

EXPANDED DIALYSIS (HDx): INTEGRATING BIOPHYSICAL INNOVATION AND CLINICAL EVIDENCE WITHIN THE EVOLVING PARADIGM OF EXTRACORPOREAL PURIFICATION

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Article Received on 30 Jan. 2026,
Article Revised on 20 Feb. 2026,
Article Published on 01 March 2026,

<https://doi.org/10.5281/zenodo.18802276>

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How to cite this Article: Duranti E.*. (2026). Expanded Dialysis (Hdx): Integrating Biophysical Innovation and Clinical Evidence Within The Evolving Paradigm Of Extracorporeal Purification. World Journal of Pharmaceutical Research, 15(5), 849-853. This work is licensed under Creative Commons Attribution 4.0 International license.

ABSTRACT

Expanded dialysis (HDx) is an emerging extracorporeal purification modality enabled by medium cut-off (MCO) membranes designed to enhance the removal of middle and large middle molecules. Positioned between high-flux hemodialysis (HF-HD) and online hemodiafiltration (HDF), HDx aims to broaden the spectrum of uremic toxin clearance while maintaining operational simplicity. This manuscript provides an integrated analysis of the biophysical rationale underlying MCO membranes, synthesizes current evidence on HDx performance, and evaluates its comparative role among contemporary renal replacement therapies. Although HDx demonstrates promising solute removal capabilities and practical advantages, long-term outcome data remain limited,

underscoring the need for further investigation.

INTRODUCTION

The evolution of dialysis adequacy has progressively shifted from a narrow focus on small-solute clearance toward a more comprehensive understanding of uremic toxicity. Middle molecules—ranging from β 2-microglobulin to free light chains and inflammatory cytokines—are increasingly recognized as key contributors to chronic inflammation, cardiovascular dysfunction, and dialysis-related morbidity. Conventional hemodialysis (HD), particularly in its low-flux form, is poorly equipped to remove these solutes, while high-flux HD offers only incremental improvements.

Online hemodiafiltration (HDF) was developed to address these limitations by combining diffusion and convection, thereby enhancing middle-molecule clearance. However, HDF requires high blood flow rates, large convective volumes, and sterile substitution fluid, limiting its feasibility in many clinical settings.

Expanded dialysis (HDx) emerged as a response to these constraints, leveraging medium cut-off (MCO) membranes to expand the solute removal profile without the infrastructural demands of HDF. HDx thus represents a conceptual bridge between diffusion-based and convection-enhanced therapies, offering a potentially scalable solution to the challenge of middle-molecule clearance.

METHODS

This manuscript synthesizes peer-reviewed literature on HDx, MCO membrane technology, and comparative extracorporeal purification techniques. Sources include nephrology journals, membrane science publications, and systematic reviews. The analysis focuses on biophysical principles, solute removal profiles, operational characteristics, and reported clinical outcomes. No patient-level data were collected, and no clinical recommendations are provided.

RESULTS

Biophysical Foundations of Medium Cut-Off (MCO) Membranes

The defining innovation of HDx lies in the architecture of MCO membranes. Compared with high-flux membranes, MCO membranes exhibit larger and more uniformly distributed pores, enabling selective permeability to solutes up to approximately 45 kDa. This pore structure produces a steep sieving curve, allowing efficient removal of middle molecules while sharply limiting albumin passage. Beyond pore size, MCO membranes incorporate reduced fiber diameter, which increases internal filtration and enhances convective transport within the dialyzer. This intrinsic convection—generated without external substitution fluid—distinguishes HDx from both conventional HD and HDF. As a result, HDx achieves a solute removal profile that extends beyond the capabilities of diffusion-based therapies while avoiding the operational complexity of convective modalities. The solute spectrum affected by HDx includes β 2-microglobulin, myoglobin, κ and λ free light chains, and selected inflammatory mediators. Albumin loss, although measurable, remains minimal and stabilizes

after the initial treatments.

Comparison with Conventional Hemodialysis

The enhanced permeability of MCO membranes translates into clinically relevant differences when HDx is compared with conventional HD. Low-flux HD is limited to small-solute clearance, while high-flux HD provides only modest improvements in middle-molecule removal. HDx, by contrast, significantly increases the clearance of solutes in the 15–45 kDa range, addressing a key gap in the performance of diffusion-based therapies. Preliminary clinical observations suggest that this expanded solute removal may reduce inflammatory burden and improve patient-reported symptoms such as fatigue and pruritus. Some studies also report reductions in hospitalization rates, although these findings remain exploratory. Importantly, HDx achieves these benefits without requiring changes in vascular access, blood flow rates, or dialysis infrastructure, making it accessible to a broader patient population.

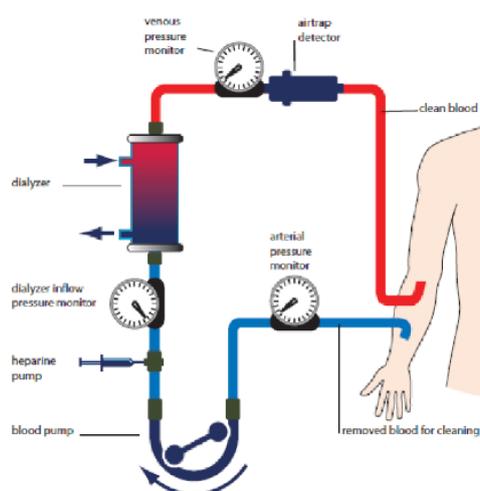
Comparison with Online Hemodiafiltration (HDF)

The comparison between HDx and HDF is particularly relevant, as both modalities target the removal of middle molecules. HDF achieves this through combined diffusion and convection, but its performance depends on achieving high convective volumes and maintaining sterile substitution fluid. HDx, by contrast, relies on membrane-driven internal convection, eliminating the need for external substitution. Evidence indicates that HDx approximates HDF for many middle molecules, particularly in the 15–30 kDa range. HDF remains superior for very large solutes (>50 kDa), but HDx offers more consistent performance in patients with limited vascular access or low blood flow rates. Operationally, HDx reduces technical complexity and resource consumption, and avoids risks associated with substitution fluid contamination. Clinical outcomes reported to date show no significant differences in all-cause mortality or hospitalization rates between HDx and HDF. HDx may offer improved tolerability in frail or elderly patients, although this requires further study.

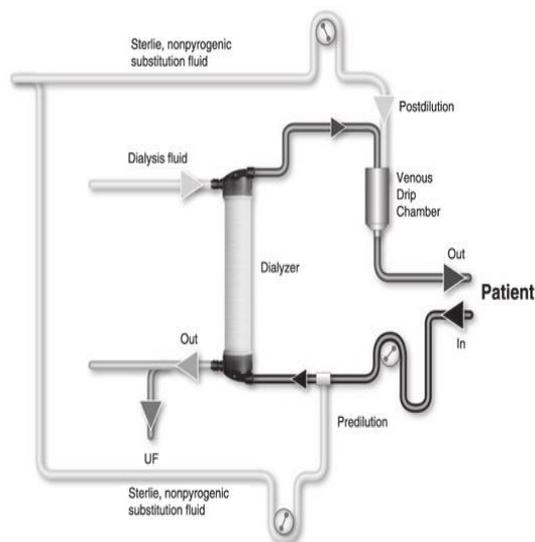
DISCUSSION

The emergence of HDx reflects a broader shift in the conceptualization of dialysis adequacy. By integrating biophysical innovation with practical feasibility, HDx addresses the longstanding challenge of middle-molecule clearance without the infrastructural demands of HDF. The MCO membrane represents a meaningful technological advance, enabling a solute removal profile that bridges the gap between diffusion-based and convection-enhanced

therapies. The clinical implications of this expanded clearance remain an area of active investigation. Early studies suggest improvements in inflammatory markers and symptom burden, but definitive evidence regarding survival, cardiovascular outcomes, and quality of life is lacking. The modest albumin loss associated with MCO membranes warrants monitoring, particularly in malnourished patients, but current data suggest that this effect is limited and stabilizes over time. HDx may be particularly valuable in settings where HDF is constrained by resource limitations or vascular access challenges. Its operational simplicity and scalability position it as a potentially transformative modality within renal replacement therapy. However, its long-term role will depend on forthcoming randomized controlled trials and cost-effectiveness analyses.



Standard and expanded hemodialysis.



On line HDF.

CONCLUSION

Expanded dialysis (HDx) represents a promising advancement in extracorporeal purification, combining enhanced solute removal with operational simplicity. While early evidence supports its efficacy and safety, long-term clinical outcomes remain insufficiently characterized. HDx may ultimately serve as a scalable and effective alternative to HDF, particularly in resource-limited settings or in patients unable to achieve high convective volumes. Continued research is essential to define its place within the evolving paradigm of dialysis adequacy.

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