillus specie isolated	No of cases	Deaths (%)
Aspergillus fumigatus	17	10/17 (58.8)
Aspergillus niger	15	4/15 (26.7)
Aspergillus terreus	9	5/9 (55.6)
Aspergillus flavus	4	2/4 (50)
Aspergillus nidulans	1	0/1
Aspergillus oryzae	1	0/1
Aspergillus sydowii	1	0/1
Aspergillus thermomutatus	1	0/1
Aspergillus spp.	6	0/6 (0)
TOTAL	**55**	**21/55 (38.2)**

Table 4
Relationship between therapeutic intervention and outcome.

Therapeutic intervention	No of cases	Deaths (%)
IV and/or IP antifungals	52	19/52 (36.5)
Catheter removal (alone)	2	1/2 (50)
Catheter removal + IV and/or IP antifungals	45	15/45 (33.3)
Amphotericin-B (monotherapy)	15	6/15 (40)
Voriconazole (monotherapy)	2	2/4 (50)
Amphotericin-B + antifungals (other than vorinocazole)	23	10/23 (43.6)
Amphotericin-B switch to voriconazole	2	0/2 (0)

IV: Intravenous; IP: Intraperitoneal.

patients, 81.8% were switched to hemodialysis while the rest remained to PD. One patient received renal transplantation immediately after FP treatment.

The frequency of *Aspergillus* peritonitis in PD per 5-year periods of publication differs as it is shown in Fig. 2. There is an increase in publications during the last two decades as compared to previous years.

Discussion

Predisposing factors for FP have not been clearly determined and include prolonged antibiotic therapy, immunosuppression, recent hospitalization and autoimmune disease [11]. Peritoneal inflammation seems to increase susceptibility to a fungal invasion, especially after bacterial peritonitis due to gram-negative bacilli and patients with prior bacterial peritonitis seem to present two times higher rate of FP [1,2]. It has been suggested that antibiotic therapy destroys the normal microflora by inducing fungal overgrowth on the skin and in the gastrointestinal tract so that contamination of the peritoneum seems to be more likely [1]. It is known that the frequent use of broad spectrum antibiotics favors colonization in the digestive system, with possible future consequence colonization of the peritoneal cavity [1,2]. Taking into account these two predisposing factors, prior peritonitis and antibiotic use, in a previous study, antibiotic use within the preceding 3 months was noted in 94% of the patients with FP complicating bacterial peritonitis, versus 61% of patients with de novo FP [1]. Based on similar findings of other studies, International Society for Peritoneal Dialysis (ISPD) recommendations suggest giving an antifungal agent in case of bacterial peritonitis as an antifungal prophylaxis as it is the main predisposing factor of fungal peritonitis [7]. However, some other studies do not confirm difference in the bacterial peritonitis rate in patients with and without FP [54]. Other risk factors include immunosuppression, such as corticosteroid therapy and immune system diseases such as systemic lupus erythematosus and HIV disease.

As far as it concerns the diagnosis of FP, it is based either on microscopic examination or on the isolation of the microbial agent in a culture of peritoneal fluid. Although, as it is known that *Aspergillus* has a growth rate of 2–5 days on SDA, isolation of the fungal agent is not always easy. It is therefore recommended that the diagnosis must be confirmed by more than one positive culture. It is also recommended the use of other methods such as microscopy, the sequence of rDNA genes, blood agar, chocolate agar, thioglycolate broth and Schiff periodic acid test PAS. In a study, it was found that direct microscopic examination of the peritoneal fluid was able to confirm a suspected IFI in 60% of patients [55]. New diagnostic techniques such as the polymerase chain reaction (PCR) are developed and evaluated and can facilitate early diagnosis [29]. In addition, although the data about sensitivity and specificity of PCR use in peritoneal fluid are very

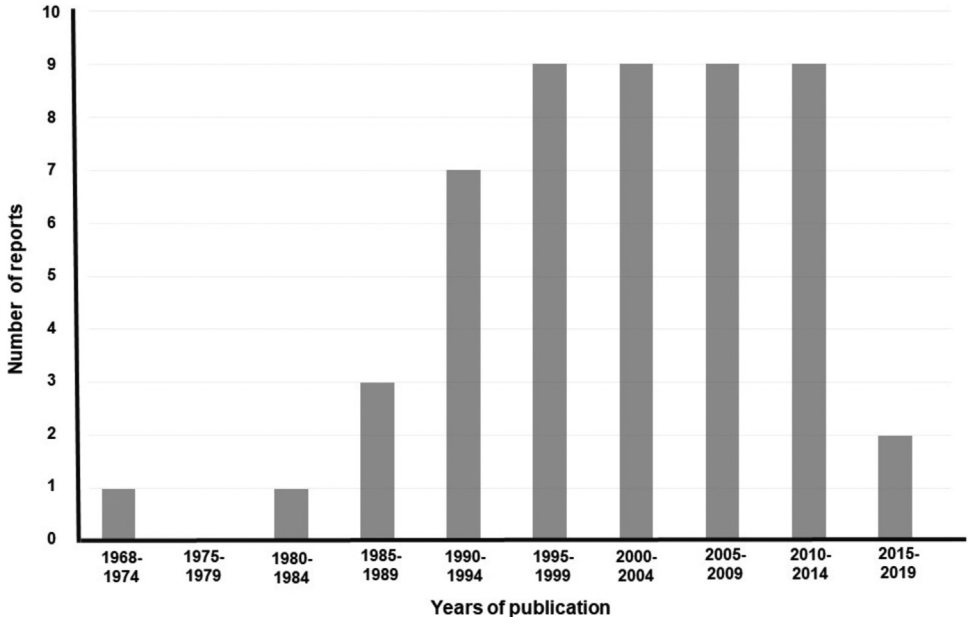

Fig. 2. Frequency of reported single cases or case series of *Aspergillus* peritonitis in peritoneal dialysis per 5-year periods of publication.

limited, this method implying increased sensitivity when compared with routine culture, especially when routine culture for *Aspergillus* remain negative. However, it is emphasized that a positive culture is sufficient for the immediate initiation of treatment that may be life-saving [26]. Since previous decade, the galactomannan test has increasingly been used as a diagnostic method, whereas the culture of peritoneal fluid in the SDA is still a safe isolation method. Furthermore, in a study it was found that galactomannan test *sensitivity ranging between* 83%–100% while *specificity ranging between* 58%–77% [56]. In our study, only 5 patients presented a positive galactomannan test among the 55 reviewed cases but unfortunately data from the rest of patients were not available.

According to the ISPD recommendations, immediate removal of the catheter with the clinical suspicion of FP and the temporary transition to hemodialysis is crucial for the final outcome as it prevents further damage of the peritoneal membrane [7]. Early onset of treatment is imperative and is aimed both at controlling the infection and in maintaining the integrity of the peritoneum. Treatment of FP involves removal of the PD catheter, treatment with antifungal agents for 4–6 weeks, and new catheter placement after 4–6 weeks [19]. The well-known antifungal polypeptides (amphotericin B and lipid formulations), older/newer azole derivatives (itraconazole, ketoconazole/posaconazole, ravuconazole, voriconazole, *isavuconazole*), fluorinated pyrimidines (fluocytosin) and echinocandins (caspofungin, micafungin, anidulafungin) are therapeutic options. Proper selection of antimycotic agent is critical and selection of the appropriate derivative should be based on antifungal susceptibility testing [13]. In our study, we found that initial antifungal treatment with amphotericin B formulations as monotherapy was used in about 47% of patients. However in total, antifungal treatment included intravenous and/or intraperitoneal administration of amphotericin B was given in about 80% of patients. Unfortunately, IP use of amphotericin B causes chemical peritonitis and pain. Although intravenous amphotericin B seems to be the treatment of choice for invasive *Aspergillus* infection, clinical studies noticed that liposomal amphotericin B is as effective as conventional, with fewer side effects [32]. In addition, with regard to penetrating infections, the use of voriconazole appears to be more effective and better tolerated by patients than amphotericin B. Up to now, intravenous liposomal amphotericin B was usually the initial treatment option either monotherapy or in combination with azole derivatives, more commonly with fluconazole or itraconazole, orally medications.

Patients on PD after FP are usually not reinstated in the method, possibly as a result of complications due to delayed administration of antifungal agents, delayed catheter removal or extensive peritoneal adhesions. In this review, the mortality rate was 38.2% and 81.8% of the surviving patients were enrolled in hemodialysis. While, *Aspergillus fumigatus*, *Aspergillus terreus* and *Aspergillus flavus* were associated with the highest mortality rates among all *Aspergillus* spp.

Limitations

A limitation of this review relates to the exclusion of case reports and case series that were not reported in English, Greek, Spanish, German or French. In addition, few case reports might have been missed because relevant search terms may not be identified in the title or abstract such that the search did not return all potentially relevant articles.

Furthermore, another limitation of this review was the bias of analysis of collected published cases in the literature that is more incentive to publish cases that were successfully treated or diagnosed with a new tool or treated with a novel therapy. In addition, although most of the published cases were proven fungal infections, unfortunately there were few cases that defined as probable or possible. The focus of the reviewed case reports and case series was mainly on the clinical and microbiological features and the treatment of *Aspergillus* peritonitis. Unfortunately, some of the articles lacked data regarding patients including age [12,31,36,46] and gender [31,36,46], the PD method [12,31,36,39,46,51], the underlying disease [12,14,18,31,36,37,39,40,46–48], the predisposing factors [12,16,18–20,22–24,26–28,30–36,38–41,43–51] and the prior peritonitis episodes [9,11,12,14,15,17–19,23–27,29–31,33–35]. Additionally, lacked data concerning also microbiological findings and management procedures. Specifically, unavailable data regarding isolation method [12,20,31,33,35,36,39,43,46,52], type of antifungal therapy [16] and duration of treatment [11–16,20,31,50,53].

Nevertheless, because of the rarity of the infection, it is important to collect information from individual cases or small case series, so that conclusions about predisposing factors, microbiology aspects and the best evidence for management are drawn.

Conclusion

This critical review supports the need for immediate initiation of treatment in clinical suspicion of *Aspergillus* peritonitis, which can be crucial not only for the maintenance of the method but also for the patient's life. It also highlights the need for systematically reporting of these patients, so that useful conclusions can be drawn for the epidemiology of *Aspergillus* peritonitis with consequent better understanding and better therapeutic options.

Disclosure of interest

The authors declare that they have no competing interest.

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