

# Clinical Effect of Purification of Dialysis Fluids, Evidence and Experience

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## Key Words

Dialysis fluid purification • Microinflammation • Dialysate contamination • Bacterial contamination

## Abstract

Microinflammation in renal failure has been the subject of numerous contributions to the literature. The bacterial contamination of dialysate and subsequent transfer of bacterial products onto the blood side is an important cause for microinflammation in hemodialysis patients. It has been suggested that the inflammatory process may not merely be an epiphenomenon but rather a pathogenetic factor in the genesis of atherosclerosis [1–3]. Thus, by promoting microinflammation, dialysate contamination may contribute directly to cardiovascular morbidity and mortality.

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A number of bacterial products such as lipopolysaccharides (LPS), exotoxins and peptidoglycans share the ability to induce cytokines and are known activators of immune functions. Several *in vitro* and *in vivo* studies investigated the permeation of these substances through dialysis membranes. In many studies, the biological test of cytokine induction in peripheral blood mononuclear cells has been used to detect these substances. By this test,

all biologically relevant bacterial substances are detected, whereas the Limulus test (LAL) detects only LPS-derived substances. The exact chemical nature of bacterial CIS is not completely understood, and most likely CIS consist of a mixture of bacterial products. LPS is not the only product in dialysate that induces cytokines and contributes only to approximately 50% of CIS. New pyrogenic candidates that may pass dialyzer membranes are bacterial-derived short DNA fragments [4]. These DNA fragments bind to Toll-like receptor 9 and are able to induce natural killer cell activity as well as IFN- $\gamma$ , TNF- $\alpha$  and IL-6 from mononuclear cells [5, 6]. Since short DNA fragments can penetrate intact high-flux membranes [4], ultrafiltration may not have removed all bacterial products that influence the immune system in clinical studies investigating the effect of ultrafiltered dialysate. To completely remove all CIS including bacterial DNA from dialysate, supplementary measures in addition to ultrafiltration may be required. In addition, the dialysate quality is currently tested by the LAL test and by counting bacterial colonies (CFU), not because these are the best test systems but for convenience. These tests may prove to be inadequate to detect all relevant bacterial products in dialysate since there is little correlation between CFU, LAL results and cytokine induction (fig. 1). For instance, in the case of biofilm on the surface there may be few CFU but lots of pyrogens. On the other hand, there may

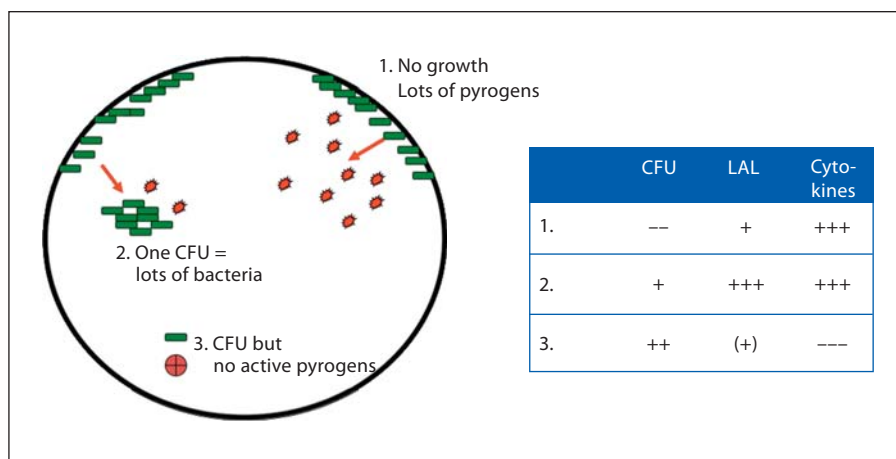
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0253–5068/09/0275–0020\$26.00/0

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**Fig. 1.** Assessment of bacterial contamination of dialysate. Three different conditions are shown.

be many bacteria (CFU) detected that do not produce significant and biologically relevant amounts of pyrogens.

Several *in vitro* studies investigated the permeability of low- and high-flux dialyzer membranes for CIS. In principle, all dialysis membranes are permeable for bacterial products when their concentration on the dialysate side is high enough. However, there are differences between membranes. Most of the *in vitro* studies demonstrated prompt transfer of CIS through low-flux cellulosic membranes but no or less transfer through high-flux polysulfone or polyflux membranes [7–9]. It was concluded that the sponge-like structure of these high-flux membranes adsorbs bacterial products; this feature even enabled the use of polysulfone and polyflux as ultrafilters to efficiently remove CIS from aqueous solutions.

In the last years, several clinical studies have been performed on the effect of ultrapure dialysate on outcomes such as CRP levels, albumin, erythropoietin efficiency and preservation of renal function. So far there have been no large, randomized controlled trials on clinical endpoints such as morbidity and mortality. Nevertheless, a number of studies have reported positive effects of ultrapure dialysate on inflammatory parameters, hemoglobin and albumin [10–12]. Most of these studies are assailable because of the few number of patients, lack of control groups, lack of data on dialysate quality and confounding factors such as dialyzer flux. However, in most of these studies, ultrapure dialysate ameliorates inflammation indicated by inflammatory markers (e.g., CRP levels). Thus, the quality of dialysate translates into clinically important measures. Future studies should reveal that ultrapure dialysate

also influences hard endpoints such as cardiovascular events. Ultrapure dialysate is not yet the standard of dialysate quality in most dialysis centers. Although the consequences of inflammation in dialysis patients are not fully understood, preventing the penetration of bacterial products from the dialysate is more than reasonable.

### Disclosure Statement

The author declares no conflicting interests.

### References

- ▶ 1 Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E: C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20–28.
- ▶ 2 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973–979. Published erratum appears in *N Engl J Med* 1997;337:356.
- ▶ 3 Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis. *Kidney Int* 1999;55:648–658.
- ▶ 4 Schindler R, Beck W, Deppisch R, Auszieker M, Wilde A, Gohl H, Frei U: Short bacterial DNA fragments: detection in dialysate and induction of cytokines. *J Am Soc Nephrol* 2004;15:3207–3214.
- ▶ 5 Wagner H: Toll meets bacterial CpG-DNA. *Immunity* 2001;14:499–502.

- ▶6 Yi AK, Yoon JG, Hong SC, Redford TW, Krieg AM: Lipopolysaccharide and CpG DNA synergize for tumor necrosis factor- $\alpha$  production through activation of NF- $\kappa$ B. *Int Immunol* 2001;13:1391–1404.
- ▶7 Lonnemann G, Behme TC, Lenzner B, Floege J, Schulze M, Colton CK, Koch KM, Shaldon S: Permeability of dialyzer membranes to TNF- $\alpha$ -inducing substances derived from water bacteria. *Kidney Int* 1992; 42:61–68.
- ▶8 Schindler R, Christ-Kohlrausch F, Frei U, Shaldon S: Differences in the permeability of high-flux dialyzer membranes for bacterial pyrogens. *Clin Nephrol* 2003;59:447–454.
- ▶9 Schindler R, Krautzig S, Lufft V, Lonnemann G, Mahiout A, Marra MN, Shaldon S, Koch KM: Induction of interleukin-1 and interleukin-1 receptor antagonist during contaminated in vitro dialysis with whole blood. *Nephrol Dial Transplant* 1996;11:101–108.
- ▶10 Arizono K, Nomura K, Motoyama T, Matsushita Y, Matsuoka K, Miyazu R, Takeshita H, Fukui H: Use of ultrapure dialysate in reduction of chronic inflammation during hemodialysis. *Blood Purif* 2004;22(suppl 2):26–29.
- ▶11 Hsu PY, Lin CL, Yu CC, Chien CC, Hsiao TG, Sun TH, Huang LM, Yang CW: Ultrapure dialysate improves iron utilization and erythropoietin response in chronic hemodialysis patients – a prospective cross-over study. *J Nephrol* 2004;17:693–700.
- ▶12 Sitter T, Bergner A, Schiffel H: Dialysate-related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 2000;15:1207–1211.