Dialysers
Increasing Cost and Treatment Efficiency

Fluid Substitution Calculator
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During the early days of dialysis, several empirical approaches were attempted to develop membranes for the treatment of acute or chronic renal failure. In 1937, cellophane in the form of a tubular film, was used as a dialysis membrane for the first time. By means of this industrially-produced membrane material, Wilhelm Kolff with his Rotating Drum dialysis machine performed the first successful dialysis treatment in 1945.

The first hollow fibre dialysers containing cellulose acetate capillary membranes were introduced in the 1960’s. These membranes enabled the basic filtration function of the natural kidney to be simulated at higher efficiency than the earlier flat sheet membranes but the elimination of uremic toxins was restricted to substances having a small molecular-weight only (low-flux dialysers). Due to their low hydraulic permeability, they were nevertheless suitable for application in diffusive haemodialysis treatments at low ultrafiltration rates.

In attempts to increase the dialysis efficiency, membranes made from synthetic polymers in the 1970’s offered the possibility to apply a higher hydraulic permeability, and, in comparison to the old low-flux membranes, these newly-developed high-flux membranes could remove larger toxins because of their larger pore sizes. Therefore, the sieving characteristics of these high-flux membranes approached that of the glomerular basement membrane.

The new high-flux membranes allowed for the realisation of the newly-developed convective treatment modalities and, for the first time, to remove substances with a higher molecular weight like $\beta_2$-microglobulin. By convention, high-flux dialysers are classified as having an ultrafiltration coefficient $> 20 \text{ mL/h} \times \text{mmHg}$ and a $\beta_2$-microglobulin sieving coefficient $> 0.6$. Moreover, the technical advancements achieved with dialysis machines (volumetric fluid control) and the development of new treatment modalities like haemofiltration demanded for dialysis membranes with a higher performance.

The purely convective treatment modality haemofiltration allows for a very good elimination of large molecules, but the elimination of small molecules is limited. By combining the diffusive (haemodialysis) and convective (haemofiltration) mechanisms, the haemodiafiltration technique was developed, which enables a high elimination of both, low and high molecular-weight substances.

One aspect that needs to be considered is that an increased elimination of substances with a higher molecular-weight with high-flux membranes and convective treatments should not cause the loss of essential proteins, such as albumin. Modern-day high-flux membranes vary considerably in their ability to curtail the loss of substances useful to the patient.
The haemodiafiltration technique has been continuously optimised since its introduction during the early 1980’s; nowadays, haemodiafiltration has reached the status whereby all solutions necessary for the treatment (ultra pure dialysis- and substitution-fluid) are produced ‘online’ by the dialysis machines, thereby allowing the exchange of large volumes of fluid in a cost-efficient way (ONLINE-HDF).

All advancements in the field of dialysis pertaining to dialysers, membranes and machines have the overall aim of improving the quality and efficiency of the dialysis treatment.

In particular, haemodiafiltration with high exchange-volumes is the most efficient treatment modality to remove a broad spectrum of uraemic toxins. Besides, a number of clinical advantages have been attributed to online-haemodiafiltration that may be the reason for the reduced mortality rates reported for HDF dialysis patients\(^4,5\).

Through a combination of innovative membranes (e. g. Fresenius Polysulfone\(^\circ\) or Helixone\(^\circ\)), dialysis machines with modern surveillance systems (Blood Volume Monitor, Blood Temperature Monitor, Online Clearance Monitoring) and effective treatment modalities (e. g. high-flux dialysis or ONLINE haemodiafiltration), modern therapy systems are thus geared towards the improvement of the quality of life of dialysis patients as well as a reduction of morbidity and mortality (Fig. 2).

This brochure is intended to provide guidance regarding the optimal usage of dialysers for the HDF treatment modality in order to achieve the largest benefit for the patient.
Dialyser Selection Criteria

The selection of the appropriate dialyser is essentially influenced by patient-related aspects such as vascular access and the achievable effective blood flow rate. In addition, factors such as body volume, sensitivity to certain sterilisation modes or polymers have also to be taken into account. Thus, the choice of the dialyser type, together with the treatment modality, has to be prescribed by the nephrologist according to the specific needs of the individual patient.

The maximal clearance that can be achieved during treatment is mainly influenced by the following parameters: the effective blood flow rate of the patient, molecular weight of the substances to be removed, permeability and effective surface area of the dialyser (Fig. 3).

Initially, the clearance of a particular substance by a specific dialyser increases linearly with an increasing blood flow rate; in this range, the blood flow rate is the limiting factor (Fig. 4). In the second phase, clearances tend to increase less rapidly, reaching the state whereby the effective blood flow rate, surface area and permeability of the dialyser have an optimal relationship.

Finally, the stage is reached whereby further increases of the blood flow rate would not result in an increase of clearance, that is, the membrane permeability and the size of the dialyser have reached a threshold.

Thus, the higher the effective blood flow rate, the higher the clearance for a given substance. However, as the selection of the effective blood flow rate is dependent on the type of vascular access, particularly the shunt function, and the cardiac situation of the individual patient, the final decision lies with the nephrologist.
To utilise a given dialyser to its full capacity, it is important to consider the relationship between its effective surface area and the achievable blood flow rate. For instance, a large dialyser with a surface area of 2.2 m² (FX 100) at a blood flow rate of only 150 mL/min would not lead to a noteworthy improvement in clearances in comparison to a smaller dialyser with a surface area of 1.4 m² (FX 60), as at a low blood flow rate of 150 mL/min the large surface area is not used to its full extent (Fig. 5).

However, the usage of a small dialyser with a surface area of 0.6 m² (FX 40) at a blood flow rate of 300 mL/min is also not appropriate, as this combination would lead to high dialyser inlet and transmembrane pressures. In this case, the selection of an FX 60 dialyser with a surface area of 1.4 m² would lead to more favourable pressure conditions and also to an increase in clearances of up to 50%.

The ratio between blood flow rate and effective surface area also influences the time that blood needs to flow through the dialyser. A low blood flow rate, in combination with a high surface area, results in an increased retention period of blood within the dialyser and an increased tendency for coagulation within the capillaries. Vice versa, a high blood flow rate in combination with a small surface area results in a very short retention period of blood within the dialyser and leads to a reduction in clearance (Fig. 6). The dotted lines in figure 6 indicate the optimal blood flow ranges of each dialyser to achieve a balance between blood retention time within the dialyser and the clearances that can be reached.

The bold lines in figure 5 represent the optimal blood flow ranges of the individual FX class dialysers. As in dialysis a broad spectrum of solutes with different molecular weights has to be removed, this figure uses vitamin B12 (1355 Da) clearances as an example, as many of the larger substances having a molecular weight above 500 Da are not adequately represented by urea (60 Da).

Fig. 5: Optimal blood flow ranges of the FX class of dialysers using vitamin B12 clearances as an example.

Fig. 6: Retention period of blood within the dialyser depends upon the blood flow rate and the dialyser surface area.
The dialysis fluid flow rate

In many dialysis centres, a dialysis fluid flow rate of 500 mL/min is used by default in haemodialysis treatments, although optimal solute clearances would already be achieved at lower dialysis fluid flow rates. As shown in figure 7, already at a dialysate flow rate equal to the blood flow rate approximately 90% of the maximum solute clearance is achieved. Thus, much higher dialysis fluid flow rates would not significantly contribute to increases in clearances and are therefore not necessary particularly from an economical point of view.

The 5008 therapy system offers the AutoFlow function, which automatically adjusts the dialysis fluid flow rate relative to the selected effective blood flow rate in order to derive an optimal ratio between blood flow rate and dialysis fluid flow rate.

Efficiency of removal depends upon the solute in question

It is conventional to consider efficiency of removal in terms of urea clearances; however urea is the smallest target substance for elimination in dialysis and removal of other solutes involves specific considerations relevant to the solute in question. If, for example, the elimination of phosphate is desired, the dialysate as well as the blood flow rates have to be adjusted and optimised to maximise phosphate clearances. More importantly, because of the distribution of phosphate in various compartments of the body, higher phosphate removal can be achieved more effectively through increased duration and frequency of dialysis, larger surface areas of dialysers as well as by selecting certain treatment modalities (e.g. haemodiafiltration).

Fig. 7: Impact of dialysis fluid flow rates on clearance relative to different blood flow rates.
Novel developments in dialysers: Internal filtration

For high-flux dialysers it is well known that, due to the pressure profiles within the dialyser, backfiltration of dialysis fluid into the blood compartment can occur (Fig. 8). This could also, analogous to fluid exchange in haemodiafiltration, be viewed as substitution fluid entering the blood compartment from the dialysis compartment; the additional fluid is removed from the blood through ultrafiltration (all contemporary dialysis machines are equipped with a precise volumetric fluid control).

The phenomenon of backfiltration has always been associated with the transfer of bacterial endotoxins into the blood from potentially contaminated dialysis fluid. It is now well recognised that the application of certain dialysis membrane materials minimises the risk of endotoxin entry into the bloodstream of the patient. The Fresenius Polysulfone membranes are recognised for their high endotoxin retention capacity, thereby providing a high level of safety to the patient.

The mechanism of internal filtration can thus be safely exploited to its full extent, in order to increase the elimination of middle molecules as long as associated requirements are met: usage of dialysis membranes with a high endotoxin retention capacity and of polysulfone-based dialysis fluid filters delivering ultrapure dialysate and substitution fluid (double safety).

In order to further increase the clearance of middle molecules, the geometry of dialysis membrane fibres of modern dialysers have been refined, resulting in different pressure profiles within the dialyser. Such modifications involve an increase in fibre length or a reduction of the inner diameter of the fibre. To illustrate this, the fluid volume which is exchanged through internal filtration during a normal high-flux dialysis ($Q_b = 300 \text{ mL/min}, Q_d = 500 \text{ mL/min}, UF = 0$) with a FX 60 dialyser (inner fibre diameter: 185 µm) is 1.0 L/h. This provides an approximately 12 % higher β2-microglobulin clearance in high-flux haemodialysis treatments with the FX class of dialysers in comparison to F-series dialysers (inner fibre diameter: 200 µm) [6].
ONLINE HDF treatment modalities

As described, ONLINE HDF in post-dilution mode currently is the most effective dialysis modality offering many advantages with respect to increased clearance of larger uraemic toxins as well as of phosphate.

As a consequence of the high filtrate flow rates (reduction of the amount of water in blood) during ONLINE haemofiltration or ONLINE haemodiafiltration treatments, the resultant haemoconcentration could increase the tendency towards coagulation within the hollow fibres. Haemoconcentration has the effect of increasing the transmembrane pressure (TMP); attention should therefore be given to any increase in the TMP, which should always be below 300 mmHg throughout the treatment, in order to ensure safer rheological and operating conditions.

The extent to which haemoconcentration occurs is dependent on patient specific values such as the haematocrit and the total protein concentration (Fig. 10). Due to the increasing usage of EPO for dialysis patients in recent years, the haematocrit values of dialysis patients are much higher now than some years ago. It is therefore necessary to monitor precisely the ratio of blood flow rate and filtrate flow rates.

For the calculation of the filtrate flow rate, the individual ultrafiltration rate of the dialysis patient and, when using modern dialysers with a reduced inner diameter of the membrane fibres, also the internal filtration rate have to be taken into consideration.

As a general rule it is accepted that the maximum total filtrate flow rate should not exceed 25 % of the effective blood flow rate. In a different approach, the calculation of the maximum filtrate flow rate is based on the maximum achievable plasma flow rate taking into account the individual haematocrit and total protein values of the patient.

Therefore, general prescriptions of filtrate flow rates to be applied should be controlled with respect to their feasibility, in order to avoid an imbalance between the effective blood flow rate and the filtrate flow rate.

While it is possible to exchange 18 L of fluid during a 4 hour ONLINE HDF treatment at an effective blood flow rate of 300 mL/min, this exchange volume cannot be realised in practice with a lower blood flow rate of 250 mL/min. In this case, the maximal substitution rate would be only 15 L, otherwise haemoconcentration would arise due to an imbalance between the effective blood flow rate and the filtrate flow rate.

Because of the effects of haemoconcentration, it is therefore better to select a somewhat lower exchange rate and complete the treatment than having higher exchange rates and having to terminate a treatment prematurely.

The Therapy System 5008 supports the user in the calculation of the correct substitution fluid flow rate: by means of the AutoSub function the dialysis machine automatically calculates the optimal substitution fluid flow rate taking into account the effective blood flow rate, patient-specific values (haematocrit value, total protein concentration, ultrafiltration rate) and the dialyser type in use.

For all other machines that do not offer the AutoSub function, it is recommended to use the Fluid Substitution Calculator included in this brochure, in order to avoid imbalances between the effective blood flow rate and the filtrate flow rate.
References


How to use the Fluid Substitution Calculator

The Fluid Substitution Calculator included within this brochure allows you to determine the maximal filtrate flow rate for a given effective blood flow rate and takes into account patient-specific parameters such as the haematocrit and total protein values.

1. Read the effective blood flow rate [mL/min] from the machine; then align the arrow on the middle disc with this blood flow rate value on the scale of the largest disc.

2. Align the patient-specific total protein value [g/dL] on the top (smallest) disc with the patient-specific haematocrit [%] on the disc below (middle disc).

3. The maximal filtrate flow rate can now be taken from the circular window on either the white, blue or pink scale according to the indicator appearing in the oval slot of the uppermost disc.

4. From this value, subtract the individual UF rate of the patient (indicated as mL/min on the dialysis machine) to get the maximum recommended substitution rate to be applied.

Fig. 11: The Fluid Substitution Calculator