Krick G, Ronco C (eds): On-Line Hemodiafiltration: The Journey and the Vision.
Contrib Nephrol. Basel, Karger, 2011, vol 175, pp 46–56

Producing On-Line Ultrapure Dialysis Fluid

Beat von Albertini

Clinique Cecil and Service de Néphrologie et Hypertension, Centre Hospitalier et Universitaire Vaudois, Lausanne, Switzerland

Abstract

The process of on-line generation of ultrapure dialysis fluid is a core prerequisite for the safe execution of modern renal replacement therapies such as on-line hemodiafiltration and high-flux hemodialysis. In these extracorporeal treatments with variable degrees of convection, significant volumes of plasma water are removed and replaced with dialysis fluid, which must occur without causing harm to the patient. Historically, on-line generation of sterile and pyrogen-free physiological substitution fluid by the process of membrane ultrafiltration of fresh dialysis fluid has its origin in hemofiltration, a purely convective therapy. Development of this and later therapies is described in the historical context of a successful effort over decades to overcome the above formidable challenge, which was provided jointly by pioneering clinical investigators and a resourceful dialysis industry.

The process of on-line generation of ultrapure dialysis fluid is a core prerequisite for the safe execution of modern renal replacement therapies such as on-line hemodiafiltration (HDF) and, to a lesser extent, high-flux hemodialysis (HD). Unlike in any other field of medicine, these extracorporeal treatments with variable degrees of convection result in the transfer of up to 1 hectoliter per week of dialysis fluid into blood, which must occur without causing harm to the patient. While absolute safety in this respect cannot be achieved, current systems lessen the probability of patients' exposure to microorganisms and pyrogens by a number of steps to diminish the burden of contamination sequentially, starting with the availability of purified water and ending with membrane ultrafiltration to obtain ultrapure dialysis fluid for use in high-flux HD and, after supplemental

In memory of the late Maurizio Gibertoni and Michael J. Lysaght.

redundant ultrafiltration or filtration of this fluid, for sterile and pyrogen-free infusate for use in on-line HDF and hemofiltration (HF). Based primarily on a validated risk analysis provided by the manufacturer of such systems for the probability of breakthrough of bacteria and pyrogens, certain regulatory authorities have approved on-line HDF for clinical use, with the proviso in Europe that the final user complies with the recommendations for use set by the manufacturer of each of such systems, in particular concerning disinfection measures. International standards exist for minimal requirements and guidelines have been developed for preparation of pure water and ultrapure dialysis fluid [1, 2]. Comprehensive reviews on this subject have been published and are highly recommended to be consulted for the clinician embarking on this therapy [3–5].

That the above challenge could be overcome and worldwide millions per year of routine treatments are now carried out safely, can be considered a success story of an effort which has lasted many years. It was achieved by drawing largely on resources available within the dialysis community itself, provided by pioneering clinical investigators and innovations of a very adaptive dialysis industry. For this historical review, this author has been asked to describe how his personal experience gained in this effort has influenced his clinical practice over the years. It is mechanistic, at times anecdotal, and certainly very incomplete in the recognition of the countless important contributions of others, for which he apologizes. It serves him to commemorate two recently deceased dear friends he has encountered early on this path.

Hemofiltration

Historically, the process of on-line generation of sterile and pyrogen-free fluid by membrane ultrafiltration has its origin in HF, a purely convective therapy. It was introduced in 1967 by Henderson, Besarab, Michaels and Bluemle [6], using a polyelectrolyte/polysulfone flat-sheet membrane with poor diffusive but high hydraulic permeability and a tailored sieving limit of 50,000 daltons for convective solute transport. At the Amicon Corp. Allan Michaels had founded, Ford, Strathmann and Lysaght developed in the following years the phase inversion spinning process to produce from this Diaflo® membrane the hollow-fiber Diafilters®. These were used for HF and in 1977 for the innovative technique of Henderson and Beans [7] for production of sterile pyrogen-free electrolyte solution by ultrafiltration. Interest in HF as an alternative to HD received a substantial boost by the seminal formulation of the square meter – hour hypothesis by Babb, Popovich, Christopher and Scribner [8] in 1971. This hypothesis proposed that the shortfalls of diffusive HD in terms of persistence of uremic toxicity in patients were a consequence of the low dialyzability of so-called middle molecules as compared to that of urea with the then available cellulosic membranes. It was based on two clinical observations: (a) that patients on peritoneal dialysis

remained free of uremic neuropathy despite higher average urea and creatinine levels and (b) that uremic neuropathy in patients could be arrested and reversed with increasing the length of each HD. Paradoxically, it was this second element of the hypothesis which later invariably stimulated clinical investigators to shorten treatment time with convective therapies.

Clinical HF as a maintenance therapy for ESRD was pioneered by Quellhorst et al. [9] in Germany since 1972. In 1976, more than a dozen clinical investigators presented their results with HF, obtained with flat-sheet filters provided by Rhône-Poulenc and Sartorius, and commercially available parenteral solutions for substitution. This meeting in Germany was also attended by Benjamin T. Burton, Associate Director of the Artificial Kidney Program of the National Institute of Health, resulting in the announcement in 1977 to sponsor a multicenter controlled study comparing HF with HD. Four groups were awarded a contract in the same year: (1) Henderson, University of California, San Diego, (2) Bosch, von Albertini, Geronemus and Glabman, Mount Sinai Medical Center, New York, (3) Quellhorst, Hann-Münden, and (4) Koch and Baldamus, University Hospital, Frankfurt. As a member of the youngest of these groups (average age 35 years) and probably because of his singular relevant qualification of being of native German tongue, this author was sent to Germany and charged with the responsibility of providing the necessary equipment and substitution fluid for conducting the committed-for clinical HF treatments in the study. Thanks to the introductions provided by Mike Lysaght, he gained access to key clinical investigators and industry. Automated gravimetric cyclers for HF were then purchased and imported from Germany, which in contrast proved impossible for substitution fluid due to regulatory obstacles. Inquiries within the industry in the USA were unsuccessful because of FDA regulations limiting the volume of parenteral solutions to 1-liter glass bottles at the time.

A system was therefore developed in early 1978 for the manufacture of sterile and pyrogen-free substitution fluid in the hospital pharmacy, with the help of Phillip Varghese, our dialysis technician. It was designed to include these five steps: (1) purification of tap water by resin column deionization; (2) distillation with a Barnstead still, resulting in sterile water as the base product; (3) admixture of a regular glucose-free acetate liquid dialysis concentrate in a holding tank; (4) removal of microorganisms and pyrogens from the fluid with ultrafiltration in two serial Amicon Diafilter 40®, identical to Henderson's just introduced technique, in a closed semi-automated circuit with the final filling of 4.5 liters each into empty collapsible PVC bags which had been imported from Germany, and (5) steam sterilization of the sealed bags for 30 min at 230°F (110°C). Incidentally, the greatest difficulty in the 3-month development of the system was related to this step. The exhaust cycle of an available disused autoclave in the hospital had to be modified to prevent rupture of the heated bags during forced cooling. This was achieved with the addition of an automated step of maintenance of a higher holding pressure in the autoclave before and

during cooling, provided with a standard air-compressor, purchased at Sears & Roebuck for this purpose. Quality control for each manufactured batch before use included chemical analysis, cultures for bacteria and fungi and testing for pyrogens. The live rabbit injection test specified by the USP was later abandoned when the more sensitive assay with limulus lysate became available.

Close to 60,000 liters of substitution fluid were produced in this fashion and used in the patients (21–32 liters per treatment, 3 times weekly). While sterility was documented throughout, a positive result for endotoxins with the limulus-lysate assay was observed at only one instance in retested fluid associated with a pyrogenic reaction of the patient, for which incidentally the rabbit injection test remained negative. Pyrogenic reactions in the patients were observed initially in about 3% of treatments. They were associated with chills and subsequent fever which, after discontinuation of treatment, would disappear without sequelae overnight. No pyrogenic reactions were observed after a reusable Amicon Diafilter 20® was routinely interposed in the infusate line for redundant final on-line filtration during treatments. For the investigators, this uncertainty represented a very stressful preoccupation throughout the study. Lysaght arranged for an expert evaluation of our system by Dinarello and took the author to a visit of Associates of Cape Cod, where he observed the bleeding of suspended live horseshoe crabs (later released to the sea) for use in a more sensitive limulus-lysate endotoxin assay.

The study was completed in 1980 without occurrence of further adverse events for the patients and resulted in progress made in two areas relevant to HF: (a) efficiency was increased by using higher blood flow rates (500+ ml/min) and the addition of a small volume of predilution (20 ml) to the postdilution mode, preventing membrane fouling for filtration by protein concentration polarization during treatment [10], and (b) guidelines were developed for adequate individualized prescription of weekly total filtration volume, based on kinetic analysis of patients' urea generation [11]. For the investigators, an important lasting effect of the experience gained in the study was twofold: it taught them (a) the necessary respect and caution to aim henceforth for the highest purity of any dialysis fluid in their clinical practice, and (b) as one of its earliest users, that with Henderson's technique of membrane ultrafiltration this could be effectively achieved, provided that it occurred as redundant final step on-line before contact with the patients' blood. The Dialfilters® used for this purpose were considered the 'gold standard' of the time. In reality, they were prone to leak because of at times incompletely achieved sealing of the hollow fibers' exterior to the housing with epoxy resin, preventing reliable testing for integrity at manufacture [H. Göhl, pers. commun.]. Retrospectively, the pyrogenic reactions observed during the study were probably related to the passing of undetected endotoxin from concentrate through leaks in the ultrafilters. That redundant final filtration alleviated this problem, was an early demonstration of the validity of fault safety as a concept in the development of on-line therapies.

The preoccupation with adverse effects in patients was not a lesser one for the clinical investigators in Germany, who had access to commercial parenteral solutions for substitution in HF. A number of severe pyrogenic reactions and sepsis, some with fatal outcome, were observed in these years with positive cultures for water-borne Gram-negative bacteria such as *Enterobacter*, *Pseudomonas* and *Corynebacteria* [12]. Recommendations were then made to altogether discontinue their use or to routinely filtrate the solutions with a reusable hemofilter during treatment [13]. The above preoccupation prompted a research effort on endotoxins and pyrogenic reactions, foremost by Koch's group in Hannover, which resulted in important contributions, such as the formulation of the interleukin-1 hypothesis by Henderson, Dinarello, Koch and Shaldon [14].

On-line HF with on-site batch preparation of substitution fluid was pioneered in 1978 by Shaldon, Mion et al. [15] and was performed with sterile and pyrogen-free infusate resulting from sequential steps of ultrafiltration of reverse osmosis-treated water, batch admixture of dialysate concentrate, redundant on-line ultrafiltration and a later added final filtration with a disposable bacterial filter. No pyrogenic reactions in the patients were observed with this system in 3,000 consecutive treatments (60,000 liters), performed in 13 homes (!) and 3 centers. From 1980 on, these and other investigators used the hollow-fiber Gambro hemofilter FH 202® for the treatments and for on-line substitution generation that Göhl et al. [16] had developed in Hechingen. Made of a physically robust asymmetric polyamide membrane with good filtration and porosity size characteristics, it was routinely pressure tested for integrity at manufacture. Gambro, which quickly became the industrial leader in development of HF, introduced in 1983 the U 7000® polyamide ultrafilter and final disposable U 2000® ultrafilter, specifically designed and validated for effective removal of bacteria and pyrogens, for use in the described 3-step configuration for on-line generation of substitution fluid. Three generations of equipment for HF were developed by Gullberg, Nilson, Bergkvist, et al. in Lund, starting in 1980 with the AK-10 HFM 10® system for gravimetric control of substitution with commercial or on-site batch prepared solutions, followed in 1985 by the GHS-10® system with a proportioning unit for continuous on-line generation of substitution solution under flowmetric control, in 1987 the MPS-10® for bicarbonate-based HD and on-line HF and HDF, in 1993 the AK 100 ULTRA®, with integrated U 8000® and final U 2000® ultrafilters, and in 1996 the more sophisticated AK 200 ULTRA® for on-line therapies. Gambro estimated that from 1981 to the beginning of 1993, more than 1.3 million liters of sterile and pyrogen-free infusate had been generated on-line with their systems and safely used in over 50,000 clinical HF and HDF treatments [17].

By this time, the popularity of HF was already waning. Other than for better vascular stability during treatment and better control of hypertension, the observed clinical results failed to demonstrate a clear superiority over HD. The latter had progressed in the intervening years with the introduction of

bicarbonate as buffer, replacing rapidly the ill-tolerated acetate in the dialysis fluid. The real challenge leading to the decline of HF resulted from the outcome of the National Cooperative Dialysis Study in 1983, highlighting the critical importance of urea generation and its quantitatively adequate removal for patient survival, which, to a variable extent, had been neglected by clinical investigators with for this purpose inherently less efficient HF.

Hemodiafiltration

Merging the advantages of HD and HF into one modality was achieved with HDF, an intermittent renal replacement therapy of combined high diffusive and convective solute transport, where the total volume of ultrafiltration exceeds the desired weight loss for the patient and is in part substituted with a physiological solution, for which a system with precise net ultrafiltration (UF) control is indispensable. It was introduced independently in 1977 by three different groups of investigators: Kunitomo, Lowrie et al. [18] in Boston, Ota et al. [19] in Japan, and Leber, Wizemann, Schuetterle et al. [20] in Germany. The first two groups used the Toray flow equalizer and Filtryzer® polymethylmethacrylate (PMMA) hollow-fiber dialyzer, while the Fresenius A 2008 system and Rhône-Poulenc RP6® polyacrylonitrile (PAN) plate dialyzer were used in Germany. Common to all three was a coupled gravimetric system for delivery of sterile normal saline or physiological parenteral solution for substitution. Ota, Leber, and after his tragic death in a car accident, Wizemann used HDF to shorten patients' treatment time to 3 × 3 h/week and less.

Self-generation of substitution for HDF was clinically introduced in 1982 by Usuda, Shinzato et al. [21] in Japan, using a push/pull system for periodic filtration of aliquots of plasma water and backfiltration of dialysis fluid during treatment under volumetric control. Shinzato, Maeda et al. [22] reported clinical use of a serial configuration of two dialyzers with a flow restriction in the blood path for ultrafiltration from blood under flow control and backfiltration of dialysis fluid for substitution under volumetric control. Cheung, Leypolt et al. [23] proposed an in-vitro tested hybrid system in a serial configuration of two hollow-fiber hemofilters for self-generation of substitution by backfiltration of on-line filtered sterile and pyrogen-free dialysis fluid under flow control, but lacked equipment to carry it out clinically.

The experience with high blood flow rates in HF stimulated this author to attempt shortening of treatment time without reducing small and large solute removal of either HD or HF. He had the chance to realize this goal by being invited in 1983 to join the group of Shinaberger, Miller and Gardner in Los Angeles. Having significantly contributed to progress in dialysis since its early days, this group had been involved with HF and HDF and had developed an at the time unique closed-circuit volumetric system, obtained from linking two recuperated Drake-Willock double-piston dialysate proportioning systems,

which was capable of performing clinical bicarbonate HD, sequential UF-HD, HF and HDF. It was used in 1983 for performing high-flux HDF in a configuration of two serial high-flux dialyzers for optimal diffusion and a simple flow restriction in the countercurrent dialysate circuit for self-adjusting optimal filtration and simultaneous substitution by backfiltration of sterile and pyrogen-free bicarbonate dialysis fluid, obtained from on-line filtration with an Amicon Diafilter 40® for safety [24]. The treatments were well tolerated and no pyrogenic reactions were observed in the patients. Coupled with high blood and dialysate flow rates, unmatched high rates of diffusive and convective solute removal can be achieved with this modality, which was later re-named double high-flux HDF and has been described again recently [25].

Relevant to the topic of this chapter, it retrospectively appears that the above modality pioneered on-line ultrafiltration of fresh dialysis fluid for ultrapurity for use in any clinical diffusive renal replacement therapy. Putative redundant sequential filtration for sterility and pyrogen removal of substitution fluid for HDF was then achieved by the backfiltration across the dialyzer membrane in the extracorporeal circuit. The hollow-fiber dialyzers used in the treatments, made of cellulose acetate, PMMA and polysulfone, were suitable for this purpose. Incidentally, this was also the first time the new Fresenius Hemoflow F 60® was clinically used in the USA, for which in 1983 the author had to obtain personal import permission by the FDA.

On-line HDF with redundant filtration of dialysis fluid for substitution was introduced in 1985 by Canaud, Polaschegg, Mion et al. [26] with one hemodiafilter in a closed-circuit under volumetric control (Fresenius A 2008 C), where fresh dialysis fluid was diverted with an additional pump for on-line filtration for sterility and pyrogen removal with two serial F 60® dialyzers and infused for substitution in post-dilution mode. This configuration was later modified to include on-line filtration of all fresh dialysis fluid and redundant on-line filtration of infusate with the Diasafe plus® system, which was integrated in 1998 into the mature Fresenius Online plus® system for HDF and HF. Gambro introduced in 2001 an equally mature AK 200 ULTRA S® system with two U 8000S® ultrafilters and final U 2000® filter for on-line HDF and HF. In Japan, Nikkiso developed a single patient dialysis system, containing a single dialysis fluid filter and a single-use final filter for HDF. The majority of on-line HDF therapies in this country are performed with central dialysis fluid delivery systems for reverse osmosis water, dialysis fluid proportioning and on-line ultrafiltration, and final redundant on-line filtration for sterility and pyrogen removal at the individual patient stations.

High-Flux Hemodialysis

This modality for efficient simultaneous small and large solute removal has its origin in 1972 with the development by Rhône-Poulenc of the AN69® PAN flat-

sheet membrane and its successful clinical introduction by Funck-Brentano, Man, Granger et al. [27] at the Necker Hospital in Paris. Compared to cellulosic Cuprophan®, it had comparable diffusive, but a tenfold higher hydraulic permeability. To prevent excessive weight loss with the clinical use of this membrane, an apparatus with closed-circuit volumetric control of recirculating countercurrent dialysate was developed, consisting of an air-tight non-compliant 60-liter vat of batch-prepared warmed dialysis fluid and a pump for continuous removal of a preset volume from the circuit into a graduated cylinder. This system was the forerunner of all modern dialysis machines with programmable weight loss for the patient, which incidentally the developers had the foresight to get patented, generating substantial royalties for Rhône-Poulenc for two decades. Consistent with the logic of the square meter-hour hypothesis, the demonstrated 2.2 times higher removal rate for vitamin B_{12} (1,335 daltons) led the clinical investigators to reduce the duration of the patients' dialysis in half, from with Cuprophan® 30 h/week to 15 with AN69®. Despite near doubling of pretreatment levels for urea and creatinine, a marked improvement of their well-being was reported and the astounding observation made that patients with paralyzing neuropathy were able to walk again after 6 months of this therapy [28]. The original apparatus was later modified by Rhône-Poulenc (which later became Hospal) and merged with a proportioning unit into the Rhodial 75 with the Cotral® system, where the recirculating dialysate was in part replenished with fresh dialysis fluid periodically during treatment. Further membrane development resulted in the hollow-fiber high-flux AN69 Nephral ST® dialyzer of today.

A single-pass volumetric flow equalizer with two small fixed volume chambers, each separated by a flexible silicone rubber membrane, for repeated cycled filling of degassed fresh dialysis fluid and withdrawing spent dialysate in a closed circuit, was developed in 1978 by Toray in Japan for clinical use of their hollow-fiber Filtryzer® PMMA dialyzer with high diffusive and hydraulic permeability. In the same year, Fresenius developed independently a very similar system for integration to their 2008 (and all subsequent systems) for precise net UF control. From the standpoint of microbiological purity of the dialysis fluid, the complexity of such hydraulic systems favors the risk of colonization with water-borne Gram-negative bacteria. While the original Rhône-Poulenc apparatus and the first Fresenius A 2008 could be steam sterilized, later models of the system, as most modern machines, offer automated cycles for frequent heat and chemical disinfection for this purpose.

Fresenius introduced in 1983 the Hemoflow F 60® hollow-fiber dialyzer with high diffusive and hydraulic permeability, made of an asymmetric membrane of hydrophobic polysulfone and hydrophilic polyvinylpyrrolidone (PVP) copolymer for enhanced diffusive permeability and biocompatibility. It was developed in collaboration with Strathmann at the Berghof Institute and Klein of Gulf South Institute, and industrially developed by Heilmann et al. at Fresenius in St. Wendel. Gambro introduced in 1989 the Polyflux® hollow-fiber high-flux

dialyzer made of an asymmetric polyamide/PVP co-polymer membrane that Göhl et al. had developed. Common to the above two membranes is their wettability, which after contact with water renders them impermeable to air. This is used for the automated procedure of an air-pressure holding test for integrity of each dialyzer or filter at manufacture.

Using the highly permeable Hemoflow F 60® with the closed-circuit volumetric control of the 2008 system, Streicher and Schneider in 1985 demonstrated efficient small and large solute (β_2-microglobulin, 12,500 daltons) removal in clinical high-flux HD. They made the relevant observation, by measurement at zero net UF, of transmembrane pressure gradients in opposite directions at inlet and outlet of the dialyzer in the countercurrent circuit, suggesting occurrence of internal filtration of plasma water into dialysate and simultaneous backfiltration of dialysis fluid into blood across the membrane [29]. Based on his experience with backfiltration in HDF, this author, after rejoining Juan P. Bosch at George Washington University and becoming head of a new dialysis unit in 1986, had, with the expert help of our technician Viroy Barlee, all installed Fresenius 2008 systems of the D, E, H series equipped with a pair of Hemoflow® and later Polyflux® high-flux dialyzers for on-line ultrafiltration of fresh dialysis fluid [30]. These were disinfected with a machine cycle of peracetic acid and heat twice daily and exchanged every 3 months. When becoming available after 1989, they were replaced with the validated Diasafe® polysulfone filter system that Fresenius had developed for this purpose. Starting with reverse-osmosis-treated water, from a loop which was disinfected weekly with formaldehyde, dialysis fluid was obtained with this technique for all treatments in the unit of HD, high-efficiency HD, high-flux HD and double high-flux HDF. No pyrogenic reactions were observed in the patients. Monthly testing with culture and endotoxin assay consistently revealed that the used dialysis fluid met and exceeded current standards for ultrapurity. This is also the case for the author's clinical practice in Lausanne since 1996, where, under the vigilance of Jacky Berger, the purity of water is maintained with a DWA-Nephrosafe® system for night-time twice weekly heat disinfection of the water loop. The Diasafe-plus®-filtered ultrapure dialysis fluid is used for all treatments, performed with single-use Gambro Revaclear® polyarylethersulfone dialyzers, with Fresenius 4008 and 5008 systems for high-flux HD and double high-flux HDF and 5008 systems for on-line HDF in post- and low-flow predilution mode for heparin-free dialysis.

Acknowledgements

The author reports no conflict of interest, but wants to express his gratitude for valuable information and help in the preparation of this chapter, provided by Hermann Göhl at Gambro and Thomas Roy at Fresenius.

References

1 ISO International Standard: Quality of dialysis fluid for haemodialysis and related therapies. ISO 2009;11663:1–15.
2 ERA-EDTA: European best practice guidelines for hemodialysis part I, section IV: Dialysis fluid purity. Nephrol Dial Transplant 2002;17(suppl 7):45–62.
3 Ledebo I: On-line preparation of solutions for dialysis: practical aspects versus safety and regulations. J Am Soc Nephrol 2002;13: S78–S83.
4 Capelli G, Ricardi M, Bonucci D, De Amicis S: Quality of water, dialysate and infusate. Contrib Nephrol. Basel, Karger, 2007, vol 158, pp 80–86.
5 Ward RA: Quality management of dialysis fluid for online convective therapies. Contrib Nephrol. Basel, Karger, 2011, vol 168, pp 78–88.
6 Henderson LW, Besarab A, Michaels A, Bluemle LW: Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans Am Soc Artif Intern Organs 1967;16: 216–222.
7 Henderson LW, Beans E: Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int 1978;14: 522–525.
8 Babb AL, Popovitch RP, Christopher TG, Scribner BH: The genesis of the square meter-hour hypothesis. Trans Am Soc Artif Intern Org 1971;17:81–91.
9 Quellhorst E, Rieger J, Doht B, Beckmann H, Jacob I, Kraft B, Mietzsch G, Scheler F: Treatment of chronic uremia by an ultrafiltration kidney: first clinical experience. Proc Eur Dial Transplant Assoc 1976;13:314–321.
10 Geronemus R, von Albertini B, Glabman S, Kahn T, Moutoussis G, Bosch JP: High-flux hemofiltration: further reduction in treatment time. Proc Clin Dial Transplant Forum 1979;9:125–127.
11 Bosch JP, von Albertini B, Glabman S: Prescription for hemofiltration. Contrib Nephrol. Basel, Karger, 1982, vol 32, pp 137–145.
12 Frei U, Koch KM: Fever and shock during hemofiltration. Contrib Nephrol. Basel, Karger, 1983, vol 36, pp 117–114.
13 Von Herrath D, Schaefer K, Hüfler M, Pauls A, Koch KM: Complications of hemofiltration. Contrib Nephrol. Basel, Karger, 1982, vol 32, pp 146–153.
14 Henderson LW, Dinarello CA, Koch KM, Shaldon S: Interleukin-1 hypothesis. Blood Purif 1983;1:1.
15 Shaldon S, Beau MC, Deschodt G, Flavier JL, Nilsson L, Ramperez P, Mion C: Three years of experience with on-line preparation of sterile pyrogen-free infusate for haemofiltration. Contrib Nephrol. Basel, Karger, 1982, vol 32, pp 161–164.
16 Göhl H, Konstatin P, Gullberg CA: Hemofiltration membranes. Contrib Nephrol. Basel, Karger, 1982, vol 32, pp 20–30.
17 Sternby J: A decade of experience with on-line hemofiltration/hemodiafiltration. Contrib Nephrol. Basel, Karger, 1994, vol 108, pp 1–11.
18 Kunitomo T, Lowrie EG, Kumazawa S, O'Brien M, Lazarus JM, Gottlieb MN, Merill JP: Controlled ultrafiltration (UF) with hemodialysis (HD): analysis of coupling between convective and diffusive mass transfer in a new HD-UF system. Trans Am Soc Artif Intern Organs 1977;23:234–243.
19 Ota K, Suzuki T, Ozaku Y, Hosino T, Agishi T, Sugino N: Short-time hemodiafiltration using polymethylmethacrylate hemofilter. Trans Am Soc Artif Intern Organs 1978;24:454–457.
20 Leber HW, Wizemann V, Goubeaud G, Rawer P, Schuetterle, D: Simultaneous hemofiltration/hemodialysis: an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clin Nephrol 1978;9:115–121.
21 Usuda M, Shinzato T, Sezaki R, et al: New simultaneous HF and HD with no infusion fluid. Trans Am Soc Artif Organs 1982;28:24–27.
22 Shinzato T, Sezaki R, Usuda R, Maeda K, Ohbayashi S, Toyota T: Infusion-free hemodiafiltration: simultaneous hemofiltration and dialysis with no need for infusion fluid. Artif Organs 1982;6:453–456.

23 Cheung AC, Kato Y, Leypoldt JK, Henderson LW: Hemodiafiltration using a hybrid membrane system for self-generation of diluting fluid. Trans Am Soc Artif Organs 1982;18: 61–65.
24 Miller JH, von Albertini B, Gardner PW, Shinaberger JH: Technical aspects of high-flux hemodiafiltration for adequate short (under two hours) treatment. Trans Am Soc Artif Organs 1984;30:377–381.
25 von Albertini B: Double high-flux hemodiafiltration. Contrib Nephrol. Basel, Karger, 2007, vol 158, pp 161–168.
26 Canaud B, N'Guyen QV, Lagarde C, Stec F, Polaschegg HD, Mion C: Clinical evaluation of a multipurpose dialysis system adequate for hemodialysis or for postdilution hemofiltration/hemodiafiltration with on-line preparation of substitution fluid from dialysate. Contrib Nephrol. Basel, Karger, 1985, vol 46, pp 184–186.
27 Funck-Brentano JL, Sausse A, Man, NK, Granger A, Rondon-Nucete M, Zingraff J, Jungers P: Une nouvelle méthode d'hémodialyse associant une membrane à haute perméabilité pour les moyennes molécules et un bain de dialyse à circuit fermé. Proc Eur Dial Transplant Assoc 1972;9:55–66.
28 Funck-Brentano J, Nguyen K, Sausse A: Effect of more porous dialysis membranes on neuropathic toxins. Kidney Int 1975;7:S51–S57.
29 Streicher E, Schneider H: The next generation of dialysis membranes – barrier or pathways? Contrib Nephrol. Basel, Karger, 1985, vol 44, pp 127–136.
30 von Albertini B, Barlee V, Bosch JP: On-line sterile rinse of reprocessed high-flux dialyzers (abstract). Congr Am Soc Nephrol 1987;94A.

Dr. Beat von Albertini
Centre de Dialyse Cecil, Avenue Ruchonnet 30
CH–1003 Lausanne (Switzerland)
Tel. +41 21 343 01 82
E-Mail Beat.vonalbertini@hirslanden.ch