Hemodiafiltration Around the Globe: Acceptance and Regulatory Issues Worldwide

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CMO, Centre of Excellence Medical, Fresenius Medical Care EMEA, Bad Homburg, Germany & School of Medicine, Montpellier University, Montpellier, France
Speaker name: **Prof. Bernard Canaud**

- I have the following potential conflicts of interest to report:
  - Consulting
  - **Employment in industry (FMC)**
  - Shareholder in a healthcare company
  - Owner of a healthcare company
  - Other(s)
  - I do not have any potential conflict of interest
Outlook of the Presentation

1. Regulatory aspects
2. Epidemiology of HDF
3. Practice patterns of HDF
4. Take home message
Outlook of the Presentation

1. Regulatory aspects
2. Epidemiology of HDF
3. Practice patterns of HDF
4. Take home message
Facing Regulatory Challenges of On-Line HDF
Producing IV Solution from Raw Material for Immediate Use

‘On-line’ Hemo Dia Filtration

Treatment system

Components 1
- Hemo-diafilter
- Tubing systems
- Dialysis machine
- Dialysis concentrate

Components 2
- Water
- Personnel
- Organization

‘On-line’ HDF filters

IV Solution

HF solution

Dialysis solution

MD = Medical device
Challenges of On-Line HDF
Producing IV Solution for Immediate Use

Hemo Dia Filtration

Solutions for hemofiltration

 Manufactured ‘in-site’
by industry

 Manufactured ‘on-line’
by customer

I. Definition

• Preparation for parenteral use
  - Sterile
  - Bacterial endotoxin/pyrogen-free
  - Containing electrolytes
  - In concentrations close to those in human plasma
  - Supplied in plastic or glass containers

• Same requirements

• Same requirements

• Not necessary

II. Tests

• Appearance of solution
  - clear
  - colorless
  - pH
  - Hydroxymethylfurfural
  - Aluminum
  - Particulate contamination
  - Sterility
  - Bacterial endotoxins/pyrogens

• Not possible

• Not possible

• Not necessary

• Not possible

• Not possible

• Not possible

• Not possible

Solving On-Line HDF Challenges
Ensuring Safety

Sterilizing Filter
Certified On-Line HDF Machine
Cleaning-Disinfecting
Water Treatment System
Water Monitoring (chemical/microbiology)
Best Practices Team Expertise
Regulatory by Country

Authorization

<table>
<thead>
<tr>
<th>Restriction</th>
<th>Approved for Use</th>
</tr>
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<tbody>
<tr>
<td>No</td>
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<tr>
<td>No</td>
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</tr>
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<td></td>
</tr>
</tbody>
</table>

Own Illustration based on Research and Survey
Regulatory by Country
Reimbursement

Restriction – Patient/Facility/Other

No

Yes

No

Incentive – Premium Reimbursement

Yes

Own Illustration based on Research and Survey
Outlook of the Presentation

1. Regulatory aspects
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3. Practice patterns of HDF
4. Take home message
## Global HDF Patient Distribution by Region in 2014

<table>
<thead>
<tr>
<th># Patients (%)</th>
<th>Global</th>
<th>EMEA</th>
<th>LA</th>
<th>AP</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>2,358,000</td>
<td>620,000</td>
<td>232,000</td>
<td>1,032,000</td>
<td>474,000</td>
</tr>
<tr>
<td>HDF</td>
<td>163,000</td>
<td>97,900</td>
<td>1,120</td>
<td>63,200</td>
<td>630</td>
</tr>
<tr>
<td></td>
<td>(7)</td>
<td>(16)</td>
<td>(&lt;1)</td>
<td>(6)</td>
<td>(&lt;1)</td>
</tr>
<tr>
<td>On-Line HDF</td>
<td>152,000</td>
<td>95,000</td>
<td>1,100</td>
<td>55,700</td>
<td>620</td>
</tr>
<tr>
<td></td>
<td>(94)</td>
<td>(97)</td>
<td>(99)</td>
<td>(88)</td>
<td>(99)</td>
</tr>
<tr>
<td>Conventional* HDF</td>
<td>10,500</td>
<td>2,900</td>
<td>10</td>
<td>7,560</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(3)</td>
<td>(1)</td>
<td>(12)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

*Bag Modality*

Source: Fresenius Medical Care

EMEA: Europe, Middle East, Africa; LA: Latin America; AP: Asia Pacific; NA: North America.
Global HDF Patient Distribution by Region in 2014

Regional Share of HDF Patients

- Global: 93% non-HDF, 7% HDF
- EMEA: 84% non-HDF, 16% HDF
- LA: 100% non-HDF, 0% HDF
- AP: 94% non-HDF, 6% HDF
- NA: 100% non-HDF, 0% HDF

Regional Distribution of HDF Patients

- EMEA: 60% of HDF patients
- LA: 39% of HDF patients
- AP: 1% of HDF patients
- NA: 0% of HDF patients

Source: Fresenius Medical Care

EMEA: Europe, Middle East, Africa; LA: Latin America; AP: Asia Pacific; NA: North America.
Global HDF Development
HDF Patients by Modality Worldwide

HDF Patients by Modality

- HDF Conventional
- HDF On-Line

Source: Fresenius Medical Care

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HDF Growth Rates

Average Patient Growth Rates 2006-2014

- HD: 6.9%
- HDF: 16%
- Conventional HDF: -2.6%
- On-Line HDF: 19%

Patient Growth Rates 2013 / 2014

- HD: 5.7%
- HDF: 10%
- Conventional HDF: -6.7%
- On-Line HDF: 12%

Source: Fresenius Medical Care
EMEA Region HDF Patient Development

# Patients by HDF Modality

Source: Fresenius Medical Care

EMEA: Europe, Middle East, Africa
EMEA Region HDF Development

Average Patient Growth Rates 2006-2014

- HD: 4.7%
- HDF: 16%
- Conventional HDF: -3.4%
- On-Line HDF: 18%

Patient Growth Rates 2013 / 2014

- HD: 4.1%
- HDF: 9.3%
- Conventional HDF: -4.7%
- On-Line HDF: 9.8%

Source: Fresenius Medical Care

EMEA: Europe, Middle East, Africa
### EMEA HDF Patient Distribution by Sub-Region in 2014

<table>
<thead>
<tr>
<th># Patients (%)</th>
<th>EMEA</th>
<th>CENE</th>
<th>WE</th>
<th>EEMEA</th>
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</thead>
<tbody>
<tr>
<td>HD</td>
<td>620,000</td>
<td>133,000</td>
<td>160,000</td>
<td>327,000</td>
</tr>
<tr>
<td>HDF</td>
<td>97,900</td>
<td>33,900</td>
<td>43,000</td>
<td>21,000</td>
</tr>
<tr>
<td>(16)</td>
<td>(26)</td>
<td>(27)</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>On-Line HDF</td>
<td>95,000</td>
<td>33,900</td>
<td>41,300</td>
<td>19,800</td>
</tr>
<tr>
<td>(97)</td>
<td>(100)</td>
<td>(96)</td>
<td>(94)</td>
<td></td>
</tr>
<tr>
<td>Conventional* HDF</td>
<td>2,900</td>
<td>0</td>
<td>1,740</td>
<td>1,160</td>
</tr>
<tr>
<td>(3)</td>
<td>(-)</td>
<td>(4)</td>
<td>(6)</td>
<td></td>
</tr>
</tbody>
</table>

(*Bag Modality)

Source: Fresenius Medical Care

EMEA: Europe, Middle East, Africa; Central, Northern, Western, Eastern Europe, Middle East, Africa
Europe may be clustered in four regions, three being close in terms of their HDF prevalent use including Northern, Central, and Western Europe with more than 25% respectively, while Eastern Europe shares only around 14%.
Top 10 Countries Ranked by **Share** of HDF Patients in Total HD Patient Population

**EMEA HDF Patient Population**

- **Switzerland**: 2,740 patients, 84% share
- **Slovenia**: 970 patients, 73% share
- **Slovakia**: 2,150 patients, 66% share
- **Czech Republic**: 3,640 patients, 60% share
- **Portugal**: 780 patients, 57% share
- **United Arab Emirates**: 750 patients, 57% share
- **Ireland**: 900 patients, 46% share
- **Denmark**: 1,380 patients, 46% share
- **Sweden**: 2,400 patients, 46% share
- **South Africa**: 2,400 patients, 44% share

*Source: Fresenius Medical Care*

- 2014 number of patients on HDF
- 2014 share of HDF patients as of total HD patients
Top 10 Countries in EMEA Ranked by Number of HDF Patient Population

EMEA HDF Patient Population

Source: Fresenius Medical Care
AP Region HDF Patient Development

# Patients by HDF Modality

Source: Fresenius Medical Care

AP: Asia Pacific
AP Region HDF Development

**Average Patient Growth Rates 2006 -2014**

- **HD**: 10%
- **HDF**: 15%
- **Conventional HDF**: -2.4%
- **On-Line HDF**: 21%

**Patient Growth Rates 2013 / 2014**

- **HD**: 8.0%
- **HDF**: 11%
- **Conventional HDF**: -7.5%
- **On-Line HDF**: 14%

Source: Fresenius Medical Care

AP: Asia Pacific
Top 5 Countries in AP Ranked by Share and Number of HDF Patients in Total HD Patient Population

AP HDF Patient Population

Source: Fresenius Medical Care
Reimbursement for On-Line HDF in Japan, 2012

- On the revision of the reimbursement for medical services in 2012, a technical fee for on-line HDF was newly established, and clearly separated from off-HDF. With this, ‘the restriction of indication’ disappeared.
- This is the first establishment of a technical fee for on-line HDF in the world.
- Technical fee for on-line HDF 22,550 JPY (184 €) (500 JPY ≈ 4€) higher than 4hrs HD) per treatment.
- Addition for maintaining dialysis fluid water quality 200 JPY (1.7€) per treatment.

https://www.jstage.jst.go.jp/browse/jsdt1968

Courtesy of Prof. Hideki Kawanishi, Hiroshima, Japan
Microbiologic Monitoring in Japan
Ultrapure Dialysis Fluid, JSDT2014

- 2014: 66.4%
- 2013: 60.8%
- 2012: 51.2%
- 2011: 41.6%
- 2010: 37.6%
HDF and On-Line HDF Trends in Japan

The claim of On-Line HDF reimbursement was controversial.

On-Line HDF Systems Recognized

Specific fee for On-Line HDF

# HD Patients

<table>
<thead>
<tr>
<th>Year</th>
<th># HD Patients</th>
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<td>2002</td>
<td>11629</td>
</tr>
<tr>
<td>2003</td>
<td>13837</td>
</tr>
<tr>
<td>2004</td>
<td>14255</td>
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<tr>
<td>2005</td>
<td>14213</td>
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<td>2006</td>
<td>16577</td>
</tr>
<tr>
<td>2007</td>
<td>18062</td>
</tr>
<tr>
<td>2008</td>
<td>17628</td>
</tr>
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<td>2009</td>
<td>17013</td>
</tr>
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<td>2010</td>
<td>15019</td>
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<td>2011</td>
<td>14115</td>
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<td>2012</td>
<td>21671</td>
</tr>
<tr>
<td>2013</td>
<td>31276</td>
</tr>
<tr>
<td>2014</td>
<td>43283</td>
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% HDF

<table>
<thead>
<tr>
<th>Year</th>
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<tbody>
<tr>
<td>2002</td>
<td>5,2</td>
</tr>
<tr>
<td>2003</td>
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<tr>
<td>2004</td>
<td>6</td>
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<tr>
<td>2005</td>
<td>5,9</td>
</tr>
<tr>
<td>2006</td>
<td>6,6</td>
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<tr>
<td>2007</td>
<td>6,8</td>
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<td>2008</td>
<td>6,5</td>
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<tr>
<td>2009</td>
<td>6,4</td>
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<td>2010</td>
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<td>2011</td>
<td>4,8</td>
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<td>2013</td>
<td>9,9</td>
</tr>
<tr>
<td>2014</td>
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</table>

https://www.jstage.jst.go.jp/browse/jsdt1968

Courtesy of Prof. Hideki Kawanishi, Hiroshima, Japan
## Impact of HDF and On-Line HDF Trends in Japan

### Japan, 2014:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>AFBF (%)</td>
<td>465</td>
<td>458</td>
<td>507</td>
<td>390</td>
<td>423</td>
<td>341</td>
</tr>
<tr>
<td>p/p HDF (%)</td>
<td>237</td>
<td>159</td>
<td>145</td>
<td>109</td>
<td>263</td>
<td>537</td>
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<tr>
<td>off-line HDF (%)</td>
<td>9,299</td>
<td>9,421</td>
<td>8,573</td>
<td>7,157</td>
<td>7,149</td>
<td>6,315</td>
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<tr>
<td>on-line HDF (%)</td>
<td>6,852</td>
<td>4,829</td>
<td>4,890</td>
<td>14,069</td>
<td>23,536</td>
<td>36,090</td>
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<tr>
<td>Center HD</td>
<td>253,807</td>
<td>262,973</td>
<td>270,072</td>
<td>268,275</td>
<td>264,211</td>
<td>255,641</td>
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<tr>
<td>Total HDF (%)</td>
<td>16,853</td>
<td>14,867</td>
<td>14,115</td>
<td>21,725</td>
<td>31,371</td>
<td>43,283</td>
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<tr>
<td>Total HD/HDF</td>
<td>270,660</td>
<td>277,840</td>
<td>284,187</td>
<td>290,000</td>
<td>295,582</td>
<td>298,924</td>
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Outlook of the Presentation

1. Regulatory aspects
2. Epidemiology of HDF
3. Practice patterns of HDF
4. Take home message
# European Practices of HDF

## HDF Prescription

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CONTRAST</th>
<th>ESHOL</th>
<th>French study</th>
<th>Turkish study</th>
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<tbody>
<tr>
<td>N (% HDF)</td>
<td>2793 (50)</td>
<td>714 (50)</td>
<td>906 (50)</td>
<td>391 (50)</td>
<td>782 (50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.1 (14.7)</td>
<td>64.1 (13.7)</td>
<td>65.4 (14.4)</td>
<td>76.2 (6.4)</td>
<td>56.5 (13.9)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1045 (37)</td>
<td>269 (38)</td>
<td>300 (33)</td>
<td>154 (39)</td>
<td>322 (41)</td>
</tr>
<tr>
<td>Vascular access, AVF (%)</td>
<td>2376 (85)</td>
<td>567 (79)</td>
<td>779 (86)</td>
<td>283 (72)</td>
<td>747 (96)</td>
</tr>
<tr>
<td>Duration of dialysis session (min)</td>
<td>233 (20)</td>
<td>226 (23)</td>
<td>235 (19)</td>
<td>236 (25)</td>
<td>237 (9)</td>
</tr>
<tr>
<td>Blood flow (mL/min)</td>
<td>337 (66)</td>
<td>301 (40)</td>
<td>386 (63)</td>
<td>336 (42)</td>
<td>294 (45)</td>
</tr>
<tr>
<td>Postdilution HDF (%)</td>
<td>(100)</td>
<td>(100)</td>
<td>(100)</td>
<td>(100)</td>
<td>(100)</td>
</tr>
</tbody>
</table>
European Practices of HDF

Convection Volume Distribution Per Session

Convection volume distribution by study

- CONTRAST
- ESHOL
- French study
- Turkish study

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HDF Prescription in Japan
JSDT, End of 2014

Dilution Modalities for HDF

<table>
<thead>
<tr>
<th></th>
<th>on-line HDF</th>
<th>off-line HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre/post</td>
<td>91.8%</td>
<td>96.8%</td>
</tr>
<tr>
<td>Post</td>
<td></td>
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Substitution fluid volume for HDF

<table>
<thead>
<tr>
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<th>on-line HDF</th>
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</thead>
<tbody>
<tr>
<td>Pre</td>
<td>39.6 L</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>10.6 L</td>
<td></td>
</tr>
</tbody>
</table>

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Key Factors Affecting HDF Practice Worldwide

- Patient Benefits & Clinical Evidence
- Healthcare Policy & Reimbursement Rates
- Regulatory & Technical Issues
- Practice Pattern

Own Illustration
Outlook of the Presentation

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Executive Summary
Global HDF Patients

• Percentage of HD patients on HDF was around 7% worldwide in 2014.

• On-Line HDF is the predominant modality with 94%, growing at a rate of around 12%.

• Growth in HDF patient population of around +10% was by far exceeding the total HD patient growth of only +5.7%.

• Huge geographical differences exist in HDF use.

• EMEA region has the largest population treating around 60% of HDF patients.

• AP region represents 39% of the global HDF population with rapid growth in Japan.

• Only minor numbers of patients in LA (0.7%) and NA (0.4%) are treated with HDF.

Source Numbers, 2014: Fresenius Medical Care
On-Line HDF: A **New Paradigm Shift** in RRT

High Volume Hemodiafiltration

![Diagram showing convective and diffusive doses leading to improved CKD patient experience and outcome.](image)
Towards HDF As A **New Standard of Care** in RRT

HDF acceptance is growing fast in the two leading regions having approved the method, i.e. **Europe and Asia Pacific**.

Interestingly, some **initiatives** have recently been launched to facilitate the implementation of HDF in the Americas.

They could even provide the push for promoting HDF as a **new standard** of care in ESKD patients on a global scale.