Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6234-20
Intern Med 60: 3447-3452, 2021
http://internmed.jp

【 CASE REPORT 】

# Peritoneal Dialysis-Related Peritonitis Caused by *Streptococcus oralis*

Akihiro Kotani[1], Yasuhiro Oda[1], Yosuke Hirakawa[1], Motonobu Nakamura[1], Yoshifumi Hamasaki[1,2] and Masaomi Nangaku[1,2]

**Abstract:**

A 77-year-old man developed peritoneal dialysis-related peritonitis caused by *Streptococcus oralis*, a rare pathogen causing the disease. The infection, which was not controlled by one-week intraperitoneal administration of cefazolin and ceftazidime, was cured only after switching to two-week intravenous administration of cefazolin and ceftazidime. The patient had no major dental disease or recent history of dental intervention. This case suggests that *S. oralis* might cause peritoneal dialysis-related peritonitis with persistent systemic inflammation via an extra-oral infection route. The clinical course is discussed along with a review of the literature.

**Key words:** infection, peritoneal dialysis, peritoneal dialysis-related peritonitis, peritonitis, *Streptococcus oralis*, viridans group streptococci

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## Introduction

Peritoneal dialysis (PD)-related peritonitis is a common complication of PD. Among Gram-positive cocci (GPC), which are responsible for 44-64% of all cases of PD-related peritonitis (1, 2), the viridans group streptococci are an infrequent pathogen of the disease, accounting for only 5-10% of all cases of PD-related peritonitis (1, 3). *Streptococcus oralis*, which is a member of the viridans group streptococci, rarely causes PD-related peritonitis.

We herein report a case of PD-related peritonitis caused by *S. oralis* via extra-oral entry complicated with prolonged systemic inflammation.

## Case Report

A 77-year-old Japanese man with end-stage renal disease caused by nephrosclerosis had been on PD for four years. The patient was performing continuous cycling PD: automated PD during the night using both 1.35% and 2.5% glucose solutions (Midpeliq L; Terumo, Tokyo, Japan) and daytime dwell of 7.5% icodextrin solution (Nicopeliq; Terumo). He used a sterile tubing welder [Capdeal TSCD SC-102 (Mukin Ace); Terumo] to connect and disconnect dialysate bags. Although PD steadily removed over one liter of water per day, excessive dietary and fluid intake caused weight gain and bilateral lower leg edema.

He underwent arteriovenous fistula creation to start combination therapy of PD and hemodialysis. The combination therapy, which comprises five or six days of PD plus one day of hemodialysis every week, is performed to obtain sufficient ultrafiltration in patients with ultrafiltration failure and limited residual urine production. The patient underwent hemodialysis sessions for the first time in his life with arteriovenous fistula in his forearm. After finishing the second hemodialysis session, the patient developed a fever. Although he had no other subjective symptoms, cloudy effluent was obtained from the bag exchange in the evening of the same day.

His medical history included hypertension, hyperuricemia, and obstructive sleep apnea syndrome. He had no history of diabetes mellitus. Three years before presentation, he had experienced an exit-site infection and tunnel infection of the

[1]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Japan and [2]Department of Hemodialysis and Apheresis, The University of Tokyo Hospital, Japan
Received: September 3, 2020; Accepted: February 25, 2021; Advance Publication by J-STAGE: May 22, 2021
Correspondence to Dr. Yoshifumi Hamasaki, yhamasaki-tky@umin.ac.jp

**Table 1. Laboratory Data.**

| Variable | Result | Reference range |
|---|---|---|
| **Blood** | | |
| White cell count (/μL) | 11,900 | 3,200-7,900 |
| Differential count (%) | | |
| Neutrophils | 80.4 | 45.3-75.0 |
| Lymphocytes | 10.4 | 19.4-47.3 |
| Monocytes | 6.5 | 1.6-8.1 |
| Hemoglobin (g/dL) | 10.0 | 11.3-15.0 |
| Hematocrit (%) | 31.3 | 34.0-46.3 |
| Red cell count ($10^6$/μL) | 3.19 | 3.70-5.07 |
| Platelet count ($10^3$/μL) | 340 | 155-350 |
| Sodium (mEq/L) | 138 | 139-146 |
| Potassium (mEq/L) | 4.5 | 3.7-4.8 |
| Chloride (mEq/L) | 101 | 101-109 |
| Urea nitrogen (mg/dL) | 32.1 | 8-21 |
| Creatinine (mg/dL) | 9.00 | 0.46-0.78 |
| Calcium (mg/dL) | 8.6 | 8.7-10.1 |
| Phosphorus (mg/dL) | 2.4 | 2.8-4.6 |
| Total protein (g/dL) | 5.8 | 6.9-8.4 |
| Albumin (g/dL) | 2.6 | 3.9-5.2 |
| Aspartate aminotransferase (U/L) | 11 | 13-33 |
| Alanine aminotransferase (U/L) | 9 | 6-27 |
| Alkaline phosphatase (U/L) | 269 | 117-350 |
| γ-Glutamyltransferase (U/L) | 33 | 9-109 |
| Total bilirubin (mg/dL) | 0.3 | 0.3-1.1 |
| C-reactive protein (mg/dL) | 3.78 | <0.3 |
| **Peritoneal dialysis effluent** | | |
| White cell count (/μL) | 2,000 | Negative |

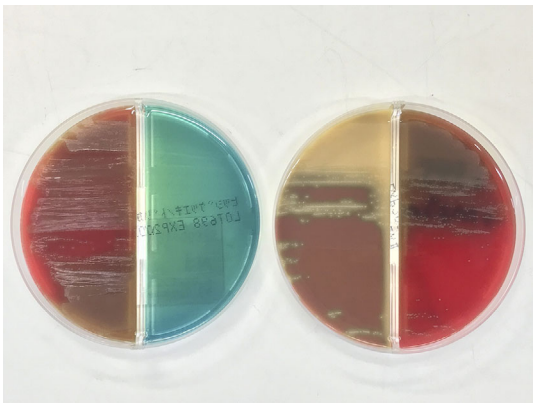

**Figure 2. No bacterial growth occurred on Drigalski agar (second medium from the left). Blood agar (media on the extreme left and extreme right) and chocolate agar (second medium from the right) grew colonies surrounded by green circles, which indicates α hemolysis. The term 'viridans' derives from the Latin word 'vĭrĭdis', meaning green.**

PD catheter. He was cured with antibiotics and a catheter diversion procedure with exit-site renewal. Pus culture showed no growth of microorganisms, including *Mycobacterium* species. No relapse of an exit-site infection or tunnel infection was observed during the next three years. He was an ex-smoker with a 20-pack-year smoking history. He did not

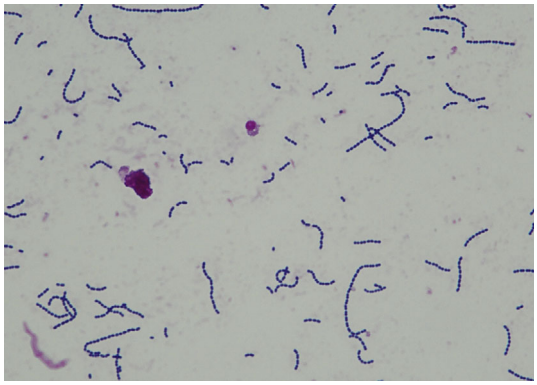

**Figure 1. Gram staining of the peritoneal dialysis effluent revealed Gram-positive cocci in chains.**

consume alcohol. He was working as a patent attorney, living with his wife, and fully able to care for himself and had been performing PD procedures independently. He was regularly taking amlodipine, azilsartan, carvedilol, furosemide, precipitated calcium carbonate, lanthanum carbonate hydrate, sucroferric oxyhydroxide, calcitriol, evocalcet, febuxostat, vonoprazan, and zolpidem.

On physical examination, the patient appeared well and was alert. His temperature was 37.9°C, blood pressure 134/82 mmHg, pulse 82 per minute, respiratory rate 14 per minute, and oxygen saturation 99% on ambient air. His height was 171 cm, weight 78.1 kg, and body mass index 26.7. Bowel sounds were normal. His abdomen was soft and nontender. Bilateral lower leg edema was mild. Neither an exit-site infection nor a tunnel infection of the PD catheter was detected. No classic physical findings of infectious diseases were observed other than a fever. Laboratory findings are shown in Table 1. His white blood cell count was 11,900/μL. His serum C-reactive protein (CRP) concentration was 3.78 mg/dL. The liver enzyme and electrolyte concentrations were normal. PD effluent was cloudy, and its white-cell count was elevated at 2,000/μL. Gram staining of the PD effluent showed GPC forming chains (Fig. 1). The patient was diagnosed with PD-related peritonitis. Intraperitoneal administration of cefazolin and ceftazidime was started in accordance with the International Society for Peritoneal Dialysis recommendations on peritonitis (4). One gram of cefazolin and one gram of ceftazidime were added to two liters of icodextrin-based PD solution, which was administered into the peritoneal cavity for nine hours every day.

On treatment day 3, *S. oralis* was detected in the PD effluent culture (Fig. 2). It was susceptible to a wide range of antibiotics (Table 2). Two sets of blood cultures obtained before starting the antibiotic therapy turned out negative. Differential counts of white cells in the PD effluent initially showed increased proportion of neutrophils (segmented neutrophils, 87%; lymphocytes, 12% on treatment day 2), which reversed over the course of time (segmented neutrophils, 35%; lymphocytes, 65% on treatment day 4). Although the white-cell count in PD effluent decreased to less than 100/μL on treatment day 4 and did not worsen thereaf-

**Table 2. Antibiotic Susceptibility Test Results of the *Streptococcus oralis* Isolate.**

| Antibiotic | Inhibition ring diameter (mm) | Minimal inhibitory concentration (μg/mL) | Susceptibility |
|---|---|---|---|
| **Disk diffusion method** | | | |
| Cefazolin | 0.23 | | N/A |
| **Broth microdilution method** | | | |
| Ampicillin | | ≤0.25 | sensitive |
| Clindamycin | | ≤0.25 | sensitive |
| Ceftriaxone | | 0.5 | sensitive |
| Meropenem | | ≤0.125 | sensitive |
| Erythromycin | | ≤0.25 | sensitive |
| Minocycline | | ≤1.0 | N/A |
| Penicillin G | | 0.125 | sensitive |
| Teicoplanin | | ≤0.5 | N/A |
| Cefepime | | 0.5 | sensitive |
| Vancomycin | | ≤0.5 | sensitive |
| Clarithromycin | | ≤0.25 | sensitive |
| Levofloxacin | | 1.0 | sensitive |
| Daptomycin | | 1.0 | sensitive |

Cefazolin was tested using the disk diffusion method. The result is reported in the diameter of the inhibition zone. Other antibiotics were tested using the broth microdilution method. The results are reported as minimum inhibitory concentration levels. Susceptibility was determined according to the breakpoints provided by the Clinical & Laboratory Standards Institute (16). Cefazolin, minocycline, and teicoplanin were not evaluated for their breakpoints for viridans group streptococci in the document and therefore have no reference to ascertain their susceptibility.

N/A: not available

ter, a persistent fever of 37-38°C was observed. On treatment day 8, his body temperature was 37.5°C. His white blood cell count and CRP level remained high at 12,000/μL and 11.76 mg/dL, respectively. Physical examination suggested no other focus of infection. Repeat blood culture tests showed no growth. Transthoracic echocardiography revealed no vegetation or valvular regurgitation. Computed tomography revealed no abscess, organomegaly or lymphadenopathy. The focus of inflammation was not identified, but the administration route of cefazolin and ceftazidime was switched to intravenous administration on treatment day 8 in an attempt to deliver the antibiotics throughout the body. The fever resolved on treatment day 11. Laboratory findings of inflammation disappeared over time (Fig. 3). Cefazolin and ceftazidime were administered intravenously without de-escalation until treatment day 22 to minimize the risk of treatment failure, although cefazolin monotherapy may have cured the infection as well. The patient was discharged on treatment day 23. At the time of writing this manuscript, he has experienced no relapse for more than nine months.

To elucidate the infection route, a dental examination was performed. Results showed mild periodontitis but no dental caries. Periodontal plaque culture grew *Streptococcus parasanguinis*, another member of the viridans group streptococci, but did not grow *S. oralis*. The patient had no recent history of dental intervention, exit-site or catheter-tunnel infection, recent catheter leakage, or gastrointestinal problems, including constipation or diarrhea. Although the patient had a history of an inappropriate PD procedure that caused PD dialysate leakage several months before the development of the peritonitis, he discarded the solution before connecting it to his PD catheter. There was insufficient evidence to ascertain the infection route objectively.

## Discussion

*S. oralis* is a member of the viridans group streptococci, which are part of the normal flora of the oral cavity, upper respiratory tract, gastrointestinal tract, and genitourinary tract (5, 6). In the literature, PD-related peritonitis caused by *S. oralis* is rarely reported. Therefore, little background information exists for the condition. This case report is the first to describe PD-related peritonitis caused by *S. oralis* with persistent systemic inflammation.

### *Infection route*

Viridans group streptococci, including *S. oralis*, are a major cause of bloodstream infection and infectious endocarditis associated with dental caries (5, 7). Cases of PD-related peritonitis caused by viridans group streptococci that developed after dental interventions have been reported in the literature (8, 9). In the present case, a dental examination revealed no dental lesions that might have caused systemic infection. Furthermore, no dental intervention had been performed recently. Blood cultures were negative. Moreover, a transthoracic echocardiogram showed no vegetation on the valves. Extra-oral entry of the bacteria was thus suspected to be the infection route. Of the two brief case reports concerning PD-related peritonitis caused by *S. oralis*, neither includes proof of oral infection (10, 11).

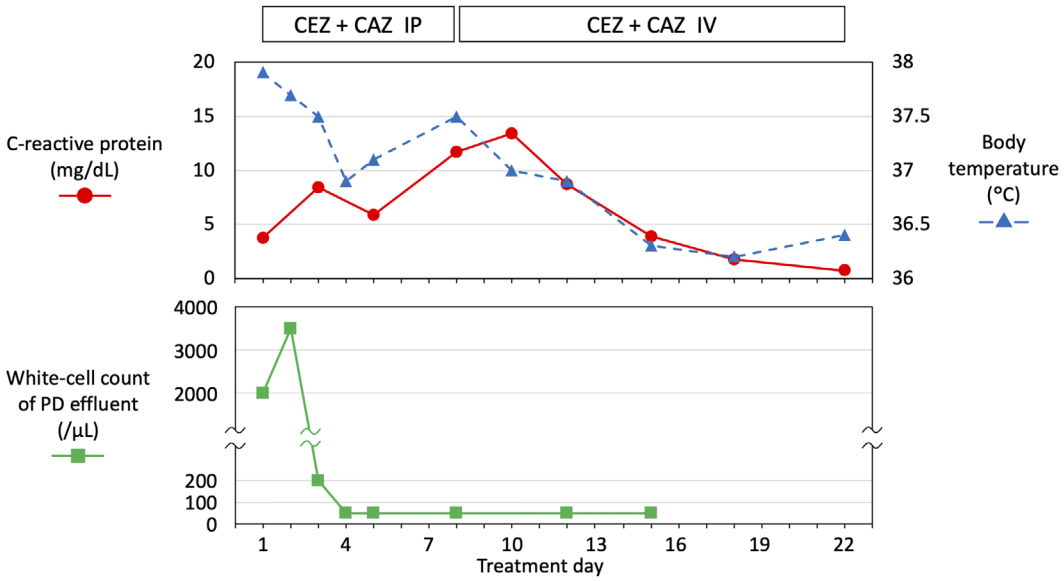


**Figure 3.** **Clinical course and treatment are described. White-cell counts of peritoneal dialysis effluent dropped below the detection threshold of 100 /μL after the intraperitoneal administration of cefazolin and ceftazidime. Signs of inflammation persisted, however, and resolved only after the administration route of cefazolin and ceftazidime was switched to intravenous injection. CAZ: ceftazidime, CEZ: cefazolin, IP: intraperitoneal, IV: intravenous, PD: peritoneal dialysis**

Touch contamination during bag exchanging procedures is reported as the cause in 89% of cases of PD-related peritonitis caused by viridans group streptococci (1). This finding suggests that not only oral infection but also touch contamination via saliva splashes is a major infection route of PD-related peritonitis caused by viridans group streptococci. One of the two earlier case reports of PD-related peritonitis caused by *S. oralis* describes a saxophone player who played the saxophone before each onset of consecutive episodes of PD-related peritonitis. Given that he no longer developed PD-related peritonitis after he quit playing the saxophone, the authors inferred that his saliva spreading all around himself heightened the risk of PD-related peritonitis via touch contamination (11). In our case, the patient used a sterile tubing welder, which minimizes the risk of touch contamination.

One might infer the arteriovenous fistula puncture for the hemodialysis sessions as the cause of undetected transient bacteremia of *S. oralis* if his limbs had been contaminated with someone's saliva. Although this was a possible route of entry, the patient and staff were wearing face masks, the puncture sites were cleansed with chlorhexidine, signs of infection were absent at the puncture site, and blood cultures were negative. All such measures and findings decrease the likelihood of such an infection. To our knowledge, there have been no case reports of arteriovenous fistula infection caused by *S. oralis*.

No other clues were available to ascertain the infection route. There was no gastrointestinal symptoms, exit-site infection, catheter-tunnel infection, or recent catheter leakage. Although the infection route was not identified, the details of this case emphasize the value of considering extra-oral infection routes even if the causative bacteria are part of the oral flora.

### Short-term outcome

In the short term, PD-related peritonitis caused by viridans group streptococci has favorable outcomes. In fact, PD-related peritonitis overall is complicated by relapse within 4 weeks in 14% of all cases, by catheter removal in 22%, and by death in 2-6% (12), whereas previous reports have found that PD-related peritonitis caused by viridans group streptococci was complicated by its relapse within 4 weeks in only 0-2% of cases and catheter removal in only 6%, with no deaths related to index peritonitis noted (1, 3). Two earlier reported cases of PD-related peritonitis caused by *S. oralis* were cured merely by the administration of antibiotics (10, 11). The peritonitis of the case reported here was also cured using antibiotics alone. The prognosis of PD-related peritonitis caused by *S. oralis* is apparently just as favorable as the prognosis of infections caused by other viridans group streptococci.

In the case presented in this report, the white-cell count in PD effluent decreased to less than 100/μL shortly after starting the intraperitoneal administration of cefazolin and ceftazidime. Nevertheless, systemic inflammation disappeared only after the antibiotic administration route was switched from intraperitoneal administration to intravenous administration. Although the etiology underlying the systemic inflammation remains unclear, several hypotheses exist as possible explanations of the clinical course. First, the existence of a different focus of infection other than peritonitis might have caused persistent inflammation. Bacteremia was inferred as a possible complication because viridans group

streptococci are a major cause of bloodstream infections. However, two sets of blood cultures were negative. The sensitivity of two sets of blood cultures for detecting streptococci bacteremia is 85% (13). No physical, laboratory or radiological findings suggest the existence of concomitant infectious diseases, including infectious endocarditis. No other focus of infection was detected throughout the clinical course. Second, residual infection of the peritoneum might have existed and might have required intravenous antibiotic administration to achieve a cure. Although the white-cell count in the PD effluent decreased to below 100/μL after the intraperitoneal administration of the antibiotics, 100/μL is the lower limit of detection and report in the PD effluent test procedure in our laboratory. Therefore, the test results might have been insufficient to reflect a low level of inflammation in the peritoneum. Conversely, previous reports suggest that the intravenous administration of antibiotics is not clinically or pharmacokinetically superior to the intraperitoneal administration for treating PD-related peritonitis with no other focus of infection (14, 15). Third, simply a longer period of antibiotic therapy might have been necessary to cure the peritonitis, irrespective of the administration route used for the antibiotics. By its nature, this hypothesis cannot be verified. The International Society for Peritoneal Dialysis recommendations on peritonitis state that effective antibiotic treatment for two weeks is generally sufficient to treat PD-related peritonitis caused by streptococci (4). One might speculate that two weeks of intraperitoneal administration of antibiotics could have treated the peritonitis of this case successfully. However, one week of a persistent fever is rarely seen in PD-related peritonitis with a fair treatment response. In addition, the resolution of a fever and systemic inflammation immediately after switching the antibiotic administration route does not favor this speculation. Despite these previous investigations and discussions, the etiology of systemic inflammation that has been cured solely after the intravenous administration of antibiotics remains unclear.

### Long-term outcome

Although PD-related peritonitis caused by viridans group streptococci shows favorable outcomes in the short term, as many as 41% of patients experience refractory peritonitis in the long term, defined by unclear effluent after 5 days of appropriate antibiotic treatment and eventual Tenckhoff catheter removal (1). This rate is markedly higher than those of refractory peritonitis caused by other GPC (1). A review of the two earlier case reports of PD-related peritonitis caused by *S. oralis* revealed mixed findings: the first case report did not mention the long-term outcomes of the case (10), and the second case report described a second episode of peritonitis occurring several months after the initial one (11). Our patient has remained free from peritonitis recurrence for over nine months at the time of manuscript submission. Further follow-up can be expected to reveal long-term outcomes.

### Conclusion

This report describes a case of PD-related peritonitis caused by *S. oralis* via extra-oral entry complicated with persistent systemic inflammation. Few reports have described cases of PD-related peritonitis caused by *S. oralis* because of its rarity. Further research is warranted to elucidate more aspects of its clinical characteristics, optimum treatment, and prognosis.

**The authors state that they have no Conflict of Interest (COI).**

Akihiro Kotani and Yasuhiro Oda equally contributed to this work.

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