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Prognosis and characteristics of *Corynebacterium* exit site infection: a single-center retrospective study

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Abstract

Background *Corynebacterium* is a rare but important cause of peritoneal dialysis (PD)-associated infection. A previous study reported that continued antibiotic use at the exit site is associated with increased *Corynebacterium* exit site infection (ESI), although the latest International Society of Peritoneal Dialysis guideline recommends its use. This study aims to verify the prognosis of *Corynebacterium*-associated PD-related infections, focusing on ESI.

Methods We conducted a single-center, retrospective study about ESI, tunnel infection (TI), and PD-associated peritonitis due to *Corynebacterium* between April 2018 and January 2023. We primarily examined the prognosis and characteristics of *Corynebacterium* ESI.

Results In this study, we included 125 patients with PD (mean age at PD onset: 69.4 ± 13.7 years, 71.2% male, 48% diabetic, mean estimated glomerular filtration rate at the introduction of PD 7.4 ± 2.6 ml/min/1.73 m^2, total follow-up 179.6 patient dialysis year). Between April 2018 and January 2023, 191 cases of ESI, 62 cases of *Corynebacterium* ESI in 24 patients, 10 cases of TI, and 32 cases of PD-associated peritonitis were detected. In total, 16 of 24 patients with *Corynebacterium*-associated ESI tested positive for *Corynebacterium* multiple times in cultures against the exit site, with a maximum of eight times. The estimated glomerular filtration rate during PD introduction was relatively lower in patients with *Corynebacterium*-associated ESI than in patients without ESI (6.4 versus 7.9 mL/min/1.73 m^2, respectively; $P = 0.052$). Although three of the *Corynebacterium* ESI cases progressed to TI, there were no cases that progressed directly to PD-associated peritonitis.

Conclusions *Corynebacterium*-associated ESI progresses to TI with a certain probability; however, it is thought that it rarely progresses to PD-associated peritonitis directly.

Keywords Tunnel infection, Peritonitis, Peritoneal dialysis-associated infection, Gentamicin ointment, Antibiotics

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Background

Improvement in exit site care and the use of antibiotic agents at the exit site have significantly decreased the incidence of Gram-positive exit site infection (ESI) [1–3]. The International Society for Peritoneal Dialysis (ISPD) Guidelines recommend daily application of topical antimicrobial agents (including mupirocin or gentamicin) at the exit site to prevent ESI [4]. *Corynebacterium* species, which are Gram-positive bacilli, are uncommon but recognizable causes of peritoneal dialysis (PD)-associated peritonitis. *Corynebacterium* species have also been increasingly recognized over the past decades, largely due to improved recognition and microbiological techniques [5–8]. Previous studies have reported that *Corynebacterium* infection accounts for a major proportion of PD-associated peritonitis [5–8]. On the other hand, we have seen only a few recent reports about how many ESIs due to *Corynebacterium* lead to PD-associated peritonitis and tunnel infection [9, 10]. ESI is one of the most common causes of PD-associated peritonitis, and it can lead to tunnel infection (TI) and catheter loss [1, 4]. We conducted a single-center, retrospective study of ESI due to *Corynebacterium*.

Methods

Study design and participants

We retrospectively reviewed the clinical data of 125 patients with end-stage renal disease who received PD and were followed up at the International University of Health and Welfare (IUHW) Hospital, Tochigi, Japan, from April 2018 to January 2023. This study protocol was approved by the ethics committee of the IUHW (approval number: 23-Im-028). Patients without submission rate data and those who opted out were excluded. This study was registered at inception in the UMIN Clinical Trials Registry under identification number UMIN000052200. In this study, we included patients aged ≥ 20 years who selected PD based on shared decision-making in renal replacement therapy selection.

Data collection and patient evaluation

Patients' demographic data were obtained from medical records. Baseline characteristics at PD initiation included sex, age, weight, primary cause of kidney disease, estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2), information about self-care PD or assisted PD, diseases that caused end-stage renal disease, and blood pressure. The Body mass index (BMI) was calculated using height (m) and body weight (kg) data at the time of PD initiation. Moreover, PD-related parameters were obtained at the first onset of ESI. PD vintage and the Charlson comorbidity index were obtained and compared between patients with ESI due to *Corynebacterium* and those with ESI associated with other pathogens. Unfortunately, markers of small solute clearance from PD—such as PD Kt/V or creatinine clearance—and those of residual kidney function—such as residual GFR—were not assessed systematically in our clinical practice. Therefore, we measured PD fluid volume as a marker of small solute clearance from PD and the serum urea-to-creatinine ratio as a marker of residual kidney function, which has been identified as an indicators of residual kidney function in patients on PD [11]. Moreover, the treatment period of each ESI was obtained.

Follow-up

All participants were followed up until PD cessation (i.e., transfer to HD alone), death, kidney transplantation, transfer to another hospital, or study completion (31 January 2023). Transfer to HD alone was defined as a transition to thrice-weekly HD.

Exit site care and definitions of PD-associated infection

We have applied gentamicin sulfate ointment at the exit site as usual care for all patients on PD. ESI diagnosis is based on the presence of a purulent discharge, with or without skin erythema at the catheter–epidermal interface [4]. The persistence of ESI due to the same pathogens for more than 4 weeks was defined as persistent pustular discharge and a positive culture from the exit site [4]. If the culture was negative for three consecutive months, the ESI was considered cured. TI is defined when we confirm the presence of clinical inflammation with or without ultrasonographic evidence of a fluid collection anywhere along the PD catheter tunnel or the presence of a low-density area around the PD catheter by computed tomography [4, 8]. PD-associated peritonitis is defined when at least two of the following three conditions are satisfied: (1) presence of fever and abdominal pain and (2) total PD effluent cell count > 100/cm^3, of which more than 50% were polymorphonuclear neutrophils, and (3) a positive culture of pathogens in the PD fluid [4–8]. In cases of polymicrobial PD-associated infection (ESI, TI, and PD-associated peritonitis), multiple isolations of the same cultured organisms with different susceptibility patterns were evaluated separately. If *Corynebacterium* was detected along with other major pathogens, such as *Staphylococcus*, the latter bacteria would be considered pathogenic. Therefore, this type of ESI was defined as "ESI due to other pathogens with *Corynebacterium* isolated" and categorized as "other pathogens-associated ESI," along with "ESI due to other pathogens alone." ESI in which only *Corynebacterium* was detected from the exit site was defined as "ESI due to *Corynebacterium*" or "*Corynebacterium*

ESI." Topical antibiotic treatment of *Corynebacterium* ESI was mupirocin ointment and minocycline ointment. Systemic antibiotics were initiated when we confirmed poor response to topical treatment. The standard systemic antibiotic treatment for *Corynebacterium* ESI includes oral levofloxacin, oral sulfamethoxazole, and intravenous vancomycin. When we confirm poor response to this series of antibiotics, we perform unroofing surgery, subcutaneous pathway diversion, or PD catheter removal. Response to medical treatment was defined as the disappearance of pustular discharge from the exit site after treatment.

Statistical analysis

Continuous variables were presented as mean values ± standard deviations or medians (25–75th percentiles) based on the normality of data distribution assessed by the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Normally and non-normally distributed continuous variables were evaluated using the one-way analysis of variance and Kruskal–Wallis test, respectively, and the chi-square test was used for categorical variables to compare parameters between groups. Infection rates were calculated as the number of infections divided by the total duration of exposure and expressed as episodes per patient-year. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [12]. A two-tailed *P*-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 125 patients underwent PD from April 2018 to January 2023. They were followed for 179.6 patient dialysis years (median follow-up period: 1.40 years per patient). A total of 191 cases of ESI, 10 cases of TI, and 32 cases of PD-induced peritonitis occurred in 125 patients with PD during the study period. The baseline characteristics of our patients are presented in Table 1.

Exit site infection characteristics

The incidence rates of all ESI and *Corynebacterium* ESI were 1.06 and 0.35 per patient dialysis year, respectively. A total of 62 cases of *Corynebacterium* ESI were detected in 24 patients during the study period. Of the 24 patients who developed *Corynebacterium* ESI, 16 had a combination of ESI due to *Corynebacterium* and ESI associated with other pathogens. We found that the eGFR during PD introduction was relatively lower in patients with *Corynebacterium* associated ESI than in patients without ESI (6.4 versus 7.9 mL/min/1.73m^2, respectively; $P = 0.052$). Meanwhile, there was no significant difference in the serum urea-to-creatinine ratio between patients with ESI due to *Corynebacterium* and patients with ESI associated with other types of pathogens (Table 2). These data are presented in Tables 1 and 2 and Fig. 1.

A total of 36 cases of ESI associated with other pathogens were identified on separate days in 14 of 24 ESI patients with *Corynebacterium* ESI. Of these, 30 cases of ESI associated with other types of pathogens, three cases of *Corynebacterium* ESI were followed by the onset of ESI associated with other pathogens, and 27 cases of *Corynebacterium* ESI were developed after the onset

Table 1 Clinical characteristics of patients at the initiation of peritoneal dialysis

	Patients with *Corynebacterium* ESI ($n = 24$)	Patients with other pathogens-associated ESI ($n = 41$)	Patients without ESI ($n = 60$)	*P*-value
Age (year)	65.0 ± 15.2	69.9 ± 11.9	70.9 ± 14.1	0.201
Sex (M/F)	20/4 (83.3/16.7%)	29/12 (70.7/29.3%)	40/20 (66.7/33.3%)	0.325
Cause of ESKD				
Diabetes mellitus	15 (62.5%)	20 (48.8%)	25 (41.7%)	0.235
Nephrosclerosis	8 (33.3%)	16 (39.0%)	25 (41.7%)	0.810
Glomerulonephritis	1 (4.2%)	0 (0%)	4 (6.7%)	0.514
ADPKD	0 (0%)	1(2.4%)	1 (1.7%)	0.737
Others or unknown	0(0%)	4(9.8%)	5 (8.3%)	0.351
eGFR (mL/min/1.73m^2)	6.4 ± 1.8	7.2 ± 2.6	7.9 ± 2.8	0.052
BMI (kg/m^2)	24.1 ± 3.1	23.9 ± 4.6	22.9 ± 4.5	0.348
CAPD/APD/hybrid	8/11/5	16/24/1	15/45/0	0.002
Self-care/assisted PD	16/8 (66.7/33.3%)	32/9 (78/22%)	35/25 (58/42%)	0.117

ESI exit site infection, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *ADPKD* autosomal dominant polycystic kidney disease, *BMI* body mass index, *CAPD* continuous ambulatory peritoneal dialysis. *APD* automated peritoneal dialysis, *PD* peritoneal dialysis

Table 2 Comparison of clinical characteristics of ESI between the two groups

	Patients with *Corynebacterium* ESI ($n=24$)	Patients with other pathogens-associated ESI ($n=41$)	*P*-value
Treatment period of each ESI (day)	25.2 ± 18.7	23.0 ± 16.4	0.404
ESI recurrence rate (%)	35.5	8.5	< 0.0001
PD fluid volume at the onset of each ESI (mL)	5072.1 ± 1833.1	4778.3 ± 2008.2	0.334
BUN at the onset of each ESI (mg/dL)	58.7 ± 14.1	54.5 ± 16.8	0.094
Serum creatinine level at the onset of each ESI (mg/dL)	8.9 ± 3.4	8.6 ± 3.6	0.530
BUN/Cre at the onset of each ESI	7.7 ± 4.1	7.2 ± 3.0	0.312
PD vintage at the onset of ESI (days)	414.3 ± 294.2	274.4 ± 267.4	< 0.050
Charlson Comorbidity Index at the onset of ESI	5.4 ± 1.7	4.4 ± 1.6	0.072

ESI exit site infection, *PD* peritoneal dialysis, *BUN* blood urea nitrogen, *Cre* creatinine, *BUN/Cre* serum urea-to-creatinine ratio

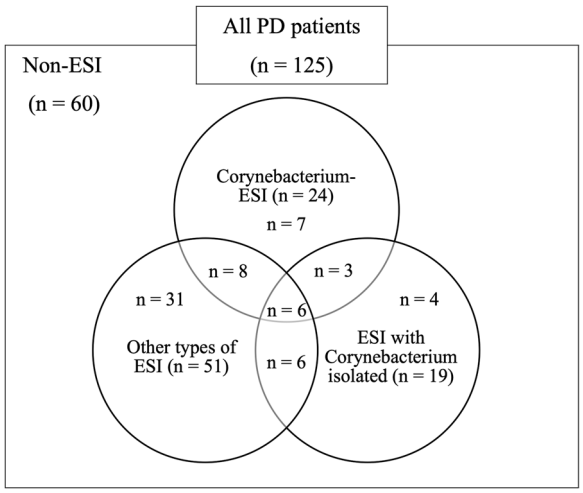

Fig. 1 The Venn diagram for ESI due to *Corynebacterium* alone, ESI due to a combination of *Corynebacterium* and other types of pathogens, and EIS due to other types of pathogens alone. *ESI* exit site infection, *PD* peritoneal dialysis

of ESI associated with other pathogens. However, 41 patients had only ESI associated with other pathogens. In this group of 41 patients, 90 cases of ESI were detected (including ESI due to other pathogens with *Corynebacterium* isolated). We observed a tendency that once *Corynebacterium* was detected at the exit site, this pathogen continued to be detected. In PD catheter exit site culture, 16 of 24 patients tested positive for *Corynebacterium* multiple times. We identified patients who tested positive on exit site culture with *Corynebacterium* up to eight times and compared the recurrence rate of ESI between ESI due to *Corynebacterium* and ESI associated with other pathogens (including ESI due to other pathogens with *Corynebacterium* isolated). Consequently, the recurrence rate of ESI due to *Corynebacterium* was 35.5%, which is significantly higher than the rate of ESI associated with other pathogens (8.5%, $P<0.001$). There was no significant difference in the treatment period of ESI between ESI due to *Corynebacterium* and ESI associated with other pathogens ($P=0.404$). PD vintage during the onset of ESI was significantly longer in patients with *Corynebacterium* ESI than in those with other pathogen-associated ESI ($P<0.050$).

Characteristics of tunnel infections

We detected ten cases of TI. The incidence rates of all TI and *Corynebacterium* TI were 0.06 and 0.02 per patient dialysis year. TI did not recur in any of these patients. Three cases of TI were caused by *Corynebacterium*, five were caused by other types of pathogens (including ESI due to other pathogens with *Corynebacterium* isolated), and two were caused by unknown bacteria. Of these ten cases of TI, eight required PD catheter removal. Of the 62 cases of ESI due to *Corynebacterium*, 3 (4.9%) progressed to TI. Among these three cases, two (3.2%) required PD catheter removal, and the other was relieved by conservative treatment with intravenous vancomycin. Of the two cases that required PD catheter removal, both had diabetes. In these two cases, one had the PD catheter removed on the fifth day of intravenous vancomycin administration and the other on the eighth day of intravenous vancomycin administration and oral combination of trimethoprim and sulfamethoxazole administration. One case that was relieved by intravenous vancomycin administration for 14 days was a nondiabetic patient case. Among the 129 cases of ESI associated with other types of pathogens, 7 (5.4%) progressed to TI directly. Among these seven cases, four required PD catheter removal followed by PD catheter replacement later. Among these 129 cases of ESI associated with other types of pathogens, *Corynebacterium* was isolated in 20 cases, of which 1 (5.0%) progressed to TI followed by PD catheter removal. There was no significant difference in the frequency of direct progression to TI between ESI due to *Corynebacterium* and ESI associated with other types of pathogens ($P=1$).

Characteristics of peritoneal dialysis-associated peritonitis

We also detected a total of 32 cases of PD-associated peritonitis. Of the 129 cases of ESI associated with other pathogens (including ESI due to other pathogens with *Corynebacterium* isolated), 2 (1.6%)—from which *Corynebacterium* was not isolated—directly progressed to PD-associated peritonitis. However, no cases of ESI due to *Corynebacterium* directly progressing to PD-associated peritonitis were confirmed. There was no significant difference in the frequency of direct progression to peritonitis between ESI due to *Corynebacterium* and ESI associated with other pathogens ($P=1$).

Discussion

Generally, ESI control is critical in PD treatment. However, the nature of ESI due to *Corynebacterium* has hardly been investigated to date. *Corynebacterium* species are Gram-positive bacilli and belong to the natural flora of the skin [4–7]. Gentamicin prophylaxis previously demonstrated efficacy in preventing most ESIs [4, 13, 14]. In the past, some researchers worried that using gentamicin cream at the exit site would increase the transmission of gentamicin-resistant pathogens; however, this concern has now largely been dispelled [15, 16]. Although some previous reports suggested that gentamicin ointment might adversely affect some specific pathogens (including *Corynebacterium*) [9, 10, 17–20], these past reports only dealt with about 20 cases of *Corynebacterium*-associated ESI at most. Additionally, the study with the most patients followed up among these ones was published more than 15 years ago, and the ISPD guidelines have changed between then and now, implying that exit site care protocols have changed in that time.

In the case of ESI in which both *Corynebacterium* and other pathogens are isolated, the presence of *Corynebacterium* in exit-site samples has been thought to indicate just contamination and not full-blown infection [9, 21]. Although we confirmed one case (5.0%) of TI following ESI due to other pathogens with *Corynebacterium* isolated, this does not necessarily indicate that *Corynebacterium* is the "true" causative pathogen. However, three (4.9%) cases of ESI due to *Corynebacterium* alone directly progressed to TI, suggesting that *Corynebacterium* cannot be overlooked as the "true" causative pathogen in ESI [21]. Moreover, the eGFR during PD introduction was relatively lower in patients with *Corynebacterium* ESI than in patients without ESI (6.4 versus 7.9 mL/min/1.73 m^2, respectively; $P=0.052$). Furthermore, PD vintage was significantly longer in patients with ESI due to *Corynebacterium*, suggesting that the residual kidney function during the onset of ESI may be decreased from baseline in patients with *Corynebacterium* ESI compared with those with other pathogen-associated ESI. Although there was no significant difference in serum BUN/Cre during the onset of each ESI between the *Corynebacterium* ESI group and the ESI associated with other types of pathogens, five of six patients on hybrid PD/HD therapy were categorized in the *Corynebacterium* ESI group, and the BUN/Cre ratio was not considered an accurate indicator of residual kidney function in such patients [11]. Considerably, lower residual kidney function may increase ESI because of *Corynebacterium*. Reportedly, skin barrier function decreases as renal function decreases [22, 23]. Additionally, *Corynebacterium* infection is more frequent in pathologies and diseases in which the skin barrier function is impaired [24–26]. Another report suggests that the risk of *Corynebacterium* infection may increase because of antibiotic use, continuous catheter placement, and increased *Corynebacterium* colonization [21]. In patients with a longer PD vintage, the periods for the application of gentamicin ointment naturally extend to a longer period. Herein, PD vintage was significantly longer in patients with *Corynebacterium* ESI. Therefore, we hypothesized that the long-term use of antibiotics such as gentamicin sulfate ointment in patients with reduced residual kidney function may increase the number of cases of ESI due to *Corynebacterium*. However, a large-scale, multicenter study is needed to validate these results and determine whether the avoidance of the ointment decreases the rate of ESI due to *Corynebacterium*. The estimated incidence of ESI is 0.53–0.6 and 0.40 per patient dialysis year in the USA and Japan [13, 27, 28]. Herein, the total incidence of all ESI—i.e., *Corynebacterium* ESI and non-*Corynebacterium* ESI—was higher (1.06 per patient-year) than that in previous reports. Because the incidence of ESI varies from country to country and region to region—typically between 0.13 and 1.28 per patient-year—the results of our study may fall into the category of such variations [29–31]. Moreover, diagnoses of each ESI were based on subjective observations [4, 30, 32]. At our facility, there is continuous education and coaching on exit site management by nurses who specialize in PD. This established system allows patients to directly visit the PD outpatient clinic if they experience any abnormality at the exit site. Therefore, culture samples collected from the exit site were possibly collected more frequently than in general facilities, which may have overestimated ESI incidence.

We found no case of ESI where *Corynebacterium* ESI directly progressing to PD-associated peritonitis in our study. Therefore, we assume that *Corynebacterium*-associated ESI may be less likely to develop into *Corynebacterium*-associated peritonitis. In other words, *Corynebacterium* may show different properties in ESI- and PD-associated peritonitis. This result is consistent with those of previous studies [4, 5, 7].

The present study has several limitations. First, since this was a retrospective study, we may have overlooked other ESIs. Second, since it was a single-center study, our findings are inconclusive and not generalizable. However, despite these limitations, we still think that the findings of this study reflect the actual situation of *Corynebacterium*-associated ESI.

Conclusions

In our current study, the incidence of *Corynebacterium*-associated ESI was higher than that in similar past studies. In patients with *Corynebacterium*-associated ESI, the eGFR at the time of PD initiation tended to be relatively low. However, such ESIs were thought to rarely develop into PD-associated peritonitis due to *Corynebacterium*.

Abbreviations

ESI	Exit site infection
TI	Tunnel infection
eGFR	Estimated glomerular filtration rate
BMI	Body mass index
ESKD	End-stage kidney disease
ADPKD	Autosomal dominant polycystic kidney disease
PD	Peritoneal dialysis

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Author contributions

K.S. and N.W. contributed equally to this study. K.S., N.W., and Y.S. contributed to conception and study design; K.S., K.H., and M.T. performed data acquisition; N.W. performed data analysis/interpretation; K.S., K.U., and N.W. contributed to the statistical analysis; Y.S. N.W., J.I., K.S., and K.U. did the supervision or mentorship and took responsibility for the honesty, accuracy, and transparency of the report and acceptance to be accountable for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Availability of data and materials

Original data cannot be openly shared to protect the privacy of study participants, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study protocol was approved by ethics committee of the IUHW (approval number: 23-Im-028). Written informed consent was waived via the opt-out method on the hospital's information website.

Consent to publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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