Managing Water and Dialysate for Hemodialysis
-Preventing Adverse Events-

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Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Overview

- Background
- Hazardous Nature of water
- Standards
- Water treatment processes
- System Monitoring and Actions
- Microbial Control
- Potential Problem areas
- Responding to results
- Summary
- Resources

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Feed Water

- Dialysis centers use water from a public supply, which may be derived from either surface-, ground or blended waters
- Source of the water may be important in terms of bacterial endotoxin, different types of microorganisms (bacteria, cyanobacteria, fungi, etc.), and even blue green algae toxins

Hazardous Nature of Water

- Very large exposure volumes; patients exposed to ≥ 360 L/week
- Little or no renal excretion
- Dialyzer semipermeable membrane is sole barrier
- Protein adsorption enhances accumulation

Uses of Water in a Dialysis Clinic

- Water is the primary component of dialysate
  - Water is proportioned with acid concentrate (acetic acid or Citrasate®) and bicarbonate concentrate
  - The final bath is made at the hemodialysis machine
- Water is also used to dilute disinfectants
  - Type of water (facility or treated) is dependent on the anticipated use of the product
- Treated water is used for dialyzer reprocessing
  - Dilution of disinfectant concentrates
  - Pre-rinsing dialyzers and for header cleaning

Relationship between concentration of Gram-negative bacteria in dialysate and pyrogenic reactions among dialysis patients

Log_{10} CFU/mL	Number of Dialysis Sessions	Pyrogenic reactions	Attack Rate (%)
1-100	25	1[a]	4
100-10,000	31	4	13
>10,000	21	5	24

[a] Questionable laboratory result

Favero MS, et al. *Trans Am Soc Artif Intern Organs* 1974;20:175-183;
Favero MS, et al. *Health Lab Sci* 1975;12(4):321-334

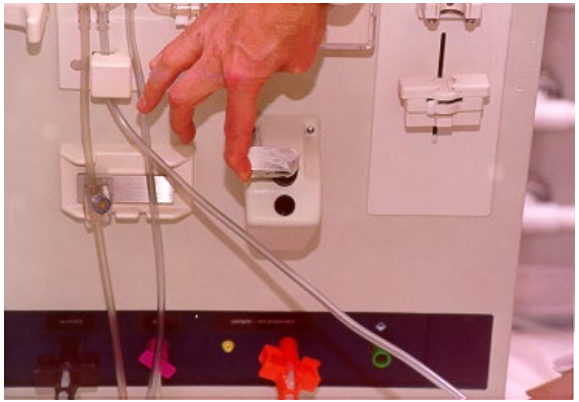
CDC Outbreaks Related to Contamination of Hemodialysis Fluids, 1980-2024

- Microbial contamination of water or dialysate (12)
  - Contaminated distribution systems
  - Contaminated water sources
  - Contaminated patient station boxes (backflow from drains)
- Chemical Contamination of water or dialysate (11)
  - Chemical contaminants included: Aluminum, monochloramine, cyanobacterial toxins, fluoride, volatile sulfur compounds
- Those associated with dialyzer reuse (14):
  - Contaminated water and distribution system
  - Insufficient amount of germicide
  - Header sepsis

CDC Outbreaks Associated with Dialyzer Reuse

- Use of multiple germicides
- Failure to rinse out dialyzer disinfectant
- Use of a chemical germicide that was not compatible with cellulosic membranes
- Inadequate concentration of dialyzer disinfectant
- Poor water quality
- Issues dealing with the removal of header caps and o -rings (“Header Sepsis”)
- Water treatment equipment malfunction or failure

So, What Can go Wrong?



Am J Nephrol 1990;10:397–403

0250–8095/90/010:

Outbreak of Gram-Negative Bacteremia and Pyrogenic Reactions in a Hemodialysis Center[1]

Consuelo M. Beck-Sague[a], *William R. Jarvis*[a], *Lee A. Bland*[a], *Matthew J. Arduino*[a], *Sonia M. Aguero*[a], *Gregory Verosic*[b]

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INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY SEPTEMBER 2009, VOL. 30, NO. 9

ORIGINAL ARTICLE

Contaminated Product Water as the Source of *Phialemonium curvatum* Bloodstream Infection among Patients Undergoing Hemodialysis

Carol Y. Rao, ScD; Constance Pachucki, MD; Salvatore Cali, MPH; Mangai Santhiraj, MPH; Kathi L. K. Krankoski, BS; Judith A. Noble-Wang, PhD; David Leehey, MD; Subhash Popli, MD; Mary E. Brandt, PhD; Mark D. Lindsley, ScD; Scott K. Fridkin, MD; Matthew J. Arduino, DrPH

OBJECTIVE. We investigated a cluster of cases of bloodstream infection (BSI) due to the mold *Phialemonium* at a hemodialysis center in Illinois and conducted a cohort study to identify risk factors.

DESIGN. Environmental assessment and cohort study.

SETTING. A hemodialysis center in a tertiary care hospital.

METHODS. A case patient was defined as a person who underwent dialysis at the center and had a blood sample that tested positive for *Phialemonium curvatum* on culture. We reviewed microbiology and medical records and tested water, surface, and dialysate samples by

Clinical Study

Am J Nephrol 1998;18:485–489

Received: October 28, 1997
Accepted: January 22, 1998

A Cluster of Bloodstream Infections and Pyrogenic Reactions among Hemodialysis Patients Traced to Dialysis Machine Waste-Handling Option Units

256 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY March 2004

EPIDEMIC PARENTERAL EXPOSURE TO VOLATILE SULFUR-CONTAINING COMPOUNDS AT A HEMODIALYSIS CENTER

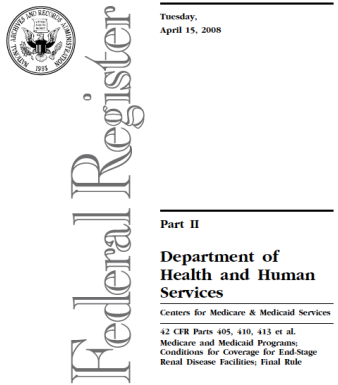
Dejana Selenic, MD; Francisco Alvarado-Ramy, MD; Mathew Arduino, MS, DrPH; Stacey Holt, MMSc; Fred Cardinali, BA; Benjamin Blount, PhD; Jeff Jarrett, MS; Forrest Smith, MD; Neil Altman, BS, MPH; Charlotte Stahl, MSN, RN, CIC; Adelisa Panlilio, MD, MPH; Michele Pearson, MD; Jerome Tokars, MD, MPH

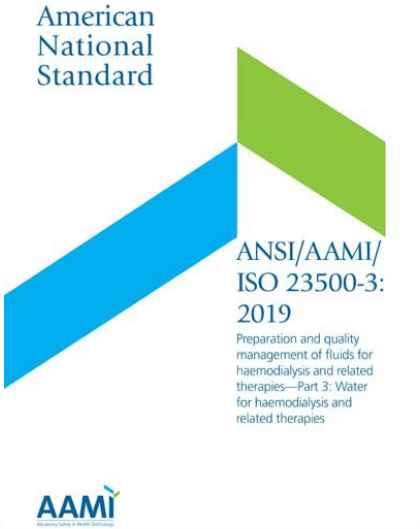
When do I suspect potential problems with water or dialysate?

- Bacteremia with waterborne opportunistic pathogen
  - *Pseudomonas aeruginosa, Burkholderia cepacia* complex, *Stenotrophomonas matlophilia, Ralstonia pickettii, Ralstonia mannitolilytica, Ralstonia eutropha, Ralstonia paucula, Klebsiella pneumoniae, Enterobacter cloacae, Ochrobactrum anthropi*
  - *Mycobacterium abscessus, Mycobacterium mucogenicum, Mycobacterium fortuitum*
  - *Candida parapsilosis, Phialemonium curvatum*
- Pyrogenic reactions
- Multiple patients with onset of acute or delayed systemic reactions

Standards and Recommended Practices
Conditions for Coverage

AAMI. RD52:2004, 09 CMS. ESRD CfC, 2008 ANSI/AAMI/ISO 23500 Series





Microbial Limits and Patient Outcomes

- Outbreaks end once water and dialysate microbial limits returned below the old AAMI Limits (ANSI/AAMI RD52:2004)*

Current Microbial Limits

AAMI. Preparation and quality management of fluids for haemodialysis and related therapies. ANSI/AAMI/ISO 23500 parts 1-5: 2019

Fluid	MCL	Action Limit
Water for dialysis	≤100 CFU/mL ≤0.25 EU/mL50	50 CFU/mL 0.125 EU/mL
Conventional Dialysate	≤100 CFU/mL ≤ 0.5 EU/mL	50 CFU 0.25 EU/mL
Ultrapure Dialysate	100 CFU/L ≤0.03 EU/ML	
Substitution fluid	Sterile and nonpyrogenic	

Check facility policies and procedures to see adopted

Chemical Contaminants with Documented Toxicity in Hemodialysis Patients

Contaminant	MCL (mg/L)	Dialysis Patient Symptoms
Aluminum	0.01	Anemia, Osteodystrophy Dialysis encephalopathy, Dialysis dementia
Total Chlorine	0.1	Hemolysis, anemia, rHEporesistance
Copper	0.1	Anemia, hemolysis, leukocytosis, metabolic acidosis and gastrointestinal symptoms muscle pain, liver damage
Fluoride	0.2	Pruritus, Cardiac arrest, chest pain, hypotension,
Lead	0.0005	Anemia, Osteodystrophy
Nitrate (as N)	2	Anemia, methemoglobinemia, hypotension
Sulphate	100	Metabolic acidosis, nausea and vomiting
Zinc	0.1	Anemia, nausea, vomiting, fever

Electrolytes normally included in dialysis fluid

Contaminant	MCL (mg/L)	Dialysis Patient Symptoms
Calcium	2 (0.05 mmol/L	Hard water syndrome (nausea, vomiting, weakness, hypertension and increased risk of arteriovenous fistula thrombosis.)
Magnesium	4 (0.15 mmol/L)	
Potassium	8 (0.2 mmol/L)	increase in serum PTH
Sodium	70 (3.0 mmol/L)	Hypertension, increased thirst, nausea and vomiting, headache, pulmonary edema, shortness of breath, tachycardia

Trace Elements Present in Dialysis Water

Contaminant	MCL (mg/L)
Antimony	0.006
Arsenic	0.005
Barium	0.1
Beryllium	0.0004
Cadmium	0.001

Contaminant	MCL (mg/L)
Chromium	0.014
Mercury	0.0002
Selenium	0.09
Silver	0.005
Thallium	0.002

These values are 1:10th the MCL for potable water; Selenium is set to the transfer level.

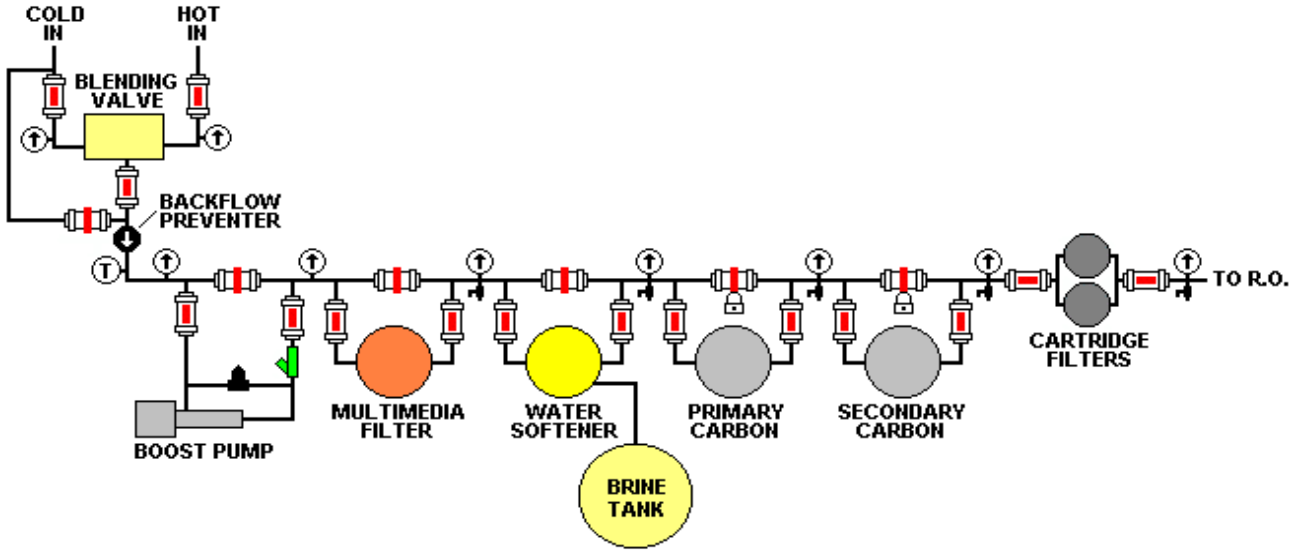
Water Treatment Processes

- **Pre-treatment**

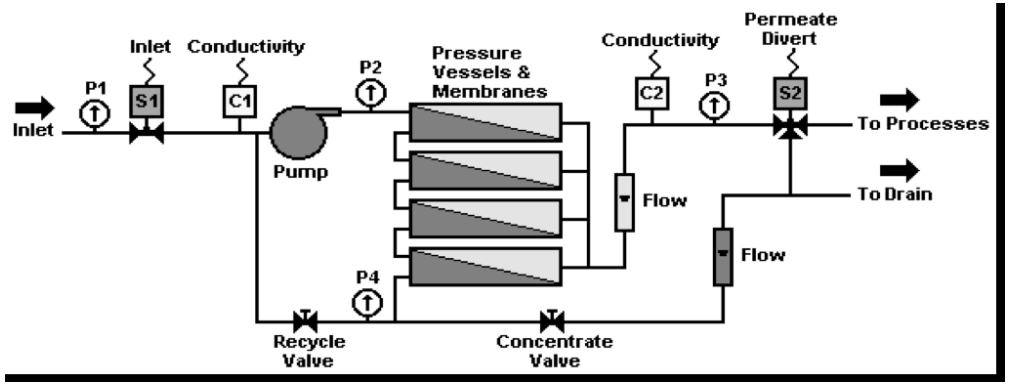
Pre-treatment Objectives

- Protect patients from drinking water disinfectants (chlorine and chloramines)
- Protect components from foulants (silts, colloids, humic acids, biologicals, etc.), scale, and oxidants
- Protect down stream components
- Provide optimum conditions for component operation

Typical Pre-treatment Chain

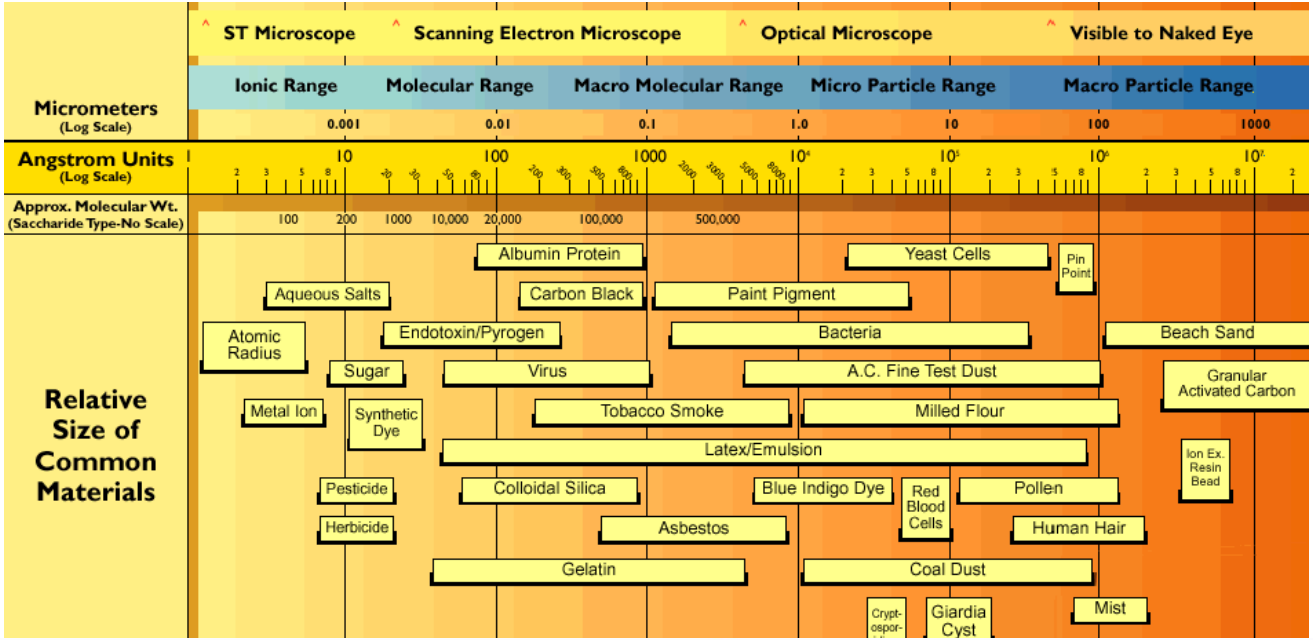


Water Treatment



Reverse Osmosis

Water Purification Processes



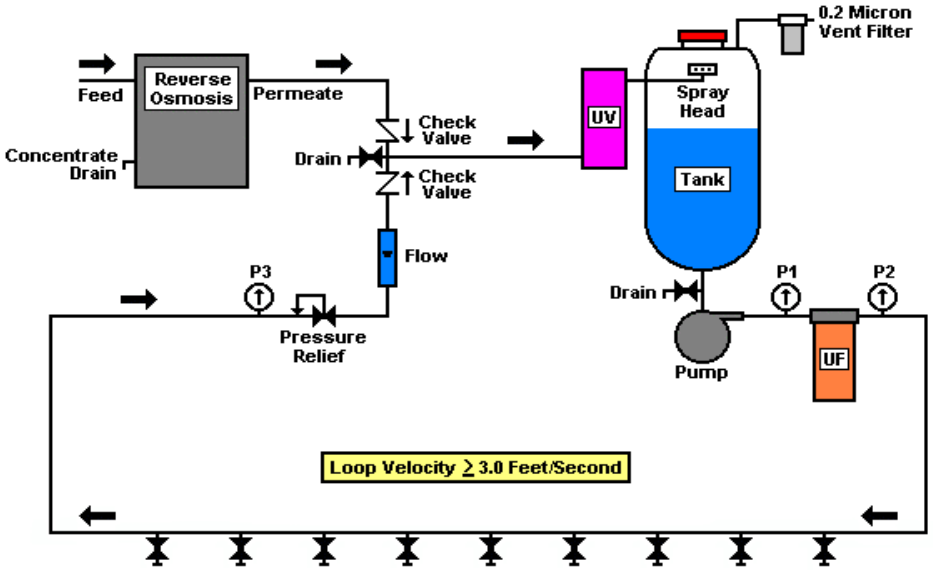
DEIONIZATION (DI)

- Ion exchange process, exchanges OH^- and H^+ to form water from anions and cations
- Produce water of highest ionic quality
- Highly dangerous when exhausted
- Bacteria & endotoxin levels increase, large surface area for microbial amplification
- Often used for RO “polish” or backup water treatment
- Requires alarms

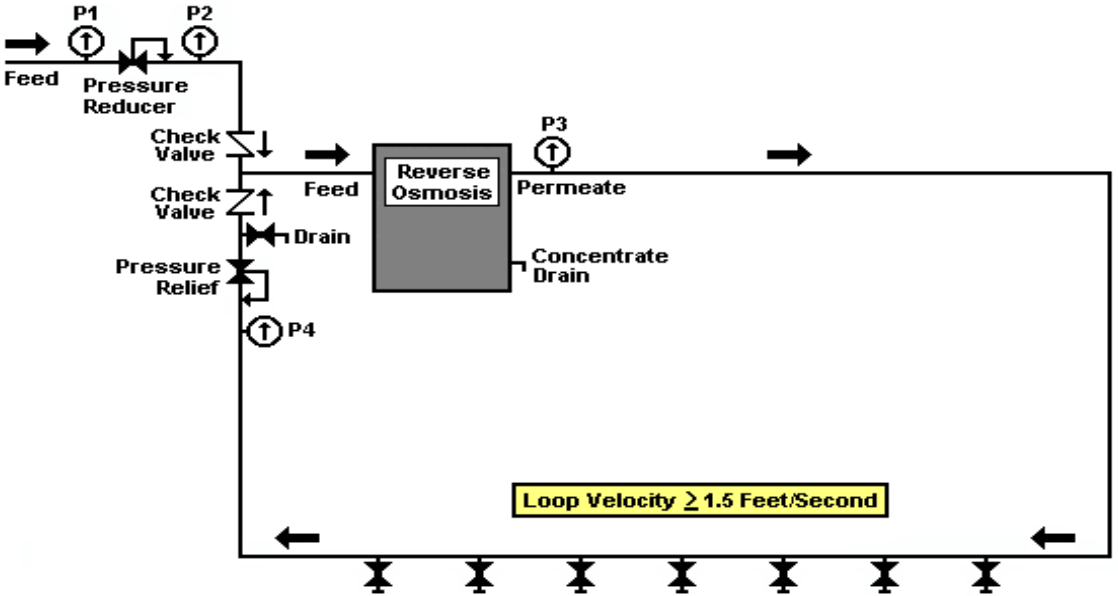
Distribution System Pitfalls

- **Non-inert materials**
- **Bacterial colonization due to:**

Indirect Feed Schematic Diagram



Direct Feed Diagram



How Often Should Monitoring Be Performed

- More is always better
- Some components are monitored daily
- Some are monitored continuously with temperature compensated audio and visual alarms
- Based on manufacturer's recommendation
- Some are monthly
- Some annually (eg. AAMI Chemicals); but seasonally may be better

Framework for Surveillance Water Treatment Equipment, Distribution Systems, and Dialysis Fluid

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Sediment filter	Pressure drop across the filter (see 7.3.2)	Pressure drop less than XXXX	Daily	NA
Sediment filter backwashing cycle	Backwash cycle timer setting (see 7.3.2)	Backwash clock set to XX:XX	Daily	NA
Cartridge filter	Pressure drop across the filter (see 7.3.3)	Pressure drop less than XXXX	Daily	NA
Water softener	Residual hardness of product water (see 7.3.4)	Hardness as specified by the manufacturer of the reverse osmosis equipment.	Daily	NA
Water softener brine tank	Level of undissolved salt in tank (see 7.3.4)	Salt level at XXX	Daily	NA
Water softener regeneration cycle	Regeneration cycle timer setting (see 7.3.4)	Regeneration cycle timer set to XX:XX	Daily	NA

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Carbon beds	Product-water total chlorine between the beds (see 7.3.5)	≤0,1 mg/l of total chlorine	Daily	Prior to each patient shift if chloramine is present in the feed water at 1 mg/l or more (see 7.3.5 for exceptions to these typical intervals). (Note that use of an online monitor can provide continuous surveillance and avoid the need for offline surveillance.)
Chemical injection system	Level of chemical in the reservoir, injector function, value of the controlling parameter (e.g. pH) (see 7.3.6)	Chemical level in reservoir ≥ XXX; controlling parameter in range XX to XX	Daily (continuous surveillance is preferable)	NA
Reverse osmosis	Product water conductivity, total dissolved solids (TDS), or resistivity and calculated rejection (see 7.3.7)	Rejection ≥ XX % Conductivity < XX µS/cm	Daily (continuous surveillance is preferable)	NA
Reverse osmosis	Product and reject flow rates, and calculated recovery (see 7.3.7)	Product water flow rate ≥ X,X l/min XX % < recovery < XX %	Daily (continuous surveillance is preferable)	NA
Deionizers	Product water resistivity or conductivity (see 7.3.8)	Resistivity ≥ 1 MΩ·cm Conductivity ≤ 1 µS/cm	Continuous surveillance	NA
Endotoxin-retentive filters	Pressure drop across the filter at a fixed flow rate or product-water flow rate at a fixed pressure drop (see 7.3.9)	Pressure drop less than XXXX or flow rate greater than XXX	Daily	NA

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Water system chemical contaminants	Chemical contaminants as listed in Tables 1 and 2 of ISO 23500-3	Maximums as listed in Tables 1 and 2 The parameters to be monitored should be defined by the validation process on the basis of the expected contaminants.	Yearly	These recommendations apply to dialysis water. However, chemical analysis of source water (or analysis results from the water supplier) is necessary to evaluate the overall performance of the water treatment system.
Dialysis water storage tanks	Bacterial growth and endotoxins (see Clause 8)	Total viable microbial count < action level (typically 50 CFU/ml); (see 4.2.4) Endotoxin < action level (typically 0,125 EU/ml); (see 4.2.4)	Monthly, or as defined by the results of the validation process for storage tanks supplying a central dialysis fluid delivery system	Specific testing at this location is performed to troubleshoot contamination of the distribution system for tanks connected to a water distribution piping system until a pattern of consistent conformity with limits can be demonstrated.
Water distribution piping system	Bacterial growth and endotoxins (see 7.4)	Total viable microbial count < action level (typically 50 CFU/ml); (see 4.2.4) Endotoxin < action level (typically 0,125 EU/ml); (see 4.2.4)	Monthly, or as defined by the validation process results	NA
UV irradiators	Energy output and/or the lamp life span (see 7.4.3.1)	Light output > XXX Lamp life span < XXXX	Monthly	NA
Ozone generators	Concentration in the water and contact time (see 7.4.3.2)	Ozone concentration > XXX Contact time > XXX Residual ozone after disinfection < X,XX mg/l	During each disinfection	NA
Hot water disinfection systems	Temperature and time of exposure of the system to hot water (see 7.4.3.3)	Temperature not less than XX °C; minimum exposure time at temperature ≥ XX min	During each disinfection	This information might be available from the data logs of automated systems.

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Chemical disinfection systems	Concentration of germicide in water and contact time	Germicide concentration > X,X mg/l; residual germicide concentration < X,XX mg/l after rinsing	During each disinfection	NA
Dialysis fluid	Conductivity, pH, electrolyte concentrations	XX,X mS/cm < conductivity < XX, X mS/cm pH in the range 6,9 to 8,0 for dialysis fluid containing bicarbonate, or as otherwise specified by the manufacturer	In accordance with local regulations or as specified by the manufacturer of the dialysis fluid delivery system (continuous surveillance for proportioning systems)	pH surveillance is necessary only if recommended by the manufacturer of the dialysis fluid delivery system.
Standard dialysis fluid	Bacterial growth and endotoxin concentration in standard dialysis fluid (see 4.4.2)	Total viable microbial count < action level (typically 50 CFU/ml); (see 4.4.2) Endotoxin < action level (typically 0,25 EU/ml); (see 4.4.2)	Monthly, rotated among machines so that each machine is tested at least once per year and different machines are sampled on each occasion	The sample should be collected at worst-case time (for example, Monday morning) if possible.
Ultrapure dialysis fluid	Bacterial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyser (see 4.4.3)	Total viable microbial count < 0,1 CFU/ml; endotoxin < 0,03 EU/ml (see 4.4.3) (see 8.3.1 and Annex E)	see footnote b	NA
Substitution fluid	Bacterial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyser (see 8.3.1 and Annex E)	Sterile and non-pyrogenic (see 8.3.1 and Annex E)	see footnote b	NA

[a] It is not possible to specify universally acceptable operating ranges for each device listed in the table since some of the specifications will be system-specific. In those cases, the facility should define an acceptable operating range based on the manufacturer's instructions or measurements of system performance.

[b] The actual interval for surveillance, testing, cleaning, and/or disinfection should be based on the results of the validation process and on going trend analysis (see Clause 6, 7.2.3, and 8.2.3).

Daily Monitoring

Item To Monitor	What To Monitor
Sediment/Depth filter	Δ Pressure
Sediment Filter (If it backwashes)	Check timer
Cartridge Filter	Δ Pressure
Softener	Product water softness @end of day
Brine Tank	Level of undissolved salt
Softener regeneration cycle	Check timer
Chemical Injection Systems	Chemical level in reservoir, controlling parameter
Carbon Adsorption	Prior to each shift: Total Chlorine
Ultrafilters	Δ Pressure

Monthly Monitoring

Item to Monitor	What to Monitor	Specification*
Water*	Microbial growth and pyrogens	HPC < 50 CFU/mL; Endotoxin 1EU/ml
Dialysate	Microbial growth and pyrogens; rotate so that each machine is tested at least once per year	HPC < 50 CFU/mL; Endotoxin 1EU/ml
UV LightSource	Energy output	
Patients	Potassium, BUN (blood urea nitrogen), creatinine, and phosphorus	On a Quarterly basis HgB, and Iron; Aluminum,

- Action Limits (ANSI/AAMI/ISO 23500 Series:2019)
- for new systems weekly until an established pattern consistent
- With compliance limits is demonstrated

Continuous Monitoring

Item to Monitor	What to Monitor	Specification
Reverse Osmosis	Product and reject water flow rates, calculated recovery (record daily)	Flow rates >X.X gpm; % recovery(eg,90-99%)
Deionizers	Resistivity	> 1 MΩ-cm

Performance Disinfection Monitoring

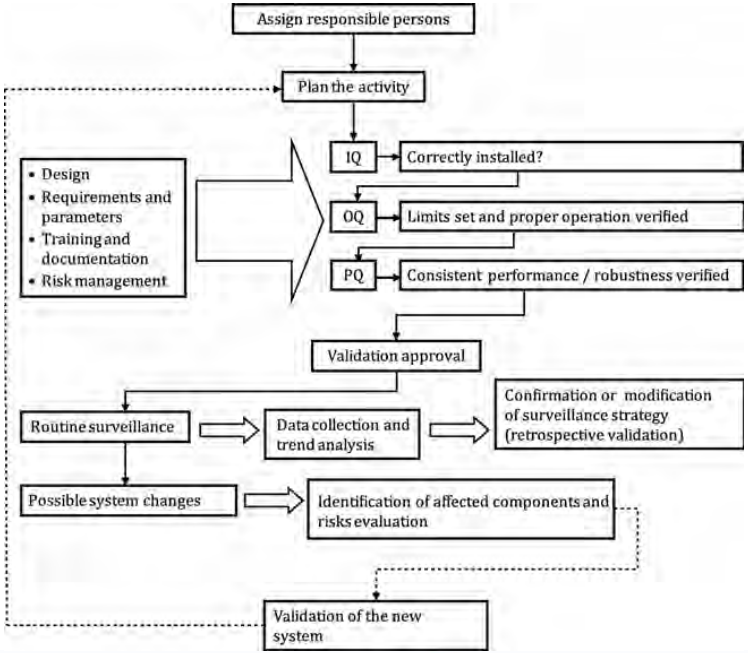
Item to Monitor	What to Monitor	Specification
Ozone generators	Concentration of O_3 in water	During each disinfection
Hot water disinfection systems	Temperature and exposure time	During each disinfection
Disinfectant (Hypochlorite, peracetic acid, Ozone, etc.)	Concentration; presence testing	Confirm contact time and rinse out
Microbial Contamination	Heterotrophic plate count and bacterial endotoxin testing	At least monthly

Microbial Control
Disinfection Strategies

- **Chemical Germicides:**
  - Aqueous formaldehyde (1-2%)*
  - Sodium hypochlorite (500 ppm-5000mg/L)
  - Hydrogen peroxide
  - Peracetic acid
  - Ozone
  - Chlorine dioxide
- **Other Mechanisms:**
  - Hot water pasteurization (>80°C)

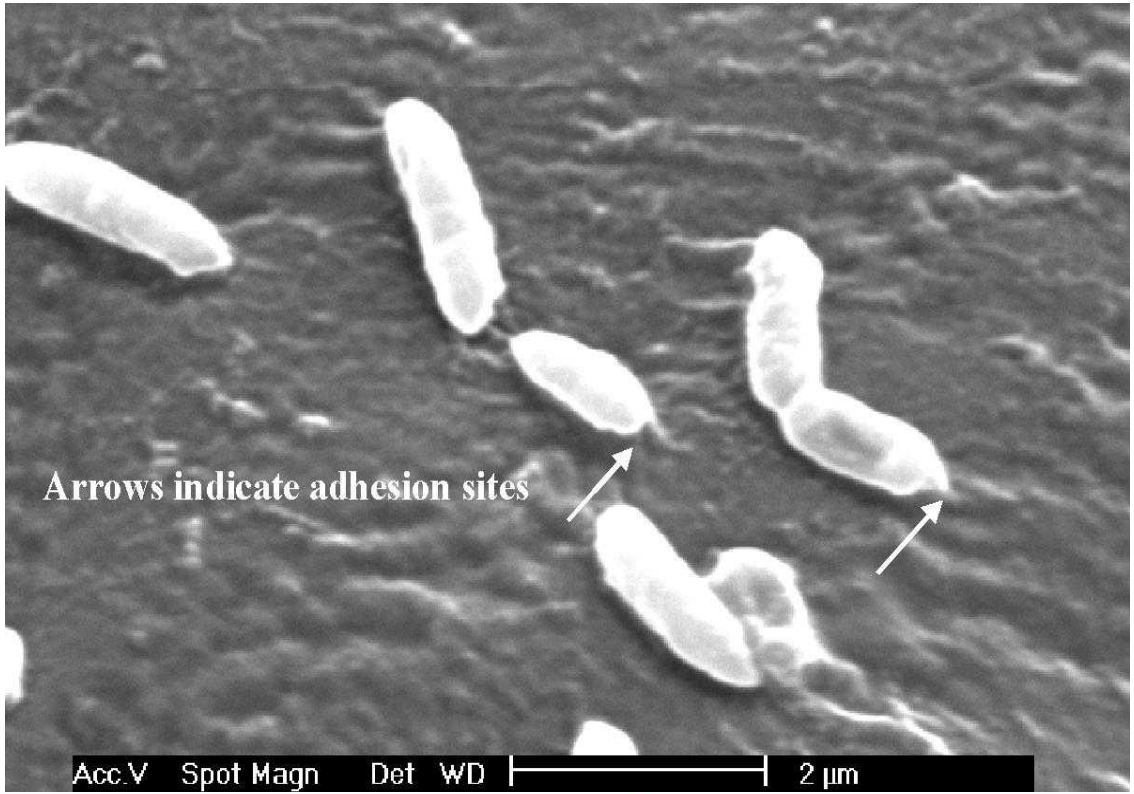
*included for historical purposes; No longer used since classified as a carcinogen and EPA set limits regarding allowable concentrations discharged to wastewater and sewer system

An Example of the Validation Process

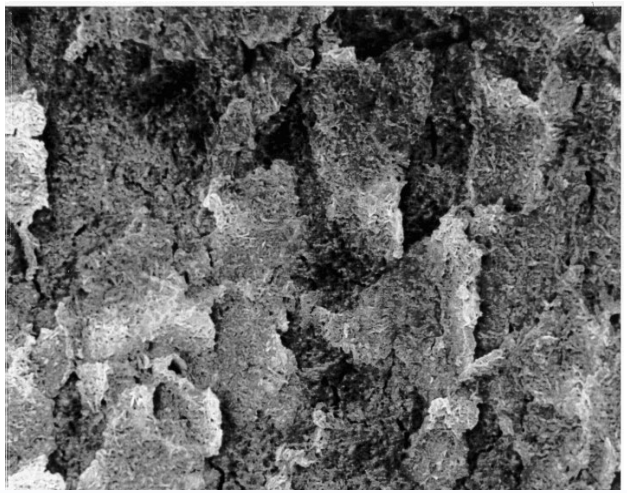


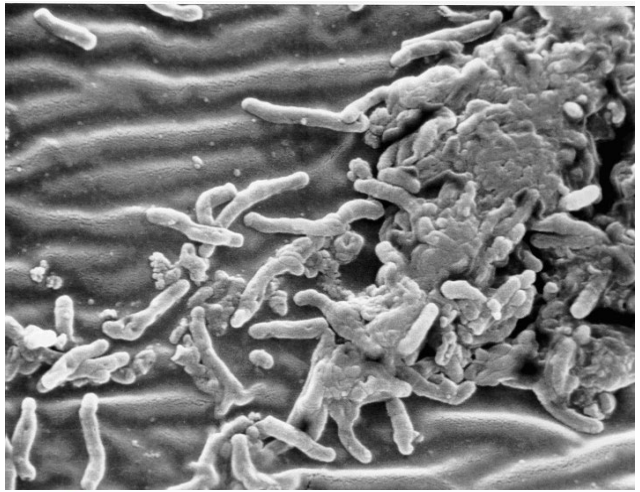
Potential Problem Areas

- **How do we truly detect biofilm if it forms on all wetted surfaces?**
  - In real world sampling of surfaces scrapings or actual visualization via fluorescent imaging or electron microscopy is used to detect the presence of biofilm
- **What microbiologic assays tell us the true story?**
  - Current culture techniques and time schedules measure planktonic (free swimming cells).
  - Microorganisms prefer to grow on surfaces

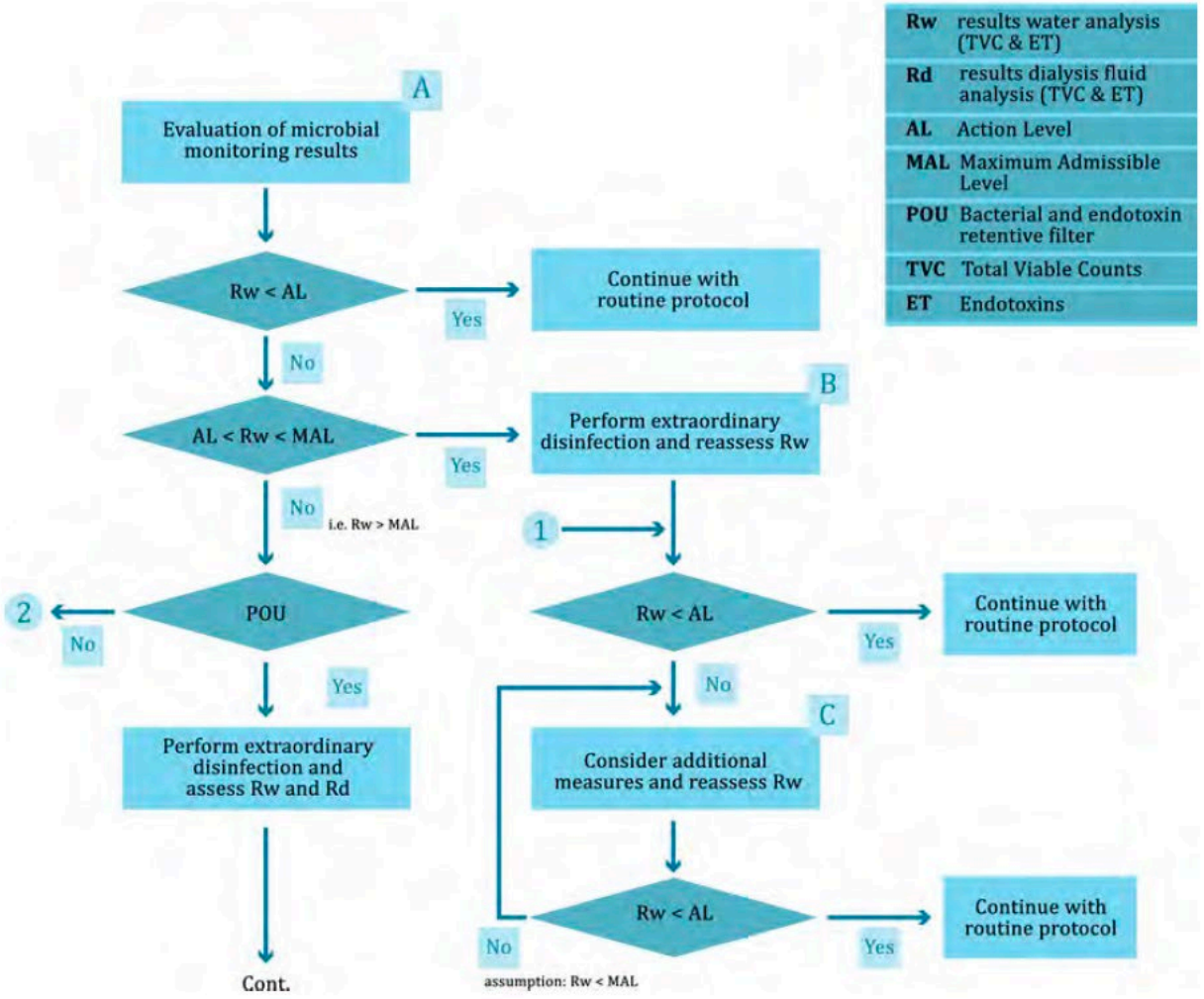

Arrows indicate adhesion sites
Acc.V Spot Magn Det WD 2 µm

Scanning Electron Micrographs of Established Bio film





- **The primary approach in respect of interpretation of microbiological test results is the use of trend analysis.**
- **Algorithm of actions to be taken in the event of Microbiologic MCLs are reached**



Responding to Results Some Examples

- Colony counts or endotoxin > than action limit: Investigate and considered disinfection distribution loops
- If chlorine break through on worker tank call vendor to replace GAC and monitor chlorine of water after 2nd serial tank (Polisher)
- Responding to alarms or Δ P:
  - investigate cause;
  - replace components as necessary;
  - Clean and disinfect RO membrane/replace membrane
  - Replacement of DI tanks (for facilities that use these)

Summary

- Water treatment systems and dialysis distribution systems should be monitored
- Results of microbiologic data and system data should be trended to inform actions
- In addition to system and environmental monitoring active surveillance for adverse dialysis events should be in place.
  - Bloodstream infections
  - Pyrogenic Reactions
  - Other adverse events (Dementia, bone disease, pruiritis, hemolysis, anemia, rhEPO resistance, hypotension, nausea vomiting, cardiac events, etc)
- Results are discussed as part of CQI/CQA meetings;
- Medical Director or designee is notified when monitoring indicates a problem

Resources

- **AAMI Complete Dialysis Collection:** https://aami.org/news-resources/publications/complete-dialysis-collection-2022
- Dialysis Safety: https://www.cdc.gov/dialysis/index.html
- Water Use in Dialysis: (https://www.cdc.gov/dialysis/guidelines/water-use.html)
- Dialysis Care After a Disaster: (https://www.cdc.gov/disasters/dialysis.html)
- CMS ESRD Center: (https://www.cms.gov/medicare/coverage/end-stage-renal-disease-center)
- AHRQ Safety Program for End-Stage Renal Disease Facilities – Toolkit: (https://www.ahrq.gov/patient-safety/settings/esrd/resource.html)

Resources II

- Nephrologists Transforming Dialysis Safety (NTDS): (https://epc.asn-online.org/projects/ntds/#gsc.tab=0)
- Forum of ESRD Networks Outpatient Medical Director Toolkit, 2021: (https://media.esrdnetworks.org/documents/Outpatient_Medical_Director_Toolkit_2021_1118_combined.pdf)
- CDC, EPA, AWWA. Emergency Water Supply Planning Guide for Hospitals and Healthcare Facilities, 2019) (https://www.cdc.gov/healthywater/emergency/pdf/emergency-water-supply-planning-guide-2019-508.pdf

Coming from AAMI In the Near Future

- Committee Review of ANSI/AAMI/ISO 23500:2019 Series
- Update to AAMI. Water testing Methodologies, AAMI TIR58:2021
- New TIR in progress on Hemodialysis distribution systems (will cover backflow prevention, distribution system components and materials, wall boxes)

Thanks!

Join the Coalition: Making Dialysis Safer For Patients Coalition

Matthew Arduino
Email: mja4@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.