OVERVIEW

• WHAT IS THE ROLE OF DIALYSIS FLUID (DIALYSATE) IN HEMODIALYSIS?
• WHY IS THE MICROBIOLOGICAL QUALITY OF THE DIALYSIS FLUID IMPORTANT?
• HOW CAN SAFE LEVELS OF MICROBIOLOGICAL 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
Minimizing the Impact of Water-Borne Bacteria on Hemodialysis Patients
Dr. Richard Ward, University of Louisville
A Webber Training Teleclass

HEMODIALYSIS

DIALYZER
DIALYSIS FLUID
BLOOD ACCESS
BLOOD TUBING
ANTICOAGULATION
BLOOD PUMP

PREPARATION OF DIALYSIS FLUID

DIALYSIS MACHINE
DIALYSER
DIALYSIS FLUID
WATER
DRAIN
ACID CONCENTRATE
BICARBONATE CONCENTRATE

DIALYSIS FLUID PREPARATION

FIXED
WATER (24 PARTS)
HEATER
ACID (1 PART)
HCO\textsubscript{3}^-
(1.83 PARTS)
DIALYSATE
C\textsubscript{t}

DYNAMIC
WATER
HEATER
ACID
HCO\textsubscript{3}^-
C\textsubscript{d}
C\textsubscript{t}
DIALYSATE

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AAMI WATER QUALITY STANDARDS - RD62:2001

<table>
<thead>
<tr>
<th>SUBSTANCES IN DIALYSATE</th>
<th>SUBSTANCES TOXIC IN DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALCIUM</td>
<td>ALUMINUM 0.01</td>
</tr>
<tr>
<td>MAGNESIUM</td>
<td>CHLORAMINES 0.10</td>
</tr>
<tr>
<td>SODIUM</td>
<td>FINE OXIDIZED 0.50</td>
</tr>
<tr>
<td>POTASSIUM</td>
<td>COPPER 0.10</td>
</tr>
<tr>
<td>TOXIC SUBSTANCES (SDWA)</td>
<td>FLUORIDE 0.20</td>
</tr>
<tr>
<td>ARSENIC</td>
<td>NITRATES (as N) 2.0</td>
</tr>
<tr>
<td>BERYLLIUM</td>
<td>SULFATE 100</td>
</tr>
<tr>
<td>BARIUM</td>
<td>ZINC 0.10</td>
</tr>
<tr>
<td>CADMIUM</td>
<td>MICROBIOLOGICAL CONTAMINANTS</td>
</tr>
<tr>
<td>CHROMIUM</td>
<td>BACTERIA 200</td>
</tr>
<tr>
<td>LEAD</td>
<td>ACTION LEVEL 55</td>
</tr>
<tr>
<td>MERCURY</td>
<td>ENDOTOXIN 2</td>
</tr>
<tr>
<td>SELENIUM</td>
<td>ACTION LEVEL 1</td>
</tr>
<tr>
<td>SILVER</td>
<td></td>
</tr>
<tr>
<td>THALLIUM</td>
<td></td>
</tr>
</tbody>
</table>

CHEMICAL CONCENTRATIONS (mg/L, BACTERIA CFU/ml, ENDOTOXIN EU/ml)

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
DIALYSIS FLUID QUALITY

AAMI RD52 - DIALYSATE FOR HEMODIALYSIS

LIMITS FOR CHEMICAL CONTAMINANTS

- SAME AS FOR WATER (RD62:2001)

LIMITS FOR MICROBIOLOGICAL CONTAMINANTS

- BACTERIA: 200 CFU/ml
  ACTION LEVEL: 50 CFU/ml
- ENDOTOXIN: 2 EU/ml
  ACTION LEVEL: 1 EU/ml

DIALYSIS FLUID

DEFINITIONS OF MICROBIOLOGICAL QUALITY

<table>
<thead>
<tr>
<th></th>
<th>Bacteria (cfu/ml)</th>
<th>Endotoxin (EU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAMI Recommended Practice</td>
<td>200</td>
<td>2</td>
</tr>
<tr>
<td>ERA-EDTA Best Practice Guidelines</td>
<td>100</td>
<td>0.25</td>
</tr>
<tr>
<td>Ultrapure</td>
<td>0.1</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Sterile</td>
<td>$10^{-6}$</td>
<td>&lt;0.03</td>
</tr>
</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

![Graph showing prevalence of pyrogenic reactions](image)


PREVALENCE OF PYROGENIC REACTIONS

![Graph showing prevalence of pyrogenic reactions](image)

Centers for Disease Control, 2000
INFLUENCE OF DIALYSIS PRACTICES ON PYROGENIC REACTIONS

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

DIALYZER REUSE: OUTBREAKS OF SEPTICEMIA AND 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 \( \beta_2 \)-MICROGLOBULIN AMYLOIDOISIS, ATHEROSCLEROSIS, AND MALNUTRITION

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**EFFECT OF WATER QUALITY ON INFLAMMATION AND β₂-MICROGLOBULIN**

![Graph showing the impact of water quality on inflammation and β₂-microglobulin](image)


**RISK OF DEVELOPING DIALYSIS-ASSOCIATED AMYLOIDOSIS WITH CONTAMINATED DIALYSIS FLUID**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂-MICROGLOBULIN AMYLOIDOSIS</td>
<td>3.308 (1.45 – 6.35) p = 0.031</td>
</tr>
<tr>
<td>BONE CYSTS</td>
<td>1.85 (1.00 – 3.42) p = 0.047</td>
</tr>
<tr>
<td>CARPAL TUNNEL SYNDROME</td>
<td>2.86 (1.35 – 6.07) p = 0.006</td>
</tr>
<tr>
<td>ARTHROPATHY</td>
<td>9.04 (2.06 – 39.6) p = 0.004</td>
</tr>
</tbody>
</table>

N = 89  
10 YEAR FOLLOW-UP  
CONTAMINATED DIALYSIS FLUID: 590 CFU/ml  
STANDARD DIALYSIS FLUID: 65 CFU/ml


**EFFECT OF IMPROVED WATER QUALITY ON ANEMIA CORRECTION**

![Graph showing the effect of improved water quality on anemia correction](image)


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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

Tubing from a dialysis machine with > 10^6 CFU/ml P. aeruginosa, Enterobacter cloacae and Candida parapsilosis
Carr J. Hospital Infections Program, CDCP

BIOMASS FROM DIALYSIS MACHINE TUBING

<table>
<thead>
<tr>
<th>Tubing From</th>
<th>CFU/cm²</th>
<th>Total Bacteria/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Path</td>
<td>23</td>
<td>1.4 x 10³</td>
</tr>
<tr>
<td>Bicarbonate Path</td>
<td>17</td>
<td>1.54 x 10³</td>
</tr>
<tr>
<td>Dialysis Fluid Path</td>
<td>12</td>
<td>3.2 x 10³</td>
</tr>
<tr>
<td>Dialysis Fluid</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

N = 3

Adapted from Man N-K et al. Artif Organs 22:596-600, 1998

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STRATEGIES FOR BACTERIAL CONTROL

• SYSTEM DESIGN
• SYSTEM OPERATION
• DISINFECTION

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.
MONITORING FOR COMPLIANCE WITH AAMI STANDARDS

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

SAMPLE COLLECTION

- SAMPLE PORTS SHOULD PROVIDE DIRECT ACCESS TO THE FLUID OF INTEREST
- FLUSH THE SAMPLE PORT FOR AT LEAST 30 sec BEFORE COLLECTING THE SAMPLE
- DO NOT DISINFECT THE SAMPLE PORT
- COLLECT THE SAMPLES DIRECTLY INTO A STERILE ENDOTOXIN-FREE CONTAINER
- ASSAY SAMPLES WITHIN 30 min OR STORE AT ≤ 5°C FOR UP TO 24 hours.

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

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EFFECT OF CULTURE CONDITIONS ON COLONY COUNT IN DIALYSATE


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EFFECTS OF CLEANING AND DISINFECTION ON BIOFILM

- Silicone rubber tubing allowed to develop biofilm by exposure to dialysate (187 CFU/ml, 1.8 EU/ml).
- Biofilm averaged 15 µm thickness, covered 96% of surface, and contained $1.7 \times 10^9$ CFU/ml (*Pseudomonas* sp.).
- Tubing was cleaned with 3% citric acid at 20°C for 5 minutes before disinfection for 40 minutes.

### EFFECTS OF CLEANING AND DISINFECTION ON BIOFILM

<table>
<thead>
<tr>
<th>CLEANING</th>
<th>DISINFECTION</th>
<th>BIOFILM (%)</th>
<th>RESIDUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>THICKNESS</td>
<td>COVERAGE</td>
</tr>
<tr>
<td>- BLEACH (0.3%, 20°C)</td>
<td>50</td>
<td>58</td>
<td>22</td>
</tr>
<tr>
<td>CITRIC ACID BLEACH (0.3%, 20°C)</td>
<td>60</td>
<td>65</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>- ACTRIL (3%, 20°C)</td>
<td>19</td>
<td>15</td>
<td>8.6 x 10³</td>
</tr>
<tr>
<td>CITRIC ACID ACTRIL (3%, 20°C)</td>
<td>54</td>
<td>68</td>
<td>2.1 x 10⁴</td>
</tr>
<tr>
<td>- CITRIC ACID (3%, 90°C)</td>
<td>0</td>
<td>7</td>
<td>3.6 x 10³</td>
</tr>
<tr>
<td>- WATER (90°C)</td>
<td>0</td>
<td>7</td>
<td>9.1 x 10³</td>
</tr>
<tr>
<td>CITRIC ACID BLEACH (3%, 20°C)</td>
<td>67-100</td>
<td>98</td>
<td>18</td>
</tr>
</tbody>
</table>


### EFFECT OF ACID CLEANING ON DISINFECTION

![Graph showing effect of acid cleaning on disfection](image)


### EFFECT OF CLEANING WITH ENZYMES AND

![Graph showing effect of enzymes and cleaning](image)


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USE OF SEQUENTIAL ULTRAFILTRATION TO PREPARE ULTRAPURE DIALYSATE

SUMMARY

• Hemodialysis patients are highly sensitive to contaminants in the water used for dialysis fluid and dialyzer reprocessing.

• In addition to the risk of septicemia and pyrogenic reactions, microbiological contaminants may contribute to many problems common in hemodialysis patients, including β2-microglobulin amyloidosis, anemia, and malnutrition.

• Avoiding complications from microbiological contaminants requires a well designed water purification and distribution system, a rigorous disinfection schedule, and constant attention to water quality.

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