Renal Replacement Therapy

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Effectiveness of additional topical antibiotics for recurrent or refractory exit-site infection: a case series

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Abstract

Background Japanese peritoneal dialysis (PD) guidelines do not suggest applying mupirocin/gentamicin ointment to the exit sites of PD patients to prevent exit-site infection (ESI). The guidelines do not mention topical antimicrobials as a treatment for ESI.

Methods We retrospectively investigated the additional use of topical antibiotic ointments on patients receiving oral or intravenous antibiotics for recurrent and/or refractory ESI at Aichi Medical University and Nagoya University Hospitals between 2017 and 2022.

Results A total of 13 patients (11 men, 2 women) were included in this study. Median age was 69.0 years, median duration of PD was 26.0 months, two patients had diabetes as a complication, and ESI incidence was 2.7 episodes per patient-year. Systemic antibacterial treatment had been administered for a median of 27.0 days before application therapy. Mupirocin was used in eight cases and gentamicin in five cases, with complete resolution in all cases. No adverse effects such as skin symptoms, antibiotic resistance, or non-tuberculous mycobacterial infections were observed. Cases were divided into two groups based on the duration of topical antibiotic use: short-term group < 90 days and long-term group ≥ 90 days. All patients in both groups achieved complete resolution, with no significant differences in time to resolution, number of recurrent ESIs, or occurrence of ESIs after discontinuation of application therapy.

Conclusion Additional use of topical antibiotic for recurrent and/or refractory ESI appears safe and effective. This study suggests that future randomized controlled trials are warranted.

Keywords Peritoneal dialysis, Topical antibiotic ointment, Exit-site infection (ESI), Recurrent ESI, Refractory ESI, Topical antibiotic ointment

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Introduction

Exit-site infection (ESI) is one cause of peritoneal dialysis (PD)-related peritonitis and subsequent catheter loss [1, 2]. In addition, some cases require surgical intervention. Peritonitis is a significant contributor to hospitalization, peritoneal membrane dysfunction, and mortality among patients undergoing PD [1–4]. Despite current prevention and treatment efforts, ESI remains an important complication in PD practice. Further innovations are needed to address this issue effectively [2, 3].

A significant body of evidence supports the application of mupirocin/gentamicin ointment to prevent ESI in PD [2]. International Society for Peritoneal Dialysis (ISPD) guidelines recommend continuous topical antibiotic use at the exit site to prevent PD-related infection (grade 1C recommendations). However, discussion on the use of antibiotic ointments in the treatment of ESI has been limited. ISPD guidelines state that "there are few data on their efficacy in the treatment of active catheter-related infections" [5]. Investigation of whether adding antibiotic ointments to oral or intravenous antibiotic therapy may provide useful insights for treating refractory ESI in Japan.

We conducted a retrospective study to examine the effectiveness of nonpermanent (limited-duration) antibiotic ointment therapy for ESI that does not resolve under oral or intravenous antibiotic therapy and for refractory ESI, exploring the feasibility of this approach in Japan through a case series.

Patients and methods

Patients and data collection

This study was approved by the Ethics Committee for Human Research at Aichi Medical University (Nagakute, Japan) and Nagoya University (Nagoya, Japan) (approval nos. 2023-001, 2005-0309 and TF19010).

We conducted a retrospective study in patients who had received topical antibiotics in addition to oral or intravenous antibiotics against recurrent and/or refractory ESI at Aichi Medical University Hospital and Nagoya University Hospital from January 2017 to September 2022. We collected data at the time of topical antibiotic ointment treatment, including age, sex, primary kidney disease responsible for renal failure, serum albumin level, duration of PD, comorbidity with diabetes, frequency of ESI occurring from the start of PD to the start of treatment (episodes per patient-year), bacterial species causing ESI, type of topical ointment, duration of systemic antibiotic treatment before topical antibiotic ointment, duration of systemic antibiotic treatment in combination with topical antibiotic ointment, treatment effect, observation period after treatment, frequency of ESI after treatment cessation (episodes per patient-year), relapse, and adverse effects.

Usual care of exit site

The exit site is disinfected with 0.02% benzalkonium chloride solution once a day. Showering is not prohibited unless ESI or bleeding is present. The PD exit site is usually protected from immersion during bathing by use of a protective cover while the infection is present.

Definition of ESI and resolution

ESI is defined as the presence of purulent discharge, with or without erythema of the skin at the catheter-skin interface according to the ISPD guideline [2]. Cases of ESI with tunnel infection assessed by imaging techniques such as computed tomography or ultrasound were excluded from this study. Recurrent ESI is defined as having two or more ESIs caused by the same organism within a 12-month period, with an initial positive response to antibiotic therapy [6]. Refractory ESI is defined as a failure to respond after 2 weeks of effective antibiotic therapy [2]. Resolution of ESI was defined as cessation of drainage, redness, and pain for more than 2 weeks. This study divided cases into two groups based on the duration of topical antibiotic ointment application: a short-term group of <90 days and a long-term group of ≥ 90 days.

Statistical analyses

Statistical analyses were conducted using SPSS version 28.0 software (IBM Corporation, Armonk, NY, USA). Continuous data are presented as medians and interquartile ranges (IQRs), while categorical data are expressed as frequencies and proportions. To evaluate differences between variables across samples, Pearson's chi-squared test and the Mann–Whitney U test were employed. The Wilcoxon signed-rank sum test was used for comparisons. Statistical significance was set at the level of $p<0.05$.

Results

Thirteen patients with refractory ESI were treated with the addition of topical antibiotic ointment to oral or intravenous antimicrobial therapy. The patient population comprised 11 men and 2 women, with a median age of 69 years (IQR, 50–73 years). The primary causes of end-stage kidney disease were chronic glomerulonephritis ($n=4$), polycystic kidney disease ($n=2$), unknown disease ($n=3$), and nephrosclerosis, diabetic nephropathy, immunoglobulin A nephropathy, and interstitial nephritis in the remaining cases (each $n=1$) (Table 1).

Patients were on PD for a median of 26.0 months (IQR, 9.0–45.0 months). Diabetes was present in two cases,

Table 1 Patient characteristics

Case	Facility	Age/sex	Primary kidney disease	Duration of PD to become refractory ESI (Month)	Comorbid diabetes	Albumin (g/dL)	Incidence of ESIs from start of PD to start of application therapy (episodes per year)	Bacterial species causaing ESI	Systemic antibiotic treatment before application therapy	Duration of systemic antibiotics before use of topical antibiotics (days)	Subcutaneous pathway diversion prior to initiation of application therapy
1	A	50 y/male	Polycystic	14	No	3.5	3.4	*Corynebacterium tuberculostearicum*	DAP RFP MINO	86	Yes; recurrence after SPD
2	A	70 y/male	Unknown	35	No	2.9	1.0	*Corynebacterium tuberculostearicum*	MINO	28	No
3	A	61 y/male	Hypertension	63	Yes	3.2	2.5	MRSA	VCM	25	No
4	A	33 y/male	Interstitial nephritis	26	No	3.7	2.3	MSSA	RFP CEX	14	No
5	A	69 y/male	Unknown	10	No	3.4	3.6	*Corynebacterium tuberculostearicum*	CEX	77	No
6	A	69 y/female	Unknown	34	No	3.1	1.4	Unknown	CEX	33	No
7	B	73 y/male	Chronic glomerulonephritis	89	No	2.9	0.9	*Corynebacterium jeikeium*	STFX MINO	14	No
8	B	68 /male	IgA nephropathy	7	No	2.7	8.6	*Corynebacterium jeikeium* / *Staphylococcus* spp, CNS	MINO RFP	0	No
9	B	45 y/female	Chronic glomerulonephritis	45	No	3.2	2.7	MRSE	VCM MINO	39	No
10	B	78 y/male	Diabetic nephropathy	9	Yes	2.5	2.7	*Corynebacterium striatum*	LVFX MINO	0	No
11	B	77 y/male	Chronic glomerulonephritis	8	No	3.2	4.5	*Staphylococcus capitis*	MINO VCM	29	No
12	B	79 y/male	Chronic glomerulonephritis	132	No	3.3	0.8	MRSE/*Streptococcus agalactiae*	MINO	0	No
13	B	50 y/male	Polycystic	7	No	3.5	5.1	MRSE	VCM MINO	27	No

MRSA, methicillin-resistant *Staphylococcus aureus*; CNS, coagulase-negative staphylococci; MRS, methicillin-resistant staphylococci; MRSE, methicillin-resistant *Staphylococcus epidermidis*; CEX, cefepime; DAP, daptomycin; LVFX, levofloxacin; MINO, minocycline; RFP, rifampin; STFX, streptomycin; VCM, vancomycin

median incidence rate of ESI was 2.7 times per patient-year (IQR, 1.4–3.6 times per patient-year), and antimicrobial therapy was administered for a median of 27.0 days (IQR, 14.0–33.0 days) before the introduction of topical antibiotic. In one case, the topical antibiotic was added after a surgical procedure to change the outlet site by subcutaneous pathway diversion [7, 8]. The specific types of bacteria causing ESI are listed in Table 1. The study identified 13 cases of ESI, with 46% due to *Corynebacterium* spp. (three cases due to *C. tuberculostearicum*, two cases due to *C. jeikeium*, and one case due to *C. striatum*), 54% due to *Staphylococcus* spp. [three cases of methicillin-resistant *S. epidermidis* and one case each of methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus*, and coagulase-negative staphylococci and *Staphylococcus capitis*], and 8% due to *Streptococcus* (one case of *Streptococcus agalactiae*) (Table 1). Refractory ESI in all cases was resolved with the addition of mupirocin or gentamicin ointment. Median interval to healing was 28 days (IQR, 21–77 days). Median duration of treatment with topical antibiotic ointment was 117 days (IQR, 71–277 days). Long-term treatment in seven patients was due to inadequate short-term response or allergies, with the most common reason being reluctance to stop due to observed improvements. During the observation period (median, 11.0 months; IQR, 6.0–26.0 months), two patients developed ESI with similar organisms 12 and 14 months post-treatment, respectively. After observation (median, 11.0 months; IQR, 6.0–26.0 months), ESI decreased to 1.1 times per person-year (IQR, 0–1.3 times per person-year), which was not significantly different compared to the preapplication period. No adverse effects such as skin symptoms, bacterial resistance, or non-tuberculous mycobacterial (NTM) infection were observed (Table 2).

The incidence of ESI before and after application decreased after application in all except one case ($p=0.019$) (Fig. 1A). Median duration of application was 63.5 days (IQR, 35.8–77.0 days) for the short-term group and 277 days (IQR, 199.5–402.0 days) for the long-term group (Table 3). No significant differences were seen between groups in terms of age, sex, presence of diabetes, serum albumin levels, proportion of ESI caused by methicillin-resistant bacteria, incidence of ESI prior to application, duration of systemic antibiotic administration, or type of antibiotic used. All patients in both groups achieved complete resolution, with no significant differences in time to resolution, number of recurrent ESIs with any organism or with similar organisms during the 5-month period of application, or incidence of ESIs after discontinuation of ointment application (Table 3). In the short-term application group, the incidence of ESI decreased after application ($p=0.028$) (Fig. 1B). In the long-term application group, no significant difference in the incidence of ESI was seen between before and after application ($p=0.176$) (Fig. 1C). One patient with a high incidence of ESI after application was observed in the long-term application group (Fig. 1C). No significant differences were identified in skin reactions or incidence of antibiotic-resistant bacteria.

Case series

Case 1: A case of recurrent and refractory ESI (Fig. 2A)

A 50-year-old man with end-stage renal failure due to autosomal-dominant polycystic kidney disease (ADPKD) had started PD 14 months earlier. On day X−98, the patient developed ESI without tunnel infection caused by *C. tuberculostearicum*.

Systemic antimicrobial therapy including daptomycin, minocycline hydrochloride, and rifampicin did not cure the infection, and *C. tuberculostearicum* continued to grow from the exit site. Subcutaneous pathway diversion was performed on day X, and systemic antibiotic therapy was continued. However, at day X+7, ESI recurred at a new exit site. *C. tuberculostearicum* was again detected from culture, and systemic antibiotic therapy with daptomycin and minocycline hydrochloride did not cure the infection. We therefore added gentamicin ointment application from day X+26, as gentamicin had been shown to be effective against *C. tuberculostearicum* in antimicrobial susceptibility testing. At day X+56, signs of inflammation disappeared and cultures from the exit site yielded negative results. Addition of topical gentamicin ointment, which had eradicated the colony of *C. tuberculostearicum*, successfully treated recurrent and refractory ESI (Fig. 2A).

Case 2: A case of recurrent and refractory ESI with persistent bacterial colony at the exit site not eradicated by systemic antibiotic therapy (Fig. 2B)

A 70-year-old man with end-stage renal failure due to nephrosclerosis was started on PD 35 months prior to presentation. *C. tuberculostearicum* was detected from surveillance cultures on day X − 14. He had previously experienced ESI due to the same organism. ESI was unimproved by minocycline but resolved with intravenous vancomycin, requiring a total treatment period of 50 days. On day X, ESI was again identified and culture grew *C. tuberculostearicum*. ESI resolved, but a small amount of exudate persisted, and *C. tuberculostearicum* continued to be detected in the culture. Gentamicin ointment, to which the *C. tuberculostearicum* had been shown to be sensitive, was initiated on day X+28 to prevent recurrence. Topical use of antibiotic ointment was terminated on day X+105. Subsequent culture from the exit site was nonviable. This case indicated the

Table 2 Therapeutic topical antibiotic ointment and outcomes

Case	Topical antibiotic	Antibiotic application period (days)	Treatment outcomes	Interval from start of topical antibiotics to resolution (days)	Recurrence with bacteria of similar strain	Observation period after completion of initial application therapy (months)	Incidence of ESIs (episodes per year) after completion of initial application therapy	Incidence of antibiotic-resistant bacteria subsequent to completion of initial application therapy	Non-tuberculous mycobacterial infection	Skin reaction to antimicrobial application
1	Gentamicin	79	Resolution	86	None	11	1.1	None	None	None
2	Gentamicin	71	Resolution	28	None	5	0.0	None	None	None
3	Muciprocin	9	Resolution	25	Recurrence of same MRSA ESI identified 14 months after treatment discontinuation	12	1.0	None	None	None
4	Gentamicin	56	Resolution	14	None	9	1.3	None	None	None
5	Gentamicin	175	Resolution	77	None	6	0.0	None	None	None
6	Gentamicin	29	Resolution	33	None	5	0.0	None	None	None
7	Muciprocin	483	Resolution	21	None	5	0.0	Unknown	None	None
8	Muciprocin	224	Resolution	21	Recurrence of same *Corynebacterium jeikeium* ESI identified 12 months after treatment discontinuation	38	1.3	Unknown	None	None
9	Muciprocin	887	Resolution	21	None	28	1.7	None	None	None
10	Muciprocin	84	Resolution	84	None	26	1.8	None	None	None
11	Muciprocin	321	Resolution	14	None	26	0.9	None	None	None
12	Muciprocin	117	Resolution	63	None	7	5.1	Unknown	None	None
13	Muciprocin	277	Resolution	277	None	47	1.0	Unknown	None	None

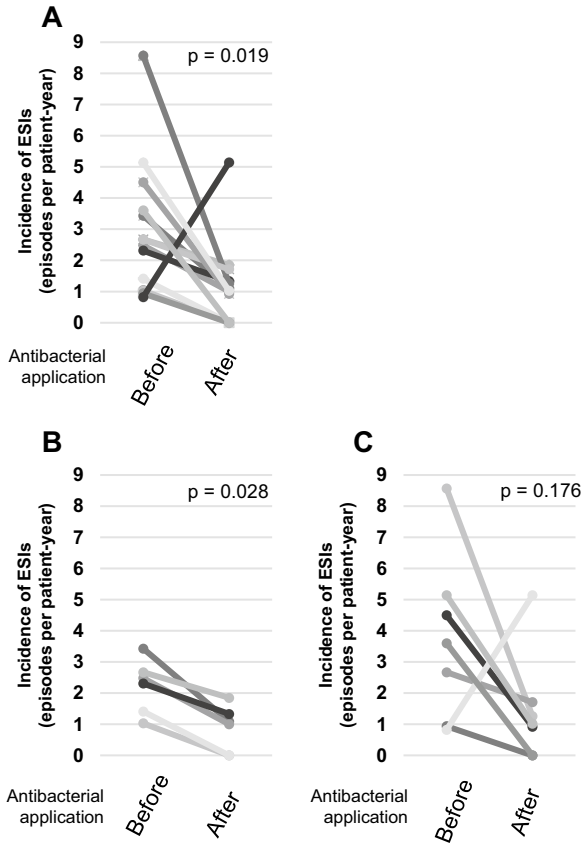

Fig. 1 Incidence rates of ESI before and after adding topical antibiotic. **A** All cases, **B** short-term application group, **C** long-term application group

effectiveness of adding topical antibiotic ointment in a patient with colonization by *Corynebacterium* at the exit site.

Case 3: A case of refractory ESI due to MRSA that did not improve with systemic vancomycin administration (Fig. 2C)

A 61-year-old man with end-stage renal failure due to nephrosclerosis, who had been on PD for 63 months, showed ESI due to MRSA on day X. Nasal cultures showed negative results for MRSA. Treatment with vancomycin was initiated, but no improvements were obtained within 2 weeks. Mupirocin ointment was added on days X + 25 to X + 34. ESI was successfully treated, and vancomycin was discontinued on day X + 30. Cultures obtained on days X + 39, X + 144, and X + 228 did not detect MRSA, suggesting that the bacterial colony had been eradicated. This was a case in which negative results for MRSA were able to be quickly achieved, removing a key risk factor for nosocomial infection.

Discussion

The pathogenesis of ESI is shown in Fig. 3. As shown in cases 1 and 3, colonized bacteria that are not eradicated by the systemic administration of antibiotics can induce persistent ESI. We therefore used an antibiotic ointment in combination with systemic administration of antibiotics, effectively improving the outcomes. The ISPD guidelines recommend constant, continuous use of antibiotic ointment at the exit site [2], but this stance was criticized in the Japanese Society of Dialysis Therapy (JSDT) guidelines due to concerns about the development of antibiotic resistance in pathogenic bacteria [1]. We thus also explored whether the use of antibiotic ointments over a limited duration would be effective against recurrent and/or refractory ESI (Fig. 4).

Although substantial evidence supports prophylactic application of topical antibiotic ointment for preventing ESI, the effectiveness of therapeutic and short-term application therapy against recurrent and/or refractory ESI has not been established. The present results suggest that the combination of oral or intravenous antibiotics and short-term topical antibiotic may be effective against refractory ESI (Fig. 1). According to the peritoneal dialysis outcomes and practice patterns study, prophylactic ointment is applied in 71–89% of cases in Europe and the USA, compared with only 4% in Japan [9]. Therefore, the effects of concomitant use appear to be best evaluated in Japan. Undertaking adequate evaluation is not really feasible in other countries where prophylactic application therapy is common practice. These data indicate that additional short-term use of topical antibiotics may be promising as a new strategy for recurrent and/or refractory ESI in Japan, while avoiding long-term use.

Many organisms can cause exit site and tunnel infections, including microorganisms belonging to the normal skin flora, such as *Corynebacterium*. Case 1 was refractory to continued intravenous antibiotic therapy and underwent subcutaneous pathway diversion [7, 8]. However, the new exit site immediately became infected with the same bacteria. A study using electron microscopy of colonies at the exit of the blood access catheter for hemodialysis found colony formation in 44.9% of cases [10]. In a study of PD outlet sites, colony formation was observed in 56% of patients who received daily washing with saline for 1 year. Colonies comprised *S. aureus* in 28.1% of cases, MRSA in 12.5%, and Gram-negative bacilli in 15% [11]. It must be noted that many organisms, including bacteria belonging to the normal skin flora, can not only cause exit site and tunnel infections, but also colonization at the exit site [2].

Although ESI can be effectively treated with systemic antibiotics, bacteria may persist on the skin surface as colonies, risking reinfection through minor wounds such

Table 3 Comparison between short- and long-term application groups

	Short-term application therapy *n* = 6	Long-term application therapy *n* = 7	*p*
Antibiotic application period, days, median (IQR)	63.5 (35.8–77.0)	277 (199.5–402.0)	0.001
Observation period after completion of initial application therapy, years, median (IQR)	0.8 (0.5–1.0)	2.2 (0.5–2.8)	0.295
Clinical features			
Age, years, median (IQR)	65.0 (52.8–69.8)	69.0 (59.0–75.0)	0.628
Male, *n* (%)	5 (83)	6 (86)	0.906
Diabetes mellitus, *n* (%)	2 (33)	0 (0)	0.097
Albumin, g/dL, median (IQR)	3.2 (3.0–3.4)	3.2 (3.1–3.4)	0.945
ESI caused by methicillin-resistant bacteria, *n* (%)	1 (17)	3 (43)	0.097
Incidence of ESIs after completion of initial application therapy, episodes per year, median (IQR)	2.4 (1.6–2.6)	3.6 (1.8–4.8)	0.295
Duration of systemic administration of antibiotics before use of topical antibiotics, days, median (IQR)	19.5 (3.5–31.0)	27.0 (7.0–34.0)	0.836
Treatment details			
Gentamicin application, *n* (%)	4 (67)	1 (14)	0.053
Mupirocin application, *n* (%)	2 (33)	6 (86)	0.053
Outcomes			
Resolution of ESI, *n* (%)	6 (100)	7 (100)	1.000
Interval from start of topical antibiotics to resolution, days, median (IQR)	30.5 (25.8–71.3)	21.0 (21.0–70.0)	0.628
Number of ESI recurrences during 5 months after the end of application therapy, median (IQR)	0 (0–0)	0 (0–2.0)	0.336
Number of ESI recurrences caused by the same bacteria within 5 months after completion of application therapy, median (IQR)	0 (0–0)	0 (0–0)	0.628
Incidence of ESIs after completion of initial application therapy, episodes per year, median (IQR)	1.0 (0.3–1.3)	1.0 (0.5–1.5)	0.945
Number of cases with skin reactions, median (IQR)	0 (0–0)	0 (0–0)	1.000
Number of cases in which antibiotic-resistant bacteria emerged after application therapy, median (IQR)	0 (0–0)	0 (0–0)	1.000

as dislodged scabs or bleeding, as in Case 2. Colonization of bacteria seems to be an important risk factor for recurrence of ESI (cases 1–3). Close monitoring of ESI resolution and appropriate measures to prevent reinfection are thus important. Poor glycemic control and high levels of air pollution and environmental particulate matter exposure represent important risk factors for catheter-related infection [12]. Which patients will be colonized and how they should be treated remains uncertain. Our study suggests that the short-term application of topical antibiotic ointment may reduce colony counts and potentially prevent re-infection in these cases (Fig. 4). This approach seems effective for repeated ESI, which suggests the presence of colonies, as in case 3.

The removal of MRSA at the exit site, as in case 3, is important to prevent the spread of MRSA infection to other patients and nosocomial infections. In clinical settings, MRSA transmission can occur through direct and indirect contact with the nasal vestibule, which is the primary reservoir of this pathogen in humans [13]. We believe that application therapy should be aggressively adopted for cases such as case 3.

The application of gentamicin ointment to the exit site reportedly increased the risk of NTM infection from 0.102 to 2.71% [14]. NTM infections often require surgical interventions, such as catheter removal or subcutaneous pathway diversion, for treatment [15–17]. Some patients will develop epidermal peeling and erosions on the skin near the exit site after antimicrobial application due to allergic reactions [18]. However, the majority of observational studies have not evaluated this side effect, and only a few studies investigated the issue [3, 19, 20]. It is necessary to be aware that some mupirocin ointments contain polyethylene glycol, which can cause degradation of the materials used in catheters [21]. Gentamicin cream has also been reported to cause catheter surface damage [22]. We did not encounter any significant adverse events in the present study.

Concerns have been raised regarding the emergence or increase of resistant strains with the long-term use of topical antibiotic ointment. In skin and soft tissue infections, rates of MRSA resistance to mupirocin ointment have been reported to range from 2% to 81%, and staphylococcal resistance to gentamicin ranges from 3% to 49%. [23–25]. Application of both mupirocin and gentamicin has been shown to increase the risk of fungal peritonitis compared with the daily application of gentamicin alone [26]. We therefore recommend short-term application to

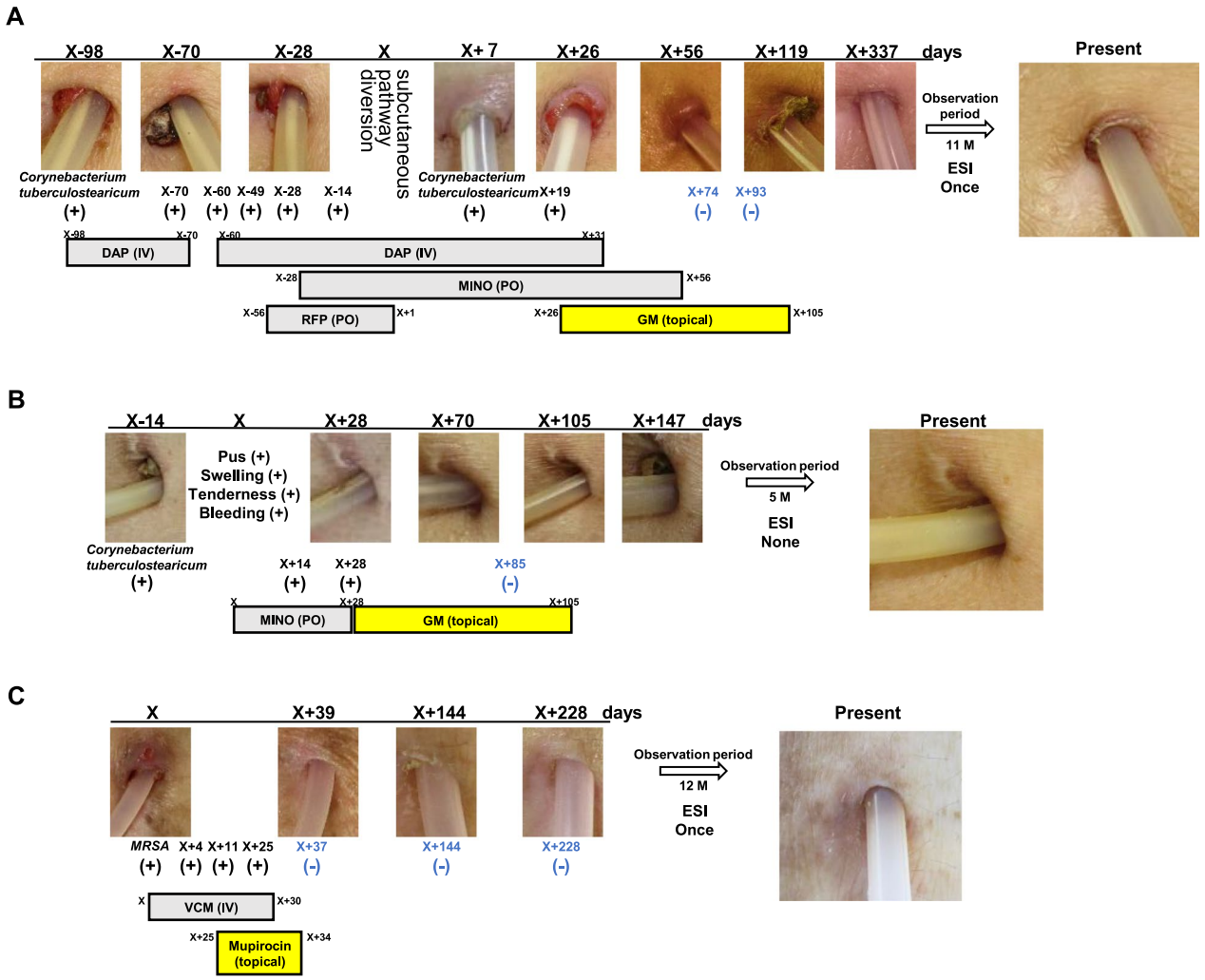

Fig. 2 Clinical course. **A** Case 1. A case of recurrent refractory ESI. Combination therapy successfully treated recurrent and refractory ESI that relapsed despite systemic administration of antimicrobials and subcutaneous pathway diversion surgery. **B** Case 2. A case with persistent bacterial colony at exit site not eradicated by systemic antibiotic therapy. This case indicates the effectiveness of adding topical antibiotic to systemic antibiotics in a patient with *Corynebacterium* colonization at the exit site. **C** Case 3. A case with recurrent MRSA ESI that did not improve with vancomycin administration. ESI was successfully treated by adding mupirocin ointment. DAP, daptomycin; MINO, minocycline; GM, gentamicin; VCM, vancomycin; IV, intravenous injection; PO, per os

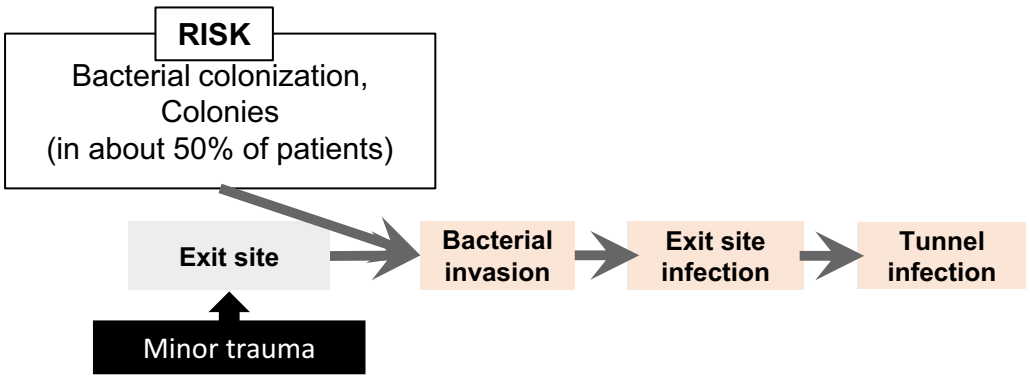

Fig. 3 The pathogenesis of ESI. About 50% of patients with normal appearance of exit sites have bacterial colonies. If a wound forms, the colonized bacteria easily invade the subcutaneous tissue, leading to ESI and tunnel infection

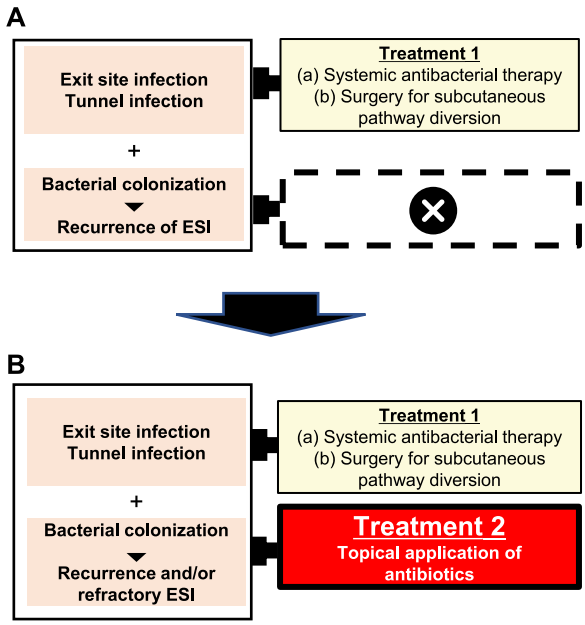

Fig. 4 Possible strategies against recurrent and/or refractory ESI with bacterial colonization. **A** Current treatments in Japan. ESI has traditionally been treated with systemic antibiotic therapy or surgery for subcutaneous pathway diversion. However, these are not always effective for eliminating bacterial colonization. **B** A new possible strategy against recurrent and/or refractory ESI. The addition of topical antibiotic to systemic antibiotic administration can successfully treat recurrent and/or refractory ESI and eliminate bacterial colonization at the exit site

prevent concomitant infections. Better determination of those patients most suited to short-term applications is necessary. The present study examined age, sex, diabetes status, serum albumin level, duration of PD, incidence of ESI before application, and number of days between the onset of ESI and administration of the drug, but none of these differed significantly between short- and long-term treatment (Table 3). In addition, all patients in both groups achieved complete cure, with no significant differences in time to cure, number of recurrent ESI with any or the same bacteria during the 5 months of application therapy, or the occurrence of ESI after stopping short-term application therapy (Table 3). Such results suggest that short-term topical antibiotic concomitant with systemic antibiotic may be an option for treating refractory ESI.

Several limitations must be considered. As this was a retrospective study, no predetermined protocol was applied. The duration of treatment was determined by each treating physician and varied between groups. The limitations include the retrospective nature of this study, highlighting the need for prospective studies in the future. The results of analyses between before and after treatment with the addition of topical antibiotics may have lacked sufficient statistical validity due to the small number of cases. Further studies with larger cohorts are therefore needed. The small number of cases can be attributed to the fact that topical antibiotic ointment is not recommended in the JSDT PD Guidelines 2019 [1]. Setting up a control group without topical antibiotic ointment was also difficult because of the complicated nature of cases with recurrent and/or refractory ESI. Moreover, differences in treatment approaches may exist between the two institutions included in this study. Finally, I would like to emphasize that we should go through the ethics committee or institutional review board before using mupirocin ointment because it is an off-label use.

In summary, the addition of topical antibiotic ointment is effective for treating refractory ESI, which does not resolve even after subcutaneous pathway diversion. If the same colony persists at the exit site after systemic antibiotic treatment for ESI, the addition of topical antibiotic can prevent ESI recurrence (Fig. 4). The strategy of using short-term topical antibiotic may be useful for preventing the emergence of drug-resistant bacteria while also reducing costs. Future prospective studies, particularly randomized controlled trials, are required to verify our findings.

Abbreviations

PD	Peritoneal dialysis
ESI	Exit-site infection
ISPD	International Society for Peritoneal Dialysis
JSDT	Japanese Society of Dialysis Therapy
MRSA	Methicillin-resistant *Staphylococcus aureus*
NTM	Non-tuberculous mycobacterial

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None.

Author contributions
N.A., Y.S., A.A., and Y.I. participated in the conception and design of the study. All authors collected, analyzed, and interpreted patient data. Statistical analysis was performed by N.A. and A.A. Drafting of the article was done by N.A., Y.S., A.A., and Y.I. All authors made important intellectual contributions during the drafting of the manuscript and approved the final version of the manuscript. All authors agreed to take responsibility for their own contributions.

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Availability of data and materials
The data underlying this article will be shared upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
All procedures performed in this study were in accordance with the ethical standards of The Ethics Committee for Human Research of Aichi Medical University Hospital and Nagoya University Hospital (Nagoya, Japan), where the studies were conducted (approval numbers: 2023-001 and TF19010, respectively), and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All data were anonymized and the requirement for informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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