

## Getting Excited about Exit Sites in Peritoneal Dialysis?

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Despite all the attention given to issues such as adequacy of clearances, ultrafiltration failure, and lack of home support, peritonitis remains the leading cause of technique failure in most peritoneal dialysis (PD) centers (1,2). Furthermore, recent audits from a number of regions suggest that peritonitis rates in unselected centers are often higher than those reported from motivated centers of excellence. For example, Brown and colleagues looked at all 10 PD units in Scotland between 2001 and 2007 and found that the peritonitis rate was 1 every 19.9 months, and Ghali *et al.* (3,4) from the Australia New Zealand Registry reported an almost identical rate of 1 in 20 months from their 72 centers between 2003 and 2008. These rather disappointing rates do contrast with better results in Canada and France, but the latter studies are based on more selected units rather than a comprehensive audit (5,6). Clearly, peritonitis is a problem that has not gone away.

Peritonitis is generally acquired by one of three major routes. These are touch contamination by the patient during connection procedures, migration of organisms from the exit site through the catheter tunnel, and transmural migration from the gut into the peritoneal cavity (7).

The first great breakthrough in preventing peritonitis occurred with the widespread introduction of Y set and double bag continuous ambulatory peritoneal dialysis connection systems in the 1980s and 1990s. Rates were typically 50% lower in randomized trials testing these systems, and there was a sense of optimism that peritonitis as a problem was largely solved when their use became widespread (8,9). Rates of peritonitis undoubtedly fell, but this was mainly because of a decline in cases caused by touch contamination organisms such as *Staphylococcus epidermidis* (10). These, however, were the mildest cases of peritonitis with the lowest rates of catheter loss and technique failure.

The second significant advance occurred in the last 15 years and was related to peritonitis that occurred via the catheter tunnel in association with exit site colonization and infection, typically with *Staphylococcus aureus* and *Pseudomonas aeruginosa* organisms. Landmark studies proved that *S. aureus* peritonitis was related to colonization of the patient, and of the exit site, by this organism (11). Subsequently, effective prevention strategies with locally applied mupirocin and gentamicin antibiotic creams were shown to

reduce exit site infection (ESI) and peritonitis rates (12,13). Intriguingly, one randomized trial showed a decline in gram-negative non-*Pseudomonas* peritonitis, which had previously been thought not usually to enter the peritoneal cavity via the exit site and tunnel (13). Despite these encouraging studies, uptake of these strategies has not been universal, and peritonitis rates do not appear to have fallen in the same way that they did when Y sets were introduced (1,2,10). This raises some questions. Why are these preventative local strategies not being more widely used? Is it physician ignorance or skepticism? Or are the strategies not as effective as the trials have suggested? Is the underlying hypothesis connecting exit site colonization and infection to peritonitis flawed in some way?

Against this background, van Diepen *et al.* (14) published an analysis of the relationship between ESI and peritonitis in this issue of *CJASN*. They use data from their recently published randomized controlled trial that compared exit site application of polysporin and mupirocin (15). This study enrolled 201 patients and found no difference in rates of peritonitis, tunnel, or ESI between the two groups. The authors then investigated the risk of developing peritonitis in the days immediately after diagnosis and treatment of an exit site infection. They found that the risk is increased >10-fold in the first 15 days, >6-fold in the first 30 days, and almost 5-fold up to 60 days. This would appear to be impressively clear evidence supporting the hypothesis that ESI is a cause of peritonitis. The authors, however, raise some caveats. They note that in only one case did peritonitis caused by the same organism occur after an ESI. Frequently, there was a discrepancy between the organism cultured from the exit site and that grown from the subsequent peritoneal effluent. They also report that the aggressiveness with which an ESI was treated, in terms of systemic versus topical antibiotics, did not alter the subsequent risk of peritonitis. These findings lead the authors to question the underlying notion that the ESI actually causes the peritonitis.

It is important to question underlying dogma in clinical medicine and dialysis is an area where research studies challenging dogma have often yielded surprising results. van Diepen *et al.* are to be congratulated for asking and attempting to answer a question that many would have considered self-evident. However, perhaps they are second guessing their own impressive findings to an excessive degree!

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First, it should be re-emphasized that their own findings are hugely supportive of a key connection between ESI and peritonitis. A 6-fold increase in the peritonitis rate in the month after an ESI is dramatic. For the period concerned, this is equivalent to a peritonitis rate of about 1 every 6 months. For anyone who doubts the significance of an ESI, this paper should be a “wake-up” call. Second, we need to recognize that the database from their randomized trial is detailed but, by its nature, small. They had just 44 ESI episodes to work with. Unfortunately, we are not told exactly how many of these were followed by peritonitis but one would suspect from the literature that it would be much less than half, so that the power of the study to say much about the relationship between ESI and peritonitis is limited. Therefore, the identification of just one pair of infections caused by the same organism cannot be considered to be proof of anything.

There is, in contrast, a wealth of information in large observational studies about this relationship. When examining this, it is best to focus on studies of the two most challenging and serious ESIs, those caused by *S. aureus* and *Pseudomonas*. These are the ESIs that matter most because they are each associated with a relatively common and very nasty peritonitis. Szeto *et al.* (16) for example, reported on 245 episodes of *Staphylococcus aureus* peritonitis from a single very large center in Hong Kong. They found that 25% of cases followed an ESI. The same group looked at 105 cases of *Pseudomonas* peritonitis and found that 45% were preceded by an ESI (17). These findings are consistent with other literature, and all of this strongly suggests a real temporal, and likely causal, relationship between ESI and important types of peritonitis. For peritonitis caused by coagulase negative staphylococci or non-pseudomonal gram-negative organisms, the proportion preceded by an ESI is much less—at 10% and 18%, respectively—but this is not surprising because these types of peritonitis are more likely to be caused by touch contamination or bowel translocation (18,19).

What, however, are we to make of the relatively common occurrence of a discordant peritonitis after an ESI? van Diepen *et al.* do not provide an exact denominator, but only one of their paired events of ESI and peritonitis showed concordance of cultures. Again, the data from the larger organism-specific peritonitis papers by Szeto and colleagues are helpful here. With *S. aureus* peritonitis, 60% of the one quarter of cases with a preceding ESI had a concordant positive exit site culture (16). With *Pseudomonas* peritonitis, just under one half of the 45% with a preceding ESI had a concordant exit site culture (17). Concordance rates were much lower for ESI preceding peritonitis caused by organisms such as coagulase-negative staphylococci and Enterobacteriaceae, but these types of peritonitis are generally not considered to be acquired via the exit site and tunnel route anyway (18,19).

How do we explain this discordance? Some possibilities are suggested by van Diepen *et al.* One is that ESI leads to peritonitis, not because the same organism tracks up the tunnel into the peritoneal cavity, but rather because ESI in some way disrupts local host defenses and therefore allows subsequent easier access of other organisms to the abdominal cavity via the tunnel. This is certainly plausible for some cases but in no way detracts from the notion that

ESIs cause peritonitis. Another is that ESI and peritonitis episodes are not causally related at all but instead each is a common consequence of being at higher risk for infection generally, either because of poor hygiene or impaired host responses. This latter explanation is less likely because, in the study of van Diepen *et al.*, the peritonitis risk varied with time, being more marked immediately after the ESI and less marked a few months later. More likely is the third explanation offered. As all PD practitioners know, growing organisms from exit sites cultures can be a challenge. Not all ESIs have ample purulent discharge available for culture. The samples taken are often inadequate and yield negative results or grow just skin commensals of dubious significance. Growing a diptheroid organism or a coagulase negative *Staphylococcus* from an ESI does not mean that this is the underlying cause of the infection and does not reassure us that there is not an underlying *Pseudomonas* or *S. aureus* that will lead to peritonitis a few weeks later.

The issue of why the risk of peritonitis after ESI did not decrease with systemic versus antibiotic treatment also merits consideration. Again, the numbers of cases are too small to draw reliable conclusions, but we should not be surprised. The equivalency of local versus systemic measures in treating ESI has been noted before (20). There is also the possibility of confounding by severity in that the worst ESI cases were probably more likely to be treated systemically, and therefore, even equivalent results may mean an advantage for systemic antibiotics.

The study by van Diepen *et al.* is a useful contribution to the literature because it quantifies better than any previous paper the extra risk of peritonitis associated with ESI. The excess risk is strikingly large but probably not surprising to PD practitioners. The data presented support rather than raise doubts about the hypothesis that ESI leads to peritonitis. As the authors propose, this area needs further investigation, but there is nothing in their findings to support a change in presently recommended practices (7,21). Acutely infected exit sites should be identified, cultured, and treated aggressively. However, antibiotics should not be casually prescribed to treat chronic changes or, worse still, positive cultures in the absence of clinical signs of infection. Both positive and negative cultures should be viewed critically, and clinical findings should guide treatment. Systemic and even intraperitoneal antibiotics should be used if there is convincing evidence of acute infection. Persistent exit site infection with clinical involvement of the tunnel, despite antibiotic treatment, should lead to consideration of catheter removal, especially if the organism is *Pseudomonas* or *S. aureus*, because progression to an unpleasant peritonitis is otherwise likely. Even more importantly, preventative strategies should be used (7). It is hard to understand why all centers do not use either topical mupirocin or topical gentamicin, given the published literature (12,13). The theoretical risks of causing an ESI due to resistant organisms or fungi seem small relative to the potential to prevent severe peritonitis caused by *S. aureus* and other organisms.

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See related article, “The Association between Exit Site Infection and Subsequent Peritonitis among Peritoneal Dialysis Patients,” on pages 1266–1271.