HDx THERAPY
Enabled by MCO THERANOVA dialyzer

Discover how HDx Therapy Expanded Dialysis may make A WORLD OF DIFFERENCE for patients, clinicians & healthcare systems

A WORLD OF DIFFERENCE
ONE CHANGE CAN TRANSFORM HD TREATMENT

Expanded Hemodialysis is a dialysis treatment where diffusion and convection are conveniently combined along a hollow fiber dialyzer equipped with a High Retention Onset (HRO) membrane\(^1\) – defined as medium cut-off, with no special requirement of a particular hardware, preparation of replacement fluid, or additional nursing skill, compared to the necessary ones required to perform conventional hemodialysis (HD) in standard mode.\(^2\)
WHAT A DIFFERENCE AN X MAKES

01
POSITIVE OUTCOMES

HDx therapy may reduce the burdens of hemodialysis therapy.3,4
Read more

02
REMOVING LARGE-MIDDLE MOLECULES

The efficient removal of large-middle molecules may reduce the risk of inflammation, toxicity, and organ damage.2
Read more

03
UNIQUE MEMBRANE

A different membrane design allows for a filtration profile that is close to that of the natural kidney.1
Read more

04
PROVEN RESULTS

HDx therapy’s large and growing evidence-base.47
Read more
HOW CAN HDx THERAPY OPEN UP A WHOLE WORLD IN HD THERAPY?

ANSWERING CRITICAL PATIENT NEEDS
Patient-reported symptom burden has a significant impact on patient quality of life.7

PATIENT-REPORTED OUTCOMES

UREMIC PRURITUS
HDx therapy may significantly lower uremic pruritus, a predictor of poor sleep, in HD patients.8
Read more

RESTLESS LEGS SYNDROME
HDx therapy may reduce the occurrence of restless legs syndrome (RLS), common in HD patients.6,9
Read more

RECOVERY TIME
HDx therapy may significantly reduce recovery time, positively associated with hospitalization and mortality, after dialysis treatments.10,11,12
Read more
CREATING POSITIVE HEALTHCARE OUTCOMES

**HOSPITALIZATION RATES**

HDx therapy may reduce hospitalization rates.\(^3,31\)

Read more

**MEDICATION USAGE**

HDx therapy has been associated with decreases in medication usage.\(^{15,16,17}\)

Read more

**COST OF CARE**

HDx therapy may reduce pressures on healthcare systems and total cost of care.\(^{3,13,14,16,31}\)

Read more
A BETTER NIGHT’S SLEEP CAN MAKE A WORLD OF DIFFERENCE

UREMIC PRURITUS
Daily bouts of itching that tend to worsen at night and may prevent sleep.8

IMPLICATIONS FOR PATIENTS18
>42% of HD patient suffer from moderate to severe pruritus

HDx THERAPY MAY IMPROVE PATIENT-REPORTED PRURITUS
One randomized clinical study found HDx therapy to deliver statistically significant improvements in key aspects of patient-reported uremic pruritus compared to conventional HD.8

MOLECULE ASSOCIATION
IL-6 is a pleiotropic cytokine that regulates the immune and inflammatory response and affects hematopoiesis, metabolism and organ development.19 IL-6 is commonly observed in Chronic Kidney Disease (CKD) patients and markedly increased in HD patients with uremic pruritus20, which is caused by increased generation resulting from oxidative stress, chronic inflammation and fluid overload.19

INTERLEUKIN-6 (IL-6)
[25 kDa]

THERANOVA dialyzers are indicated for treatment of chronic and acute renal failure by Hemodialysis.
Do not use in Hemodiafiltration or Hemofiltration mode or isolated Ultrafiltration.
RESTLESS LEGS SYNDROME (RLS)
A neurological condition characterized by an irresistible urge to move the limbs accompanied by uncomfortable sensations.23

HDx THERAPY MAY PREVENT DISCOMFORT
A large observational study in prevalent HD patients found an approximate 55% reduction in the number of patients meeting RLS criteria after 12 months on HDx therapy.9

MOLECULE ASSOCIATION
A1M is a microglobulin, belonging to a protein family. It is described as a circulating “waste bin” which continuously removes free radicals and oxidizing agents, particularly heme, from the tissues. It is subsequently transported to the kidneys, where it is broken down. A1M’s urinary excretion is associated with faster Chronic Kidney Disease (CKD) progression and high mortality as well as restless syndrome.25

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**HDx THERAPY CAN HELP PATIENTS ENJOY MORE OF LIFE**

**RECOVERY TIME**
The time in minutes that it takes a patient to recover after a hemodialysis session.\(^{28}\)

**FASTER RECOVERY WITH HDx THERAPY**
HDx therapy may significantly reduce dialysis recovery time and improve perceived fatigue level.\(^{11}\)

**MOLECULE ASSOCIATION**
IL-6 is a pleiotropic cytokine that regulates the immune and inflammatory response and affects hematopoiesis, metabolism and organ development.\(^{10}\) In people on chronic HD, fatigue appears associated with the serum level of interleukin, supporting that inflammation plays a role.\(^{30}\)

**IMPLICATIONS FOR PATIENTS**

68% of patients report >2 hours to recover.\(^{12}\)

- Poor quality of life scores\(^{12}\)
- Activities of daily living\(^{12}\)
- Dialysis-related stress\(^{12}\)
- Associated with hospitalization\(^{12}\)
- Higher mortality risk\(^{12,29}\)

**INTERLEUKIN-6 (IL-6)**

[25 kDa]
HOSPITALIZATION RATES
Research reveals that HDx therapy is likely to significantly lower hospitalization rates.3,31

REDUCTION IN HOSPITALIZATION EVENTS
A randomized controlled trial of 171 prevalent HD patients showed a 45% lower all-cause hospitalization rate over 12 months with HDx therapy compared to the control high-flux HD arm.31

<table>
<thead>
<tr>
<th>Health resource utilization</th>
<th>THERANOVA dialyzer (n = 86)</th>
<th>high-flux HD (n = 85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization events</td>
<td>18</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Total hospital days</td>
<td>74</td>
<td>139</td>
<td>-</td>
</tr>
<tr>
<td>Total patient-years</td>
<td>32.4</td>
<td>30.5</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalization rate per PY (SE)</td>
<td>0.56 (0.13)</td>
<td>1.02 (0.12)</td>
<td>0.042</td>
</tr>
<tr>
<td>Hospital length of stay (mean days [SE])</td>
<td>4.11 (0.57)</td>
<td>4.63 (0.58)</td>
<td>0.406</td>
</tr>
</tbody>
</table>

* One high-flux HD randomized participant did not complete baseline.
WHERE LESS CAN BE MORE

FEWER MEDICATIONS
HDX therapy has the potential to reduce the need for medication for conditions related to uremic toxins such as anemia and inflammation.16

LOWER DOSES
Research has shown that patients under HDX therapy may have a decreased Erythropoietin Resistance Index (ERI). Also, these patients may need a lower ESA dose over time without a concomitant reduction in hemoglobin level, when compared with patients under High-Flux HD and HDF therapies.14,15,16,17

LOWER USE
Patients receiving HDX therapy may have a decreased use of supportive medications such as iron, insulin and antihypertensive medications vs those treated with conventional high-flux HD.16

MEDICATION UTILIZATION PER PATIENT YEAR

<table>
<thead>
<tr>
<th></th>
<th>ESA - INTERNATIONAL UNITS</th>
<th>Percent change</th>
<th>IRON - MILIGRAMS</th>
<th>Percent change</th>
<th>INSULIN - INTERNATIONAL UNITS</th>
<th>Percent change</th>
<th>HYPERTENSION MEDICATIONS - TABLETS</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD HF mean (95% CI)</td>
<td>181318</td>
<td></td>
<td>HD HF mean (95% CI)</td>
<td>959</td>
<td>HD HF mean (95% CI)</td>
<td>5383</td>
<td>HD HF mean (95% CI)</td>
<td>1188</td>
</tr>
<tr>
<td>N = 81</td>
<td></td>
<td></td>
<td>N = 81</td>
<td>759&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 81</td>
<td>3434&lt;sup&gt;a&lt;/sup&gt;</td>
<td>N = 81</td>
<td>731&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDX therapy mean</td>
<td>168124&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-7%</td>
<td>HDX therapy mean</td>
<td>759&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HDX therapy mean</td>
<td>3434&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HDX therapy mean</td>
<td>731&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI) N = 81</td>
<td></td>
<td></td>
<td>(95% CI) N = 81</td>
<td></td>
<td>(95% CI) N = 81</td>
<td></td>
<td>(95% CI) N = 81</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Statistically significant difference found in corresponding univariate GLM analysis of outcome on HDX therapy. All had a P-value <0.01.

Adapted after Ariza: An initial evaluation of HDX therapy on hospitalizations, drug utilization, costs, and patient utility in Colombia.16

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CHAPTER 01 – POSITIVE OUTCOMES
ECONOMIC OUTCOMES

BETTER CARE CAN LOWER EXPENSES

FREEING UP RESOURCES
Recently published research has shown promising signs that HDx therapy has the potential to positively impact the burden on healthcare systems.14,16,31

REDUCING THE COST OF CARE
HDx therapy may offer health care systems the opportunity to reduce the total cost of care, primarily driven by potential reduction of cardiovascular events, infections, medication usage, all-cause hospitalizations, hospitalization rate and length of stay.3,13,14,16,17,31

ECONOMIC OUTCOMES

HOSPITALIZATION EVENTS31
Probabilistic analysis determined that THERANOVA dialyzer was associated with lower costs in 96% of the 10,000 simulations.

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit cost (USD)</th>
<th>THERANOVA high-flux HD</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause Hospitalization</td>
<td>$2518 per day</td>
<td>$5756</td>
<td>$11,853</td>
</tr>
<tr>
<td>Dialyzer cost</td>
<td>$15.00 ea/$6.50 ea</td>
<td>$2340</td>
<td>$1014</td>
</tr>
<tr>
<td>Cumulative</td>
<td>$8096</td>
<td>$12,867</td>
<td>-$4771</td>
</tr>
</tbody>
</table>

a All-cause hospitalization was defined as any serious adverse event that resulted in hospitalization
b THERANOVA dialyzer was priced at $15 in the United States and high-flux dialyzer was assumed to cost $6.50

Adapted after Blackowicz: Economic evaluation of expanded hemodialysis with the THERANOVA 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States.31

MEDICATION UTILIZATION16

<table>
<thead>
<tr>
<th>ESA*</th>
<th>IRON</th>
<th>INSULIN</th>
<th>ANTIHYPERTENSIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7.27%</td>
<td>-20.83%</td>
<td>-32.64%</td>
<td>-30.18%</td>
</tr>
</tbody>
</table>

*Erythropoietin stimulating agents

Adapted after Ariza: An initial evaluation of HDx therapy on hospitalizations, drug utilization, costs, and patient utility in Colombia.14

CARDIOVASCULAR EVENTS
A retrospective, observational study found that HDx therapy compared to HD-HF is likely to significantly lower nonfatal cardiovascular events by 35%.3
IS IT POSSIBLE TO GET CLOSER TO THE NATURAL KIDNEY?

USING A MEMBRANE WITH EXPANDED PERMEABILITY AND SELECTIVITY

Until now, current dialytic therapies have had limited capability in removing large-middle molecule uremic toxins. Large-middle molecules can contribute to inflammation, cardiovascular events and other dialysis-related co-morbidities.

<table>
<thead>
<tr>
<th>Uremic Toxin Classes by molecular weight (Daltons)</th>
<th>Evolution of dialysis therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (60 Da)</td>
<td>Small Molecules (&lt;0.5 kDa)</td>
</tr>
<tr>
<td>Phosphate (96 Da)</td>
<td>Small-middle Molecules (0.5-15 kDa)</td>
</tr>
<tr>
<td>PTH (9.5 kDa)</td>
<td>Medium-middle Molecules (&gt;15-25 kDa)</td>
</tr>
<tr>
<td>Beta₂ microglobulin (12 kDa)</td>
<td></td>
</tr>
<tr>
<td>Myoglobin (17 kDa)</td>
<td></td>
</tr>
<tr>
<td>Kappa free-light-chains (23 kDa)</td>
<td>Large-middle Molecules (&gt;25-58 kDa)</td>
</tr>
<tr>
<td>Complement factor D (24 kDa)</td>
<td></td>
</tr>
<tr>
<td>Interleukin-6 (25 kDa)</td>
<td></td>
</tr>
<tr>
<td>TNF-alpha (26 kDa)</td>
<td></td>
</tr>
<tr>
<td>FGF-23 (32 kDa)</td>
<td></td>
</tr>
<tr>
<td>Alpha 1 microglobulin (33 kDa)</td>
<td></td>
</tr>
<tr>
<td>YKL-40 (40 kDa)</td>
<td></td>
</tr>
<tr>
<td>Lambda free-light-chains (45 kDa)</td>
<td></td>
</tr>
<tr>
<td>Albumin (67 kDa)</td>
<td>Large Molecules (&gt;58 kDa)</td>
</tr>
</tbody>
</table>

GOING BEYOND UREA AND BETA₂ MICROGLOBULIN

The clinical symptoms and conditions associated with uremic toxins differ according to their molecular weight, with the large-middle molecules being linked to several clinical effects.  

<table>
<thead>
<tr>
<th>Large-middle molecules</th>
<th>Relevant clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-alpha (26 kDa)</td>
<td>• Sepsis³³</td>
</tr>
<tr>
<td></td>
<td>• Chronic Inflammation³³</td>
</tr>
<tr>
<td></td>
<td>• Cardiovascular Disease³⁴</td>
</tr>
<tr>
<td></td>
<td>• Protein-energy wasting in CKD³⁴</td>
</tr>
<tr>
<td>FGF-23 (32 kDa)</td>
<td>• Secondary Immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>• Cardiovascular Disease³⁴</td>
</tr>
<tr>
<td>Alpha 1 microglobulin  (33 kDa)</td>
<td>• Restless Legs Syndrome (RLS)³⁵,³⁶</td>
</tr>
<tr>
<td>YKL-40 (40 kDa)</td>
<td>• Inflammation³⁷</td>
</tr>
<tr>
<td>Lambda free-light-chains (45 kDa)</td>
<td>• Chronic Inflammation</td>
</tr>
<tr>
<td></td>
<td>• Secondary Immunodeficiency³⁴</td>
</tr>
</tbody>
</table>

Adapted after Wolley: Exploring the Clinical Relevance of Providing Increased Removal of Large Middle Molecules.⁴⁹

EXPERTISE IN MEMBRANE MANUFACTURING: MCO MEMBRANE TO PERFORM HDx THERAPY

Membrane formation technologies have enabled precise control of pore size distribution which results in a narrow pore size distribution with a significant number of pores that are large enough for middle molecules to penetrate, but small enough for albumin to not pass through.³⁸,³⁹

Number of pores

Adapted after Wolley: Exploring the Clinical Relevance of Providing Increased Removal of Large Middle Molecules.⁴⁹
HDx THERAPY: DIFFUSION AND CONVECTION COMBINED INSIDE A DIALYZER

A HEMODIALYZER WITH AN EXPANDED SOLUTE REMOVAL PROFILE

HDx therapy is a dialysis treatment where diffusion and convection are conveniently combined inside a hollow fiber dialyzer. MCO THERANOVA membrane provides the patented Molecular Weight Retention Onset (MWRO) and Molecular Weigh Cut-Off (MWCO) range to target the efficient removal of large-middle molecules. This results in a sieving curve closer to the natural kidney.

A NEW CLASS OF DIALYZERS

THERANOVA dialyzer is the only device falling in the classification of Hemodialyzers with an expanded solute removal profile, as defined by the US Food and Drug Administration (FDA). THERANOVA dialyzer also falls into the new class of medium cut-off dialyzers, based on the in vitro and clinical use methodology published by the Chinese Nephrology & Blood Purification Innovation Alliance.
FOUR THERAPEUTIC PRINCIPLES THAT MAKE HDx THERAPY POSSIBLE

The clearance profile provided by HDx therapy enabled by MCO THERANOVA dialyzer is made possible using regular HD workflow and infrastructure thanks to the combination of 4 principles in a single dialyzer device design.

- **A UNIQUE MEMBRANE**
  - The membrane structure is asymmetric and can be seen in cross section as three distinct layers:
    - A finger-like macro-porous outer layer
    - A very thin inner layer (skin)
    - A sponge-like intermediate layer

1. **HIGH PERMEABILITY TO LARGE-MIDDLE MOLECULES**
   - Membrane with increased nominal pore size that provides significantly higher permeability for large-middle molecules when compared to high-flux membranes used for conventional HD and HDF.

2. **EFFECTIVE SELECTIVITY BY SIZE EXCLUSION**
   - A unique asymmetric 3-layer structure controls the distribution of pore sizes for a stable separation profile.

3. **AUGMENTED INTERNAL FILTRATION**
   - A reduced inner diameter increases the convective transport along the membrane, within the same hollow fiber dialyzer performing diffusion.

4. **RETENTION OF ENDOTOXINS**
   - The adsorptive properties of the MCO membrane make it a safe and effective barrier against potential dialysis fluid contaminants despite the higher permeability.

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### Internal filtration IF at 500mL/min Qd

<table>
<thead>
<tr>
<th>Blood flow (QB), mL/min</th>
<th>THERANOVA 400 dialyzer</th>
<th>THERANOVA 500 dialyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF mL/min</td>
<td>29.7</td>
<td>41.6</td>
</tr>
<tr>
<td></td>
<td>31.6</td>
<td>53.1</td>
</tr>
</tbody>
</table>

Adapted after Lorenzin: Classification of hemodialyzer clinical performance.
HOW HDx THERAPY IS CHANGING DIALYSIS ONE STUDY AT A TIME

HDx therapy evidence on patient-reported, clinical and economic outcomes continues to grow.⁴⁶

If you want to visit the Compendium of Studies click here
Visit the HDx therapy website click here
REFERENCES


