

## Expanded haemodialysis: news from the field

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### ABSTRACT

Expanded haemodialysis (HDx) has emerged as a promising solution to improve haemodialysis effectiveness. A medium cut-off membrane allows the removal of a wider range of uraemic toxins. However, little is known about the potential interesting applications of HDx therapy. Feedback from the first routine use of HDx therapy under real-life conditions in European facilities was excellent for priming and rinse back. There was no adverse event after 5191 HDx treatments. Patients suffering from itching, restless legs syndrome, persistent asthenia or malnourishment could benefit from HDx therapy. Moreover, we discuss here the promising applications in which HDx could be valuable (myeloma, rhabdomyolysis or cardiovascular diseases). This enthusiastic message is mitigated by reminding why and how prudence should be taken in the design of future HDx studies.

**Keywords:** chronic haemodialysis, haemodialysis membrane, HDx, medium cut-off, uraemic toxins

### INTRODUCTION

There has been considerable progress in haemodialysis (HD) that has met many of the needs of patients with end-stage renal disease (ESRD). Technical advances in membrane architecture, water treatment and HD monitor-embedded technology have led to a better survival and lower morbidity. Nevertheless, HD remains a heavy burden for the patients as complications from vascular access or from the procedure itself are still major concerns.

Despite the evident progress over recent decades, there are still unmet needs in HD. Many complications, such as pruritus, malnourishment, restless legs, cramps or headaches remain for which treatment is currently limited. In most cases, these complications result from the interaction between the uraemic milieu, the bio-incompatibility of fluids and materials and the unique phenotype of the patient.

Haemodiafiltration (HDF) has emerged as an interesting and promising technology, but its worldwide spread is still delayed by logistical, regulatory and economic issues as it requires investments in an ultrapure water-loop and extra

devices to be added to the HD monitor. These highly regulated technologies also need frequent upkeep to maintain the quality of water that is delivered to the patient. Unfortunately, many centres have decided not to invest in HDF due to the high cost of the required infrastructure. Moreover, the added benefit of HDF requires high convective volumes that are hard to achieve in routine clinical use. This restrains the potential benefits of HDF to patients with a functional vascular access. Nevertheless, to date, this is the only new method to have demonstrated improved patient survival compared with conventional HD.

Expanded haemodialysis (HDx) has emerged as a breakthrough in HD as it can achieve the same removal performance as that achieved by HDF. This is related to the cut-off of the pores combined with a unique internal architecture that allow HDx membranes to achieve interesting removal capacities for middle molecules and large middle molecules in standard HD procedures.

Combining unmet needs and the limitations of HDF availability, the value of HDx therapy in the management of patients with HD in routine care requires evaluation. Based on existing clinical experience and feedback, we describe in the present review what could be the clinical benefits of this method in an HD centre.

### FIRST FEEDBACK OF HDx FROM THE FIELD

During a limited control distribution study after CE marking approval, 18 dialysis units tested HDx therapy from November 2015 to February 2016. A total of 5191 HDx treatments were performed during this period in the participating HD centres in Germany (Uni München, DaVita Düsseldorf, Nephrologisches Zentrum Eckernförde, Uni Rostock, Uni Tübingen, Uni Mainz), Italy (La Peccarella Padre Pio Benevento, La Peccarella SannioMedica Telesse T, Omega Messina, NCDC Decimomannu, Ippocrate DC Agrigento, Ippocrate SMAC Canicatta, Ippocrate Aurora Agrigento) and France (St Côme Compiègne, Parc Monceau Paris, Polyclinique Bordeaux Nord Aquitaine, CHU Poitiers, Hôpital Edouard Herriot Lyon). The main goal of this study was to evaluate HDx therapy in routine

use. Nurses and nephrologists answered questionnaires about everyday use of Theranova<sup>®</sup> in their HD centres. The satisfaction with regards to packaging, priming and the rinsing of the membrane was collected using a three-level scale (full, medium and poor satisfaction, scored, respectively, 1, 2 and 3). Concerning the overall evaluation for priming and rinseback, the mean score among all participating centres was favourable (respectively, 1.2 and 1.3, Baxter data on file). Satisfaction for priming varied among the different type of monitors; the best mean score (1.0) was obtained for Nikkiso DBB05 (Nikkiso, Langenhagen, Germany), and the worst (1.9) for BBraun Dialog (BBraun, Melsungen, Germany). Satisfaction for priming was excellent when the priming protocol was fully respected (volume greater than 500 mL and blood pump speed between 100 and 149 mL/min); except in two centres in Germany, the mean priming satisfaction score of centres was lower (i.e. better) than 1.3. Concerning rinseback, mean satisfaction score ranged from 1.3 for FMC 5008 (Fresenius, Bad Homburg, Germany) and Gambro AK 200 (Gambro, Lund, Sweden) to 1.1 for BBraun Dialog. The mean satisfaction scores for rinseback were lower than 1.6 irrespective of anticoagulant protocol used for the session. The mean satisfaction score for rinseback was <1.8 among all the centres; there were 16 centres with a mean score <1.5. Among the 5191 treatments, only three adverse events were reported with the Theranova<sup>®</sup> membrane over the study period and all occurred in the same centre. These events were itching during the session, an aborted session due to breathlessness and circulatory insufficiency, and cramps. However, the causal relationship with Theranova<sup>®</sup> membrane is debatable.

Despite overall satisfaction with HDx therapy, there was negative feedback for certain aspects. First, some nurses experienced poor de-aeration of the filter in automatic mode and manual interventions were required to successfully prime the membrane. This issue can be avoided using a low blood pump speed during priming. Second, some patients required more anticoagulation using the Theranova<sup>®</sup> membrane, but for all such patients there was an increase in membrane surface area compared with that usually used, and this finding may also be explained by the transparency of the dialyser. Second, despite the warning with a 'no HDF' logo on the cassette, there were a few incidents of HDF use with the Theranova<sup>®</sup> membrane. Nevertheless, no adverse events were reported in these patients. Thus, to avoid these issues in HDF-using centres, strengthened prevention through training of nurses is required and nephrologists should pay particular attention to HD session prescription.

More generally, the study found that HDx therapy was easy to handle in routine use. However, particular precaution is needed to avoid the use of medium-cut off membranes in HDF therapies. In light of these results, the clinical applications of HDx therapy need to be evaluated.

## UNMET NEEDS: IS THERE A PLACE FOR HDx?

### Can the armistice be signed between HD and HDF?

HDF has emerged as a valuable alternative to high-flux HD during the last decade. Despite an interesting postulate,

the evidence of superiority is weak. The ESHOL study found superiority of HDF compared with HD in reducing mortality among patients with HD [1]. Nevertheless, these results were obtained with a convective volume of at least 23 L in a post-filter reinjection. This level of reinjection requires a perfect conjunction of HD parameters to be obtained in routine practice; the vascular access needs to deliver sufficient blood flow, the hydraulic permeability of the dialysis membrane needs to be adapted for high convective volumes and the session to have few interruptions. However, most of the HDF-ready centres deal with frail and elderly patients with catheters as vascular access, and the target volume is difficult to reach.

HDx can be a valuable option for patients who are not reaching systematically the target volume in HDF because of their vascular access. These patients could thus benefit from a treatment as effective as HDF for toxin removal [2]. Moreover, patients treated with HDF could also benefit from HDx whenever HDF needs to be suspended (dialysis without anticoagulation, one-needle puncture, suspension of HDF for safety reasons).

### Pruritus, restless legs syndrome and asthenia

Pruritus is one of the most tenacious and disabling symptoms in patients with HD [3]; most suffer from a *sine materia* pruritus that resists intervention during HD, and this remains an unsolvable problem [4]. Pruritus among patients with HD results from an interaction of many factors: accumulation of large uraemic toxins, high phosphorus levels and biocompatibility of the HD procedure [5]. With a potential for better removal of large middle molecules, HDx may improve pruritus in some patients with HD. Nevertheless, because of the wide range of causes leading to pruritus, this potential benefit could remain insufficient.

**Case report 1.** We describe here the case of a 50-year-old patient who had received HD for 5 years. He was healthy and had nocturnal HD in our centre. He suffered from a tenacious pruritus that would start during the HD session and last until a few hours before the following session. Many interventions were tried to avoid itching, such as membrane switch and various medications. None of these was effective; intravenous antihistamine therapy before each session mitigated slightly the pruritus. HDx treatment was initiated and resulted in a significant reduction of the symptoms and the discontinuation of the intravenous antihistamine medication.

Restless legs syndrome (RLS) is another disturbing symptom related to HD. Pathogenesis is unclear but uraemic toxicity and ESRD-induced disorders seem to play an important role as its occurrence is significantly lowered by transplantation [6]. Many treatments have been tested but their effectiveness remains partial [7]. HDx could be an interesting option for these patients, but as RLS remains poorly understood it is not possible to predict its effects.

**Case report 2.** This describes an 88-year-old patient who was suffering from a persistent RLS during and after each HD session despite a maximal neurologist-guided drug therapy. HDx

was started and led to slight lowering of the doses of drugs and the RLS intensity.

Among all the burdens of routine HD, the length of time recovery after a session was frequently reported by patients to be the most disabling. This persistent asthenia heavily impacted the quality of life of patients with HD, rendering their free-from-dialysis time difficult to enjoy. Based on our observations, HDx seems to shorten this in some patients. Nevertheless, rendering the effects of HDx is hard to extrapolate in all the HD patients.

**Case report 3.** We report here the cases of two patients receiving HDF treatment but suffering from a persistent and disabling asthenia after the session. Despite many interventions, such as isonatric dialysis, tight adaptation of their dry weight or prescription cleaning, the asthenia remained. HDx was tried in these two patients and dramatically improved the recovery after the HD session.

### Dietary intake and malnourishment

Albumin leak with HDx has been raised as a potential limitation for its widespread use, especially among malnourished patients. Nevertheless, many patients receiving HDx therapy in our centre reported a better appetite after switching to this therapy. Many uraemic compounds can be linked to a reduced appetite in HD. For instance, leptin, pro-inflammatory cytokines such as IL-6, or more recently obestatin and acyl-ghrelin, have been associated with diminished appetite among patients with HD [8, 9], and a wide range of accumulated middle molecules inhibited the ingestive behaviour in rats [10]. Thus, a better appetite associated with HDx may be in relation to more effective removal of these molecules when a medium cut-off membrane is used. Further studies are needed to explore the effect of HDx on the appetite and nutritional status of patients with HD. Moreover, albumin leak could be considered as positive as it could enhance protein-bound uraemic toxin removal and clearance of toxic modified forms of albumin [11, 12].

### Myeloma and rhabdomyolysis

Recent data suggest that free light chains (FLC) removal in patients suffering from cast nephropathy could be an interesting therapy to improve renal injury and mortality. The use of a high cut-off (HCO) membrane was associated with a lower rate of HD independence at 6 and 12 months [13]. However, these membranes were expensive and cumbersome. Adsorptive membrane, such as polymethylmethacrylate-based BK-2.1 membrane, was also associated with better outcomes among patients with myeloma and cast nephropathy [14]. However, despite a lower cost with respect to HCO membranes, this membrane remains expensive. As HDx improved the clearance of FLC, it could be an interesting and cost-effective therapy among patients with a cast nephropathy. Thus, further studies need to investigate the potential effects of HDx on FLC removal in multiple myeloma.

Similarly, the clearance of myoglobin during acute kidney injury (AKI) due to rhabdomyolysis highlighted the potential value of HCO membranes [15, 16]. However, despite this theoretical advantage, HCO membrane still suffers from a high

albumin and protein leakage and a prohibitive cost. HDx therapy could be an interesting option to improve myoglobin clearance in rhabdomyolysis-related AKI, and further studies need to be conducted to shed light on its potential benefits (Figure 1).

### Inflammation and cardiovascular diseases

Despite continuous improvements in HD procedures, cardiovascular mortality and morbidity remain a concerning issue among patients with HD. Many intertwined factors lead to this higher risk, including accumulation of uraemic toxins, anaemia, phospho-calcic disorders, inflammation and bio-incompatibility. HDF emerged as an interesting approach to enhance removal of middle molecules, whose benefits were expected on cardiovascular morbidity. Unfortunately, in the ESHOL study, cardiovascular mortality was not impacted using HDF (with the exception of stroke-related death) [1]. In addition to HDF-removed toxins, larger ones might be removed by HDx therapy, and this could tip the balance; medium cut-off membranes could enhance the removal of middle molecules, such as FLC, pentraxin 3 or chitinase-3-like protein 1, which are involved in cardiovascular diseases among patients with HD [17]. Furthermore, improvement of toxin removal could also improve anaemia and calcium-phosphate balance. These effects put together could have a positive effect on cardiovascular morbidity (Figure 1).

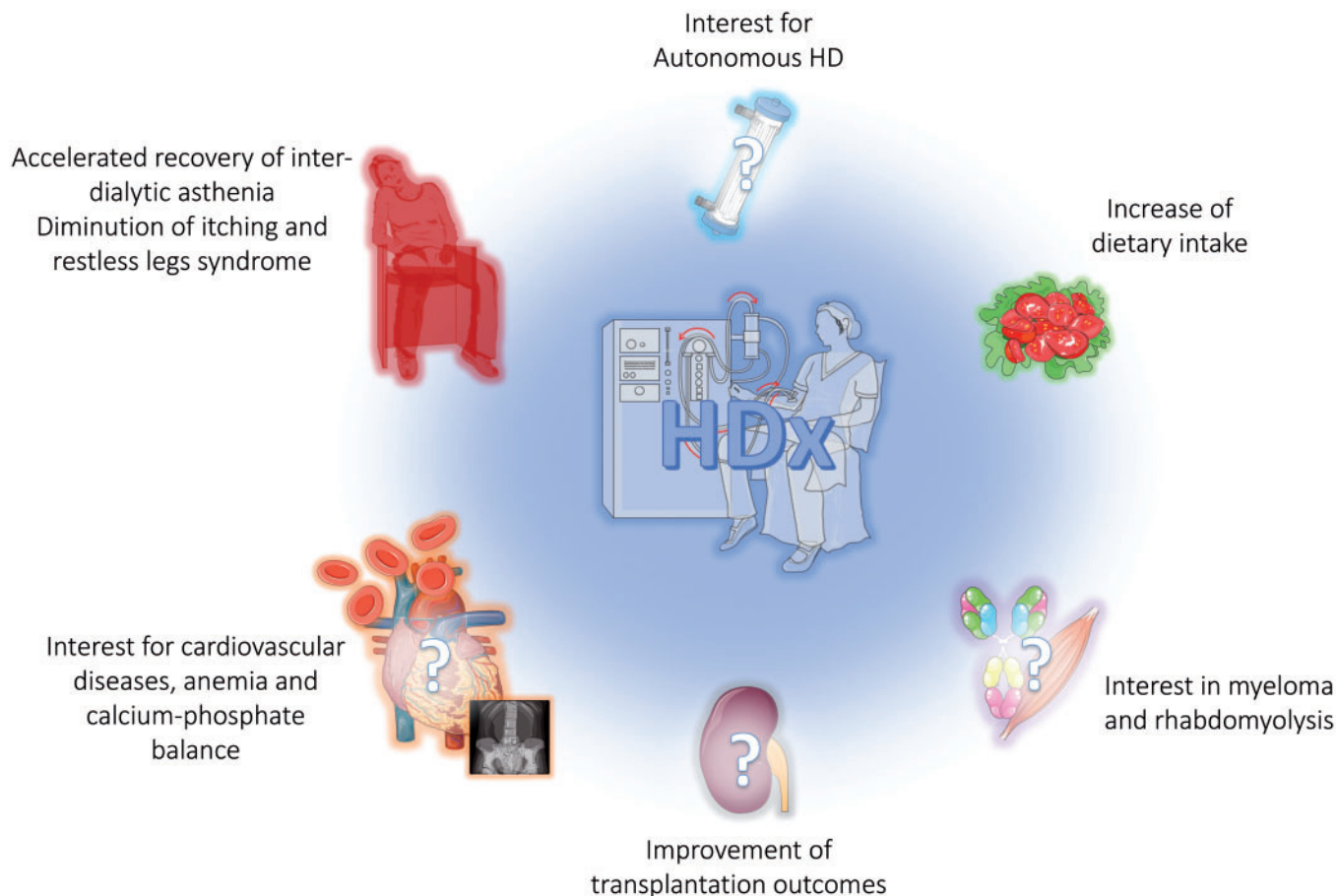
### Self-care units and home HD

Autonomous dialysis is dedicated to healthy and young patients because it is suited to their lifestyle, and therefore is associated with better survival than in-centre HD [18]. Due to logistical reasons, self-care and home dialysis cannot offer HDF and despite a better survival because of younger age and healthier condition, long-term development of vascular calcifications and cardiovascular morbidity remain high. Moreover, such patients are often on transplant waiting lists and better dialysis could improve transplantation outcomes. HDx could be a promising solution for these patients and needs to be evaluated for long-term outcomes (Figure 1).

## HDx UNSOLVED CHALLENGES

First, despite the potential applications of HDx, future studies need to take into account the complexity of patients with HD. Little is really known about the real pathogenesis of almost all the symptoms experienced by patients with HD. For instance, the improvement of asthenia or dietary intake observed in our patients treated by HDx cannot be fully explained by conventional evaluation of dialysis performance. Consequently, it remains difficult to understand positive or negative results arising from dialysis studies. The use of sensitive and exhaustive techniques, such as proteomics, could be of interest to identify the spectrum of toxins that are involved. This would lead to a better understanding of the uraemic milieu, which is urgently required to evaluate the benefits of HDx.

Second, the benefit of an enhanced toxin removal could be mitigated by the leak of important solutes. HDx may suffer from the same limitations as HDF, and efforts need to be made to describe the real effect of dialysis on non-toxic solutes. Again, high sensitivity of the proteomic approach could be



**FIGURE 1:** Potential development paths and clinical applications of HDx therapy. Thanks to an overall increase in toxin removal, the impact of HDx on cardiovascular diseases, anaemia and calcium-phosphate balance needs to be tested. HDx could be also beneficial for healthy patients receiving HD via autonomous techniques. Then, its effects on long-term outcomes such as success of transplantation or occurrence of cardiovascular diseases need to be investigated. Among patients who underwent HDx therapy in various clinical situations, most reported an increase in appetite, which could be interesting in malnourished patients. We saw a potential interest in patients with pruritus or RLS. Moreover, HDx therapy seemed to reduce the recovery time of inter-dialytic asthenia. Nevertheless, interventional studies are required to confirm or overturn these statements.

valuable to understand the balance between the solutes removed that are beneficial and those that are toxic.

Third, the case of protein-bound toxins (PBTs) and very large uraemic toxins is not solved with HDx. However, enhancement of removal of a wide spectrum of uraemic toxins could already be beneficial for patients with HD. Furthermore, an acceptable but greater albumin leak could improve the removal of some PBTs. Large uraemic toxins could be targeted in selected patients with emerging techniques such as rheopheresis, in particular in situations such as peripheral artery disease or calciphylaxis.

## CONCLUSION

HDx could be an interesting solution in several clinical situations. The first feedback from the battlefield is promising but the evidence is still incomplete. Future studies should focus on the potential benefits for pruritus, asthenia or cardiovascular disease. Simultaneously, we urgently need to better understand the removal pattern of our devices (membrane and dialysate) evaluated through sensitive technologies such as proteomics.

## IN BRIEF: WHEN SHOULD HD<sub>x</sub> BE USED IN CLINICAL PRACTICE?

When?	Why?	Level of proof
<b>When HDF is not possible or valuable</b>		
<ul style="list-style-type: none"> <li>• Difficulty to achieve the targeted post-reinjection volume</li> <li>• Logistical issues (single-needle puncture and other temporary vascular access malfunction, water loop maintenance ...)</li> </ul>	HDx may have the same effectiveness of removal of middle molecules as HDF	No proof Real benefits are unknown, and further studies are needed
<b>Pruritus and RLS</b>		
<ul style="list-style-type: none"> <li>• After the failure of all the routinely used medical interventions</li> <li>• After a well-conducted work-up for secondary causes</li> </ul>	HDx could improve the removal of larger uraemic toxins such as FLC, myoglobin	No proof Case report Real benefits are unknown, and further studies are needed
<b>Asthenia and timeliness of recovery after a HD session</b>		
<ul style="list-style-type: none"> <li>• Based on patient's grievances</li> </ul>	Better biocompatibility?	No proof Case report

*Continued*



## Continued

When?	Why?	Level of proof
	Role of large middle molecules?	Real benefits are unknown, and further studies are needed
<b>Cardiovascular and transplantation outcomes</b>		
• Not defined yet	Better removal of large middle molecules?	No proof Real benefits are unknown, and further studies are needed
<b>Self-care haemodialysis</b>		
• Whenever HDx is medically appropriated	Better removal of uraemic toxins such as high flux HD?	No proof Real benefits are unknown, and further studies are needed

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## CONFLICT OF INTEREST STATEMENT

L.J. performed occasional lectures for Baxter. N.F. and L.J. received a grant Investigator Initiated Research for the evaluation of HDx in clinical practice.

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