# Ultrapure Dialysate Present & Future Impact on Biomed Techs

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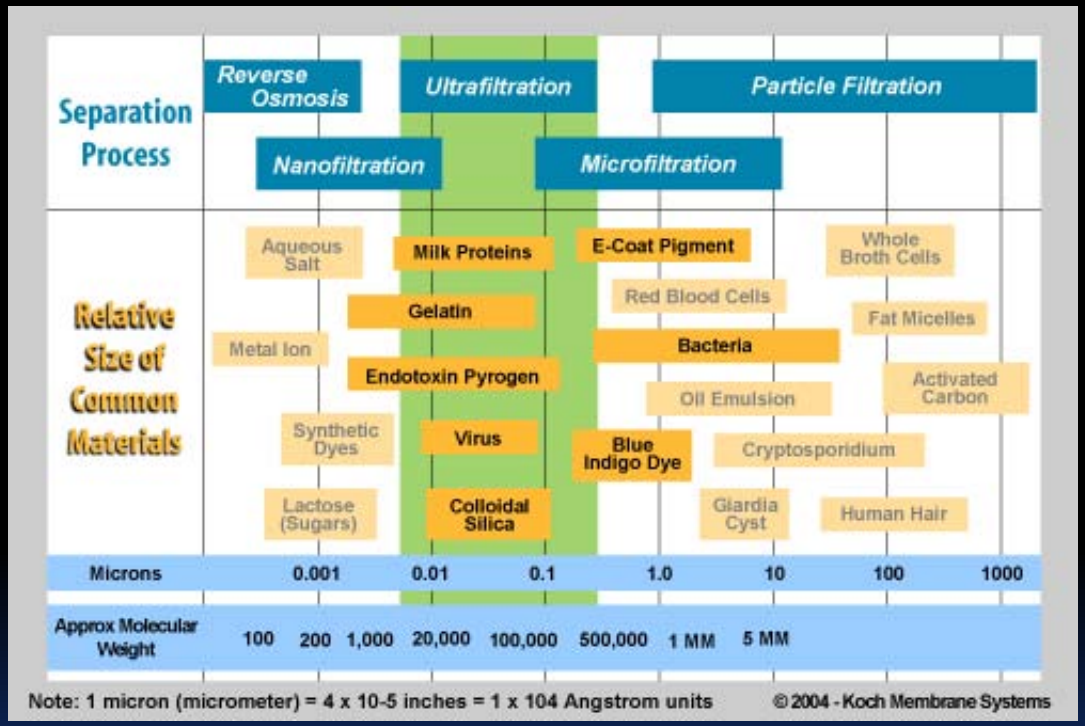
# What is Ultrapure Dialysate?




- 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 β2 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

# Ultrapure Dialysate

## THE PRESENT

# Comparison of Dialysates

| | Standard Dialysate | Ultrapure Dialysate | Dialysate for Infusion |
|---|---|---|---|
| Bacterial Limits | <200 CFU/mL | <0.1 CFU/mL | <1 CFU/1000 liters (Sterile) |
| Endotoxin Limits | <2 EU/mL | <0.03 EU/mL | <0.03 EU/mL (Pyrogen-free) |
| Monitoring Method/Frequency | Spread plate LAL Testing Monthly | Spread Plate or Membrane Filtration; LAL Testing | Validation and Process Control; Monitor Water & Dialysate |
| Sample Vol Tested | 0.5 mL | 0.5 mL plated or ISO 10 mL to 1L membrane filtration | NA |
| Media, Incubation Time & Temperature | 35$^0$C, 48 hr TSA | 35$^0$C, 48hr TSA ISO TGEA or R2A 17-23$^0$C, 7 days | NA |
| Production Method | Mix concentrate with hemodialysis quality water | Ultrafilter standard dialysate | On-line generation, validated & controlled processing or Pre-packaged sterile |
| Therapy Type | Standard Hemodialysis | Standard Dialysis with Ultrapure Dialysate | Convective Therapies |

# 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

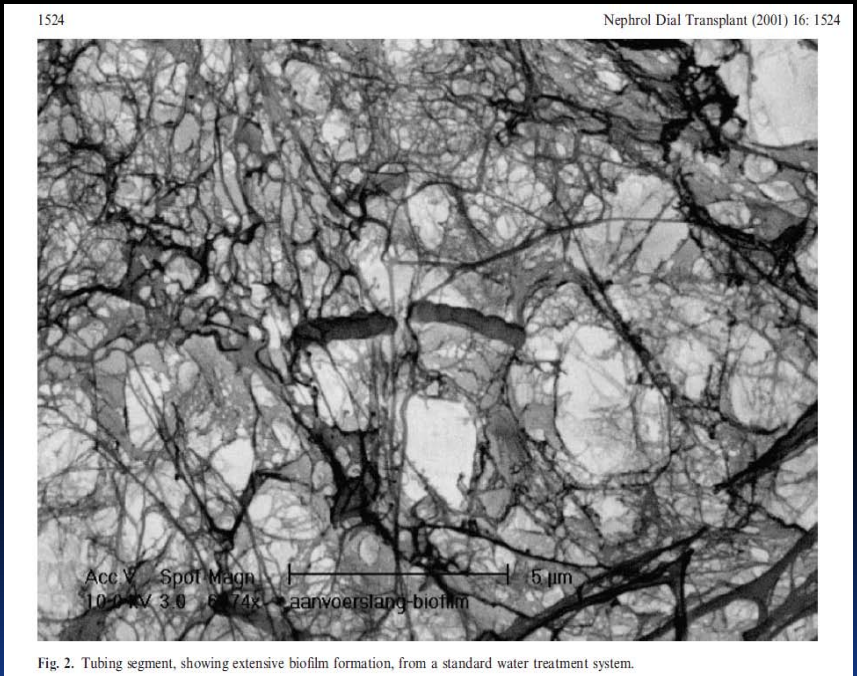



Fig. 2. Tubing segment, showing extensive biofilm formation, from a standard water treatment system.

## Ultrapure Water

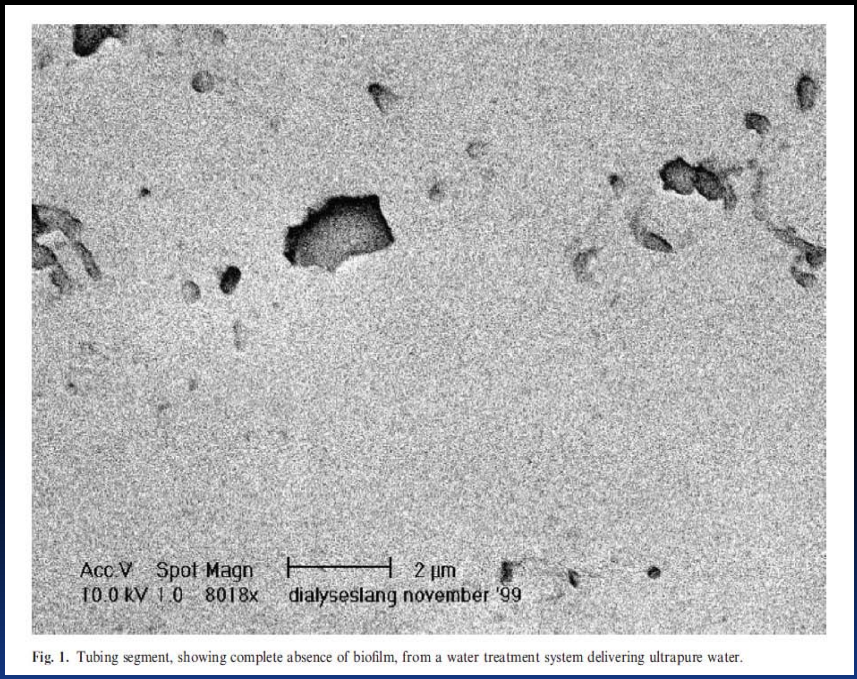



Fig. 1. Tubing segment, showing complete absence of biofilm, from a water treatment system delivering ultrapure water.

# 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

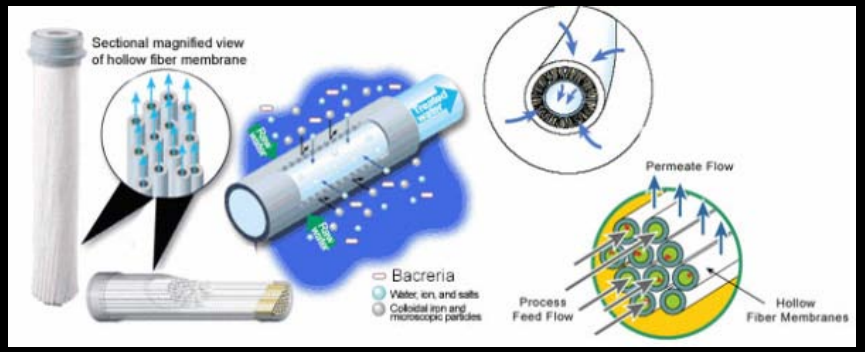
# REDUCE PATIENT EXPOSURE TO CONTAMINANTS & THE EFFECTS OF CHRONIC MICRO-INFLAMMATION

# 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



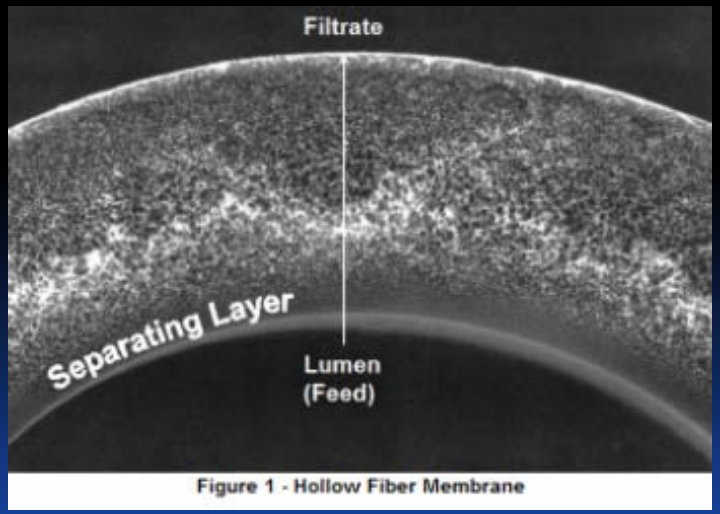



Figure 1 - Hollow Fiber Membrane

# 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

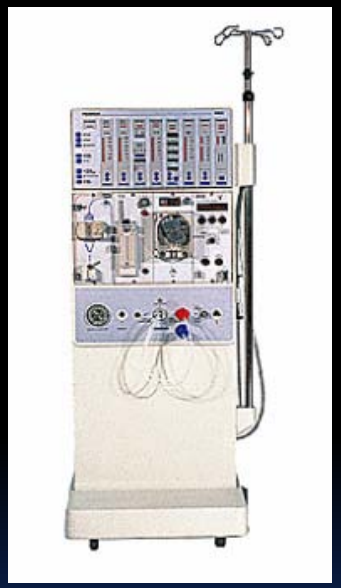
**Gambro DIACLEAR**


**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

# IMPACT ON BIOMED TECHS

# 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 $<10^{-6}$ CFU/mL (<1 CFU/1000L = <1 CFU/250 gallons)
    - Endotoxin <0.03 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 1st 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 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

# PERFORMANCE QUALIFICATION COMPLETED

# 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 Qualfication

- 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 Qualfication

- 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!