Online haemodiafiltration: definition, dose quantification and safety revisited

James E. Tattersall¹
Richard A. Ward² on behalf of the EUDIAL group*

Correspondence and offprint requests to: EuDial@era-edta.org

¹Department of Renal Medicine, St James’s University Hospital, Leeds, UK and
²Department of Medicine, University of Louisville, Louisville, KY, USA

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ABSTRACT

The general objective assigned to the EUropean DIALysis (EUDIAL) Working Group by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) was to enhance the quality of dialysis therapies in Europe in the broadest possible sense. Given the increasing interest in convective therapies, the Working Group has started by focusing on haemodiafiltration (HDF) therapies. Several reports suggest that those therapies potentially improve the outcomes for end-stage renal disease patients. Europe is the leader in the field, having introduced the concept of ultra-purity for water and dialysis fluids and with notified bodies of the European Community having certified water treatment systems and online HDF machines. The prevalence of online HDF-treated patients is steadily increasing in Europe, averaging 15%. A EUDIAL consensus conference was held in Paris on 13 October 2011 to revisit terminology, safety and efficacy of online HDF. This is the first report of the expert group arising from that conference.

INTRODUCTION

Conventional haemodialysis is the most widely used therapy for the replacement of renal function. Haemodialysis is based on the diffusive transport of solutes across a semipermeable membrane and is effective in removing small solutes, such as urea, and correcting electrolyte, acid–base and fluid imbalances. However, it is poorly suited to the effective removal of larger solutes, such as β2-microglobulin, even when high-flux membranes are used because solute diffusion coefficients decrease rapidly with the increasing molecular size. As the importance of larger uraemic toxins has become recognized, the need for alternative therapies that provide better removal of those solutes has become evident. It has long been known that convective transport of solutes across membranes decreases less rapidly as the solute size increases than does diffusive transport because solute sieving coefficients are less dependent on the molecular size than are diffusion coefficients. This knowledge led to the development of convective therapies (haemofiltration) in the 1970s [1], followed later by combined convective and diffusive therapies (haemodiafiltration, HDF) [2]. Today, several different convection-based therapies are available for use in treating both acute kidney injury and end-stage renal disease. For end-stage renal disease, HDF is the most widely used of those convective therapies.

The term HDF has been used to describe a range of modes of therapy that include both diffusion and convection (Table 1). These therapies are not all equivalent, leading to the potential for confusion in interpreting clinical outcomes. Moreover, therapies coming under the broad umbrella of HDF involve exchanging large volumes of fluid with the patient. This process adds to the risks associated with conventional haemodialysis and mitigation of this additional risk requires measures to ensure the safe and effective delivery of therapy. This review seeks to establish a common terminology for HDF, summarize currently existing guidelines relevant to its application and suggest areas where more work might be required. By intention, this document does not provide recommendations on when and how HDF should be used or the optimal dose. It is recognized that HDF is only one way to increase large solute clearance. Other methods include the use of dialysers with pores of larger diameter and total surface area, while increasing the total weekly treatment time will proportionally increase the removal of all solutes.
Table 1. Modes of controlled haemodiafiltration

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Post-dilution haemodiafiltration</td>
<td>Ultrafiltration followed by infusion of replacement fluid</td>
</tr>
<tr>
<td>Pre-dilution haemodiafiltration</td>
<td>Infusion of replacement fluid followed by ultrafiltration</td>
</tr>
<tr>
<td>Mid-dilution haemodiafiltration</td>
<td>Infusion of replacement fluid at the mid-point of ultrafiltration (post-dilution followed by pre-dilution)</td>
</tr>
<tr>
<td>Mixed-dilution haemodiafiltration</td>
<td>Infusion of replacement fluid before and after ultrafiltration (pre-dilution followed by post-dilution)</td>
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</table>

**TERMINOLOGY**

The Consensus Conference on Biocompatibility held in 1993 [3] defined HDF as follows:

[HDF is] a treatment designed to remove accumulated metabolic products from blood by a combination of diffusive and convective transport through a semi-permeable membrane of high-flux type. Fluid is removed by ultrafiltration and the volume of filtered fluid exceeding the desired weight loss is replaced by sterile, pyrogen-free infusion solution. HDF provides a better elimination of higher-molecular weight solutes than HD.

The European DIALysis (EUDIAL) group considered the above definition to be too broad. In theory, standard high-flux haemodialysis, with the addition of a 10 mL infusion and 10 mL ultrafiltration ‘exceeding the desired weight loss’, would satisfy that definition of HDF without any benefit to the patient. *Post-hoc* analyses of recent studies suggested that any improved survival associated with HDF did not occur until the effective convection volume exceeded 18–20 L [4, 5]. (As discussed under quantification, the effective convection volume includes both the replacement fluid volume and fluid removed for weight loss.) Therefore, the EUDIAL group felt that it was necessary to add a lower limit to the convection volume, below which the treatment would not qualify as HDF. A convection volume equivalent to 20% of the total blood volume processed for the treatment was chosen as the lower limit because it is achievable with post-dilution HDF in the majority of patients without excessive haemoconcentration. Using typical treatment times and blood flow rates, this will result in effective convection volumes close to or exceeding the volumes which have been associated with clinical benefit [4–6]. It follows from this definition of HDF that high-flux treatments, with effective convection volumes <20% of the blood volume processed, should be termed high-flux dialysis.

The blood volume processed will vary by indication, being lower in children and higher in patients with a larger body size who require a larger dose of dialysis. Expressing the limit for the convection volume as a fraction of the blood volume processed, rather than as an absolute volume, results in a proportional and achievable increment in higher molecular weight clearance, regardless of the dose and blood flow rate prescribed. In theory, it would be more correct to prescribe the convection volume as a proportion of the plasma water volume processed rather than the blood volume processed. However, the EUDIAL group felt that this would introduce additional complexity. The blood volume processed—not the plasma water volume processed—is displayed on the HDF machine control panel.

Some definition of ‘high-flux’ was also felt to be required. The traditional definition of ‘high-flux’ was based on the hydraulic permeability. Since high-hydraulic permeability does not necessarily equate to high large solute permeability, the EUDIAL group felt it important to add a characteristic of middle-molecule clearance and the definition of a ‘high-flux’ membrane used by the membrane permeability outcome study investigators [7] (sieving coefficient >0.6 for β2-microglobulin) was selected.

These considerations led to a revised definition of HDF as follows:

HDF is a blood purification therapy combining diffusive and convective solute transport using a high-flux membrane characterized by an ultrafiltration coefficient greater than 20 mL/h/mm Hg/m² and a sieving coefficient (S) for β2-microglobulin of greater than 0.6. Convective transport is achieved by an effective convection volume of at least 20% of the total blood volume processed. Appropriate fluid balance is maintained by external infusion of a stable, non-pyrogenic solution into the patient’s blood.

**MODES OF HDF**

Various modes of HDF, differing by the site of replacement fluid infusion, are in use (Table 1).

**Post-dilution HDF**

In post-dilution HDF, the replacement fluid is infused downstream of the dialyser, usually into the venous bubble trap [8]. For solutes which can pass the membrane unimpeded (sieving coefficient = 1), the concentration in the ultrafiltrate is the same as in the plasma water. The high ultrafiltration rates used in HDF effectively prevent back-filtration which normally occurs in high-flux dialysis. Post-dilution HDF is the most efficient method of HDF in terms of solute removal. A potential disadvantage is that haemoconcentration at high ultrafiltration rates can result in the...
deposition of plasma proteins on the membrane surface, clogging the membrane pores and occluding the blood channels of the dialyser. These effects can raise transmembrane pressure (TMP), causing alarms, reducing clearance and possibly resulting in clotting of the extracorporeal circuit.

The degree of haemoconcentration is dependent on the filtration fraction. Strictly defined, the filtration fraction is the ratio of the ultrafiltration rate to the plasma water flow rate. For practical clinical purposes, however, it is usually defined as the ratio of the ultrafiltration rate to the blood flow rate and, thus, depends on haematocrit and protein concentration, as well as on the ultrafiltration rate and the blood flow rate. Because the intention of the EUDIAL group is to provide clinically relevant guidance, the latter definition is used in this review. Haemoconcentration generally limits the filtration fraction to 20–25% of the blood flow rate in post-dilution HDF. The ultrafiltration rate is controlled in proportion to the actual blood flow rate or guided by TMP. A filtration fraction up to 30% of the blood flow rate is possible using systems designed to optimize the filtration rate, based on automatic adjustment of TMP according to the ultrafiltration flow rate measurements [9].

**Pre-dilution HDF**

The haemoconcentration associated with post-dilution HDF can be avoided by infusing the replacement fluid upstream of the dialyser [10]. With pre-dilution HDF, higher filtration rates are possible than with post-dilution HDF, and ultrafiltration rates up to 100% of the blood flow rate are used. However, pre-dilution reduces the efficiency of both the diffusive and convective components of solute removal by reducing the solute concentrations in the blood compartment. In some situations, small solute clearance by pre-dilution HDF may be lower than by conventional high-flux haemodialysis. For equivalent clearance, the ultrafiltration rate needs to be at least two times greater for pre-dilution HDF compared with post-dilution (Table 2).

**Mid-dilution HDF**

In this technique, the replacement fluid is infused partway down the blood pathway using specially designed dialysers or systems [11]. Thus, the first part of the blood circuit is operated in the post-dilution mode and the second part in the pre-dilution mode. While mid-dilution HDF can provide more efficient removal of middle molecules than post-dilution HDF [12], there is a risk of high TMP in the post-dilution section of the filter when used in its original configuration [13]. High TMP can be minimized by using large-surface filters and reversing the blood-side flow configuration [15].

**Mixed dilution HDF**

In mixed dilution HDF, the replacement fluid is infused both upstream and downstream of the dialyser [14]. The ratio of the upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximizing clearance and avoiding the consequences of a high TMP and haemoconcentration.

<table>
<thead>
<tr>
<th>Blood flow (mL/min)</th>
<th>UF rate (mL/min)</th>
<th>Effective convection rate (% of blood flow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>50</td>
<td>20%</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
<td>30%</td>
</tr>
<tr>
<td>350</td>
<td>70</td>
<td>20%</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>30%</td>
</tr>
<tr>
<td>450</td>
<td>90</td>
<td>37.7%</td>
</tr>
<tr>
<td>UF rate (mL/min)</td>
<td>Effective convection rate (% of blood flow)</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>30%</td>
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<tr>
<td>120</td>
<td>20%</td>
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</tr>
<tr>
<td>135</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>37.7%</td>
<td></td>
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<tr>
<td>210</td>
<td>20%</td>
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<tr>
<td>240</td>
<td>30%</td>
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</tr>
<tr>
<td>270</td>
<td>37.7%</td>
<td></td>
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<tr>
<td>400</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>450</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

Rates assume a haematocrit of 35%.

*A filtration fraction of 30% in post-dilution is only possible using methods designed to optimize filtration.

**Enhanced internal filtration**

Various methods have been described to enhance the ultrafiltration and 'back-filtration' of dialysis fluid which normally occurs during high-flux haemodialysis. These methods include creating oscillations in the TMP (push–pull HDF) [15] and increasing the resistance to blood flow in the dialyser, either by reducing the internal diameter of the fibres [16], increasing the dialyser length or using two dialysers in series [17]. In general, these techniques do not result in a sufficient convection volume to qualify the treatment as HDF as defined by the EUDIAL group; however, it is conceivable that this will be possible in future.

Techniques that enhance internal filtration have the advantage that they can be performed with relatively minor modifications to standard dialysis hardware. However, back-filtration will increase the risk of transfer of biological contaminants from dialysis fluid to blood. That risk may be reduced by decreasing the dialyser permeability to biological contaminants in the dialysis fluid and by increasing the purity of the dialysis fluid.

A second disadvantage of enhanced internal filtration is that the convection volume cannot be measured or controlled directly, except in certain types of push–pull HDF (see below).

**Push-pull HDF**

In push–pull HDF, variations in dialysis fluid pressure cause alternating filtration and back-filtration of dialysis fluid.
The effective convection volume is the total volume of undiluted fluid ultrafiltered during the treatment, including the fluid removed for weight loss. In post-dilution HDF, the effective convection volume will be equal to the total volume ultrafiltered, including the weight loss. When some or all of the replacement fluid is infused upstream of the ultrafiltration process (pre-, mid- or mixed-dilution), the ultrafiltration volume must be adjusted for the degree of dilution using a dilution factor (DF) which takes into account the effect of any upstream infusion on the concentration of solute in the ultrafiltrate (see below). In the case of enhanced internal filtration, the total convection volume is difficult to determine. For systems intended to provide enhanced internal filtration, the manufacturer should provide reference tables or equations to allow the user to estimate the effective convection volume.

A measure of serum β₂-microglobulin clearance or plasma level would also be a logical quantifier of the effect of HDF. However, those measurements are relatively expensive and confounded by calibration differences and variations in the generation rate. As long as the β₂-microglobulin sieving coefficient is >0.6, the β₂-microglobulin clearance will be predictable and proportional to the effective convection rate. When the β₂-microglobulin clearance is calculated from concentrations in blood, the concentration should be corrected for the presence of protein and lipid [22].

Calculating the dilution factor

For pre-dilution and mixed-dilution modes, the DF is the total plasma water volume processed divided by the total non-erythrocyte water volume passed through the dialyser (plasma water plus upstream infused fluid). For solutes other than urea, diffusion through erythrocyte walls is too slow to allow significant clearance of erythrocyte water. The DF can be calculated using the equations below from the plasma water flow rate (Qpw), flow infused upstream (Qinf), blood flow rate (Qb), haematocrit (Hct) and protocrit (Pct). The protocrit is the volume fraction of plasma proteins, which may be calculated as the product of 0.000718 and the total protein concentration of plasma proteins in g/mL. Lipids occupy 0.016 of the plasma volume. In the following equation, the term (1 – 0.016 – Pct) can be approximated by 0.93.

\[
Q_{pw} = Q_b \times (1 - Hct) \times (1 - 0.016 - Pct),
\]

\[
DF = \frac{Q_{pw}}{Q_{pw} + Q_{inf}}.
\]

In the case of mid-dilution HDF, the DF is more difficult to determine. The dialyser manufacturer should provide reference tables or equations to allow the user to estimate the DF from information provided by the dialysis machine.

Calculating the UF rate to be used in pre-dilution

To achieve a target effective convection flow rate (Qeff), the ultrafiltration rate in pre-dilution (Qlpref) must be increased by a factor of 1/DF so that Qlpref = Qeff/DF. Table 2 shows the various Qlpref required to achieve an adequate Qeff.
In pre-dilution HDF, the actual filtration rate will need to be at least 30–50% of blood flow entering the dialyser to achieve the target of an effective convection rate of at least 20% of the undiluted blood flow rate (see Table 2).

Calculating clearance

Clearance can be calculated in HDF using blood or blood and dialysis fluid samples in the same way as for conventional haemodialysis. However, the dialyser inlet blood sample must be taken upstream of any pre-dilution infusion port (from the arterial needle or the initial segment of the arterial blood line) and the dialyser outlet blood sample must be taken downstream of any post-dilution infusion port (from the venous needle or the final segment of the venous blood line). Online clearance methods designed for conventional dialysis may need to be adapted to account for the effect of ultrafiltration rate in HDF.

Clearance can also be estimated from dialyser $K_uA$ and the blood, dialysis fluid, and convection flow rates. However, in HDF there is interference between clearance by diffusion and convection, so that overall clearance is significantly less than the simple addition of each component. For post-dilution HDF, the convective component of urea clearance is $\sim 50\%$ of the convection rate. Urea clearance may actually be slightly reduced by pre-dilution, although the effect on the clearance of larger molecular weight solutes is always positive. Appendix 1 describes how clearance can be estimated in HDF.

The measurement of non-urea solutes in samples taken during or after dialysis needs to take into account disequilibrium between erythrocytes and plasma [23]. The concentrations in plasma are likely to change in the blood samples due to re-equilibration during the time between sampling and analysis.

The per cent reduction in solute concentration from pre- to post-treatment is a more practical and easier way to evaluate the performance of an HDF session. In calculating the per cent reduction in solute concentration, it is necessary to take into account the effects of haemoconcentration and disequilibrium and rebound phenomena. For $\beta_2$-microglobulin, which is excluded from erythrocytes, plasma water concentrations should be used. Post-treatment disequilibrium and rebound can be adjusted for by using the equilibrated concentration ($C_{eq}$), calculated from:

$$C_{eq} = C_{pre} \times \left( \frac{C_{post}}{C_{pre}} \right)^{t_d/(t_d+110)},$$

where $C_{pre}$ and $C_{post}$ are the measured pre- and post-treatment concentrations, respectively, and $t_d$ is the treatment time (min) [24].

Regulation of HDF

The EU Medical Device Directive can be interpreted to state that convective therapies, including the replacement fluid, are medical devices [26]. At present, not all aspects of convective therapies are addressed by European Norms (see the section on standards). In the absence of a clear detailed EU position, some countries have filled the void by publishing national laws and regulations or by referencing the European Pharmacopoeia for the quality of replacement fluid. A preliminary review of those laws and regulations show differences in how HDF is regulated in different countries. The European Pharmacopoeia gives quality requirements for pre-packaged i.v. replacement fluid, including a proposed maximum endotoxin level of 0.05 EU/mL, but does not consider replacement fluid prepared online. In spite of the inability of available culturing methods to demonstrate that online prepared replacement fluid is sterile, French regulations require culturing of 500 mL of replacement fluid via the membrane filtration method and determining endotoxin levels at least once every 3 months to demonstrate no growth of bacteria and an endotoxin concentration <0.05 IU/mL [27]. Swedish regulations require that, if replacement fluid is sampled after the final step of filtration, it shall be sterile [28], but provide no information on how sterility can be demonstrated with an online HDF system.

In the opinion of the EUDIAL group, the current situation is unsatisfactory and the group encourages the development of a harmonized set of norms and regulations. It is also recommended that any dialysis facility providing online HDF develop a database of clinical events and microbiological monitoring results for use in quality control.
Standards for HDF

International standards organizations have issued standards that address HDF. The International Electrotechnical Commission (IEC) has published a standard (IEC 60601-2-16) for equipment [29], and compliance with this standard is required to obtain a CE Mark for equipment used to perform HDF. The second edition of IEC 60601-2-16, which was adopted as EN 60601-2-16:1998, sought to ensure safety by establishing certain performance criteria for the equipment. A third edition of IEC 60601-2-16 was published in 2008. This third edition seeks to ensure safety by requiring manufacturers to perform a risk analysis for their equipment and incorporate means to mitigate identified risks in the design and operation of the equipment. The third edition of IEC 60601-2-16 has yet to be adopted as a European Norm.

The International Organization for Standardization (ISO) has published a series of standards addressing fluids for haemodialysis and related therapies, including HDF. Specifically, ISO 11663:2009, 'Quality of dialysis fluid for haemodialysis and related therapies', requires that replacement fluid used for HDF be sterile and non-pyrogenic [25]. The ISO standard recognizes that it is not possible to test for compliance with this requirement under clinical conditions. Instead, the standards require that online replacement fluid be prepared using a process validated by the manufacturer of the equipment. The ISO standards for fluid quality are being proposed for adoption as European Norms. Until such an adoption occurs, there are no European Norms that address fluid quality for online HDF.

The emphasis on risk analysis and process validation places the onus on individual machine manufacturers to carefully consider all aspects of the operation of the equipment, identify the potential risks to patients of equipment failure, and put in place preventive measures to minimize those risks. The results of those risk analyses are seldom available to the users of the equipment, making it harder for them to fully understand the risks associated with performing HDF and developing strategies designed to mitigate those risks in individual dialysis centres. Furthermore, different manufacturers might assess the risk differently and adopt different protective measures, an example being the different approaches used in currently available equipment to ensure replacement fluid quality.

The EUDIAL group encourages machine manufacturers to be more transparent and make the risk analyses available to users to better allow them to implement appropriate safety measures in their centres.

Bacteria- and endotoxin-retentive filters installed on the inlet dialysis fluid circuit are the key components of the online HDF safety system. Those filters are disinfected after each dialysis treatment according to manufacturer’s recommendations and the repetitive disinfection cycles can alter the membrane characteristics. Therefore, the filters should be replaced periodically to ensure proper operation of the cold sterilization process. The number and type of filter used and the frequency of replacement should comply with the HDF machine manufacturer’s instructions. The integrity of the filters may also be assessed online by regularly pressure testing or use of other validated tests according to the manufacturer’s instructions.

The EUDIAL group encourages machine and filter manufacturers to provide the user with clear and concise protocols for disinfecting, testing and replacing sterilizing filters.

While replacement fluid for convective therapies is required to be sterile and non-pyrogenic, ISO 11663:2009 recommends that the quality of dialysis fluid for high-flux haemodialysis meets the less demanding standard of ultrapure. It is widely understood that high-flux haemodialysis involves filtration and back-filtration within the dialyser that provides a certain amount of uncontrolled convective solute transport. The phenomenon of filtration and back-filtration has led some to question whether or not dialysis fluid used for high-flux haemodialysis should also be sterile and non-pyrogenic. Back-filtration and back-diffusion occur with all membranes, both low-flux and high-flux, with the dialyser membrane acting as a final barrier between the patient and any microbiological contaminants in the dialysis fluid. Clinical experience suggests that the combination of ultrapure dialysis fluid and the barrier provided by the dialysis membrane is safe for back-filtration volumes of up to 8 L per treatment. Not all currently available dialysis membranes have the same ability to limit transfer of microbiological contaminants from dialysis fluid to blood and, at present, it is not known whether the use of ultrapure dialysis fluid would continue to be safe for all, or any, dialysis membranes if back-filtration volumes were increased >8 L by manipulating the dialyser design.

The current ISO standard for replacement fluid used in HDF focuses on bacteria and endotoxin. It is clear that the dialysis fluid used for the online preparation of replacement fluid can be contaminated with other bioactive microbial contaminants, such as peptidoglycans [30] and fragments of bacterial DNA [31]. The extent to which the latter contaminants are removed by the techniques currently used for the online preparation of replacement fluid is unclear, as are the consequences of inadequate removal. Moreover, whether or not patients treated with online HDF are at greater risk from chemical contaminants by virtue of direct infusion of replacement fluid into the blood has received little study. In the opinion of the EUDIAL group, more research is needed in these areas of replacement fluid quality.

Implementation of HDF by dialysis centres

The current regulatory environment emphasizes risk analysis by the device manufacturer as the principal means of ensuring the safe and effective use of a medical device. There is no certainty, however, that the manufacturer’s risk analysis will foresee every conceivable risk that might arise at an individual dialysis centre, leaving some residual risk that must be addressed by the centre through the establishment of policies and procedures that minimize the risks associated with HDF.
at that centre, including those related to replacement fluid quality.

The EUDIAL group recognizes the need for risk assessment and quality management at individual dialysis centres performing online HDF and the need for resources to guide users in setting up an HDF program and in routinely ensuring safe operation of the equipment used to perform convective therapies.

What is not so clear is who should be responsible for providing the resources necessary for establishing an online HDF program. At present, there is no user guideline specifically addressing safe operation of equipment for performing HDF. The IEC has recently published a user guidance based on IEC 60601-2-16 [32]. ISO has published a guideline for users on how to routinely comply with the quality requirements of ISO 11663:2009 as part of its series of standards related to fluid quality [33]. Some recommendations related to HDF are also included in the European Best Practice Guidelines [34]. However, those guidelines are directed at the broad spectrum of dialytic therapies and are not specific for HDF.

The formal risk analysis of an individual centre’s HDF operations does not appear to be common, most likely because there is little to guide users who engage in such an effort for the first time and because a proper risk analysis requires a considerable commitment of time and resources, including the formation of a multidisciplinary group comprising both medical and technical personnel. An appreciation of what is involved in performing a risk analysis related to dialysis can be obtained from the work of Lodi et al. [35], but that analysis is from the point of view of an equipment manufacturer, rather than the operator of a dialysis facility. The use of failure mode and effects analysis (FMEA), a tool long used outside the health care environment, has been described in the setting of dialysis by Bonfant [36]. FMEA is a procedure for identifying potential adverse events associated with a process, such as the delivery of HDF, and classifying them according to their likelihood of occurring and the severity of subsequent patient injury. Analyzing risk in this way might allow a centre to manage the centre-specific risks associated with HDF through their continuous quality improvement programme. At a more fundamental level, the development of a checklist of the basic prerequisites might prevent a centre from prematurely initiating an HDF program. Such a list should cover both technical requirements and staff attitudes. For example, the patients need to have blood accesses capable of routinely delivering a high enough blood flow rate and staff must be committed to using those high blood flow rates to provide a therapy meeting the new definition of HDF presented above.

The EUDIAL group recommends the development of a ‘checklist’ of the basic prerequisites and protocols covering both technical requirements, clinical practices and staff attitudes for reducing specific risks associated with online HDF.

APPENDIX 1: CALCULATION OF SOLUTE CLEARANCES IN HDF

The diffusive component (\(K_D\)) of clearance in HDF can be estimated using Michael’s equations [37] from the blood flow rate (\(Q_b\)), the dialysis fluid flow rate (\(Q_d\)) and the solute-specific dialyser mass transfer-area coefficient (\(K_{CA}\)).

\[
K_D = \frac{1 - e^{-K_{CA}\times(\frac{Q_b}{Q_d} - \frac{Q_b}{Q_d})}}{(1/Q_b) - (1/Q_d) \times e^{-K_{CA}\times(\frac{Q_b}{Q_d} - \frac{Q_b}{Q_d})}}.
\]

For pre-dilution, the actual blood and dialysis fluid flow rates at the inlet ports of the dialysers should be used by correcting for pre-dilution infusion, which will add to the blood flow rate and subtract from the dialysis fluid flow rate. For clearance of urea, \(Q_b\) is considered to be the blood water flow rate, while for other solutes \(Q_b\) is considered to be the plasma water flow rate since only urea diffuses rapidly enough across erythrocyte membranes to allow erythrocyte water to be cleared [23, 38].

The convective component (\(K_C\)) is calculated as follows [39, 40] taking the sieving coefficient, \(S\), into account.

\[
K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S,
\]

where \(Q_f\) is the convection rate.

Finally, the total clearance, \(K_T\), is calculated by adding the diffusive and convective components and taking the DF into account.

\[
K_T = (K_D + K_C) \times DF
\]

APPENDIX 2: MEMBERS OF THE EUDIAL GROUP CONTRIBUTING TO THIS WORK

Bernard Canaud, Montpellier, France (Chair until May 2012)
Peter J. Blankestijn, Utrecht, the Netherlands (Secretary until May 2012, Chair from May 2012)
Michiel Bots, Utrecht, the Netherlands; Adrian Covic, Iasi, Romania; Andrew Davenport, London, UK (Secretary from May 2012); Muriel Grooteman, Amsterdam, the Netherlands; Victor Gura, Beverly Hills, USA; Jörgen Hegbrant, Lund, Sweden; Joerg Hoffmann, Bad Homburg, Germany; Daljit Hothi, London, UK; Colin Hutchison, Birmingham, UK; Fatih Kircelli, Izmir, Turkey; Detlef Krieter, Würzburg, Germany; Martin Kuhlmann, Berlin, Germany; Ingrid Ledebo, Lund, Sweden; Francesco Locatelli, Lecco, Italy; Francisco Maduell, Barcelona, Spain; Alejandro Martin-Malo, Cordoba, Spain; Philippe Nicoud, Sallanches – Courriel, France; Menso Nubé, Bergen, the Netherlands; Ercan Ok, Izmir, Turkey; Luciano Pedrini, Bergamo, Italy; Friedrich Port, Ann Arbor, USA; Alain Ragon, Marseille, France; Antonio Santoro, Bologna, Italy; Ralf Schindler, Berlin, Germany; Ruksana Shroff, London, UK; James Tattersall, Leeds, UK; Raymond Vanholder, Ghent, Belgium; Richard Ward, Louisville, USA.

J. E. Tattersall and R. A. Ward
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Johannes Werzowa¹,
Michael Haidinger¹,
Walter H. Hörl¹,
Julio Pascual²,
Klemens Budde³,
Fu L. Luan⁴,
Akinolu Ojo⁴,
Aiko P. J. de Vries⁵,
Esteban Porrini⁶,
Giovanni Pacini⁷,
Friedrich K. Port⁸,
Adnan Sharif⁹
and Marcus D. Säemann¹

European-New-Onset Diabetes After Transplantation Working Group

Correspondence and offprint requests to: Marcus D. Säemann; E-mail: marcus.saemann@meduniwien.ac.at

Abstract

New-onset diabetes after transplantation (NODAT) is associated with increased risk of allograft failure, cardiovascular disease and mortality, and therefore, jeopardizes the success of renal transplantation. Increased awareness of NODAT and the prediabetic states (impaired fasting glucose and impaired glucose tolerance, IGT) has fostered previous and present recommendations, based on the management of type 2 diabetes mellitus (T2DM). Unfortunately, the idea that NODAT...