Ultrapure Dialysate
Present & Future
Impact on Biomed Techs

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What is Ultrapure Dialysate?

- Dialysis fluid produced from
  - Hemodialysis quality water
  - Bicarbonate concentrate
  - Controlled Ultrafiltration
    - Ultrafilter pore size 0.1 to 0.001 μ
- High Quality requirements
  - Total viable bacterial count < 0.1 CFU/mL
  - Endotoxin concentration < 0.03 EU/mL
Why Use Ultrapure Dialysate?

Microbial contamination of water and dialysate purported to cause acute and chronic, inter- & intra-dialytic complications

- **Acute**
  - Pyrogenic reactions

- **Chronic**
  - Cardiovascular instability
  - Headache
  - Nausea
  - Cramps
Long-term Effects Attributed to Chronic Micro-Inflammation

- Malnutrition
- Low albumin
- Muscle protein wasting
- Protein catabolism
- Increased CRP
- Atherosclerosis
- Low cholesterol synthesis
- Increased ferritin levels
- Resistance to EPO therapy
- Bone disease, cysts, fractures
- Sleep disorders
- Anti-endotoxin antibodies
Hypotheses

- Interleukin Hypothesis
  - Chronic state of micro-inflammation induced
    - Long term exposure to low levels of microbial contamination and debris
  - Contaminants cross dialyzer membranes due to backfiltration
  - Cytokines induced
  - Inflammatory response -- fever and hypotension

- MIA Syndrome
  - Malnutrition, Inflammation and Atherosclerosis
  - Contributes to morbidity and mortality
Microbial Contaminants with Cytokine Inducing Activity

- Endotoxin fragments
- Muramylpeptides
- Polysaccharides
- Lipopolysaccharides (LPS)
- DNA fragments
- Oligode-oxynucleotides
Evidence to Support Improved Clinical Outcomes Using Ultrapure Dialysate

- Improved Morbidity
  - Reduced $\beta_2$ microglobulin & associated amyloidosis
  - Decreased markers of inflammation & oxidative stress
  - Increased responsiveness to EPO
  - Improved nutritional status
  - Improved preservation of RRF
  - Slowing of onset carpal tunnel syndrome

- Complications return when standard dialysate treatment re-initiated
## Comparison of Dialysates

<table>
<thead>
<tr>
<th></th>
<th>Standard Dialysate</th>
<th>Ultrapure Dialysate</th>
<th>Dialysate for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial Limits</strong></td>
<td>&lt;200 CFU/mL</td>
<td>&lt;0.1 CFU/mL</td>
<td>&lt;1 CFU/1000 liters (Sterile)</td>
</tr>
<tr>
<td><strong>Endotoxin Limits</strong></td>
<td>&lt;2 EU/mL</td>
<td>&lt;0.03 EU/mL</td>
<td>&lt;0.03 EU/mL (Pyrogen-free)</td>
</tr>
<tr>
<td><strong>Monitoring Method/Frequency</strong></td>
<td>Spread plate LAL Testing Monthly</td>
<td>Spread Plate or Membrane Filtration; LAL Testing</td>
<td>Validation and Process Control; Monitor Water &amp; Dialysate</td>
</tr>
<tr>
<td><strong>Sample Vol Tested</strong></td>
<td>0.5 mL</td>
<td>0.5 mL plated or ISO 10 mL to 1L membrane filtration</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Media, Incubation Time &amp; Temperature</strong></td>
<td>35°C, 48 hr TSA</td>
<td>35°C, 48hr TSA ISO TGEA or R2A 17-23°C, 7 days</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Production Method</strong></td>
<td>Mix concentrate with hemodialysis quality water</td>
<td>Ultrafilter standard dialysate</td>
<td>On-line generation, validated &amp; controlled processing or Pre-packaged sterile</td>
</tr>
<tr>
<td><strong>Therapy Type</strong></td>
<td>Standard Hemodialysis</td>
<td>Standard Dialysis with Ultrapure Dialysate</td>
<td>Convective Therapies</td>
</tr>
</tbody>
</table>
Factors Affecting Transport of Bacterial Products to the Patient thru Dialysate

- Backfiltration
  - Higher dialysate than blood compartment pressures
  - Blood outlet, dialysate inlet side of dialyzer
  - Fluid flows from dialysate side to blood side
- Conditions that increase backfiltration
  - Dialyzers with large surface area
  - High blood flow rates
  - High dialysate flow rates
Importance of Water in Ultrapure Dialysate

- Water -- the main component of dialysate
- Water is the main source of contaminants in dialysate
  - Bacterial
  - Endotoxin
  - Biofilm
- Large volumes of water are used in dialysis
  - Concentrate preparation
  - Dialysate proportioning
  - Rinsing dialysis machines
  - Disinfection of water treatment system components and dialysis machines
  - Reprocessing of dialyzers for reuse
**BIOFILM: IN STANDARD DIALYSIS & ULTRAPURE WATER**

**Standard Dialysis Quality Water**

Fig. 2. Tubing segment, showing extensive biofilm formation, from a standard water treatment system.

**Ultrapure Water**

Fig. 1. Tubing segment, showing complete absence of biofilm, from a water treatment system delivering ultrapure water.
Effect of Biofilm Presence on Dialysate Quality

- Biofilm is a source of contaminants that can be transferred to patients during dialysis thru dialysate
  - Bacteria
  - Debris
    - Endotoxin
    - Exotoxin
    - Peptidoglycan
    - LPS, Lipid A
    - DNA & RNA fragments
    - Low molecular weight by products of bacterial metabolism
    - Carbohydrate slime layer
    - Matrix Proteins
    - Cytokine inducing substances

- Most undetectable with current testing methods
Thus Ultrapure Dialysate is One Way to REDUCE PATIENT EXPOSURE TO CONTAMINANTS & THE EFFECTS OF CHRONIC MICRO-INFLAMMATION
Strategies to Achieve Ultrapure Dialysate

- Design and operate Water Treatment Systems to consistently produce
  - At a minimum -- Hemodialysis Quality Water
    - Monitored, trended and disinfected regularly as per AAMI 52 & 62
    - Keep Biofilm under control
  - Ideal – use Ultrapure Water

- Design features in hemodialysis systems to reduce biofilm formation

- Use Ultrafilter(s) to remove/reduce contaminants in dialysate pre-dialyzer
Ultrafiltration

- Ultrafiltration
  - Filtration through a semipermeable membrane resulting in retention of endotoxin and microbial products by size exclusion and adsorption.
  - Hydrophobic Domains
  - Pore size dictates size exclusion
    - Generally 0.1 to 0.001 µ
Properties of Ultrafilters

- Diffusive resistance
  - Cellulosic Low-Flux membranes
    - 6.5-8µm thick
  - Synthetic High Flux membranes
    - 40-60µm thick

- Hydrophobic vs Hydrophilic domains
  - Hydrophobic domains adsorb CIS and pyrogens
    - Cellulosic Low-Flux membranes -- hydrophilic
    - Synthetic High Flux membranes – hydrophobic domains & large surface area
Some Currently Available Systems to Achieve Ultrapure Dialysate

Gambro DIACLEAR

Fresenius DIASAFE Plus
Ultrapure Dialysate Capable Hemodialysis Systems

Gambro Phoenix

B. Braun

Fresenius 4008 H/S
Why Is Usage of Ultrapure Dialysate Controversial and Limited?

- Cause & Effect not conclusively established
- Not part of Standard of Care
- Most data are retrospective or anecdotal
- No long term, large population, prospective, controlled clinical trials
- Poor study design, poorly controlled studies
- Inadequate comparison groups
- Confounding variables
- No data to correlate dependency between level of microbial quality of dialysate and clinical outcomes
- Not practical or feasible to implement
- Cost constraints
Challenges to Implementation of Ultrapure Dialysate

- What are the correct parameters for water and dialysate to achieve the therapeutic effects desired?
  - Many current water treatment systems inadequate
- Are the correct standards in place yet?
- Are the techniques available for assessing and insuring compliance?
- Will it have meaningful clinical benefit for a significant number of patients?
- Can ultrapure dialysate be delivered cost effectively?
Preparation & Delivery of Ultrapure Dialysate
Role of BioMed Techs -- The Present

- Maintain Quality of Water
  - Water treatment system
- Maintain Systems to Produce Ultrapure Dialysate
  - Ultrafilters and dialysis machines
- Disinfect &/or replace Ultrafilters as per manufacturer’s validated instructions or as needed
- Monitor water and dialysate quality and trend data
- Make adjustments to disinfection plan based on trending results
Role of BioMed Techs -- The Future

Increased use of Ultrapure Dialysate in Standard Dialysis Tx
- More emphasis on Quality of Water and Dialysate
- On-line preparation of bicarbonate dialysate
- Regulatory requirements more stringent
  - Bacteria <0.1 CFU/mL
  - Endotoxin <0.03 EU/mL
- Monitoring & trending become even more critical
- Monitoring focus on water entering dialysis machine
- Validation and process control become important
Role of BioMed Techs—The Future

- Improvements in Water Treatment Systems and materials capable of withstanding heat for daily disinfection
- Increased use of ozone for disinfection and biofilm removal
- More on-line delivery systems
  - Product produced used immediately—no time for “batch control” testing
  - Validation plan required
  - Operation and maintenance as per manufacturer’s validated instructions
Role of BioMed Techs–The Future

• More convective therapies?
  ▫ Dialysate for infusion or substitution fluid
  ▫ More stringent bacterial and endotoxin requirements
    ▪ Bacteria $<10^{-6} \text{CFU/mL} \ (<1 \text{CFU/1000L} = <1 \text{CFU/250 gallons})$
    ▪ Endotoxin $<0.03 \text{EU/mL}$
  ▫ Cannot monitor with conventional techniques
  ▫ Validation and process control required
VALIDATION
What is Validation?

Validation is a process consisting of a series of activities and documents to ensure that a given piece of equipment or process can consistently meet its design and performance requirements in a given setting.
What Does a Validation Include?

- Validation Plan
- Installation and Operational Qualification (IQ & OQ)
- Performance Qualification (PQ)
- Documentation
- Revalidation through routine monitoring
Validation Plan

- Validation Plan
  - Level of detail reflects risk, complexity and novelty of the system
  - Define all responsibilities during validation, system operation, monitoring and maintenance
Installation & Operational Qualification

- IQ and OQ
  - Installed following the installation instructions from the manufacturer
  - Operates as per the technical manuals and does all the required actions
Performance Qualification

- Performance Qualification—PQ
  - Phase 1
    - Full chemical and microbiological analysis of water and dialysate
    - Weekly microbiological analysis for 1\textsuperscript{st} month
    - All information on system behavior documented
    - Trend Analysis of data
    - Identify and correct deviations to protect patient safety
    - Fine tune action levels
    - Performance during 3 \textit{consecutive} runs must meet all acceptance criteria
Performance Qualification

- Phase 2-- Monitoring Phase (Normal Operations)
  - Must successfully pass Phase 1 first
  - Monthly microbial monitoring & disinfection
    - Sampling prior to disinfection -- demonstrates control
    - Sampling post disinfection-- demonstrates effective disinfection process
  - High quality results within parameters demonstrated for extended time period
  - Continuous monitoring covers all critical aspects of the system performance
Two Consecutive Months Within Action Level Performance
Why is Validation Necessary at the Clinic Level for Ultrapure Dialysate?

- Water and dialysate quality critical
- Microbiological and endotoxin levels difficult to measure with traditional methods
- Process control is the only way to ensure continuous conformance
  - Deviations may occur between sampling
- Early and timely identification of potential problems early is easier – Necessary to protect patients
You Do It Now And Don’t Realize It

BIOMED TECHS ALREADY DO VALIDATIONS
Validation Just Involves Documenting What You are Already Doing

- INSTALLATION Qualification
  - A new piece of equipment arrives at the clinic
  - You unpack the equipment, check that all the components are there and find the Instruction Manual
  - You follow the INSTALLATION instructions and put the equipment together
  - RESULT-- INSTALLATION Qualification
Validation: Operational Qualification

- Operational Qualification (OQ)
  - You connect the equipment to the water and concentrate supplies
  - Plug it in
  - Turn it on and check that it works—
  - RESULT-- OPERATIONAL Qualification
Validation: Performance Qualification

- **Performance Qualification (PQ)**
  - You run the equipment at least 3 times under normal use conditions to make sure---
    - Everything is running properly and consistently
    - Problems are not caused with/for other equipment or systems already in place & vice versa
    - Microbiological & endotoxin levels are acceptable
    - Critical performance parameters are met
  - You document everything you did
  - **RESULT -- PERFORMANCE Qualification**
Validation: Process Control

- Your process is now validated
- Process control takes over during operations
  - Identify areas that are critical to monitor to keep the equipment meeting all its critical operational and performance criteria
  - Include the equipment in your routine monitoring, maintenance, cleaning and disinfection program to ensure continued performance
  - Establish alert and action levels and how you will respond at each level to keep the system in control
Is Ultrapure Dialysate In Your Future?

Be prepared to play your part.
YOU ARE THE DEFENDERS!