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VIRIDANS STREPTOCOCCI IN PERITONEAL DIALYSIS PERITONITIS: CLINICAL COURSES AND LONG-TERM OUTCOMES

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♦ ***Background:*** **The clinical courses and long-term outcomes of viridans streptococcus (VS) peritoneal dialysis (PD) peritonitis remain unclear.**

♦ ***Methods:*** **We conducted a retrospective analysis of all PD patients in a single center with gram-positive cocci (GPC) peritonitis between 2005 and 2011, and divided them into 3 groups: VS, other streptococci and other GPC (apart from VS). Clinical characteristics and outcomes of the VS group were compared with the other streptococci and other GPC groups, with prognostic factors determined.**

♦ ***Results:*** **A total of 140 patients with 168 episodes of GPC peritonitis (44% of all peritonitis) were identified over 7 years. Among these, 18 patients (13%) developed VS peritonitis, while 14 patients (10%) developed other streptococcal peritonitis. Patients with VS peritonitis had a high cure rate by antibiotic alone (94%), despite a high polymicrobial yield frequency (28%). We found that VS peritonitis carried a lower risk of Tenckhoff catheter removal and relapsing episodes than other GPC peritonitis (6% vs 11%), and a lower mortality than other streptococci peritonitis (0% vs 7%). However, after the index peritonitis episodes, VS, other streptococci, and other GPC group had a significantly increased peritonitis incidence compared with the period before the index peritonitis (all $p < 0.01$). Patients with VS peritonitis had a significantly higher incidence of refractory peritonitis compared with other streptococci or other GPC peritonitis in the long term (both $p < 0.01$).**

♦ ***Conclusions:*** **VS poses a higher risk of subsequent refractory peritonitis after the index episode as compared with other streptococcal or GPC peritonitis. It might be prudent to monitor the technique of these patients with VS peritonitis closely to avoid further peritonitis episodes.**

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Peritonitis is a leading complication during peritoneal dialysis (PD), and remains a major cause of technique failure (1,2). Gram-positive cocci (GPC) account for 43 – 64% of all PD peritonitis episodes (3–5), and over half are caused by coagulase-negative *Staphylococci* (6). *Streptococcal* species constitute around 10 – 15% of GPC peritonitis episodes (3,7–9).

Streptococcal PD peritonitis have favorable outcomes, with more than a 90% cure rate (7,8). However, the taxonomy of *Streptococcal* species has changed over the past decades (7). *Enterococcus* have been re-located out of the genus *Streptococcus* since the early 1990s, but previous streptococcal peritonitis studies often included *Enterococcus* species in their reports (9,10). This obscures the clinical picture of streptococcal peritonitis, since enterococcal peritonitis demonstrates distinct courses and antibiotic susceptibility from streptococcal peritonitis (11,12). Such findings raise the importance of examining different members of the *Streptococcus* species to discern their clinical features.

Viridans streptococci (VS) are normal flora of humans, especially in the oral cavity, upper respiratory tract and all parts of the gastrointestinal (GI) tract (13). They are usually deemed to be of low virulence, except in infective endocarditis (13,14). However, reports about VS were

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often confusing in the past since the classifications were based upon hemolytic patterns on agar plates (14). Consequently, reports of VS peritonitis were mostly anecdotal (15–17). Furthermore, subsequent outcomes of patients with VS peritonitis had never been described before and clinicians often extrapolate the findings from streptococcal peritonitis to VS episodes. It is presumed that VS peritonitis might have higher cure rates compared with other GPC (7,8), but whether VS peritonitis demonstrate different clinical courses when compared with the other streptococcal species or even GPC remains unclear. Therefore, the current study analyzed our peritonitis episodes to describe the clinical characteristics and outcomes of VS peritonitis compared with other GPC peritonitis. In addition, the influence of index peritonitis on long-term PD outcomes was analyzed.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

This is a retrospective analysis of a prospectively followed-up cohort in the National Taiwan University Hospital PD program (18–20). We identified all episodes of culture-proven GPC peritonitis between January 2005 and December 2011. Diagnosis of peritonitis was made by the presence of peritoneal signs and cloudy effluent with white blood cell counts >100/μL and > 50% neutrophils. Relapse peritonitis was defined as episodes of peritonitis recurring within 4 weeks after treating previous episodes by the same pathogens, while repeat peritonitis was defined as episodes recurring after 4 weeks of previous episodes by the same pathogens (21–23).

ETHICAL CONSIDERATIONS

This study was approved by the ethics committee of the National Taiwan University Hospital (No. 201212165RINC).

CLINICAL DATA COLLECTION

We collected patients' demographic profiles including age, gender, as well as their comorbidities including diabetes mellitus (DM), hypertension, dyslipidemia, coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), liver cirrhosis, and malignancy.

For each episode of peritonitis, we collected data on the date of peritonitis, dialysis modality of continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD), presenting symptoms, pathogen identification and antibiotic susceptibilities. Causes of peritonitis were divided into 5 categories: contamination during exchanging procedure, GI flora translocation (accompanied by GI symptoms and/or lesions), hematogenous spread (from other primary infective sites), catheter related (concomitant exit-site or tunnel infections), and undetermined. In our PD program, all patients were treated initially with empirical intraperitoneal antibiotics according to standard recommendations (21–23), including cefazolin/ceftazidime (after 1998). A subsequent switch of antibiotic choices and relapse or repeat peritonitis was documented.

OUTCOMES

The outcomes included two parts: short-term outcomes included antibiotic response (primary or secondary), Tenckhoff catheter removal, relapsing peritonitis, or death during the index peritonitis episodes. We defined death associated with index peritonitis as mortality that occurred during treatment or within the first 2 weeks after completing antibiotic treatment for index peritonitis. The latter definition was based upon the fact that peritonitis could at least be an indirect predisposing factor for mortality in such a scenario. Tenckhoff catheter removal due to peritonitis was coded if catheter removal was due to lack of improvement during index peritonitis treatment, or fungal peritonitis, as determined by nephrologists. Long-term outcomes included the subsequent development of refractory peritonitis, all-cause hospitalization, technique failure with permanent transfer to hemodialysis of any causes, and death, at least 3 months after index peritonitis episodes. Refractory peritonitis was defined as failure of effluent to clear after 5 days of appropriate antibiotic treatment with resultant Tenckhoff catheter removal. All the patients were followed up until mortality or November 2012.

STATISTICAL ANALYSIS

All statistical analyses were performed with SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). All variables are reported as mean ± SD for continuous variables and as frequencies or percentages for categorical variables. Student's *t*-test was used for analysis between groups, wherever appropriate. Differences in frequency were tested using chi-square analysis. Peritonitis incidence in each group of PD patients before and after the index peritonitis was compared by Poisson analysis. Kaplan-Meier survival analysis was used to

compare survival between groups and constructed survival curves. The adjusted variables were stated for each analysis. Two-sided *p* values < 0.05 were considered statistically significant.

RESULTS

A total of 140 patients with 168 episodes of GPC peritonitis were identified over 7 years, constituting 44% of the total peritonitis episodes. The average incidence of total and GPC peritonitis in our cohort was one episode per 71.4 patient-months and per 125 patient-months respectively during this period. Among all GPC peritonitis episodes, 18 patients developed 18 episodes of VS peritonitis (11%). The 18 patients with VS peritonitis also developed 28 episodes of other GPC peritonitis (all from non-*Streptococci* species) in the study period, and therefore these 28 episodes of GPC peritonitis were excluded from our subsequent analysis.

The demographic profiles and etiologies of end-stage renal disease (ESRD) among VS, other streptococci and other GPC peritonitis are outlined in Table 1. The mean age was not significantly different between the three groups of patients, but there were significantly fewer male patients (28% vs 43%; $p < 0.001$) in patients with VS and other streptococcal peritonitis, and more CAPD users ($p < 0.001$) in those with VS peritonitis. Comorbidities, causes of ESRD, and PD vintage were not significantly different between patients with VS and other GPC peritonitis, but patients with VS peritonitis were more likely to have CAD and CHF than those with other streptococcal peritonitis. All patients presented with cloudy effluent and abdominal pain, with effluent white blood cell higher than 100/μL.

For patients with VS peritonitis and other streptococcal peritonitis, no catheter infection was reported, while there were 3% of patients with other GPC peritonitis developing exit-site infection concomitantly. No cases of mechanical complications including peritoneal leakage or hernia were found in patients with VS peritonitis. Among the VS peritonitis patients, 5 patients (28%) had polymicrobial growth, and one was impressed as minor hollow viscera perforation and permanently transferred to hemodialysis.

TABLE 1
Baseline Clinical Features of Patients with Viridans Streptococcus (VS), Other Streptococcal, and Other Gram-Positive Cocci (GPC) Peritonitis

Characteristics	VS (*n*=18)	Other streptococci (*n*=14)	Other GPC (*n*=122)	P1 value[a]	P2 value[b]
Age (years)	63±15	60±16	54±17	0.6	0.59
Gender (male%)	28%	29%	43%	0.92	<0.01
CAPD %	94%	71%	62%	<0.01	<0.01
Comorbidities					
Hypertension	89%	86%	89%	0.61	0.95
DM	28%	14%	29%	0.07	0.94
Dyslipidemia	11%	14%	21%	0.61	0.35
CAD	33%	14%	22%	0.01	0.30
CHF	22%	7%	14%	0.02	0.36
CVA	0%	7%	11%	0.02	0.15
Malignancy	0%	7%	7%	0.02	0.24
Cirrhosis	0%	0%	1%	1.0	0.70
Etiology of ESRD				0.09	0.07
DM	22%	14%	25%		
CGN	33%	29%	27%		
Hypertension	6%	21%	16%		
Miscellaneous	39%	36%	33%		
Vintage (months)	38±64	35±43	40±37	0.81	0.42

VS = viridans streptococcus; GPC = gram-positive cocci; CAPD = continuous ambulatory peritoneal dialysis; DM = diabetes mellitus; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; ESRD = end-stage renal disease; CGN = chronic glomerulonephritis.

[a] VS compared with other streptococci.

[b] VS compared with other GPC.

The precipitating causes of peritonitis in all 3 groups are displayed in Table 2. Contamination during the exchange procedure constituted the most common cause (VS vs other streptococci, 89% vs 57%; VS vs other GPC, 89% vs 75%), followed by GI bacterial translocation. The causes also differed between the three groups, with more contamination in patients with VS peritonitis, while less GI bacterial translocation and hematogenous spread, than in patients with other streptococcal or other GPC peritonitis (Table 2, $p < 0.05$ for both comparisons with chi-square test). None of the patients with VS peritonitis had relevant records of dental clinic visits or receipt of dental procedures within the year before VS peritonitis episodes.

The susceptibility of VS in our cohort showed that all strains were susceptible to clindamycin, levofloxacin, penicillin, vancomycin, linezolid and rifampin. In all VS isolated, 6 (33%) were resistant to tetracycline, while 1 (6%) was intermediately resistant to erythromycin. There were 5 patients with 7 co-existing bacteria isolated, including *E. coli* (11%), *Klebsiella pneumoniae* (6%), *Bacteroides vulgaris* (6%), *Citrobacter freundii* (6%), *Neisseria* species (6%), and *Corynebacterium* species (6%).

The microbiologic spectrum of other GPC peritonitis is provided in Table 3. Coagulase-negative *Staphylococci* were the most frequently isolated bacteria (48%), followed by *Staphylococcus aureus* (21%) and *Enterococcus* species (16%). Other less-frequently found bacteria included group B *Streptococci* (not classified further), *Streptococcus bovis*, *Lactococcus* and *Micrococcus* species. Polymicrobial growth occurred in 18 episodes (15%).

After antibiotic treatment, 78% of peritonitis episodes were cured by antibiotics, in which 14% necessitated antibiotic switch for cure. Another 10% of patients required catheter removal (Table 4). The overall mortality rate for the index peritonitis was 4%. Patients with VS peritonitis had a similar primary and secondary antibiotic response rate compared with those with other streptococcal or other GPC peritonitis, but a lower rate of catheter removal ($p < 0.05$) and relapsing peritonitis ($p < 0.01$) compared with those with other GPC peritonitis. Patients with other streptococcal peritonitis had significantly higher mortality during index peritonitis than patients with VS peritonitis ($p = 0.02$). Overall, the average time from peritonitis onset to Tenckhoff catheter removal and death was 11.5 days and 9.8 days, respectively, in patients with VS peritonitis.

After an average of 2.3 years of follow-up, 70 patients (58%) had technique failure with permanent modality switch, while another 22 patients (18%) died in the follow-up period. Patients with VS peritonitis had similar long-term hospitalization rates, technique failure and mortality compared with those with other GPC peritonitis, but significantly higher rates of refractory peritonitis in the long term than patients with other streptococcal or other GPC peritonitis (VS vs other streptococci, 41% vs 8%; VS vs other GPC, 41% vs 8%; both $p < 0.001$). Before the index peritonitis, patients in all three groups had

TABLE 3
Microbiologic Spectrum of Other Gram-Positive Cocci (GPC) Peritonitis in the Current Cohort (n=122)

Organisms	Frequency
Coagulase-negative *Staphylococci*	59 (48%)
Staphylococcus aureus	
Methicillin-susceptible	23 (19%)
Methicillin-resistant	3 (3%)
Enterococcus species	20 (16%)
Group B *Streptococcus*	13 (11%)
Streptococcus bovis	1 (1%)
Lactococcus species	1 (1%)
Micrococcus species	2 (2%)

GPC = gram-positive cocci.

TABLE 2
Etiology of Viridans Streptococcus (VS) Peritonitis, Other Streptococcal Peritonitis, Group 2, and Other Gram-Positive Cocci (GPC) Peritonitis

Origin[a]	VS	Other streptococci	Other GPC
Contamination	16 (89%)	8 (57%)	91 (75%)
GI flora translocation	1 (6%)	2 (14%)	13 (11%)
Hematogenous spread	0 (0)	0 (0%)	2 (2%)
Catheter related	0 (0)	0 (0%)	4 (3%)
Undetermined	1 (6%)	4 (28%)	12 (10%)

VS = viridans streptococcus; GPC = gram-positive cocci; GI = gastrointestinal.
[a] $p<0.05$ for comparison between VS/other streptococci and between VS/other GPC (both with chi-square test).

similar peritonitis incidences. However, peritonitis rates rose in the subsequent follow-up period significantly in all groups ($p < 0.001$; Table 5). We also identified that, in our cohort, the trends of PD peritonitis diverge after the index peritonitis: for VS peritonitis patients, the incidence rate increases further compared with the other two groups (Table 5). The etiologies of technique failure in the long term are displayed in Table 6. A Kaplan-Meier survival curve was also constructed for the refractory peritonitis-free survival in all three groups (Figure 1).

DISCUSSION

In the current study, we describe the clinical features and courses of VS peritonitis in the PD population, which is a rarely touched topic in the literature. Compared with other streptococcal and other GPC peritonitis episodes, VS peritonitis is more likely to result from contamination. Current episodes of GPC peritonitis predict a higher incidence of peritonitis after the index events, and this effect is more obvious in the VS peritonitis group. The experience of VS peritonitis also signifies a higher risk

TABLE 4
Clinical Outcomes of Viridans Streptococcus (VS) Peritonitis, Other Streptococcal Peritonitis, and Other Gram-Positive Cocci (GPC) Peritonitis

Outcome (index peritonitis)	Total (*n*=140)	Other VS (*n*=18)	Other *streptococci* (*n*=14)	GPC (*n*=122)	P1 value[a]	P2 value[b]
Antibiotics						
Primary response	90 (64%)	14 (78%)	11 (79%)	76 (62%)	0.1	0.26
Secondary response	19 (14%)	3 (17%)	1 (7%)	16 (13%)	0.11	0.19
Tenckhoff catheter removal	14 (10%)	1 (6%)	1 (7%)	13 (11%)	0.72	<0.05
Relapse peritonitis	11 (8%)	0 (0%)	0 (0%)	11 (9%)	1.0	<0.01
Death (index peritonitis)	6 (4%)	0 (0%)	1 (7%)	6 (5%)	0.02	0.34
Outcomes (long-term)	**Total (*n*=120)**	**Other VS (*n*=17)**	**Other *streptococci* (*n*=12)**	**GPC (*n*=103)**	**P1 value[a]**	**P2 value[b]**
Refractory peritonitis	15 (13%)	7 (41%)	1 (8%)	8 (8%)	<0.01	<0.01
Hospitalization (>1 time)	70 (58%)	12 (71%)	5 (42%)	58 (56%)	0.01	0.14
Technique failure	70 (58%)	11 (65%)	7 (58%)	59 (57%)	0.68	0.57
Death	22 (18%)	3 (18%)	3 (25%)	18 (18%)	0.13	0.87

VS = viridans streptococcus; GPC = gram-positive cocci.
[a] VS compared with other streptococci.
[b] VS compared with other GPC.

TABLE 5
Peritonitis Rate Before and After Index Gram-Positive Cocci (GPC) Peritonitis

	Before (patient-months required for one peritonitis episode)	After (patient-months required for one peritonitis episode)	*p* value
VS	76.9	26.3	<0.001
Other *streptococci*	72.8	39.2	0.002
Other GPC	66.7	35.7	<0.001
P1 value[a]	0.61	<0.01	
P2 value[b]	0.41	<0.01	

VS = viridans streptococci; GPC = gram-positive cocci.
[a] Comparing VS/other streptococci with Poisson analysis.
[b] Comparing VS/other GPC with Poisson analysis.

TABLE 6
Reasons for Long-Term Technique Failure in the Entire Cohort (VS Peritonitis, Other Streptococcal Peritonitis, and Other GPC Peritonitis)

Reasons	Total cohort (*n*=70)	VS (*n*=11)	Other *Streptococci* (*n*=7)	Other GPC (*n*=59)
Refractory peritonitis	15 (21%)	7 (64%)	1 (14%)	8 (14%)
Fungal peritonitis	4 (6%)	0 (0)	0	4 (7%)
Recurrent peritonitis	8 (11%)	0 (0)	0	8 (14%)
Repeat peritonitis	2 (3%)	0 (0)	0	2 (3%)
Tunnel infection/ESI	5 (7%)	0 (0)	0	5 (9%)
Mechanical complication	3 (4%)	0 (0)	1 (14%)	3 (5%)
Renal transplantation	6 (9%)	0 (0)	1 (14%)	6 (10%)
Death	13 (19%)	3 (27%)	3 (43%)	10 (17%)
Miscellaneous[a]	14 (20%)	1 (9%)	1 (14%)	13 (22%)

VS = viridans streptococcus; GPC = gram-positive cocci; ESI = exit-site infection.
[a] Miscellaneous: including socio-economical reasons, major intra-abdominal surgeries, ultrafiltration failure or inadequate clearance.

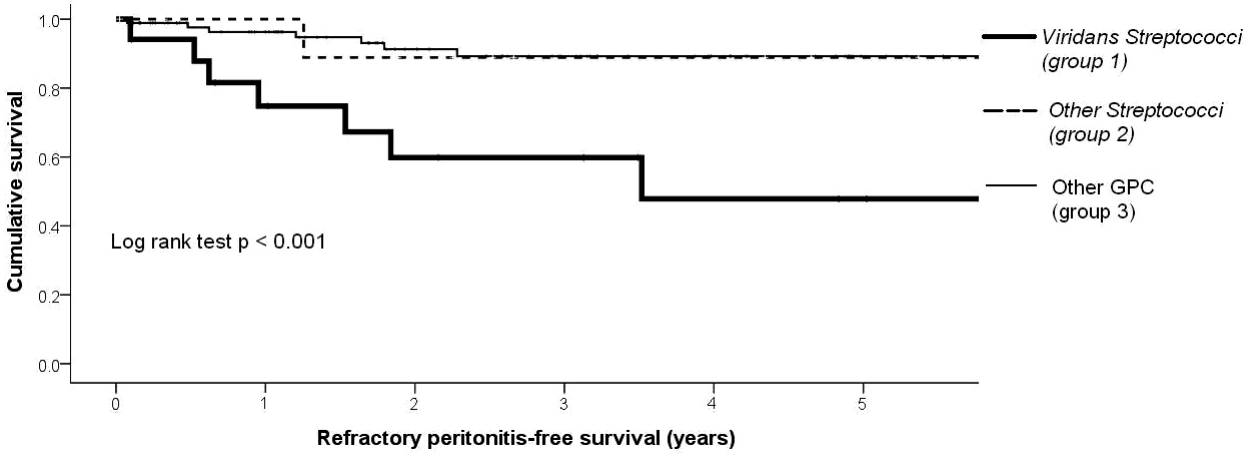

Figure 1 — Kaplan-Meier curve of refractory peritonitis-free survival between VS, other streptococci, and other GPC peritonitis. VS = viridans streptococcus; GPC = gram-positive cocci.

of subsequent refractory peritonitis and hospitalizations than other streptococcal or other GPC peritonitis. These features have never been described before, and merit our further attention.

The incidence of PD peritonitis in our cohort (one episode per 71.4 patient-months) is lower than most reports (21,24,25). However, the percentage of total GPC peritonitis is similar to other reports, and the distribution of microbiologic spectrum of our GPC episodes is also akin to other studies in the literature. We believe that the low incidence did not affect the results of the present study on VS peritonitis.

VS peritonitis is still rather under-investigated, possibly owing to the variable inclusion of different bacterial species and the changing microbiologic spectrums (14,26,27). Most reports are single species limited and of low case numbers, but different VS members might demonstrate distinct antibiograms and different ports of entry. *Streptococcus parasanguis*, a species of VS group, reportedly showed high resistance to penicillin while retaining susceptibility to vancomycin, fluoroquinolone, clindamycin and erythromycin (28). *Streptococcus oralis* was also found to display penicillin resistance while susceptible to vancomycin (29). Several case reports favored poor dental hygiene as a main predisposing factor, while others indicated that contamination is the most likely route (16,28,29). In our experience, we identified no relevant dental defect history in our VS peritonitis patients, and contamination was probably a more important risk factor (Table 2). In addition, VS peritonitis

showed quite consistent susceptibility to vancomycin, fluoroquinolone and clindamycin but variable resistance to tetracycline and erythromycin, similar to previous isolated case reports (26,28–30). Contamination was also the main port of entry (89%, Table 2), and we did not identify any case with clinically significant poor dental hygiene. However, there was no case of penicillin resistance found in our VS patients. Several studies have shown that *Streptococci* might demonstrate resistance to macrolides (23 – 58%) and tetracycline (28 – 45%) as well as low-level penicillin resistance (13 – 17%) (31,32). Among these, *Streptococcus sanguinis* shows a high frequency of penicillin resistance in most reports (30 – 45%), compared with other members of VS (1 – 3%) (32). This species is a minor pathogen in our study, as reported in the literature (7), therefore explaining the absence of penicillin-resistance. Consequently, the use of penicillin-group antibiotics in patients with VS peritonitis could be a reasonable first-line choice.

In our study, 94.4% of VS peritonitis was cured by antibiotics alone without relapse or permanent HD transfer, and there was no mortality in VS peritonitis, in contrast to other GPC peritonitis (Table 4). This finding is also consistent with previous reports that the catheter loss rate of streptococcal peritonitis is only 1.1% (7).

Currently, the available predictive factors of PD peritonitis prognosis all address short-term outcomes (33). The long-term clinical courses and outcomes of VS peritonitis had never been investigated. Specifically, we reported on the occurrences of refractory peritonitis, hospitalization, and technique failure for these patients, owing to their relevance to overall patient survival in the long run (1,2). In our study, more than half of all patients with GPC PD peritonitis would eventually be hospitalized or develop technique failure, within an average of 2.3 years of follow-up. The average duration of technique survival after peritonitis is similar to other reports (1.7 – 2.2 years) (34).

Infection is the single most important origin of PD failure (28 – 35%) (35,36). However, the relevant factors influencing long-term technique failure after index peritonitis events are still unknown, and reports investigating this issue are rare. PD vintage could be an important factor in determining infection-related technique failure (34). Our study contributes to this research gap by identifying that the offending pathogens might offer a clue to PD peritonitis long-term outcomes. Patients with VS peritonitis did have a higher risk of subsequent refractory peritonitis than those with other streptococcal and other GPC peritonitis (Table 4). It is unlikely that the legacy of single peritonitis episode exerts any effect on the subsequent patient outcomes. Other factors might be in effect in this scenario. First, according to our findings, patients with VS peritonitis had better outcomes than those with other GPC peritonitis (Table 4). This positive short-term outcome of VS peritonitis could potentially lower patients' alertness to maintaining exchange sterility, leading to a paradoxical increase in subsequent peritonitis incidence (Table 5). Refractory peritonitis could then ensue in the following period. Second, in our cohort, patients with VS peritonitis had a significantly higher percentage of contamination as their peritonitis origin, compared with other streptococcal and other GPC peritonitis (Table 2). This phenomenon suggests that developing VS peritonitis might serve as an indicator of poorer exchange technique beforehand. Rather than being causative for poor outcome mechanistically, VS PD peritonitis might be a potential marker for patients requiring technical re-education. Consequently, it would be optimal to improve patients' exchange skills if they develop VS PD peritonitis.

This study is the first to specifically focus on the clinical features of VS peritonitis. In addition, we also provide information on the long-term outcomes of these patients. However, there are limitations to this study that are worth noting. First, the case number of VS peritonitis patients in this study, though higher than other reports, is still not high enough. This is likely the result of a lower incidence of PD peritonitis in our cohort. Second, other factors determining subsequent refractory peritonitis are still lacking and we could not investigate this issue thoroughly. Further study is warranted to elucidate this interesting finding.

CONCLUSION

In conclusion, VS is an under-recognized pathogen in GPC peritonitis, and penicillin groups could be reasonable first-line antibiotics. VS peritonitis is usually benign with a high antibiotic cure rate, but the long-term course of these patients might not be as benign as it initially appears. Continuous monitoring of PD exchange technique for patients with VS PD peritonitis after index episodes are cured might be necessary to reduce their risk of subsequent peritonitis occurrence.

DISCLOSURES

The authors have no relevant financial or non-financial competing interests to declare in relation to this manuscript.

CTC and JWH conceived and designed the study. CTC, SYL, WSY, HWC, CCF, CJY, CKC, KYH and JWH interpreted

the results. CTC, JWH drafted the manuscript. CTC, SYL, WSY, HWC, CCF, CJY, CKC, KYH and JWH critically revised the manuscript. All authors approved the submission of this manuscript.

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