Dialysis Water Quality:

Does it really matter with today`s inline water filters?

Satellite CME symposium: basics in nephrology
Hemodialysis: slightly beyond basics
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Quality of water and dialysate

• Background
• History
• Biofilm
• Microbiological aspects
• Experimental and clinical issues
• Actual standards
• Future goals

➔ Clinical correlations to intoxication and inflammation
Background
Is drinking water clean?

Contamination

1. Solid particles

2. Solved particles
   - Ions, colloides, organic substances

3. Mikroorganisms
   - Bacterias and endotoxin, viruses, fungi
Parameters regularly examined:

- **Particles** (minerals, sand, Si-comp....)
- **Organic substances** (tannines, oil, N-comp....)
- **Anorganic substances** (Ca, Mg, Al, Cu, F, Zn....)
- **Bacteries** (E. coli, pseudom., enterococc., Mycobact....)

➡ Intoxications and infections

Tolerance and limits for drinking water:

- Total CFU: 100 CFU/ml
- E. coli / enteroc.: 0 CFU/100ml
- Salmonella spp.: 0 CFU/5000ml
- Campylobacter spp.: 0 CFU/5000ml
We all know ……

Peel it

Cook it

or

Leave it !!!

➔ Infections and intoxications
➔ Most important rule on trips in the third world
History
Dialysate in the early days

- Tanksystems
- Water heated and boiled
- “No” microbiol. contamination
- Chemical “contamination”
- Concentrate was added
## Signs and symptoms and possible water contaminant-related causes

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Water Contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Al. chloramine, Cu, Zn</td>
</tr>
<tr>
<td>Bone Disease</td>
<td>Al, Fl</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Cu, nitrates, chloramine</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Ca. Na</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Bacteria, endotoxin, nitrates</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>low pH, sulfates</td>
</tr>
<tr>
<td>Neurological deterioration</td>
<td>Al</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Bacteria, Ca, Cu, endotoxin, low pH, Mg, nitrates.</td>
</tr>
<tr>
<td>Pyrogen reactions</td>
<td>Sulfates, ETO</td>
</tr>
<tr>
<td>Death</td>
<td>Al, Fl, endotoxin, bacteria, chloramine</td>
</tr>
</tbody>
</table>
Frequency of pyrogen reactions during hemodialysis as a function of dialysate contamination

<table>
<thead>
<tr>
<th>Dialysate Microbial Contamination CFU/ml</th>
<th>No. of Dialysis Sessions</th>
<th>No. of Pyrogenic Reactions</th>
<th>Attack Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-100</td>
<td>25</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>100-10000</td>
<td>31</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>&gt; 10000</td>
<td>21</td>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

The Philadelphia incident

- 1960-80 many incidents due to contaminated dialysate
- 1987 Chloramin intoxication in Philadelphia
  - Nurse noted in many patients anemia, headache, nausea and hypotension
  - Chloramine was the cause for hemolysis
  - 44 of 107 patients needed transfusions – 10 were hospitalized
  - Investigations revealed – insufficient quality of the RO-water

→ Regular control of the water quality and the water treatment system
Aluminium intoxications: still a problem in nephrology?

- **Belgium** (1987-90): Inproper water treatment in 2 dialysis centers (s-Al 78-154 mcg/l)
- **Egypt** (1992): Contamination of ROW in collection tank (s-Al 119mcg/l)
- **Portugal** (1993): Dialysate Al-intoxication due to improper water treatment (11 pts. died)
- **Spain** (1993): Dialysate Al-intoxication due to an inadequate connection of RO system (s-Al 147mcg/l)
- **Russia** (1995): Improper water treatment
- **USA** (1995): Epidemic Al-intoxication caused by the use of electric pumps with Al-housing (s-Al>100mcg/l)

D’Haesee et al NDT 11 (Suppl 2): 92-97; 1996
Water-contamination and solutions

<table>
<thead>
<tr>
<th>Period</th>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960-1970</td>
<td>Colloid-particles, Ca, Mg, Microorganisms</td>
<td>➜ Aluminiumsulfat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➜ Softner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➜ Chloride</td>
</tr>
<tr>
<td>1970-1980</td>
<td>Aluminium, Chloramine</td>
<td>➜ Softner / RO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>➜ Carbon filters</td>
</tr>
<tr>
<td>1980-2000</td>
<td>Microorganisms, Endotoxins</td>
<td>➜ RO and ultrafiltration</td>
</tr>
</tbody>
</table>

Schindler and Lonnemann Wasser und Dialysataufbereitung
Dialyseverfahren in Klinik und Praxis – Thieme 2004
Biofilm
This SEM micrograph shows a knot tied in a suture. The suture was used to hold a small tube in place. The micrograph shows that a mucous like material has started forming around the knotted suture. The suture material is about 30 microns in size.

The large cylindrical structure on the left is the actual suture thread. There are indications of red blood cells, which look like somewhat deformed donuts. The red blood cells are slightly deformed, resulting from the sample preparation used in creating the micrograph.
Biofilm on silikon catheter

SEM Micrograph of a Biofilm formed by Bacterial Colony on Silicon Catheter
Biofilm formation

Induktionphase: thin layers of organic substances on surfaces

→ Mikroorganisms attach easily on these organic layers
Cytokine induction during dialysis

**Membrane effects**

- Blood
- Membrane
- Dialysate

**Endotoxin effects**

- Endotoxin

Schindler & Dinarello Bio Techniques Vol. 8: 408, 1990
Risks of biofilm formation

• Many nosocomial infections due to biofilm formation
• Catheter related infections
• Foreign body infections (biomaterials)
• Pseudomonas pneumonia in ventilated patients
• Biofilm formation in all water systems (tubing / app.)

⇒ Increasing bacterial growth
⇒ Endotoxin formation

Hoenich et al Seminars in Dialysis 16, 492-497; 2003
Microbiology
Gram-negative bacteria in ROW and dialysate

- Pseudomonas species (P. maltophilia, P. aeruginosa, P. vesicularis, P. cepacia, P. putida, P. stutzeri, P. fluorescens, P. testosteroni)
- Moraxella species
- Alcaligenes species (Flavobacteria)
- Acinetobacter species (Serratia, Klebsiella)
- Enterobacter cloacae

G. Lonnemann, Kidney Int Vol. 43, Suppl. 41, S-195-200; 1993
## Water contamination due to aquatic microorganisms and their degradation products

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Metabolites and Other Degradation Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative Bacteriae</td>
<td>Endotoxins (LPS, Lipid A, PS-core) Peptidoglycans (Muramyl dipeptide)</td>
</tr>
<tr>
<td>Gram-positive Bacteriae</td>
<td>Peptidoglycans, Teichoic acid, Exotoxins, Proteins</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Peptidoglycans Polysaccharides, Proteins</td>
</tr>
<tr>
<td>Algae</td>
<td>Peptidoglycans</td>
</tr>
<tr>
<td>Molds and Yeasts</td>
<td>Peptidoglycans</td>
</tr>
<tr>
<td>Virus</td>
<td>Proteins Hemaglutinin</td>
</tr>
</tbody>
</table>

Dinarello CA; Contr Nephrol Vol. 36, 90-90; 1983
Effectiveness of various membrane separation processes as a function of particle size in the liquid to be filtered

Comparison of different media

CFU

<table>
<thead>
<tr>
<th>CFU</th>
<th>Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Blut Agar</td>
</tr>
<tr>
<td>57</td>
<td>Tryptone Soya Agar</td>
</tr>
<tr>
<td>368</td>
<td>R 2 A</td>
</tr>
<tr>
<td>493</td>
<td>Tryptone Glucose Extract Agar</td>
</tr>
</tbody>
</table>

Nystrand pers. comm. 1996
Experiments
Materials and Methods

- Bacterial filters in swinnex holders filtering fluids
- Cultivation special agar at 20°C for 7 days
How to obtain sterile dialysate?

**Condition I**

<table>
<thead>
<tr>
<th></th>
<th>ROW</th>
<th>Dialysate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bact. %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ETO pg/ml</td>
<td>12</td>
<td>48</td>
</tr>
</tbody>
</table>

Kiss et al. Kidney Int 34, 573-574; 1988
How to obtain sterile dialysate?

Condition II

<table>
<thead>
<tr>
<th>ROW</th>
<th>Dialysate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bact. %</td>
<td>10</td>
</tr>
<tr>
<td>ETO pg/ml</td>
<td>4</td>
</tr>
</tbody>
</table>

Kiss et al Kidney Int 34, 573-574; 1988
How to obtain sterile dialysate?

Condition III

<table>
<thead>
<tr>
<th></th>
<th>ROW</th>
<th>Dialysate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bact. %</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>ETO pg/ml</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Kiss et al Kidney Int 34, 573-574; 1988
Bacteria and endotoxins in bicarbonate concentrate

- Bacteria CFU/ml
- ETO ng/ml

Na-Bicarbonate-powder for on-line preparation

Ebben et al. 1987
Ultrafiltration of dialysis fluid

→ In-line dialysate ultrafilter

Water treatment for Dialysis:
Chemical and microbiological aspects

Development of disinfection systems
Actual Standards
Standards & Controls

Water quality controls:

- Bacterial- and ETO contamination $4x/year$.
- Chemical analysis $1x/year$
Summary and Future goals
Why do we need a Water Treatment System?

1960-70: Pionierphase – Dialysis-program was more important than survival
   ➔ Hard-water syndrome and pyrogen-reactions

1970-80: Problemphase – Aluminiumsulfate and bacteriol. contamination
   ➔ Dialysis-Dementia due to aluminium-overload

1980-90: Problems due to new technologies – Bicarbonate und high-flux Filter
   ➔ Bacterial and endotoxin contamination
   ➔ Acute- and chron. Inflammation (beta2 MG)

After 2000: online HDF ➔ Ultrapure water is necessary to reduce biofilm formation
   ➔ Reduce inflammation to improve treatment outcome

Alfrey et al NEJM 294:184, 1976
Hoenich et al Seminars in Dialysis 16, 492-497; 2003
Conclusions & Future Goals

- Further reduction of biofilm formation in tubing system and dialysis machines
  - Optimal water treatment system
  - Regular (heat) disinfection
  - Regular controls
  - Improvement of surface (nano-) technology
  - Better disinfectant systems
  - "No" or minimal biofilm formation

Hoenich et al. Seminars in Dialysis 16, 492-497; 2003
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a contaminated issue!

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