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EXIT-SITE INFECTIONS IN PERITONEAL DIALYSIS: PREDICTIVE FACTORS FOR ADVERSE OUTCOMES

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Filipa Silva, Joana Tavares, Sofia O Correia, Cristina Freitas, Olívia Santos, Maria João Carvalho, Jorge Malheiro, António Cabrita, Anabela Rodrigues

Peritoneal Dialysis Unit, Centro Hospitalar e Universitário do Porto, Portugal

Résumé

Les complications liées à l'infection chez les patients en dialyse péritonéale (DP) sont importantes. Notre objectif était d'évaluer le type d'infections d'orifice de sortie (ESI) et l'évolution naturelle chez une cohorte de patients admis en DP ces dix dernières années au sein de notre service.

Les données du registre des événements ESI (n = 126, chez 74 patients) ont été récupérées. Les protocoles ESI ont suivi les directives internationales standard. Un contrôle qualité systématique est effectué. Le suivi médian était de 29,1 mois (14,0 à 47,4). Dans cette population, les résultats défavorables du taux de tunellites (TI) et du taux de péritonite étaient respectivement de 0,12 et 0,13 patient / an. Le sexe masculin (0,048), l'âge (0,007) et l'agent *Staphylococcus aureus* (0,006) étaient prédictifs de l'IT, l'IT là où la mise obligée en DP et des taux faibles d'albumine étaient des facteurs prédictifs de la péritonite.
Après avoir groupé les ESI en fonction de la date d'apparition de l'infection (groupe 1: 2008 à 2012, groupe 2: 2013 à 2017 et groupe 3: 2018), une augmentation substantielle de l'IT en 2018 était évidente (p <0,001 lorsque le groupe de comparaison 3 vs 1 et 0,005 en comparant les groupes 2 et 3).

Lorsque l'ESI survient en même temps que l'IT, le taux d'echec de guérison est de 65%. On observe 50 % d'abandons en cas d'ESI sans péritonite, contre 86% des patients ayant une péritonite (p <0,001). Le *Staphylococcus aureus* est le microorganisme le plus souvent responsable de l'échec de la guérison (P = 0,002) et de l'abandon de la technique (P = 0,01).

En dépit de nombreux efforts visant à réduire les ESI, un audit régulier a quand même mis en avant le besoin de réviser les protocoles en vue d'éviter des résultats défavorables. Une formation ciblée des patients est obligatoire, mais les protocoles prophylactiques et antibiotiques devraient être améliorés.

Mots clés : dialyse péritonéale, infections de l'orifice de sortie, cathéters

Summary

Infection-related complications in patients on peritoneal dialysis (PD) is a leading complication.
Our aim was to evaluate the type and natural course of Exit site infection (ESI) events in a cohort of PD treated in last decade of our PD program.

Our hospital database of ESI events (n=126, in 74 patients) were retrieved. ESI protocols followed standard international guidelines. A systematic quality control is performed.

The median follow-up was 29.1 (14.0-47.4) months. In this population the adverse outcomes of tunnel infection (TI) rate and peritonitis rate was 0.12 and 0.13 patient/year, respectively.
Male sex (0.048), older age (0.007) and *Staphylococcus aureus* (SA) agent (0.006) were predictive of TI while non-optional PD and lower levels of albumin were predictive of peritonitis.

After grouping the ESI events according to the date of the occurrence of infection (group 1: 2008 to 2012, group 2: 2013 to 2017 and group 3: 2018) a substantial increase of TI in 2018 was evident (P <0.001 when comparing group 3 vs 1 and 0.005 when comparing group 2 and 3).

When ESI occurs simultaneous with TI, the probability of not reaching cure is 65%. Drop-out occurred in 50% of ESI without peritonitis vs 86% with peritonitis (P <0.001). SA is the microorganism most implicated in the failure to heal (P 0.002) and drop-out (P 0.010).

In spite of a number of efforts to reduce ESI, a regular audit still point to the need for protocols review in order to avoid adverse outcomes. Focused training of patients is mandatory but also prophylaxis and antibiotic protocols deserve improvement.

Keywords : peritoneal dialysis, exit site infections, outcomes

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INTRODUCTION

Infection-related complications in patients on peritoneal dialysis (PD) is a leading complication and despite major technique advances and cumulative experience still is a major cause of technique dropout and switch to hemodialysis.

Catheter-related infections are used as the collective term to describe both exit-site infection (ESI) and tunnel infection (TI). These two conditions may occur on their own or simultaneously. ESI is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface [1,2]. TI is defined as the presence of clinical inflammation or ultrasonographic evidence of collection along the catheter tunnel. May present as erythema, edema, induration or tenderness over the subcutaneous pathway. Usually occurs simultaneously to an ESI but could occur alone [3]. ESI caused by *Staphylococcus aureus* (SA) or *Pseudomonas aeruginosa* are often associated with concomitant tunnel infections [4].

METHODS

Our hospital database of ESI events were retrieved from January 2008 to December 2018, in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or automated cycling peritoneal dialysis (APD), including epidemiological, modality variables, microbiologic agent and outcomes. During this period a total of 126 infections occurred in a total of 74 patients, who represent the study population.

Catheter exit-site is done by exteriorization of the "buried" catheter, implanted by the Moncrief Popovich technique. ESI protocols followed standard international guidelines. Salvage ESI/TI therapy with external cuff extrusion/shaving is done according to clinical criteria.
The focus was on quality control, analyzing rates of infection, identifying the most common microbiologic agents and their susceptibilities to antimicrobials and outcomes. A multivariable logistic regression model was used to determine significant risk factors for tunnel infections, peritonitis and drop-out as adverse outcomes of ESI.

RESULTS

Exit site episodes and population characteristics

The 126 ESI episodes included 98 ESI exclusively and 28 ESI concomitant with peritonitis. These episodes occurred in 74 patients followed for 79.342 patient-days and the median time since the start of DP to the first episode of ESI were 281 days (8-1990). In this population the adverse outcomes of TI rate and peritonitis rate was 0.12 and 0.13 patient/year, respectively. In 15 patients (20%) the ESI occurred in the first 30 days, and only 2 of them had simultaneous TI. The majority of this early infections occurred in patients on DPCA as this is the modality of choice for the beginning of the technique in our DP program. No characteristics, either patient or infection related, had statistical significance when early and late ESI were compared.

The average number of ESI episodes per patient was 1,8 (range from 1 to 6 episodes); 45,7% of patients had 1 ESI, 40% has 2 episodes, 8,6% had 3 and 5,7% has more than 3 episodes of ESI.
The median age of this cohort were 54 years (38-64) and most of all were men (54%, n=40). The majority were on CAPD modality (59%).
Most of the patients were hypertensive (92%) but only 19% had diabetes mellitus. The other population characteristics were detailed in table 1.

Table I : Characteristics and comorbidities of patients with ESI

Characteristics	N	%	Comorbidities	N	%
Age, median (IQR)	54 (38-64)		Current smoker	5	7
Women	34	46	Chronic lung disease	13	18
Men	40	54	Hypertension	68	92
			Cardiopathy	24	32
Residual renal function	44	59	Dyslipidemia	59	80
CAPD	40	54	Peripheral vascular disease	6	8
APD	34	46	Cerebrovascular disease	8	11
			Diabetes mellitus	14	19
ESRF cause			Insulin therapy	12	86
Unknown	22	30	HIV positive	4	5
Chronic glomerulonephritis	16	22	HCV positive	2	3
Diabetic nephropathy	11	15	Abdominal hernia	9	12
Reflux nephropathy	9	12	Corticotherapy exposure	15	20
Polycystic kidneys	8	11			
Renovascular disease	2	3			
Other	6	7			

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Identified microorganisms in ESI

The most common isolated organisms (table II) were Gram positive (n=81) included *Staphylococcus aureus* (n=43), Corynebacterium species (n=27), other *Staphylococcus* than aureus (n=6), Enterococcus faecalis (n=3) and Streptococcus species (n=2). Gram negative were identified in 36 cases, including *Pseudomonas aeruginosa* (n=15), *Proteus mirabilis* (n=13), Serratia marcescens (n=4), *Escherichia coli* (n=3) and *Haemophilus parainfluenzae* (n=1). In 4 cases, ESI were caused by both Gram positive and negative agents, in 2 by fungal and in 11 the agent was not identified. Only in 60% of IOS the microorganisms were multisensitive, while in the others cases the agents had at least one antimicrobial resistance. From all SA identified, only 4 were methicilin-resistant (MRSA). Two of the *Pseudomonas* isolated has extended-spectrum B-lactamases (ESBL) and 1 were carbapenemase producing bacteria (KPC). In all cases the antibiotic therapy took at least 2 weeks.

Table II : Identified microorganisms in ESI

		N =130	Multi-sensible (n=76)
Gram positive	*Staphylococcus aureus*	43	39 (4 MRSA)
	Corynebacterium species	27	12
	Other *Staphylo* than aureus (*coagulase negative, lugdunensis, epidermidis*)	6	4
	Enterococcus faecalis	3	0
	Streptococcus species (*pyogenes, viridans*)	2	1
Gram negative	*Pseudomonas aeruginosa*	15	11 (2 ESBL, 1 KPC)
	Proteus mirabilis	13	6
	Serratia marcescens	4	2
	Escherichia coli	3	1
	Haemophilus parainfluenzae	1	0
Fungal	*Candida albicans*	2	
Non-identified		11	
Mixed ESI	*Proteus mirabilis + enterococcus faecalis*		0
	Proteus mirabilis + Corynebacterium species		0
	Corynebacterium species + Streptococcus pyogenes		0
	Corynebacterium species + Enterococcus faecalis		0

Outcomes

The cure was achieved in almost 48% of cases (n=60), 26% (n=33) failed in cure and 26% (n=33) were responsible for the drop out of technique. When tunnel was involved the drop out reached 60%. Shaving of the external cuff was performed in 24 refractory ESI episodes but 12 (50%) still ended in catheter removal.
All the outcomes were described in table III

Table III. Events and outcomes of all ESI in our center

Outcome	N	%
Cure	60	48
Chronic infection	33	26
Relapse	25	19,7
Drop-out	**30**	**24**
Temporary hemodialysis	5	6,7
Permanent hemodialysis	25	33,8
Death	0	0

Predictors of adverse outcomes in ESI

In multivariate logistic regression male sex (0.048), older age (0.007) and *Staphylococcus aureus* agent (0.006) were predictive of TI, while non-optional PD (PD due to vascular access failure) and lower levels of serum albumin were predictive of peritonitis (Table IV). Diabetes, anuria, and PD modality were not predictive.

After grouping the ESI events according to the date of the occurrence of infection (group 1:2008 to 2012, group 2: 2013 to 2017 and group 3:2018) a substantial increase of tunnel infections in 2018 was evident (P <0.001 when comparing group 3 vs 1 and 0.005 when comparing group 2 and 3) (table V). There was no significant difference in patients' characteristics between the 3 groups and no cause has been identified for this occurrence.

When ESI occurs simultaneous with tunnel infection, the probability of not reaching cure is 65%. Drop out occurred in 50% of ESI without peritonitis vs 86% with peritonitis, P <0.001). *Staphylococcus aureus* is the microorganism most implicated in the failure to heal (P 0.002) and drop out (P 0.010).

DISCUSSION

Skin infection at the catheter exit-site remains a relevant problem in PD patients. The wide variations in is appearance leads to inconsistent monitoring and difficulties in

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Table IV : Multivariate logistic analysis of predictors of adverse outcomes in ESI, adjusted to variables with P<0.02

Significant risk factor for		OR	95% CI	P
Tunnel infection	Male gender	3.44	1.01-11.72	**0.048**
	Age	1.05	1.01-1.08	**0.007**
	Staphylococcus aureus	6.09	1.69-22.01	**0.006**
Peritonitis	Albumin	0.31	0.13-0.77	**0.011**
	Non-option vs option of technique	3.23	1.05-9.95	**0.041**
Non cure	Age	0.96	0.94-0.99	**0.009**
	Tunnel	4.89	1.45-16.49	**0.010**
	Staphylococcus aureus	3.37	1.12-10.13	**0.031**
	Others gram +	3.50	1.06-11.56	**0.039**
Drop-out	Peritonitis	8.28	2.56-26.83	**<0.001**
	Tunnel	9.42	2.56-34.65	**0.001**

Table V : ESI adverse outcome events according to date of occurrence

	Group 1 (2008-2012) Patient-time (days): 25572	**Group 2** (2013-2017) Patient-time (days): 44535	**Group 3** (2018) Patient-time (days): 9235	P Group 1vs2	P Group 1vs3	P Group 2vs3
Tunnel infection rate patient-year	0.04 (3 events)	0.11 (14 events)	0.39 (10 events)	0.107	**<0.001**	**0.005**
Peritonitis infection rate patient-year	0.21 (15 events)	0.06 (8 events)	0.20 (5 events)	**0.006**	0.910	0.072

interpreting study results. Although there has been no change in our unit protocols, there has been a staggering increase in ESI, particularly TI in 2018 whose cause was unclear to us. We then made a quality assessment brainstorming in order to disguise opportunities of improvement.

Relative to incidence rates, most of studies reports a range from 0.05 to 1.02 episodes/patient-year. We report the incident rate of this affected population, which for itself is more susceptible to ESI. Although it might be a negative methodological bias, our rates of ESI per patient-year are relatively low: 0.58 for ESI (126 events), 0,12 for tunnel infection (27 events) and 0.13 for peritonitis (28 events). Gram-positive agents were responsible for most peri-catheter infectious episodes, and SA was the primary cause of ESI. *Pseudomonas aeruginosa* was the most frequent gram-negative agent, followed by other Enterobacteriaceae, according to the literature evidence [5,6].

Implantation protocol

In our center the double-cuffed Tenckhoff catheters were placed in all patients by an expert team (a nephrologist and a surgeon) using mini-laparotomy and the Moncrief–Popovich method, in an operating room under sterile conditions.

Several randomized trials have compared laparoscopic or peritoneoscopic catheter placement with standard laparotomy, but none of them reported catheter-related infection as a secondary outcome [7]. There are two studies that compare midline and lateral incision but neither found any difference in the risk of catheter-related infection [8,9]. Although the best strategy for catheter placement has been questioned, several studies have shown that with appropriate training there is no difference in the rate of ESI in what concerns to catheter placement (by nephrologists or surgeons) or different techniques or incisions [7, 10-18]. Although an uncontrolled study suggests that the technique of burying the PD catheter in subcutaneous tissue for 4 to 6 weeks after implantation is associated with a lower rate of catheter-related infections [19], two randomized controlled studies found no difference as compared with the standard technique [20,21].

In all cases we administered intravenous prophylactic cephazolin immediately before implantation and before the exteriorization of external segment of the catheter.
Nowadays, it is widely recommended to do prophylactic antibiotics before catheter insertion. However, several prospective trials found that prophylactic perioperative intravenous antibiotics had no significant effect on the rate of early catheter-related infections, although it significantly reduces the risk of early peritonitis [22-26].
A break-in period of more than 4 weeks before exteriorization of the external segment of catheter was standard, usually extended to additional months until dialysis was needed [16]. It remains controversial whether immediate commencement of PD after catheter insertion is associated with a higher risk of catheter-related infections [27-30].

Nasal carriage of *Staphylococcus aureus* is seen as a major risk factor of catheter-related infections. Besides, one prospective study showed that intranasal mupirocin reduced SA ESI but not tunnel infection [31], there are no data on efficacy of its routine screening and eradication

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in patients prior to insertion of the peritoneal dialysis catheter. In our unit we use nasal mupirocin as part of the pre-implantation protocol in nasal carriers of S. aureus.
Facing the increase of ESI with tunnel infection we decided to 1) change the implantation procedure with a soaking step the catheter in cefazoline before introducing it in the pelvis and in the subcutaneous tunnel and 2) change the procedure of catheter exteriorization by using a skin biopsy needle to do the exit side to reduce trauma in the early cicatrization process and avoid early exist side colonization.

Exite site care

After exteriorization of the catheter's external segment, patients were taught to clean the exit site every day with saline solution (0.9% NaCl) and to keep it dry. They were prescribed 2% mupirocin cream to be used at the exit site once daily.

Guidelines recommend daily topical application of antibiotic cream or ointment on the catheter exit side since it prevents ESI caused by SA. This strategy is proved to be effective by a number of observational studies, randomized controlled trials, and meta-analyses [7,22,32-38] and has also been shown to be cost-effective [39]. Xu et al demonstrated that topical mupirocin over the exit-site reduced the risk of SA ESI by 72% [37]. The optimal frequency, however, is not well stablish, but mupirocin resistance has been reported predominantly with intermittent but not daily administration [15, 32-42]. The long-term implication of mupirocin resistance, however, remains unclear and may have been overstated [43]. Daily application of gentamicin cream to the exit site was used in order to try to reduce the ESI caused by Pseudomonas species, but no superiority to mupirocin was described and it was associated with an increase in ESI caused by Enterobacteriaceae, Pseudomonas species and probably non-tuberculous mycobacteria [33, 35, 44-46]. The incidence and implications of gentamicin resistance are uncertain [47]. Thokhonelidze et al, in a small randomized trial reported that topical application of 3% hypertonic saline is as effective as topical mupirocin cream for the prevention of ESI [48].
No cleansing agent has been shown to be superior with respect to preventing catheter-related infections. Studies with head-to-head comparison of hypochlorite, chlorhexidine or povidone-iodine reported conflicting advantage of one agent over another [49-51].
General measures on exit-site care and meticulous hand hygiene are generally recommended, but none has been proved by randomized controlled trial to reduce the rate of catheter-related infections [52]. In general, the exit site should be cleansed at least twice weekly and every time after a shower [53, 54]. Although gauze is commonly used for exit-site dressing and protection, a recent study suggested that regular dressing may not be necessary [53] and is what we recommend in our DP unit.

Exite site infection

At each clinic visit, an expert nurse classified the exit-site as "infected," "equivocal," or "good" according to a classification adapted from Twardowski [55]. A diagnosis of ESI was made when clinical signs of infection led to an exit-site swab and a positive culture. Equivocal exits were kept under surveillance, with topical antibiotic, saline soak, or silver nitrate granuloma cauterization. Exits that did not improve within 1 month were classified as "infected" and a systemic oral antibiotic was prescribed.

The first choice of empiric antibiotic was cotrimoxazole, usually taken for 2 weeks or until a week had passed since the cessation of signs of ESI. Once a culture report became available, the patient was switched to an appropriate antibiotic (if necessary). Pseudomonas ESI were treated with two antipseudomonal antibiotics: oral ciprofloxacin and intraperitoneal ceftazidime. Slow-responding SA ESI were treated with the addition of oral rifampicin. Prophylaxis against fungal peritonitis was undertaken by adding oral fluconazole in cases of recurrent or prolonged antibiotic prescriptions for ESI.
A recurrence of ESI caused by the same organism 30 days or more after appropriate therapy was considered chronic [24]. The presence of peritonitis caused by the same organism or by a fungus within 1 month after diagnosis of an ESI was considered an ESI-related peritonitis.

If prolonged therapy with appropriate antibiotics failed to resolve the infection, external cuff shaving was performed. The peritoneal catheter was removed after unsuccessful cuff shaving in patients with persistent chronic ESI, when the ESI progressed to peritonitis, when there was concomitant tunnel infection or when ESI occurred in conjunction with a peritonitis caused by the same infectious agent (with the exception of coagulase negative *Staphylococcus*). Catheter removal was considered to be related to ESI if it was performed within 3 months after the ESI diagnosis.

Rates of ESI have decreased substantially over the years through improvements in equipment, techniques, and prophylactic measures. It was required a multifaceted process, starting with extensive patient training and fo-

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cusing on proper technique [56].

In our unit however, the increase on tunnel infection rate induced a more aggressive empirical antibiotic protocol with intravenous vancomycin and oral ciprofloxacin, soon adjusted after the agent is diagnosed.

CONCLUSION

The natural history of ESI and timely strategies to promote cure remain challenging. In spite of a number of efforts to reduce ESI (prophylactic antibiotic administration at catheter implantation, nasal MRSA eradication in the carriers, topical use of mupirocin/gentamicin, improved connective systems) continuous monitoring of infection protocols, together with routine microbiologic assessment and quality control, is mandatory for individualized strategies.
Clinical trials are required on the primary and secondary prevention of ESI, specifically the optimal method of exit-site care and the fundamental strategies for a good patient-training program. Furthermore, the biology and management of catheter biofilm is another area which should be explored in the near future.

CONFLITS D'INTERET

Les auteurs déclarent ne pas avoir de conflit d'intérêt pour cet article.

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