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**Which dialyser membrane to choose?**

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**Introduction**

Exchanges through dialyser membranes aim: (i) at the removal of uraemic solutes that are retained because of renal failure (e.g. urea) and (ii) at the restoration of depleted compounds (e.g. bicarbonate).

The originally used cellulotic membranes were derived from cotton and therefore named ‘natural’. They activated complement and leukocytes, inducing an inflammatory reaction as one of the indices of ‘bioincompatibility’ [1]. Later on, chemically developed ‘synthetic’ polymers appeared to mitigate this activation [2]. Furthermore, masking hydroxyl groups, which are responsible for the complement activation with cellulotic membranes, also resulted in more biocompatibility [3]. Therefore, cuprophan and its analogues were called ‘unmodified cellulotic’ vs the more biocompatible, later developed ‘modified/regenerated cellulotic’ membranes.

Many synthetic membranes have large pore sizes allowing higher rates of water flux and permitting a higher ultrafiltration capacity as well as a better removal of high molecular weight ‘uraemic solutes’ than membranes with smaller pore size. Therefore, although a high ultrafiltration rate and the capacity to remove large molecules do not strictly run in parallel, large pore membranes are mostly referred to as ‘high-flux’, in contrast to ‘low-flux’ membranes with smaller pores. Five general types of membranes are available at present (Table 1).

In this review, the most relevant membrane characteristics allowing a rational choice for treatment are discussed. More extensive relevant data can be found in the European Best Practice Guidelines for haemodialysis, part I [4,5].

**Relevant membrane characteristics**

*Biocompatibility towards leukocytes and the complement system*

Biocompatibility describes materials, which cause only minor biochemical and biological effects. In this review,
we will concentrate on leukocyte and complement activation, which occur predominantly when unmodified cellulosic membranes are used.

Baseline activation of leukocytes results in inflammation, which is related to vascular disease, the first cause of death in dialysis patients [6]. C-reactive protein, a marker of inflammation that is related to mortality [7,8], is lower when synthetic, biocompatible, high-flux polysulfone is used, compared with unmodified cellulose [9]; this difference is present both pre-dialysis, as a carry-over effect of previous dialyses, and is further accentuated several hours after dialysis [9].

Subsequently, functional impairment of leukocytes develops as well, e.g. the impaired function of stimulated granulocytes and monocytes, of phagocytosis, of chemotaxis and of surface molecule expression. All these functional defects predispose to infection [10], the second most frequent cause of death in dialysis patients [6]. The bioincompatibility concerning complement and leukocytes, is not so strong when synthetic and modified cellulosic membranes are used [11,12].

Impermeability against dialysate impurities

Dialysate may be contaminated by bacteria, which release lipopolysaccharides, peptidoglycans, DNA and other pro-inflammatory products when they traverse the membrane and enter the blood stream. The risk for inflammation is even higher when backfiltration occurs, i.e. when dialysate enters the blood by convection in the distal part of the dialyser to compensate for net ultrafiltration, which occurs in the more proximal parts of the dialyser. Paradoxically, bacterial products penetrate more easily across small-pore cellulosic membranes into the blood compartment than across large-pore synthetic membranes, which adsorb such bacterial products. As a result of this transfer of bacterial products, leukocytes are activated [13]. Applying as pure dialysate as possible is the optimal approach to avoid transfer of impurities. Nevertheless, using a synthetic membrane as an additional precaution, will offer extra protection.

Adsorption

Adsorption onto the membrane, a characteristic of synthetic membranes, contributes to the removal of noxious compounds such as interleukin-1, tumour necrosis factor, peptides, interleukin-6 and β₂-microglobulin (β₂-M) [14]. Not all synthetic membranes have the same adsorptive capacity. Adsorption is most pronounced for polymethylmethacrylate and AN69.

As a result of the restricted surface area of dialysers, adsorption capacity will rapidly be saturated. Acceptable rates of net removal by adsorption can only be achieved if the surface area is drastically increased by the development of specific devices that have adsorption as only aim. These devices should then contain beads to which well-defined adsorptive properties are conferred.

Pore size

Recently, an increasing number of larger compounds (so-called middle-molecules, > 500 Da), which are bioactive and may contribute to the uraemic syndrome have been recognized (Table 2) [15]. Enlarging pore size and increasing flux allows high rates of removal of these solutes.

β₂-M has been implicated in the genesis of uraemic amyloid disease [16]; the concentration of β₂-M decreases progressively when patients are treated on high-flux membranes [17]. A further decrease in the concentration of β₂-M can be achieved by changing the duration and strategic concept of dialysis sessions, e.g. by adopting daily long slow overnight on-line haemodiafiltration [18].
As a further example of a ‘middle molecule’, the concentration of leptin, which causes decreased appetite and malnutrition [19], is reduced only during high-flux dialysis [20].

Advanced glycation end products (AGEs) are involved in the genesis of an inflammatory state and cardiovascular disease [21]. Their concentration is significantly decreased during dialysis with super-flux membranes, a new generation of devices, which have an even higher capacity to remove middle molecules than high-flux membranes [22].

Homocystein, a small protein bound compound, is related to vascular damage [23]. Its concentration is decreased when patients are switched from high-flux to super-flux dialysis [24]. Likewise, pre-dialysis indoxyl sulfate concentration is also decreased by super-flux dialysis (R. De Smet, unpublished data). Both studies have been conducted with cellulosic super-flux membranes, which are also more leaky for albumin. This characteristic might explain the high rate of removal of the two protein bound compounds.

Summary

The presently available membranes cover a broad spectrum from unmodified cellulose low-flux to synthetic high-flux membranes (Tables 1 and 3). Unmodified low-flux cellulose: (i) is bio-incompatible (i.e. activates complement), (ii) does not prevent the penetration of impurities from the dialysate into the blood stream, (iii) does not adsorb unwelcome compounds and (iv) does not remove middle molecules.

High-flux synthetic membranes are bio-compatible, reflect dialysate impurities, adsorb compounds and remove middle molecules. All other membrane types show intermediate characteristics.

Clinical consequences

Several controlled studies suggest the superiority of high-flux membranes for isolated aspects of the uraemic syndrome, such as β2-M amyloidosis [25], loss of residual renal function [26], dyslipidaemia [27], polyneuropathy [28] and infection [10], although other studies remained inconclusive [5,17,29,30].

Regarding mortality, at least eight observational studies showed superiority of high-flux dialysis [5, 31–38], and at least two studies suggested that this benefit was in part related to removal of middle molecules [37,38].

In contrast, the only controlled mortality study, the HEMO study, failed to document the superiority of high-flux compared with low-flux membranes. Secondary analysis showed a trend, which could be compatible with a certain superiority [39], since a benefit with respect to cardio-vascular events was shown for high-flux membranes. The shortcomings of this study were, however, that relatively short dialysis times and reuse, which may have an unpredictable impact on membrane flux, were allowed. Also, prevalent dialysis patients were enrolled so that the outcome may have been confounded by morbidities, which had been acquired in the pre-study treatment period.

Hence, although there might be a trend for superiority of high-flux membranes regarding mortality, this finding must be confirmed by further studies, before definite conclusions can be drawn. The data suggesting superiority regarding morbidity are more convincing.

Conclusion

On theoretical grounds, dialysis membranes with the best biological properties should be bio-compatible, exclude impurities in the dialysate and have a large pore size (Table 3). A high adsorptive capacity is less essential, but may increase the total amount of solutes removed. Clinical arguments supporting the notion of a superiority of high-flux synthetic membranes relate to certain facets of the uraemic syndrome, e.g. the quality of life, but whether they have a beneficial impact on mortality remains an unresolved issue.

Conflict of interest statement. None declared.

References
