DIALYSIS FLUID QUALITY: AN IMPORTANT PART OF THE DIALYSIS PRESCRIPTION
Presented by Dr. Richard Ward
A Webber Training Teleclass, March 11, 2004

OVERVIEW
- WHAT IS THE ROLE OF DIALYSIS FLUID (DIALYSATE) IN HEMODIALYSIS?
- WHY IS THE QUALITY OF THE DIALYSIS FLUID IMPORTANT?
- WHAT ADVERSE OUTCOMES MAY BE RELATED TO CONTAMINATED DIALYSIS FLUID?
- HOW CAN SAFE LEVELS OF THESE CONTAMINANTS BE ASSURED?

HEMODIALYSIS
- REPLACES THE EXCRETORY FUNCTIONS OF THE KIDNEY
  - REGULATES WATER BALANCE
  - REGULATES ELECTROLYTE BALANCE
  - ELIMINATES WASTE PRODUCTS OF METABOLISM
- DOES NOT REPLACE ENDOCRINE AND METABOLIC FUNCTIONS OF THE KIDNEY

PREPARATION OF DIALYSIS FLUID
- WATER
- BICARBONATE CONCENTRATE
- ACID CONCENTRATE

DIALYSIS FLUID PREPARATION
- FIXED
  - WATER (34 PARTS)
  - ACID (1 PART)
  - HCO₃⁻ (1.83 PARTS)
- DYNAMIC
  - WATER
  - ACID
  - HCO₃⁻
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WATER TREATMENT SYSTEM

- REQUIRED FOR ALL DIALYSIS FACILITIES
- MUST PRODUCE WATER OF APPROPRIATE QUALITY FROM THE WORST CASE FEED WATER
- MUST MEET THE PEAK DEMAND FOR WATER (SOME EXCESS CAPACITY IS DESIRABLE)
- SHOULD BE DESIGNED FOR EASE OF MAINTENANCE

PURIFICATION PROCESSES

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>CONTAMINANT</th>
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<tbody>
<tr>
<td>CARBON ADSORPTION</td>
<td>CHLORAMINES, ORGANICS</td>
</tr>
<tr>
<td>SOFTENER</td>
<td>CALCIUM</td>
</tr>
<tr>
<td>REVERSE OSMOSIS</td>
<td>IONIC CONTAMINANTS, BACTERIA, ENDOTOXIN</td>
</tr>
<tr>
<td>DEIONIZATION</td>
<td>IONIC CONTAMINANTS</td>
</tr>
<tr>
<td>ULTRAFILTRATION</td>
<td>BACTERIA, ENDOTOXIN</td>
</tr>
</tbody>
</table>

PRE-TREATMENT

- PROTECTS THE PRIMARY PURIFICATION PROCESS
  - DEPTH FILTER REMOVES LARGER PARTICULATES (> 15 µm) THAT CAN FOUL DOWN-STREAM PROCESSES
  - SOFTENER REMOVES CALCIUM THAT CAN FOUL REVERSE OSMOSIS MEMBRANES
  - CARBON REMOVES CHLORINE THAT CAN DEGRADE REVERSE OSMOSIS MEMBRANES
- ESTABLISHES OPTIMUM OPERATING CONDITIONS FOR PRIMARY PURIFICATION PROCESS
- PROTECTS PATIENTS BY REMOVING CHLORAMINES

REMOVAL OF CHLORAMINES

- CARBON ADSORPTION WITH GRANULAR ACTIVATED CARBON OR CATALYTIC CARBON IS GENERALLY THE MOST EFFECTIVE MEANS OF REMOVING CHLORAMINES
- CARBON ADSORPTION MAY NOT BE EFFECTIVE UNDER RARE CIRCUMSTANCES:
  - HIGH LEVELS OF N-CHLORAMINES
  - USE OF ORTHOPHOSPHATE TO REDUCE LEAD AND COPPER LEVELS IN THE MUNICIPAL WATER
  - HIGH pH IN THE MUNICIPAL WATER
- UNDER THESE CIRCUMSTANCES, CARBON ADSORPTION MAY NEED TO BE SUPPLEMENTED; FOR EXAMPLE, BY INJECTION OF METABISULPHITE

PRIMARY PURIFICATION

REVERSE OSMOSIS versus ION EXCHANGE

- REVERSE OSMOSIS
  - REMOVES A WIDE RANGE OF IONIC AND NON-IONIC CONTAMINANTS (DOES NOT REMOVE CHLORAMINES)
  - PROVIDES A BARRIER AGAINST MICROBIOLOGICAL CONTAMINANTS
  - GENERALLY REQUIRES PRE-TREATMENT OF FEED WATER (CALCIUM, CHLORINE, COLLOIDS)
  - SIGNIFICANT CAPITAL COST, BUT LOW OPERATING COST
- ION EXCHANGE
  - DOES NOT REMOVE NON-IONIC CONTAMINANTS (MAY LIMIT AI REMOVAL)
  - HAS A FINITE CAPACITY
  - PROMOTES BACTERIAL PROLIFERATION
  - RISK OF ACUTE FLUORIDE TOXICITY IF ALLOWED TO EXHAUST
  - LOW CAPITAL COST, BUT SIGNIFICANT OPERATING COST

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WHAT ABOUT DIALYSIS FLUID QUALITY?

DIALYSIS FLUID QUALITY
AAMI RD52 - DIALYSATE FOR HEMODIALYSIS

PROPOSED LIMITS FOR CHEMICAL CONTAMINANTS
- SAME AS FOR WATER (RD62:2001)

PROPOSED LIMITS FOR MICROBIOLOGICAL CONTAMINANTS
- BACTERIA: 200 CFU/ml
  - ACTION LEVEL: 50 CFU/ml
- ENDOTOXIN: 2 EU/ml
  - ACTION LEVEL: 1 EU/ml

DEFINITIONS OF MICROBIOLOGICAL QUALITY

<table>
<thead>
<tr>
<th>Bacteria (cfu/ml)</th>
<th>Endotoxin (EU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAMI Recommended</td>
<td>200</td>
</tr>
<tr>
<td>ERA-EDTA Best Practice (Proposed)</td>
<td>100</td>
</tr>
<tr>
<td>Guidelines UltraPure</td>
<td>0.1</td>
</tr>
<tr>
<td>Sterile</td>
<td>$10^6$</td>
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</tbody>
</table>

SEPTICEMIA AND PYROGENIC REACTIONS

- BACTERIA
  - DO NOT CROSS DIALYZER MEMBRANES
  - MAY INFECT BLOOD COMPARTMENT DURING PROCESSING OF DIALYZER FOR REUSE
  - CAN CAUSE SEPSIS CHARACTERIZED BY WATER-BORNE ORGANISMS
- ENDOTOXIN
  - FRAGMENTS MAY CROSS DIALYZER MEMBRANES
  - MAY CONTAMINATE BLOOD COMPARTMENT DURING PROCESSING OF DIALYZER FOR REUSE
  - CAUSE PYROGENIC REACTIONS CHARACTERIZED BY SHAKING CHILLS, FEVER AND HYPOTENSION

INTRADIALYTIC PYROGENIC REACTIONS

Favero MS et al. Trans Am Soc Artif Int Organs 20:175-183, 1974
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INFLUENCE OF DIALYSIS PRACTICES ON PYROGENIC REACTIONS

CHRONIC INFLAMMATION

• CYTOKINE-INDUCING SUBSTANCES (ENDOTOXIN FRAGMENTS, PEPTIDOGLYCANs, MURAMYL Dipeptides, Exotoxins)
  ❖ CROSS LOW- AND HIGH-FLUX MEMBRANES
  ❖ STIMULATE MONONUCLEAR CELL CYTOKINE PRODUCTION
  ❖ ARE ASSOCIATED WITH INCREASED LEVELS OF ACUTE PHASE PROTEINS (C-REACTIVE PROTEIN)
  ❖ PRODUCE A MICROINFLAMMATORY STATE THAT MAY PLAY A ROLE IN β2-MICROGLOBULIN AMYLOIDOSIS, ATHEROSCLEROSIS, AND MALNUTRITION

RISK OF DEVELOPING DIALYSIS-ASSOCIATED AMYLOIDOSIS WITH CONTAMINATED DIALYSIS FLUID

Odds Ratio (95% CI)

- β2-MICROGLOBULIN AMYLOIDOSIS: 3.308 (1.45 – 6.35) p = 0.031
- BONE CYSTS: 1.85 (1.00 – 3.42) p = 0.047
- CARPAL TUNNEL SYNDROME: 2.86 (1.35 – 6.07) p = 0.006
- ARTHROPATHY: 9.04 (2.06 – 39.6) p = 0.004

N = 88
10 YEAR FOLLOW-UP

CONTAMINATED DIALYSIS FLUID: 550 CFU/ml
STANDARD DIALYSIS FLUID: 65 CFU/ml

POTENTIAL ADVANTAGES OF WATER AND DIALYSIS FLUID OF HIGH MICROBIOLOGICAL PURITY

- LESS INFLAMMATORY STIMULUS
- REDUCED INCIDENCE OF β2-MICROGLOBULIN AMYLOID DISEASE
- IMPROVED RESPONSIVENESS TO ERYTHROPOIETIN
- IMPROVED NUTRITIONAL STATUS
- BETTER PRESERVATION OF RESIDUAL RENAL FUNCTION

DIALYZER REUSE: OUTBREAKS OF SEPTICEMIA AND PYROGENIC REACTIONS

- INCORRECT GERMICIDE CONCENTRATION: 5/10
- INAPPROPRIATE GERMICIDE: 2/10
- USE OF TAP WATER TO CLEAN OR RINSE DIALYZERS: 3/10
- USE OF MULTIPLE GERMICIDES: 1/10
- USE OF WATER NOT MEETING AAMI STANDARDS: 10/10


INFLUENCE OF DIALYSIS PRACTICES ON PYROGENIC REACTIONS

Tokars JI et al. ASAIO J 40:1020-1031, 1994

Risk of developing dialysis-associated amyloidosis with contaminated dialysis fluid

Odds Ratio (95% CI)

- β2-Microglobulin Amyloidosis: 3.308 (1.45 – 6.35) p = 0.031
- Bone Cysts: 1.85 (1.00 – 3.42) p = 0.047
- Carpal Tunnel Syndrome: 2.86 (1.35 – 6.07) p = 0.006
- Arthropathy: 9.04 (2.06 – 39.6) p = 0.004

N = 88
10 Year Follow-Up

Contaminated Dialysis Fluid: 550 CFU/ml
Standard Dialysis Fluid: 65 CFU/ml


Potential advantages of water and dialysis fluid of high microbiological purity

- Less inflammatory stimulus
- Reduced incidence of β2-Microglobulin Amyloid Disease
- Improved responsiveness to Erythropoietin
- Improved nutritional status
- Better preservation of residual renal function

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BIOMASS FROM DIALYSIS MACHINE TUBING

<table>
<thead>
<tr>
<th></th>
<th>CFU/cm²</th>
<th>TOTAL BACTERIA/cm²</th>
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<tbody>
<tr>
<td>TUBING FROM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WATER PATH</td>
<td>23</td>
<td>$1.4 \times 10^5$</td>
</tr>
<tr>
<td>BICARBONATE PATH</td>
<td>17</td>
<td>$1.54 \times 10^5$</td>
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<tr>
<td>DIALYSIS FLUID PATH</td>
<td>12</td>
<td>$3.2 \times 10^5$</td>
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<tr>
<td>DIALYSIS FLUID</td>
<td>0</td>
<td>0</td>
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N = 3
Adapted from Man N-K et al. Artif Organs 22:596-600, 1998

DESIGN TO LIMIT BACTERIAL PROLIFERATION

- USE A DISTRIBUTION LOOP
- AVOID STAGNANT FLOW
  - NO DEAD ENDS, PRESSURIZING TANKS, OR MULTIPLE BRANCHES
  - SIZE PIPES TO MAINTAIN VELOCITY > 3 ft/sec
- INCLUDE BACTERIAL CONTROL DEVICES
  - ULTRAFILTERS
  - ON-LINE HOT WATER DISINFECTION
- IF A STORAGE TANK IS USED
  - MINIMUM SIZE NEEDED TO ENSURE TURN-OVER OF WATER
  - TIGHT-FITTING LID WITH A HYDROPHOBIC 0.2 µm FILTER AIR VENT
  - CONICAL BOTTOM WITH DRAIN AT LOWEST POINT
  - ADEQUATE DISINFECTION MECHANISM

DISINFECTION

- DISINFECTION SCHEDULES SHOULD BE DESIGNED TO PREVENT, NOT ELIMINATE, CONTAMINATION WITH BACTERIA AND BIOFILM.
- DISINFECTION SHOULD INCLUDE THE WATER STORAGE AND DISTRIBUTION SYSTEM, CONCENTRATE PREPARATION AND DISTRIBUTION SYSTEM, AND THE PROPORTIONING SYSTEM.
- MONITORING WITH CULTURES AND ENDOTOXIN LEVELS IS INTENDED TO VERIFY THE ADEQUACY OF DISINFECTION, NOT INDICATE WHEN DISINFECTION IS NEEDED.

NO MAN’S LINE

MONITORING FOR COMPLIANCE WITH AAMI STANDARDS

<table>
<thead>
<tr>
<th>CULTURING CONDITIONS</th>
<th>TECHNIQUE</th>
<th>MEDIUM</th>
<th>TEMPERATURE</th>
<th>TIME</th>
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<tbody>
<tr>
<td></td>
<td>MEMBRANE FILTER, SPREAD PLATE</td>
<td>TRYPTIC SOY AGAR OR EQUIVALENT</td>
<td>35 - 37°C</td>
<td>48 hours</td>
</tr>
<tr>
<td>ENDOTOXIN MEASUREMENT TECHNIQUE</td>
<td>LIMULUS AMEBOCYTE LYSATE ASSAY</td>
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</table>
ALTERNATIVES TO SPREAD-PLATE CULTURES

- **CALIBRATED LOOP**
  - Standard technique in clinical laboratories
  - Sample volume is too small for required sensitivity
  - Specifically prohibited for dialysis applications

- **PADDLES**
  - Convenient for on-site testing
  - Require a magnifier and light-source for accurate enumeration of colonies
  - May give an apparent false negative with heavily contaminated samples

- **MEMBRANE FILTRATION**
  - Very sensitive
  - Requires filtration system and large sample volumes

EFFECT OF CULTURE CONDITIONS ON COLONY COUNT IN DIALYSATE

<table>
<thead>
<tr>
<th>Culture Conditions</th>
<th>Bacteria Count (log CFU/ml)</th>
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<tbody>
<tr>
<td>Blood Agar 37°C</td>
<td>1</td>
</tr>
<tr>
<td>TSA 37°C</td>
<td>2</td>
</tr>
<tr>
<td>TGEA 37°C</td>
<td>3</td>
</tr>
<tr>
<td>TGEA 20°C</td>
<td>4</td>
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SUMMARY

- Hemodialysis patients are highly sensitive to contaminants in the water used for dialysis fluid and dialyzer reprocessing
- Water contaminants can cause many problems common in hemodialysis patients, including anemia, bone disease, and intra-dialytic nausea and vomiting
- No water supply can be considered suitable for dialysis applications without purification
- Avoiding complications from water contaminants requires constant attention to water quality

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