High-Flux Dialysis
Good Dialysis Practice

... the leader in dialysis care
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Global Trends

World-wide more than 1,000,000 patients are dependent on renal replacement therapy. Of these patients, approximately 89% are treated by a haemodialysis mode.

When dialysis became established as a routine therapeutic measure more than 30 years ago, the treatment chosen was low-flux haemodialysis across a cellulose membrane.

Today the treatment of choice is that best suited to the individual needs of the patient. Selection can be made from a range of dialysers and treatment modes.

Trends in dialysers used and treatment modes selected correlate with mounting evidence for the benefits of certain treatment strategies.

Eight years ago, more than 80% of haemodialysis treatments employed low-flux dialysers.

Today this number has significantly decreased to around 50% with an ever increasing number of patients having access to biocompatible membranes and treatments with high fluid fluxes supporting the removal of a wider range of uraemic toxins.

In the last four years the number of high-flux dialysers used world-wide has increased significantly. With this development we also observe an increase in alternative treatment modes such as haemofiltration and more significantly haemodiafiltration. From these trends we recognise a development towards high quality treatment strategies to improve the long-term well-being of ESRD patients.

![Chart showing changes in membrane characteristics used in haemodialysis over a seven year period.](image-url)
High-Flux Dialysis and Clinical Benefits

Trends in dialysis indicate the increasing recognition of the benefits of selecting biocompatible and high-flux membranes and their contribution to the quality of dialysis. The increasing availability of high-flux dialysers and technology to implement such treatments have contributed to this development. On the other hand, the natural desire to adhere to known practices and the additional costs generally associated with high-flux dialysis have served as a deterrent. These issues are addressed here, where we consider the prerequisites to be met before starting high-flux dialysis and to what extent high-flux dialysis results in additional expense.

However, attention is first given to the clinical benefits of high-flux dialysis. Today, a pathway is evolving leading from blood-material interactions and membrane permeability characteristics to clinical outcome and patient well-being.

This pathway must be contemplated when seeking the best and most cost-effective dialysis treatment. Clinical studies and reported clinical experience suggest that high-flux dialysis with blood compatible dialysis membranes has a positive impact on the long-term well being of the dialysis patient by influencing for example:

- Residual Renal Function (RRF)
- Inflammatory Reactions
- Vascular Disorders
- Lipid Profiles
- Dialysis-Related Amyloidosis

High-flux dialysis addresses dialysis mortality and morbidity aspects. High-flux dialysis is a tool to support adequate patient treatment in the most biocompatible way and as such is an integral element in the Fresenius Medical Care BioAdequacy™ concept for patient care management.
Preservation of Residual Renal Function (RRF)

Although it is recognised that renal function deteriorates rapidly after starting haemodialysis recent studies have indicated that even after 4 years of dialysis a significant percentage of patients still have a glomerular filtration rate which can contribute to the dialysis requirement (1) (Fig. 2).

Even the best dialysis treatment cannot replace the function of the natural kidney, thus the importance of selecting a treatment strategy which maintains any remaining function as long as possible is evident. Again, studies have in fact shown that the treatment strategy selected contributes to the maintenance of residual renal function. Patients dialysed with biocompatible, high-flux dialysers have been reported to maintain a higher degree of RRF than those treated with other types of dialysers (1, 2, 3, 4, 5) (Fig. 3).

Maximising the preservation of RRF may have a far-reaching impact on the well-being of the long-term dialysis patient. Maintenance of RRF may influence fluid balance, nutritional status, renal anemia, β₂-microglobulin-related amyloidosis and thus contribute to the quality of life of the renal failure patient.

Fig. 2:
Patients (%) with glomerular filtration rate ≥ 2, 4, 8 and 12 ml/min versus time on dialysis. (adapted from Van Stone, 1995)

Fig. 3:
Progressive decline of (A) urine volume (ml) and (B) creatinine clearance (ml/min) after onset of hemodialysis. (adapted from Hartmann et al, 1997)
Reduction of Inflammatory Reaction

Relation to albumin – a key mortality predictor

An inflammatory response has been consistently demonstrated during haemodialysis with bioincompatible membranes in contrast to biocompatible membranes (6, 7, 8, 9, 10, 11). Chronic stimulation of lymphokines and acute phase reactive proteins have been implicated in a multitude of disease stigmata prevalent in the dialysis population (infection, amyloidosis, vascular lesions).

Recent studies suggest that hypoalbuminemia does not primarily arise from low protein intake or albumin losses but is primarily connected to reduced albumin synthesis due to chronic inflammatory processes (12, 13, 14, 15). Increasing dietary protein intake will be supportive in the care of malnourished patients but normal albumin levels and synthesis will not be restored if the source of inflammation is not eliminated (Fig. 5).

A strategy for the care of malnourished patients is to provide high adequacy dialysis while avoiding or minimising chronic and acute activation of the inflammatory response by selecting blood compatible membranes and eliminating any potential stimulation from an external source such as dialysis fluid contaminated with bacteria and/or bacterial fragments.

The inflammatory response is also believed to be involved in hypoalbuminemia a major concern in dialysis patients. An inverse correlation has been found between albumin concentration and acute phase reactive proteins in haemodialysed patients (12) (Fig. 4).

Fig. 4:
Correlation between albumin concentration and log concentration of acute phase reactants in haemodialysis patients. (adapted from Kayser et al. 1997)

Fig. 5:
Albumin concentration and synthesis is primarily determined by non-nutritional factors
Reduction of Vascular Disorders

Leading cause of premature death in dialysed patients

Complement activation is involved in the stimulation of oxidative metabolism in dialysed patients (16, 17). Oxidative stress is involved in the genesis of advanced glycation end products (AGEs). Recent evidence suggests that enhanced oxidative stress and accompanying elevation of AGEs contribute to vascular disorders (18, 19, 20) (Fig. 6).

AGE transformation of a variety of proteins in blood vessel walls might contribute to the premature aging of dialysis patients as well as to the development of vascular lesions.

The higher permeability of the high-flux membrane may further combat this process especially in case of diabetics by removal of AGEs during dialysis (21) (Fig. 7).

**Fig. 6:** Pathway from blood-material interactions to protein modification and clinical stigma evident in the long-term dialysis patient.

**Fig. 7:** High-flux dialysis enables reduction of serum levels of LMW AGEs (adapted from Mekite et al., 1994).
Correction of Lipid Profiles

Implicated in cardiovascular disease as major cause of morbidity and mortality

Cardiovascular disease is the single highest cause of morbidity and mortality in the dialysis population. The abnormal lipid profiles present in renal failure patients would be associated with an increased risk of cardiovascular disease in the normal population. Studies have indicated that the dyslipidaemia of the dialysis patient is reduced when treated with a high-flux and blood compatible dialysis membrane (22, 23) (Fig. 8).

Various, non-mutually exclusive explanations have been proposed for these clinical observations: removal of an inhibitor of lipoprotein uptake, decreased level of AGE modified lipoproteins and lowered oxidative stress with the attendant decrease of oxidized and AGE modified lipoprotein levels. High-flux dialysis with a blood compatible membrane may have a long-term impact on patient morbidity and mortality with respect to cardiovascular disease.

Fig. 8:
Improved lipid profiles through use of high-flux biocompatible dialyser, (adapted from Blankstein et al, 1994) (TG: triglyceride, CHOL: cholesterol, VLDL: very low density lipoprotein)
Delayed Onset of Dialysis-Related Amyloidosis

90% prevalence after 7 years dialysis

High-flux biocompatible membranes can significantly lower serum levels of β₂-microglobulin (β₂-m) and postpone clinical manifestations of amyloid depositions. This observation is primarily related to the porosity of the membrane enabling β₂-m elimination (24) (Fig. 9). Advanced glycated β₂-m levels and amyloidosis are enhanced by oxidative stress which is related to membrane characteristics (25).

Further, the use of ultrapure dialysis fluid and dialyser membranes preventing the passage of cytokine inducing substances is believed to contribute to the delayed onset of clinical manifestations of amyloidosis (26) (Fig. 10a).

The biocompatibility of the membrane may play a further role in the inflammatory reactions leading to the clinical manifestations of amyloidosis (Fig. 10b).
High-Flux Dialysis in Clinical Practice

Only a few hurdles must be overcome before making high-flux dialysis the routine treatment method in the centre.

The quality of dialysis fluid is a critical aspect for all dialysis treatment modes. Attention to quality of dialysis fluid is essential but practicable (Fig. 11).

![Graph showing endotoxin concentration (EU/ml) for water, unfiltered dialysate, and filtered dialysate with values of 1, 0.8, 0.003, and < 0.004 respectively.](image)

**Fig. 11:** A dialysis fluid filter enables ready preparation of ultrapure dialysis fluid. (adapted from Weber et al. 1996)

### Ultrapure Dialysis Fluid: Today a Necessity

Already in 1961 bacterial contamination of dialysis fluid was reported and instances of "transient bacteraemia" observed in dialysis patients. In a publication in 1964 it was concluded that contamination of dialysis fluid presented a potential danger to the patient and should be eradicated but "at the present time no completely satisfactory method is available" (27).

Today we can address this problem. Ultrapure dialysis fluid should be considered a prerequisite for performing dialysis, whether high- or low-flux, as bacterial debris and metabolites may cross some dialysis membranes either by backdiffusion or backfiltration (28, 29, 30, 31). The former transport mechanism is common to both high- and low-flux dialysis whereby the latter predominates during high-flux where it is desirable to have high fluid fluxes across the membrane to support the convective transport of large toxins.

Due to its high retention properties for microbiological contaminants the Fresenius Polysulfone® dialysate fluid filter DIASAFE® plus (Fig. 12) prevents the passage of microbial substances and assures ultrapure dialysis fluid, independent from the type of dialyser and treatment modality selected.

Maximum safety is achieved due to an automated filter integrity test prior to each treatment.

![DIASAFLF plus device](image)

**Fig. 12:** The DIASAFE®plus – a newly developed dialysis fluid filter, aids achieving and maintaining ultrapure dialysis fluid.
Bicarbonate Dialysis Fluid:  
A further contribution to biocompatibility

The dialysis fluid contributes to the biocompatibility of the treatment. The benefits of using bicarbonate are numerous due to bicarbonate being the physiological buffer substance (32, 33, 34). Bicarbonate dialysis fluid is recommended for all modes of dialysis.

However, bicarbonate concentrate can result in bacterial contamination in the dialysis fluid. To assure high quality dialysis fluid, dry online bicarbonate concentrate such as bibag® is recommended. bibag® enables online preparation of bicarbonate dialysis fluid combining the benefits of high safety with easy handling, minimal storage requirements and reduced waste (Fig.13).

Attention: Machine hygiene is important

Maintenance and disinfection of all systems with which the dialysis fluid comes into contact before entering the dialyser is necessary. Even the dialysis machine can be a source of contamination. Reduced flow zones, warm temperatures and dialysed blood components support the formation of biofilms on the surfaces of the hydraulic components within the machine. Regular cleaning and disinfection of the dialysis machine is thus essential.

Disinfection should be performed prior or subsequent to every treatment. Attention should also be given to the quality of fluids entering the machine to minimise the presence of bacterial contaminants and thus reduce the formation of biofilms.
High-Flux Dialysis Demands Accurate Fluid Control

The benefit of high-flux dialysers lies in their increased permeability to potentially toxic substances in blood. In comparison to a low-flux membrane, a high-flux membrane has larger porosity. The size of toxin removed depends on the size of the pores introduced into the membrane during the manufacturing process.

The amount of fluid removed during a treatment is regulated by the ultrafiltration pump.

Even in such cases where fluid removal is zero, fluids still flow across the membrane due to the pressure profiles in the blood and dialysis fluid compartments which again support convective transport processes. The higher the fluid flux across the membrane then the higher the driving force for molecular movement.

A dialysis machine therefore must be selected which enables volumetric dialysis fluid and ultrafiltration control (Fig. 15). This means that fluid loss during dialysis can be accurately and safely performed and monitored. Backfiltration does not disturb fluid balance. Concern due to backfiltration and/or back-diffusion of contaminants in the dialysis fluid does not arise if due attention is given to the quality of dialysis fluid as previously considered (Ultrapure Dialysis Fluid: Today a necessity).

![Fig. 14:
Sieving characteristics of low- and high-flux membranes compared to the natural kidney](image1)

![Fig. 15:
The dialysis fluid circuit for safe and accurate fluid control](image2)
Some Essential Differences between Low- and High-Flux Dialysis in Clinical Practice

Today high-flux dialysis and the associated benefits are accessible to an ever-increasing patient population. Modern haemodialysis machines assure accurate fluid control while high-quality dialysis fluid can be prepared from well-maintained reverse osmosis systems and cartridges for the online preparation of bicarbonate dialysis fluid.

Dialysers containing blood compatible membranes with performance characteristics appropriate for high-flux therapies and the individual patient requirements are available. Some such dialysers offer the added advantage of a high retention capacity for pyrogenic materials thus assuring a further level of safety. Enhancing modules like OCM (online Clearance monitor), BVM (Blood volume monitor) and BTM (Blood temperature monitor), enable accurate treatment settings and parameter control during dialysis thus contributing to a comfortable and adequate dialysis treatment.

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<tr>
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<th>High-flux dialysis</th>
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<tr>
<td>Volumetric UF control</td>
<td>recommended</td>
<td>required</td>
</tr>
<tr>
<td>Blood flow</td>
<td>standard range</td>
<td>standard range</td>
</tr>
<tr>
<td>Dialysate flow</td>
<td>standard range</td>
<td>standard range</td>
</tr>
<tr>
<td>Dialysate composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Buffer</td>
<td>bicarbonate recommended</td>
<td>bicarbonate recommended</td>
</tr>
<tr>
<td>• Electrolytes</td>
<td>standard range</td>
<td>standard range</td>
</tr>
<tr>
<td>• Glucose</td>
<td>recommended</td>
<td>required</td>
</tr>
<tr>
<td>• Sterile &amp; ET* free</td>
<td>recommended</td>
<td>normally yes</td>
</tr>
<tr>
<td>Backfiltration of dialysate</td>
<td>normally not</td>
<td>normally yes</td>
</tr>
<tr>
<td>Convective CIS* backtransport</td>
<td>normally not</td>
<td>yes, membrane dependent</td>
</tr>
<tr>
<td>Diffusive CIS backtransport</td>
<td>yes, membrane dependent</td>
<td>yes, membrane dependent</td>
</tr>
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</table>

Table 1: Key parameters to be considered when comparing low- and high-flux dialysis.

*This table serves only as a guide. Parameter settings and fluid compositions must be prescribed by the physician according to the needs of the individual patient
* ET = endotoxin
* CIS = cytokine inducing substances

Table 1 summarises some key parameters and aspects and their relevance to low-and high-flux dialysis treatments.

Fig. 16: Components contributing to the treatment quality
Optimised Patient Treatment Parameters

contribute further to the biocompatibility and efficacy of high-flux dialysis and maximise the benefits for the patient.

As in any dialysis treatment, parameters must be selected to maximise treatment efficacy and comfort for the individual patient (35, 36, 37). Technological developments render control of parameters such as blood temperature and volume, access recirculation and dialysis adequacy practicable and readily integrated in routine dialysis treatments. The blood temperature monitor (BTM) and blood volume monitor (BVM) are modular components of the 4008 machine generation.

The BTM and the BVM detect alterations in body temperature and haematocrit, respectively, and consequently decreases in blood volume.

The BVM is an operator tool to improve haemodynamic stability and thus help minimise side-effects such as hypotension caused by fluid removal during haemodialysis (Fig. 18).

Predefined profiles for dialysate sodium and ultrafiltration may be additional useful tools to effect fluid removal while maintaining maximum comfort for individual patients.

The online Clearance monitor measures sodium dialysance online from which the adequacy of the ongoing treatment can be assessed and directs the operator to select or modify the parameters to maximise the treatment efficacy (39). The adequacy of the treatment in terms of \( \text{Kt/V} \) can thus be readily calculated. An equilibrated \( \text{Kt/V} \) of > 1.2 should be our objective (40). High-flux dialysis should thus not result in short treatment times.
High-Flux Dialysis and „Good Dialysis Practice“

Opens up New Perspectives to High Quality and Cost-effective Treatments.

Establishing ultrapure dialysis fluid and high-flux dialysers in routine dialysis practices opens the door to the introduction of new modalities.

The innovative ONLINEplus™ System enables haemo(dia)filtration (HF/HDF) to be performed simply and cost-effectively. The ONLINEplus™ System prepares sterile dialysis fluid and substitutale solution online through double filtration by two DIASAFeplus fluid filters (Fig. 19). The sterile fluid primes the extracorporeal circuit and retransfuses the blood to the patient at the end of the treatment. A fluid bolus can also be infused during the treatment and an unlimited amount of substitution fluid (20 to max. 350 ml/min) is available online for performing HDF and HF treatments (also within SN-mode).

Fig. 19.
Schematic flowchart for ONLINEplus™ for ONLINE HF/HDF, priming, rinsing, volume bolus and reinfusion

BioAdequacy™

High-Flux Dialysis
State-of-the-Art Clinical Practice
High-Flux Dialysis and Cost Implications

Economical constraints

There is a world-wide challenge of setting dialysis procedures within rigorous financial boundaries. We better understand now that cost analysis cannot be limited to the direct cost of the dialysis treatment but must consider the overall expenditure allocated to a dialysis patient. The dialysis treatment contributes 20% to the overall financial cost of a dialysis patient in the United States, while hospitalisation alone accounts for 50% (41). Similar contributions may be expected in other geographical areas.

Does high-flux dialysis decrease the cost of health-care?

There is not a detailed financial evaluation of the cost of high-flux dialysis. Clinical observations reported to result from the use of high-flux dialysers suggest that high-flux dialysis, appropriately delivered, can reduce health-care costs:

- Delayed surgical intervention for dialysis related amyloidosis when high-flux dialysis is performed and the chronic inflammatory response is reduced by selection of ultrapure dialysis fluid and biocompatible materials (24, 26).

- High-flux dialysis has been reported to correct dyslipidaemia effectively (22, 23),
- High-flux biocompatible dialysis has been reported to have a positive impact on parameters influencing nutritional status (12, 13, 14, 42),
- Biocompatible dialysis reduced hospitalisation due to chronic inflammatory processes (7, 43, 44),
Recent publications have addressed this aspect in quantitative terms:

- Increased survival and decreased hospitalisation costs were associated with the use of biocompatible and high-flux dialyzers (43).
- Less-well-dialysed patients resulted in 13% higher expenditure on erythropoietin (EPO) (45). The EPO dose responsiveness has been shown to be higher in patients receiving a higher dose of dialysis (46) (Fig. 20). The enhanced correction of anemia resulting from an increased level of dialysis may reduce cardiovascular morbidity and poor functional status associated with anemia and prolong survival.

When dialysis is needed, the modality that provides the highest quality of care for an individual should be used. If it is, it will be the most cost-effective as well, by maintaining patient health, minimising hospitalisations and prolonging survival (47).

Fig. 20:
Effect of an increased level of dialysis on haematocrit (adapted from Ifudu et al, 1996)

BioAdequacy™
High-Flux Dialysis Impacts Dialysis Care Costs – Long-Term!
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