The Association between Exit Site Infection and Subsequent Peritonitis among Peritoneal Dialysis Patients

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Summary

Background and objectives Peritonitis is the most common infectious complication seen in peritoneal dialysis (PD). Traditionally, exit site infection (ESI) has been thought to predispose PD patients to peritonitis, although the risks have not been quantified. This study aimed to quantify the risk of PD peritonitis after ESI.

Design, setting, participants, & measurements Data from 203 clinically stable PD patients >18 years of age who were followed as part of a randomized controlled trial over 18 months were used to estimate the risk of developing peritonitis within 30 days of an ESI compared with individuals who did not have a recent ESI. Sensitivity analyses were performed at 15, 45, and 60 days.

Results Patients were mostly male (64.5%) and Caucasian, with a mean age of 60.5 ± 14.4 years. There were 44 ESIs and 87 peritonitis episodes during the 18-month study. Seven patients had an ESI followed by peritonitis within 30 days. Using a frailty model, patients who had an ESI had a significantly higher risk of developing peritonitis within 30 days, even if the ESI was appropriately treated. This risk was maximal early on and diminished with time, with hazard ratios (95% confidence interval) of 11.1 at 15 days (HR=11.1, 95% CI=4.9–25.1), 5.3 at 45 days (2.5–11.3), and 4.9 at 60 days (2.4–9.9). In 2.3% of patients, subsequent peritonitis was caused by the same organism as the previous ESI.

Conclusions A strong association between a treated ESI and subsequent PD peritonitis was present up to 60 days after initial diagnosis.

Introduction

Treatment-related infections, such as peritonitis, continue to be the leading cause of morbidity and mortality in peritoneal dialysis (PD) patients. In addition, PD-related infection is the most common cause of technique failure (1–5). Much effort is placed on the prevention of peritonitis and the avoidance of the resulting severe complications (4–6). Traditionally, it has been thought that exit site infection (ESI) increases the risk of peritonitis via transmigration of organisms from the exit site along the PD catheter tunnel into the peritoneal cavity (3–6). Earlier studies that suggest a relationship between ESI and peritonitis have been largely retrospective or conducted using data from prospective observational cohorts or databases, with the majority being published before 2000. Although most of these studies have been consistent with the premise that an ESI places a PD patient at increased risk of peritonitis (7–27), none have quantified the strength of the reported relationship nor defined the period of time after ESI that was associated with increased peritonitis risk. Furthermore, in recent years, the spectrum of organisms causing infections in the PD population has changed, with a significantly higher proportion of Gram-negative organisms being seen due in part to a decline in infections with skin organisms (28–30). International Society for Peritoneal Dialysis guidelines have led to a wider use of topical antibiotic prophylaxis at the catheter exit site and more aggressive management of ESIs (31–35). We therefore hypothesized that the relationship between ESI and peritonitis might no longer be seen in a contemporary cohort of patients. We used data collected as part of a blinded multicenter randomized controlled trial (RCT) (36) to assess whether a temporal relationship between ESI and peritonitis truly exists and to quantify the risks in those treated with systemic and nonsystemic therapy for their ESI.

Materials and Methods

Patients

Data were extracted from a multicenter RCT comparing two PD catheter exit site ointments, mupirocin and Polysporin Triple (36,37). Patients were taught to apply the study ointment to the exit site with each dressing change. All aspects of medical care, including exit site care, dressing change frequency, dialysis...
protocols, and management of PD-related infections, were left to discretion of the patient’s primary nephrologist. All ESIs and peritonitis episodes were recorded prospectively as part of the study protocol using rigorous methods (ongoing direct patient contact and review of all dialysis unit logs and charts as well as formal study incident reports). As per local training procedures, patients were reminded to contact their dialysis team if either ESI or peritonitis was suspected. This included data on microbiology of ESI and peritonitis episodes as well as treatment for these infections. The choice of treatment for ESIs was left to the physician’s discretion. Trial results showed no significant decrease in PD-related infections with the routine use of Polysporin Triple at the exit site (37).

Definitions
The International Society for Peritoneal Dialysis definitions were used (35). ESIs were defined as purulent drainage from the exit site with or without erythema. Peritonitis was defined as the presence of two of the following three findings: abdominal pain, cloudy effluent with ≥100 white blood cells/μL and ≥50% polymorphonuclear cells, or positive microbiological culture of dialysate fluid. ESI and peritonitis were considered to be associated with each other if peritonitis followed within 30 days of the diagnosis of an ESI. In addition, sensitivity analyses for 15, 45, and 60 days were performed.

Treatments of the ESI were classified as systemic (oral, intravenous, or intraperitoneal antibiotics) or nonsystemic (topical antibiotics or other localized treatments).

Statistical Analyses
A Cox proportional hazards model was used to assess the relationship between ESI and peritonitis, with a frailty term to account for repeated episodes of peritonitis in each person. Each person was considered at baseline risk of an episode of peritonitis between the beginning and the end of the study period. We used a time-dependent variable for ESI, in which the first 30 days after an ESI were considered “exposed” to additional risk due to concomitant ESI. The variables for age, sex, and presence of diabetes were included as covariates. The 30 days after ESI were considered as an “additional risk time period,” whereas the remaining time and time in participants who did not have an ESI were considered as the “baseline peritonitis risk period.” In addition, sensitivity analyses were performed using time epoch methodology (38) and by using the time for ESI-related risk as 15, 45, and 60 days after an ESI. Crude rates of peritonitis (episodes per 100 days) in the time after ESI and the ESI-free time were reported.

Prespecified Secondary Analyses
Three prespecified secondary analyses were performed. First, time dependency was assessed by performing the analysis using 15, 45, and 60 days after an ESI for the period of time at risk. Second, the analysis was limited to those episodes of peritonitis that occurred with identical organisms to those seen causing the ESI, based on the cultured organism. For the purposes of the analysis, organisms were condensed into the following eight groups: Streptococcus spp., Staphylococcus aureus, other Gram-positive organisms, Pseudomonas spp., other Gram-negative organisms, Candida spp., other organisms, and culture negative. Finally, the effect of exit site treatment was explored. Patients who were treated with oral, intravenous, or intraperitoneal therapy were said to have received systemic therapy, whereas those who had been managed with only topical therapies were said to have received nonsystemic therapy.

Results
Population Characteristics
The study population consisted of 203 PD patients, both incident (n=63) and prevalent (n=140). The demographic and baseline clinical characteristics of the study population are summarized in Table 1. Most patients were male (64.5%) with a mean age of 60.5±14.4 years (range, 22.8–96.6). Patients were on PD for a median time of 9.7 months (25th and 75th percentiles: 2.1 and 28.5 months, respectively). Demographic data are shown in Table 1. The patients were followed prospectively for a total of 2756 patient-months (median 18 months; range, 0.1–18.0 months), and 173 patients (85.2%) completed 18 months of follow-up or were followed up to catheter removal or death. The total follow-up after ESI was 271 months (median 6.3; range, 1–17 months).

Incidence
Thirty-four patients experienced 44 ESIs during the study period (overall exit site rate: 1 episode per 62.6 patient-months, 0.19 episodes per patient-year). ESIs were treated using systemic (i.e., oral, intravenous, or intraperitoneal) antibiotics in 18 patients (41.1%), a combination of systemic antibiotics with modified topical therapy in 2 patients (4.5%), or nonsystemic therapies such as topical ointments or hydrogen peroxide in 24 patients (54.4%). Eight patients with ESIs received multiple systemic antibiotics. Peritonitis occurred in 57 individuals experiencing a total of 87 episodes (overall peritonitis rate: 1 episode per 31.7 patient-months, 0.38 episodes per patient-year). Causative organisms are shown in Table 2. The predominant organisms causing ESI and peritonitis were skin organisms. A negative culture occurred more frequently in peritonitis than in ESI. Five ESIs (11.4%) and 17 peritonitis episodes (19.5%) were culture negative. The single episode of peritonitis after an ESI that had the identical organism occurred with a corynebacterium infection in which peritonitis occurred 1 week after the ESI. The ESI was originally treated with increased dressing changes and topical hydrogen peroxide but no antibiotic.

Risk of Developing Peritonitis after a Recent ESI
A strong association was found between a recent ESI and the development of subsequent peritonitis. The association was present after adjustment for age, sex, and presence of diabetes. Of the 44 ESIs, 7 were followed by subsequent peritonitis within 30 days and 12 within 60 days. The risk of developing peritonitis declined with time. Maximal risk was seen within 15 days of ESI, with a hazard ratio (HR) of 11.1 (95% confidence interval [CI], 4.9–25.1; P<0.001). The risk became attenuated with time; however, it remained clinically important up to 60 days after the onset of an ESI, with HRs of 6.3 at 30 days (95% CI, 2.9–14.0; P<0.001), 5.3...
at 45 days (95% CI, 2.5–11.3; \( P < 0.001 \)), and 4.9 at 60 days (95% CI, 2.4–9.9; \( P < 0.001 \)) (Figure 1). Further assessment of the risk estimate at 90 and 120 days was not possible due to the relatively small number of ESI events.

Secondary Analyses

Results from evaluation of the relationship using time epochs (38) yielded similar results (data not shown). As noted previously, the management of ESI was highly variable because the study protocol left management of the ESI to the physician’s discretion. No statistical difference was seen between patients receiving systemic or nonsystemic treatment of ESI, although a trend to harm associated was seen with systemic treatment (HR, 16.7; 95% CI, 6.4–43.6) compared with nonsystemic treatment (HR, 6.0; 95% CI, 1.4–25.5). Because only one episode of both ESI and peritonitis was seen with the same organism, no further analysis was attempted.

Discussion

Our study estimates the hazard of peritonitis, shortly after an ESI is diagnosed, to be six-fold higher than baseline. This has major implications for clinicians involved with PD patients, particularly as ESI management strategies vary highly between physicians and units. We were surprised to find such a high estimated risk associated with ESI, particularly because most ESIs were managed promptly with either topical or systemic therapies. With the current strategies to detect and treat ESIs promptly, we anticipated that we would see considerably lower risks. In addition to confirming previous reports (7–27) that patients with an ESI are at increased risk of peritonitis in the immediate post-ESI period, and quantifying this risk, our data showed two additional observations: microbiological inconsistency and lack of effect with aggressive ESI treatments.

Before obtaining the study results, we anticipated that ESIs with Gram-positive organisms or *Pseudomonas* spp. would be highly associated with corresponding bacterial peritonitis infections. We hypothesized that peritonitis would be caused by the same organisms because of contamination of the patient’s hands and equipment when performing exit site care, the presence of catheter biofilm and, to a lesser extent, because of bacterial tracking along the catheter wall. In contrast, we found that the bacterial cultures from the ensuing peritonitis were often different from the organisms causing ESI. We considered three

| Table 1. Demographic and baseline clinical characteristics of the study population |
|---------------------------------------------------|---------------------|---------------------|
| Characteristic                     | Value, \( n (%) \) |                     |
| Patients (\( n \))                    | 203                 |                     |
| Male                                | 131 (65)            |                     |
| Age (yr), mean ± SD                 | 60.5±14.4           |                     |
| Diabetic                            | 88 (43)             |                     |
| On immunosuppressive drugs at study start | 22 (11)           |                     |
| Peritoneal dialysis technique prevalent |                     |                     |
| APD                                 | 78 (39)             |                     |
| CAPD                                | 60 (29)             |                     |
| Incident                            |                     |                     |
| APD                                 | 29 (14)             |                     |
| CAPD                                | 36 (18)             |                     |

APD, ambulatory peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

| Table 2. Detailed microbiology of ESIs and peritonitis events |
|---------------------------------------------------------------|---------------------|---------------------|
| Organism                                      | ESI | Peritonitis |
|                                               | P3 | Mupirocin | P3 | Mupirocin |
| Gram positive                                  |   |     |     |
| *Staphylococcus aureus*                        | 3 | 3    | 1  | 2        |
| Diphtheroid spp.                               | 4 | 5    | 3  | 3        |
| *S. epidermis*                                 | 1 | 0    | 5  | 6        |
| Coagulase negative *Staphylococcus* (excluding *S. epidermis*) | 0 | 0    | 8  | 9        |
| *Streptococcus viridans*                       | 1 | 0    | 3  | 1        |
| *Streptococcus*, other                         | 2 | 0    | 1  | 3        |
| *Pseudomonas* spp.                             | 3 | 3    | 3  | 2        |
| *Proteus* spp.                                 | 2 | 0    | 0  | 0        |
| *Serratia* spp.                                | 2 | 0    | 0  | 0        |
| *Klebsiella*                                   | 1 | 0    | 0  | 2        |
| *Citrobacter* spp.                             | 0 | 0    | 1  | 0        |
| *Neisseria* spp.                               | 0 | 0    | 0  | 1        |
| *Enterobacter*, other (e.g., coliforms)        | 0 | 0    | 0  | 1        |
| *Escherichia coli*                             | 0 | 0    | 0  | 4        |
| *Enterococcus* (*S. faecalis, S. faecium*)     | 0 | 0    | 1  | 3        |
| *Candida* spp.                                 | 4 | 0    | 4  | 1        |
| Other                                          | 4 | 1    | 2  | 2        |
| Culture negative                               | 3 | 2    | 8  | 9        |

ESI, exit site infection; P3, Polysporin Triple.
possible explanations for the microbiological inconsistency. First, it is possible that the relationship we observed is purely an artifact of our study design. Because we identified patients at the time of their first ESI after recruitment into the study, it is plausible that we simply identified a high-risk group. Patient-specific factors (hygiene, immunocompetence, psychosocial circumstances, etc.) may place some individuals at a higher baseline risk of infection compared with others. These individuals would present earlier with their first infection, and then have a higher incidence of subsequent random infections that would look similar to an increased risk of peritonitis after the first infection. We believe this to be an unlikely explanation because one would then expect little or no change in the estimated risk of peritonitis over time (because these individuals are always at high risk). In contrast, we observed a trend to decreasing risk over time from ESI diagnosis. A second explanation is that it is possible that ESI affects immunomodulatory pathways and is associated with an overall increase in predisposition to bacterial infection, much in the same way that patients with sepsis or influenza are at increased risk of secondary bacterial infections. The dialysis population is already known to be immunocompromised, and we thus thought that this may be plausible and searched the literature for similar data. Although we identified patients at the time of their first ESI after recruitment into the study, it is plausible that we simply identified a high-risk group. Patient-specific factors (hygiene, immunocompetence, psychosocial circumstances, etc.) may place some individuals at a higher baseline risk of infection compared with others. These individuals would present earlier with their first infection, and then have a higher incidence of subsequent random infections that would look similar to an increased risk of peritonitis after the first infection. We believe this to be an unlikely explanation because one would then expect little or no change in the estimated risk of peritonitis over time (because these individuals are always at high risk). In contrast, we observed a trend to decreasing risk over time from ESI diagnosis. A second explanation is that it is possible that ESI affects immunomodulatory pathways and is associated with an overall increase in predisposition to bacterial infection, much in the same way that patients with sepsis or influenza are at increased risk of secondary bacterial infections. The dialysis population is already known to be immunocompromised, and we thus thought that this may be plausible and searched the literature for similar data. Although we were unable to find any published data relating increased infection associated with tunneled hemodialysis catheters, or in other immunocompromised nonrenal populations that support bacterial super-infection after mild skin infections, we still believe this to be plausible and suggest that further research may be required to evaluate this hypothesis. Last, we questioned if laboratory culture techniques could lead to the observed microbiological inconsistency. Skin swabs would likely be cultured in a laboratory setting for a specific time or until a positive growth. The samples are unlikely to be cultured for much longer, particularly if the organism grown is consistent with skin infection. Culture plates would be discarded and likely cultures not observed further for alternative slow growing or unusual organisms. Consequently, the treatment used for the skin organism may be appropriately targeted at the skin organism detected, but not target any other associated organisms. These may then grow and subsequently lead to peritonitis. Although this is an interesting theory, using the data collected as part of this study, we are unable to further comment on whether this may be true and again await further research in the field.

In addition to the microbiological inconsistency detailed above, we also found that treatment of the exit site did not reduce the risk of subsequent peritonitis. At the time of the study design, there were no widely available evidence-based protocols for the management of ESIs and the protocol allowed for individualized management of the ESI. The aggressiveness of treatment seemed to vary widely between the five different primary nephrologists who provided regular dialysis care (data not shown). As a result, many cases of ESI were treated with systemic antibiotics (41.1%), whereas others were treated only with topical therapies. We were again intrigued to find a nonstatistical trend to lower rates of peritonitis in those with topical therapies and higher in those who received systemic treatments (defined as oral, intraperitoneal, or intravenous antibiotics). Although these data are difficult to interpret because of low numbers of ESI infections, and consequently low power and confounding by indication, they do raise the question of whether systemic therapy is warranted or better.

One of the strengths of this study is that data were collected as part of a blinded multicenter RCT (36,37). It is unlikely that biases arising from missed or undocumented ESI are present. In addition, because of the long prospective follow-up, it is also unlikely that any peritonitis episodes were missed. On the other hand, we have shown wide CIs around the HRs because of a relatively small sample of patients enrolled in our RCT and the low rate of infection. The data, however, still support increased risk in the immediate post-ESI period because, in all cases, the lower CI limits remained substantially >1. It is worth noting that some patients had <60 days of follow-up after the ESI start, including 22.7% with <30 days of follow-up after the ESI. This could potentially have led to an underestimation of
the extent of the increase in peritonitis risk after ESI. Further extrapolation beyond 60 days was not possible because of the low incidence of ESI. In the context of a RCT, one may arguably see an atypical relationship that arises from the use of an experimental therapy. Our primary results showed that the use of Polysporin Triple was associated with an increase in observed fungal infections; however, because none of the peritonitis events after an ESI were fungal, this is unlikely to have affected the association reported in this manuscript.

In conclusion, we have demonstrated the presence of a strong association between ESI and the development of peritonitis in PD patients. The risk of peritonitis was maximal shortly after the diagnosis of an ESI and decreased over time but remained above baseline even 60 days after the ESI. These data suggest that research is required to assess if strategies to improve the early detection of ESIs may be useful in the prevention of peritonitis and serve to question whether current treatment of ESIs are beneficial.

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Disclosures
None.

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