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NEPHROLOGY - EDITORIAL

Our war against bacteria in peritoneal dialysis, the last 40 years!

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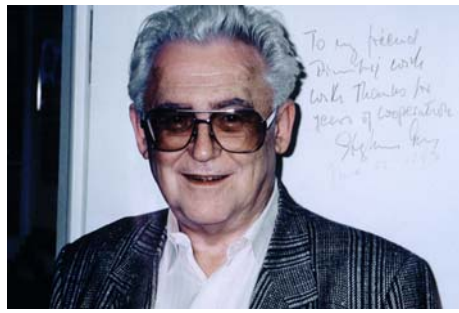
The late Stephen Vas often used to remind us, "Bacteria can never be defeated". Our lives are a continuous struggle against bacteria. They try continuously to invade us and take over our bodies and, sometimes when our defense mechanisms are low, they succeed and we lose the battle. In the field of peritoneal dialysis there is evidence that our fight against bacteria has greatly benefited our patients, although there is still room for improvement.

The enemy

Unfortunately we are not dealing with a small number of bacteria. Almost any bacterium, yeast or filamentous fungi can invade the peritoneal cavity and under the conditions of peritoneal dialysis, even some non-pathogenic agents may become pathogenic [1–4]. Among all these bacteria, it is infections by *Staphylococcus aureus*, *Pseudomonas* species and fungi that do the greatest damage to the patient on peritoneal dialysis.



Stephen Vas: Microbiologist "Par excellance"—*1926–2006*

Routes of invasion

The first step in our efforts to protect the peritoneal dialysis patients is to understand the routes through which bacteria invade the peritoneal cavity. Stephen Vas identified the five routes of invasion [5]: (1) The intraluminal—contamination during the connection procedure; (2) the extraluminal—infection from around the exit site; (3) the transmural—infection through the bowel wall, and two infrequent ones; (4)

1st Stephen Vas Memorial Lecture, Annual Dialysis Conference, around 2008.

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the hematogenous (blood-borne) organism like TB and (5) the ascending route—rarely women may become infected from a communication between the peritoneal cavity through the fallopian tubes via the vagina.

Intraluminal infections

We have achieved our major successes against bacteria to date by preventing infections through the intraluminal route i.e. during the connection between catheter and the administration tube and the administration tube and the new bag. Work in this area has given rise to the term "connectology". Initially when Popovich, Moncrief and Nolph started doing continuous ambulatory peritoneal dialysis (CAPD) in 1975, they had to use dialysis solutions in glass containers, hence their patients had to do many connections and disconnections in the process of dialysis solution exchanges. Under these conditions, the peritonitis rate was high; one episode every 3–4 patient months [6].

The introduction by Baxter Canada of plastic bags made it easier to handle the bags but also made way for the introduction of the Toronto Western Hospital Technique for CAPD. This technique, first described in the *Transactions of the American Society for Artificial Internal Organs* in 1978 [7], connected the new plastic bag with fresh dialysis solution with the peritoneal dialysis catheter via a connection tube with a Luer connection at the catheter end and at the other end, a spike that penetrated the port of the bag. After the fresh solution is infused, the empty bag is folded still connected to the tubing, and is attached to the patient's clothes for the next 4–8 h. At the end of this period, the fluid drains out from the peritoneal cavity into the unfolded empty bag, and the spike is removed from the empty bag, under sterile conditions and connected to a new bag. When it was introduced, this technique reduced the original peritonitis rate (with glass containers) of 1 episode every 3–4 patient months to 1 episode every 11–12 months. This major advancement made CAPD acceptable to the wider nephrology community.

Subsequently, two further modifications of this technique, both from Italy, lowered peritonitis rates even further. In 1980, Bazzato presented his twin bag system. Here a Y-set is attached to a full and an empty bag and with a needle at the third arm of the Y-set that pierces a rubber stopper in the end of a special adapter in the peritoneal catheter. After the fluid drains out of the peritoneal cavity into the empty bag, the new solution from the full bag is infused into the patient and the needle is removed from the rubber stopper. Using this technique in seven patients, Bazzato was able to lower the peritonitis rate to 1 episode every 21 patient months [8].

In a subsequent development, Buoncristiani from Perugia introduced his Y-set technique. With this technique [9], a short Y-set is attached at the end of the peritoneal catheter and, between exchanges, is filled with a small volume of sodium hypochloride. A small clamp at the peritoneal catheter prevents the sodium hypochlorite from entering the catheter. When the patient is ready to carry out his exchange, he connects the Y-set to a bag that comes with a long tube. Then in succession, he flushes the sodium hypochloride from the Y-set with a small volume of the fresh dialysate solution, drains the fluid from the peritoneal cavity, and opens the clamp that allows infusion of the new solution into the peritoneal cavity. When the infusion of the new solution is completed, the bag is disconnected from the Y-set which again is filled with a solution of sodium hypochlorite. Italian investigators, under Maiorca, undertook a prospective controlled trial to compare this technique with the standard spike system (Toronto Western Hospital Technique), and found that the peritonitis rate with the new system was one-third of that with the standard system [10]. This revolutionary technique was not accepted in North America for 4–5 years because neither Vas nor Oreopoulos believed than an Italian technique could provide results better than their own. Only after the Toronto Western Hospital group in collaboration with Dr. David Churchill undertook their own prospective, controlled multicenter trial that confirmed this benefit [11], this technique was accepted in North America. In this technique sodium hypochloride may not be necessary because the "flush after connect" step ensures that any organisms that may have accidentally contaminated the system are flushed out before new fluid is infused to the peritoneal cavity. No one is using sodium hypochloride now. With this Y-set technique, peritonitis rates have been stabilized at between 1/30 and 1/40 patient months.

In an overview of peritonitis rates of nine hospitals in the Province of Ontario, the rate of peritonitis ranged

from one episode every 17.6–49.5 patient months with an average of 1 episode every 29 patient months.

Extraluminal infections

We have also made progress in the prevention of extraluminal infections. In a recent meta-analysis on the relationship of the types of catheter with the incidence of peritonitis, Strippoli et al. [12] showed that neither a particular PD catheter design nor the implantation technique gave an advantage with respect to peritonitis rates. Individual experience that guides our practice in our hospitals shows that: the double-cuff catheters achieve a lower exit-site infection rate than single-cuff catheters [13]; the type of catheter makes no major difference in the peritonitis rate [14]; and prophylactic use of antibiotics at the time of implantation may prevent early post-surgical peritonitis [15]. Some workers report that presternal catheters may have lower peritonitis rates [16].

Biofilm

The formation of biofilm on the peritoneal catheter may play some role in the perpetuation of peritonitis or its recurrence [17]; this phenomenon may be prevented with the use of embedded catheters [18]. Certain investigators tried antibiotic-coated or silver-impregnated catheters in an attempt to prevent the formation of biofilm but have reached no conclusions. In addition, whether laparoscopic placement of peritoneal dialysis catheters has an effect on peritonitis rates remains to be established [19].

Transmural infections

These infections are caused by enteric bacteria, with Gram-negative bacteria predominating. The studies of Gram-negative peritonitis in PD patients have come to two sobering conclusions. First, unlike the rates of transluminal and, apparently, periluminal infections that have decreased considerably, the rates of Gram-negative peritonitis have not been affected by the improvements in PD connectology and PD technique overall. Second, Gram-negative peritonitis increases the mortality in PD populations [20]. Prevention of Gram-negative peritonitis will require our undivided attention. Timely diagnosis and management of intraabdominal conditions, such as ischemic bowel disease or diverticulitis, that can promote transmural infection, could potentially reduce the rate of transmural peritonitis. Whether the diagnosis of any of these conditions calls for treatment with intermittent courses of antibiotics even when there are no signs of infection is a question that has not been addressed. Endoscopic procedures in PD patients have been reported to be the cause of peritonitis with enteric organisms and should be "covered" by short antibiotic courses, although the efficacy of prophylactic antibiotics in this setting is still debated.

Prevention of exit-site infection and peritonitis

Of the major developments in this area, a prospective randomized study showed that application of mupirocin ointment in the nasal nares prevents staphylococcal colonization of the nose and decreases the rate of staphylococcal exit site infection [21]. Bernardini et al. [22] have proposed the use of mupirocin at the exit site with significant decrease in exit-site infections due to *Staphylococcus aureus*. Thodis et al. [23] in our unit confirmed the value of these measures. Exit-site infections due to *Staphylococcus aureus* and even *Staphylococcus aureus* peritonitis declined significantly after the application of muporicin at the exit site. More recently Bernardini and Piraino compared the effect of gentamicin ointment at the exit site with that of mupirocin; they found that gentamicin was more effective than mupirocin; and, in addition to preventing gram-positive infections, gentamicin also prevented pseudomonas exit-site infections [24]. Although they have not studied the effects of gentamicin ointment on pseudomonas peritonitis, one would expect fewer cases of such peritonitis, because often exit-site infections with pseudomonas lead to peritonitis with the same organism. Finally, investigators in Hong Kong [25] have proposed use of oral Nystatin to prevent fungal infections. The Toronto Western Hospital group [26] repeated this study but could not confirm the success of the Hong Kong Group. However, because this is a safe intervention, the ISPD guidelines recommend that peritoneal dialysis

patients who are on antibiotics for any length of time should take oral Nystatin as long as they are on antibiotics.

Other areas where prophylactic antibiotics may have some effect, although we lack supportive evidence obtained through prospective studies, are before dental work, before colonoscopy and before D&C.

Peritoneal defenses and prevention of bacterial infections

We expect great benefits from studies of the peritoneal defenses based on humoral factors such as, haptoglobin and opsonins and cellular factors like mesothelial cells, macrophages, eosinophils, and lymphocytes. Although we have considerable knowledge in this area, todate no new approach in the prevention and treatment of peritonitis has been based on this knowledge. A prospective study failed to show any benefit of addition of immunoglobulins to the dialysis fluid on the rate of peritonitis [27].

Peritonitis treatment and catheter removal

We have greatly improved the treatment of peritonitis but there is still much to do. ISPD Ad Hoc Committee recommends that, during a peritonitis episode, one should expect an 80% cure rate a 15–18% catheter removal rate and 2–3% deaths [28]. We hope that these results, though "adequate" will improve in the future.

The key to the treatment of persistent peritonitis is catheter removal. Indications for such removal include: persistent peritonitis despite the use of appropriate antibiotics for more than 5–7 days; fungal peritonitis, as soon as the diagnosis is made; and pseudomonas peritonitis if the infection persists for more than 4–5 days, especially if pseudomonas peritonitis and pseudomonas exit site infection develop in the same patient.

New dialysis solutions and peritonitis rates

Low GDP neutral pH solutions

Initially evidence from Registry data suggested that patients using the new biocompatible solutions have lower peritonitis rates than those using standard solutions. This improvement could be due to the fact that in vitro new solutions show better bacterial killing action than standard dialysis solutions [29]. In two subsequent uncontrolled studies peritonitis rates with the new solutions, were significantly lower [30, 31]. However Fan et al. [32] dashed these promising observations after a prospective randomized study in 100 PD patients. Fan's study found no difference in peritonitis rate between patients randomized to receive neutral pH bicarbonate/lactate solutions and those randomized to receive the standard PD solutions. However the primary objective of this study was to study the effect of the new solutions on the residual kidney function; the effect on peritonitis was a secondary objective. We believe that further studies have to be done to confirm the observations of Fan and his colleagues.

The future

Overall the last 30 years have seen a reduction in peritonitis rates from 1 episode every 4 months in the beginning to 1 episode every 30–36 months now. However, the nephrology community and our patients should expect even better results in the future.

Over the years several workers have noted that peritonitis rates reported from Eastern Asian centers like Japan, Korea and more recently from China were significantly lower than those observed in other countries, whatever technique they were using [33]. This was confirmed when two large centers of similar size and experience, one in Shanghai and one in Toronto compared their peritonitis rates. Indeed the peritonitis rate in the Chinese center was one episode every 61 patient months versus one every 36 patient months in the Canadian center. Future developments in our understanding of the reasons for this difference may give us a greater insight in our war against bacteria.

Conclusion

In conclusion, bacteria are formidable enemies. They have many ways of entering our bodies and to defeat our defenses. However, over the years, a combination

of ingenuity and research has helped us to protect our patients from this enemy for significant periods. We believe that there is still room for improvement and hope that a study of peritoneal defenses and possibly genetic studies will bring further success in our war against bacteria.

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