Peritoneal Dialysis–Related Peritonitis due to Coagulase-Negative Staphylococcus: A Review of 115 Cases in a Brazilian Center

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Abstract

Background and objectives Coagulase-negative Staphylococcus (CNS) is the most frequent cause of peritoneal dialysis (PD)–related peritonitis in many centers. This study aimed to describe clinical and microbiologic characteristics of 115 CNS episodes and to determine factors influencing the outcome.

Design, setting, participants, & measurements This study reviewed the records of 115 CNS peritonitis episodes that occurred in 74 patients between 1994 and 2011 at a single university center. Peritonitis incidences were calculated for three consecutive 6-year periods (P1, 1994–1999; P2, 2000–2005; P3, 2006–2011) and annually. The production of biofilms, enzymes, and toxins was evaluated. Oxacillin resistance was evaluated based on its minimum inhibitory concentration and the presence of the mecA gene.

Results The overall incidence of CNS peritonitis was 0.15 episodes per patient per year and did not vary over time (0.12, 0.14, and 0.16 for P1, P2, and P3, respectively; P=0.21). The oxacillin resistance rate was 69.6%. Toxin and enzyme production was infrequent and 36.5% of CNS strains presented the gene encoding biofilm production. The presence of icaAD genes associated with biofilm production was predictive of relapses or repeat episodes (odds ratio [OR], 2.82; 95% confidence interval [95% CI], 1.11 to 7.19; P=0.03). Overall, 70 episodes (60.9%) resolved; oxacillin susceptibility (OR, 4.41; 95% CI, 1.48 to 13.17; P=0.01) and vancomycin use as the first treatment (OR, 22.27; 95% CI, 6.16 to 80.53; P<0.001) were the only independent predictors of resolution.

Conclusions Oxacillin resistance and vancomycin use as the first treatment strongly influence the resolution rate in CNS peritonitis, which reinforces the validity of the International Society for Peritoneal Dialysis guidelines on monitoring bacterial resistance to define protocols for initial treatment. These results also suggest that the presence of biofilm is a potential cause of repeat peritonitis episodes.


Introduction

Peritonitis remains a major cause of technique failure in peritoneal dialysis (PD) (1) and affects patients’ morbidity and mortality (2). In many centers, coagulase-negative Staphylococcus (CNS) species are its most frequent causes. In general, CNS peritonitis presents a mild clinical course and has a high resolution rate; however, CNS has shown an increasing methicillin resistance rate (3,4). The CNS group comprises >40 species (5), some of which are already well established as causes of PD-related peritonitis, particularly Staphylococcus epidermidis (6,7). Methicillin (or oxacillin, similar and stable penicillin) resistance is mediated by mecA (8), a gene located on the transferable element SCCmec, which allows transmission of the resistance trait (9). Methicillin resistance has important implications, including restriction of the use of β-lactams (7). In addition, bacterial virulence factors and patient characteristics can influence the peritonitis outcome. For instance, we demonstrated an association between biofilm production and nonresolution of CNS peritonitis (10), and we showed that both β-hemolysin production and diabetes mellitus are independent predictors of the nonresolution of Staphylococcus aureus peritonitis (11). Furthermore, studies comparing the outcome of peritonitis caused by different CNS species have not been reported.

The two largest published series of CNS peritonitis by Szeto et al. and Fahim et al. confirmed high methicillin resistance rates of 49.5% and 68%, respectively (12,13). Unexpectedly, in both studies, there were no differences in the outcomes of episodes treated with vancomycin or a first-generation cephalosporin. Although these results may be associated with bias in the initial prescription, it is also possible that some nonevaluated host or bacterial factors influenced the outcome. To provide information regarding the microbiologic and clinical characterization of CNS peritonitis, we reviewed all CNS peritonitis episodes that occurred over an 18-year period. Our main objective
was to identify microbiologic and clinical predictors of outcome.

Materials and Methods

Study Population

When patients started their treatment, they gave written consent for the use of their clinical and laboratorial data for research purposes. Thus, the institutional research ethics committee approved this study and exempted it of any specific written informed consent. We reviewed all episodes of PD-related peritonitis caused by CNS that occurred between June 1994 and December 2011. Exclusion criteria were the presence of concomitant exit site or tunnel infections and incomplete information. A peritonitis diagnosis was based on at least two of the following: abdominal pain or cloudy dialysate, dialysate white cell count >100/μL with at least 50% neutrophilic cells, and positive culture of dialysate (14). A repeat refers to an episode that occurs >4 weeks after completion of therapy of a prior episode with the same CNS species (14). Recurrence refers to an episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different CNS species (14). A relapse is an episode caused by the same CNS species, or a negative culture result accompanied by signs or symptoms of peritonitis within 28 days of completion of antibiotic therapy (14). Resolution was defined as the disappearance of signs and symptoms within 5 days after the beginning of antibiotic therapy (14). Refractory peritonitis is the failure of the effluent to clear after 5 days using appropriate antibiotics (14). Peritonitis-related death refers to the death of a patient with active peritonitis or to a patient who had an episode within the previous 2 weeks (14). Nonresolution refers to the patients who required catheter removal by refractory peritonitis, needed a second antibiotic regimen, relapsed, or progressed to death.

Patients and/or caretakers received at least 20 hours of theoretical and practical PD training by a senior nurse. Retraining was performed if peritonitis occurred. If the patient reported contamination, a single dose of cefazolin (1 g intraperitoneally) was given.

Data Collection

The following information was recorded for each case: (1) episode: date, clinical findings, previous peritonitis episodes, vancomycin use, outcome (resolution, relapse, catheter removal, or death); (2) presence of diabetes; (3) demographics: age, sex, and race (Caucasian, non-Caucasian), and (4) dialysis vintage and modality.

Patients were initially treated within 24 hours of the onset of signs or symptoms using contemporary antibiotic recommendations (7,14,15). The peritonitis rate (episodes per patient per year) and the proportion of oxacillin-resistant isolates were calculated for three periods of 6 years.

During period 1 (1994–1999), antibiotic prophylaxis was not prescribed, and the connection systems were the Y set (1994-1998) or the twin bag (introduced in 1999). Automated PD was introduced in 1998, and its indication for prevalent patients was based only on clinical criteria; for incident patients, the main criterion was the patient’s option. During period 2 (2000–2005), antibiotic prophylaxis was not prescribed until 2003, when daily application of mupirocin cream at the exit site was introduced; the twin bag system was used in all patients. During period 3 (2006–2011), daily application of mupirocin was prescribed until December 2006, and it was replaced by gentamicin cream in January 2007; the twin bag system was used in all patients.

Cultures were performed with the Bactec System (Becton Dickinson Company, Sparks, MD) and then seeded onto blood agar. The isolates were submitted to catalase and coagulase tests (16) and were identified according to the recommendations of Cunha et al. (17). After identification and susceptibility testing, strains were stored frozen at −80°C in Trypticase Soy Broth with 15% glycerol. Phenotypic identification was confirmed by internal transcribed spacer PCR, after extraction of bacterial whole nucleic acids (18). Discrepancies were resolved using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (19,20) using a MALDI-TOF Biotyper (Bruker Daltonik, Bremen, Germany), and/or partial sequencing of RNA polymerase β-subunit gene rpo B (21) followed by Basic Local Alignment Search Tool analysis (22).

The in vitro susceptibilities to oxacillin and vancomycin were determined based on minimal inhibitory concentrations by the E test (bioMérieux, Inc., Durham, NC) and the broth microdilution technique, respectively. The microdilution test was performed according to Clinical and Laboratory Standards Institute (CLSI) recommendations (23) utilizing cation-adjusted Mueller Hinton Broth (Becton Dickinson [BD]) and vancomycin hydrochloride (Sigma-Aldrich, Shanghai, China). Standard reference strains (S. aureus ATCC 29213; Enterococcus faecalis ATCC 29212, and E. faecalis ATCC 51299) were utilized for quality control. The susceptibility was defined based on the 2013 CLSI breakpoints (8). Strains presenting intermediate values were considered resistant.

PCR amplification of bacterial DNA was performed to detect the mecA gene, biofilm-related gene (icaAD), and the genes encoding enterotoxins A–D (sea, seb, sec, and sed), TSST-1 (tst), and Panton-Valentien leukocidin ( lukPVE). Reactions were carried out in 0.2-ml microcentrifuge tubes containing 10 pmol of each primer, 2.0 U of Taq-DNA polymerase, 100 μM of deoxyribonucleotide triphosphates, 10 mM Tris-HCl (pH 8.4), 0.75 mM MgCl2, and 3 μL nucleic acid in a total volume of 25 μL. Primer sequences and amplification conditions of the PCR reactions were published elsewhere (24–27). The following S. aureus reference strains were included in the reactions as positive controls: ATCC 33591 (mecA positive), ATCC 13565 (sea positive), ATCC 14458 (seb positive), ATCC 19095 (sec positive), ATCC 23235 (sed positive), ATCC 51650 (tst positive), and ATCC 49775 (lukPVE positive); water was used as a template for negative control PCR reactions. The efficiency of amplification was monitored by electrophoresis on 1.5% agarose gel prepared in 1× Tris-borate-EDTA buffer and stained with ethidium bromide. The size of amplified products was compared with a 100-bp standard and the gels were photographed under ultraviolet transillumination.

Production of α- and β-hemolysin was determined on plates containing a blood agar base supplemented with 5% rabbit blood and 5% sheep blood, respectively. The plates were incubated for 24 hours at 37°C. The formation of hemolysis zones around the isolated colonies indicated a
positive result. Lipolytic activity was determined on plates containing blood agar enriched with 0.01% CaCl$_2$/2H$_2$O and 1% Tween 80. A positive result was defined as the formation of opacity around the colony after incubation at 37°C for 18 hours, followed by incubation at room temperature for 24 hours (28). The production of lecithinase was evaluated using Baird-Parker medium. The formation of an opaque halo around the colony indicated positivity (29). Nuclease (DNAse) and thermonuclease (TNAse) production were detected using the metachromatic Toluidine blue O agar diffusion-DNA technique as described by Lachica et al. (30). Supernatants obtained by the sac culture method described by Donnelly et al. (31) were transferred to the wells of plates containing metachromatic Toluidine blue O agar. The culture supernatant was first heated in a water bath for 20 minutes for the detection of TNAse. Nuclease (DNAse and TNAse) activity was evaluated by measuring the diameter of pink halos (in millimeters) formed on the medium. Positive results were interpreted by comparing the halos with those obtained for a standard DNAse and TNAse-positive *S. aureus* strain (ATCC 25923).

Statistical Analyses
Chi-squared or Fisher’s exact tests were used to compare frequencies. Incidences were compared using the Poisson regression model. Multivariate analysis by logistic regression was used to determine independent predictors of outcomes (resolution or nonresolution). Collinearity among variables was tested and, if statistically significant interactions were presented, one of them was excluded. Univariate logistic regression was performed to select variables for the final model, using $P>0.20$ as the elimination criterion, and to evaluate the association between microbiologic factors and repeat or relapse episodes. The Hosmer and Lemeshow test was used to assess the fit of logistic regression models. A $P$ value $<0.05$ was considered significant.

Results
Between 1994 and 2011, 878 peritonitis episodes were diagnosed; CNS caused 135 of them. After the exclusion criteria were applied, 115 episodes were enrolled. The

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Frequency, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloudy dialysis effluent</td>
<td>106 (92.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>89 (77.4)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>47 (40.9)</td>
</tr>
<tr>
<td>Fever</td>
<td>17 (14.8)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>12 (10.4)</td>
</tr>
</tbody>
</table>

Figure 1. Annual rate (episodes per patient per year) of CNS peritonitis from June 1994 to December 2011 and introduction of changes in peritoneal dialysis practice. Dashed line represents a trend curve of peritonitis rate. APD, automated peritoneal dialysis; CNS, coagulase-negative *Staphylococcus.*
overall peritonitis rate was 0.89 and the CNS peritonitis rate was 0.15 episodes per patient per year. The incidences of CNS peritonitis were 0.12, 0.14, and 0.16 in periods 1, 2, and 3, respectively (P=0.21). There was a nonstatistically significant decline after introduction of the Y set system (1995) (P=0.10) and a slight increase of incidence over time (P=0.19) (Figure 1).

The 115 peritonitis episodes occurred in 74 patients; 47 patients had one, 16 had two, and 11 had three or more episodes. Demographic and clinical data at the first episode showed that the patient’s mean age was 53.6±15.9 years, 43 were women (58.1%), 60 were Caucasians (81.1%), 35 were aged 60 years (47.3%), 30 presented with diabetes (40.5%), and 59 were treated by continuous ambulatory PD (79.7%). Eighty-eight cases (76.5%) were new episodes, 19 (16.5%) were repeat or recurring, and eight (6.6%) were relapses. Clinical findings at the initial presentation are shown in Table 1.

Vancomycin was used in 81 episodes (70.4%; as the initial treatment in 40 episodes and as a second regimen in 41 episodes), whereas cefazolin was initially prescribed in 75 cases. Overall, 70 episodes (60.9%) resolved. Among nonresolved infections, 18 (15.7%) required catheter removal because of refractory peritonitis, 14 (12.2%) relapsed, 10 (8.7%) were cured with a second antibiotic, and 3 (2.6%) progressed to death. Figure 2 expresses the outcomes according to oxacillin susceptibility and initial therapy.

S. epidermidis was the most frequent cause (62.6%), followed by Staphylococcus haemolyticus (11.3%), Staphylococcus warneri (7%), Staphylococcus cohnii (5.2%), and Staphylococcus hominis (4.3%). Seven other species were identified, accounting for 9.6% of episodes (Table 2).

Oxacillin resistance was detected in 80 strains (69.6%), with rates of 62.7%, 84%, and 70.9% in periods 1, 2, and 3, respectively (P=0.18). The mecA gene was detected in 55 isolates (47.8%), correlating in 75.3% with oxacillin resistance detected by the E test. All strains were susceptible to vancomycin. Species-specific patterns of susceptibility are shown in Table 3. Analysis of the five most frequent species revealed similar oxacillin resistance rates except S. warneri strains, which had a lower rate than S. haemolyticus (P=0.02). Enzyme-, toxin-, and biofilm-encoding genes were detected mainly in S. epidermidis isolates (Table 4).

At least one enterotoxin gene was found in 20 strains (17.4%), the simultaneous presence of sec and sed was verified in one strain of S. epidermidis and one of S. hominis, and another S. epidermidis strain carried sea, sec, and sed genes. Toxic shock syndrome toxin-1 and Panton-Valentine leukocidin encoding genes (tst and lukF-PV, respectively) were not detected.

A multivariate logistic regression model showed that oxacillin susceptibility (odds ratio [OR], 4.41; 95% confidence interval [95% CI], 1.48 to 13.17; P=0.01) and vancomycin use as the first treatment (OR, 22.27; 95% CI, 6.16 to 80.53; P<0.001) were the only independent predictors of resolution. Clinical, demographic, and dialysis-related factors (e.g., sex, race, age, diabetes, dialysis vintage, number of previous peritonitis episodes, and PD modality) did not influence the outcome. In addition, factors such as CNS species, toxin and enzyme production, or the presence of the mecA and icaAD genes were not associated with the outcome. On the other hand, the presence of the mecA (OR, 3.11; 95% CI, 1.17 to 8.27; P=0.02) and icaAD (OR, 2.82; 95% CI, 1.11 to 7.19; P=0.03) genes were associated with relapse and repeat episodes.

The resolution rate was 53.4% in a second analysis enrolling only new episodes (n=88). Oxacillin susceptibility (OR, 4.64; 95% CI, 1.14 to 18.3; P=0.03) and vancomycin as Figure 2. | Clinical outcomes of coagulase-negative peritonitis, according to oxacillin susceptibility and initial antibiotic therapy.
the first treatment (OR, 25.13; 95% CI, 4.89 to 129.04; 
P<0.001) remained the only independent predictors of res-
olution. The P values from Hosmer and Lemeshow tests 
for the first and the second multivariate models were 0.72 
and 0.43, respectively.

Discussion

Although our center has experienced a reduction in 
peritonitis rates over the last 2 decades (32), the incidence 
of CNS peritonitis did not vary. After an initial reduction 
associated with Y set use, a trend to increase occurred over 
time. By contrast, we recently reported a strong decline in 
the S. aureus peritonitis rate (11) similar to that observed in 
other centers (4). It is possible that the introduction of safer 
dialysis connections and antibiotic prophylaxis had a 
greater effect on S. aureus than CNS peritonitis prevention. 
A high prevalence of S. aureus nasal carriage in our 
country (33) could explain, at least in part, these contrast-

A high oxacillin resistance rate was observed, which 
likely explains the number of episodes treated by vancomycin.

Table 2. Causative agents of 115 episodes of peritoneal 
dialysis–associated peritonitis caused by coagulase-negative 
Staphylococci

<table>
<thead>
<tr>
<th>Staphylococcus Species</th>
<th>Frequency, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. epidermidis</td>
<td>72 (62.6)</td>
</tr>
<tr>
<td>S. haemolyticus</td>
<td>13 (11.3)</td>
</tr>
<tr>
<td>S. warneri</td>
<td>8 (6.9)</td>
</tr>
<tr>
<td>S. colnii</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>S. hominis</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>S. capitis</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>S. capra</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>S. lugdunensis</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>S. pasteur</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>S. sciuri</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>S. xylosus</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Total</td>
<td>115 (100.0)</td>
</tr>
</tbody>
</table>

Table 3. Vancomycin and oxacillin susceptibility patterns of coagulase-negative Staphylococci isolated from peritoneal dialysis–associated peritonitis

<table>
<thead>
<tr>
<th>Staphylococcus Species</th>
<th>n</th>
<th>MIC50 μg/ml</th>
<th>Oxacillin Resistance Rate, n (%)</th>
<th>meCA Gene, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
<td>Oxacillin</td>
<td></td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>72</td>
<td>2.0</td>
<td>1.0</td>
<td>50 (71.4)</td>
</tr>
<tr>
<td>S. haemolyticus</td>
<td>13</td>
<td>1.0</td>
<td>4.0</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>S. warneri</td>
<td>8</td>
<td>1.0</td>
<td>0.25</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>S. colnii</td>
<td>6</td>
<td>1.5</td>
<td>0.5</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>S. hominis</td>
<td>5</td>
<td>0.5</td>
<td>0.38</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td>4</td>
<td>1.0</td>
<td>0.38</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>S. capitis</td>
<td>2</td>
<td>1.0</td>
<td>0.38</td>
<td>2 (100)</td>
</tr>
<tr>
<td>S. xylosus</td>
<td>1</td>
<td>1.0</td>
<td>0.38</td>
<td>1 (100)</td>
</tr>
<tr>
<td>S. sciuri</td>
<td>1</td>
<td>1.0</td>
<td>0.5</td>
<td>1 (100)</td>
</tr>
<tr>
<td>S. pasteur</td>
<td>1</td>
<td>1.0</td>
<td>0.75</td>
<td>1 (100)</td>
</tr>
<tr>
<td>S. lugdunensis</td>
<td>1</td>
<td>0.5</td>
<td>0.75</td>
<td>0</td>
</tr>
<tr>
<td>S. capra</td>
<td>1</td>
<td>0.25</td>
<td>0.125</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
<td>1.0</td>
<td>0.75</td>
<td>80 (69.6)</td>
</tr>
</tbody>
</table>

MIC50, minimal inhibitory concentration that inhibited the growth of 50% of isolates.
Table 4. Rates of enzyme production and detection of biofilm- and toxin-encoding genes in coagulase-negative \textit{Staphylococcus} isolated from peritoneal dialysis–associated peritonitis cases

<table>
<thead>
<tr>
<th>\textit{Staphylococcus} Species</th>
<th>n</th>
<th>α-Hemolysin</th>
<th>β-Hemolysin</th>
<th>Lipase</th>
<th>Phospholipase</th>
<th>DNase</th>
<th>DNAse</th>
<th>TNAse</th>
<th>icaAD</th>
<th>sec</th>
<th>sed</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{S. epidermidis}</td>
<td>13</td>
<td>10 (76.9)</td>
<td>7 (53.8)</td>
<td>1 (7.7)</td>
<td>1 (7.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{S. haemolyticus}</td>
<td>8</td>
<td>4 (50.0)</td>
<td>2 (25.0)</td>
<td>6 (75.0)</td>
<td>4 (50.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{S. warneri}</td>
<td>6</td>
<td>3 (50.0)</td>
<td>2 (33.3)</td>
<td>3 (50.0)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>\textit{S. cohnii}</td>
<td>1</td>
<td>1 (100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>\textit{S. hominis}</td>
<td>5</td>
<td>4 (80.0)</td>
<td>1 (20.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>\textit{S. saprophyticus}</td>
<td>4</td>
<td>1 (25.0)</td>
<td>3 (75.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{S. capitis}</td>
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<td>0</td>
<td>0</td>
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<td>\textit{S. xylosus}</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>\textit{S. sciuri}</td>
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<tr>
<td>\textit{S. caprae}</td>
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<td>1 (100.0)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>\textit{Total}</td>
<td>115</td>
<td>44 (38.3)</td>
<td>28 (23.9)</td>
<td>35 (30.4)</td>
<td>31 (26.6)</td>
<td>32</td>
<td>15</td>
<td>8</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are given as n (%) unless otherwise indicated. DNase, deoxyribonuclease; icaAD, biofilm-related genes; sec, sed, and sec, enterotoxin A-D-encoding genes, respectively; TNAse, thermonuclease.

Oxacillin resistance, detected phenotypically, had a 73% concordance with meca detection. This was influenced mainly by the low breakpoints from the 2013 CLSI (8), once 35% of resistant strains were meca negative, whereas only 8.6% of susceptible were meca positive. Similar resistance profiles were observed among CNS species, although \textit{S. warneri} and \textit{S. haemolyticus} trended toward low and high oxacillin resistance rates, respectively.

Beyond peritonitis, an increasing CNS oxacillin resistance rate has been observed in cases of outpatient and nosocomial infections at our hospital, particularly among outpatient infections, with a current rate of >50% (unpublished data). The SENTRY Antimicrobial Surveillance Program has documented a high and slightly increasing methicillin resistance rate among CNS around the world (37).

Oxacillin susceptibility was an independent predictor of resolution. Methicillin resistance has been associated with an increased risk of relapse in CNS peritonitis (13) and with worse outcomes of \textit{S. aureus} infections (38,39). The largest report of CNS peritonitis showed that detection of methicillin resistance and prompt change of the treatment to vancomycin improved the cure rate (12).

Vancomycin had high in vitro activity against all of the strains, with minimum inhibitory concentration values ≤2.0 µg/ml. Resistance to vancomycin is seldom observed in staphylococci, even in CNS in which glycopeptide resistance is more frequent (40).

The initial vancomycin prescription was a predictor of resolution, possibly because of the high oxacillin resistance rate. However, its use as a second treatment was associated with a low resolution rate. We speculate that a delay in the vancomycin prescription or its use in patients with severe infections could explain these findings.

CNS strains had low expressive enzyme and toxin production, although the icaAD gene-encoding biofilm was found in approximately 35% of them. However, these factors were not associated with the outcome. This finding differs from the observed in \textit{S. aureus} episodes, in which β-hemolysin production was a predictor of a poor outcome (11). Even if we have not used techniques for direct observation of biofilm, the presence of icaAD was associated with relapse and repeat peritonitis, reinforcing that biofilm increases the risk for relapse (41). However, its association with repeated infections was not previously reported. Interestingly, Nessim et al. (42) reported that prior CNS peritonitis was associated with an increased risk of CNS peritonitis within the subsequent year. This result may be associated with the presence of biofilm in the catheter of patients suffering a repeat CNS episode. Our results suggest that catheter removal should be considered for patients presenting with high peritonitis rates and repeat infections.

This study had limitations such as the small number of cases and its single-center characteristic, which limits wide extrapolation of its results. However, this work presents novel information regarding CNS peritonitis, such as a detailed characterization of the species and the identification of the meca gene as well as the association of biofilm with repeat peritonitis. Furthermore, this is the first Latin American study analyzing a long-term series of CNS PD-related peritonitis.
In conclusion, the odds of resolution were strongly influenced by oxacillin susceptibility and initial vancomycin prescription, emphasizing the pertinence of ISPD guidelines (7,14) regarding antimicrobial resistance monitoring in every dialysis center toward a rational definition of peritonitis treatment protocols.

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Disclosures

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