MINIMIZING THE IMPACT OF WATER-BORNE BACTERIA ON HEMODIALYSIS PATIENTS

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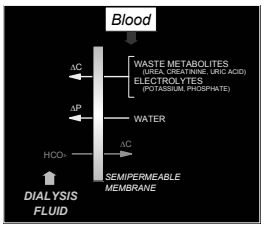
OVERVIEW

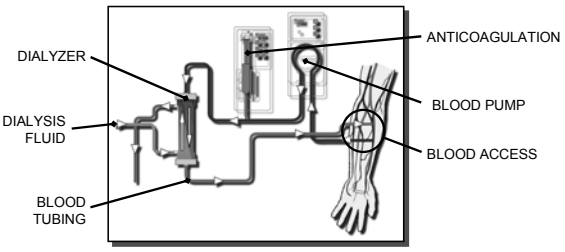
- WHAT IS THE ROLE OF DIALYSIS FLUID (DIALYSATE) IN HEMODIALYSIS?
- WHY IS THE MICROBIOLOGICAL QUALITY OF THE DIALYSIS FLUID IMPORTANT?
- HOW CAN SAFE LEVELS OF MICROBIOLOGICAL CONTAMINANTS BE ASSURED?

HEMODIALYSIS

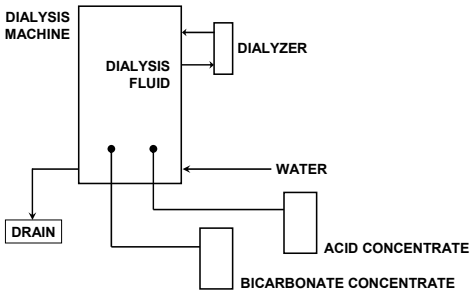
- **REPLACES THE EXCRETORY FUNCTIONS OF THE KIDNEY**
  - ✓ REGULATES WATER BALANCE
  - ✓ REGULATES ELECTROLYTE BALANCE
  - ✓ ELIMINATES WASTE PRODUCTS OF METABOLISM
- **DOES NOT REPLACE ENDOCRINE AND METABOLIC FUNCTIONS OF THE KIDNEY**



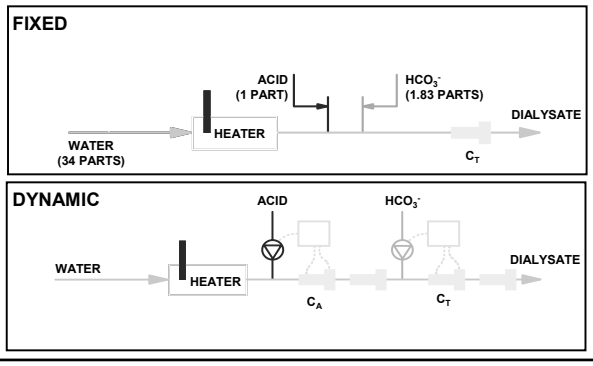
HEMODIALYSIS

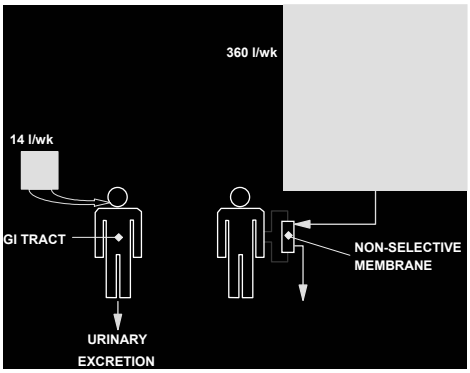


PREPARATION OF DIALYSIS FLUID



DIALYSIS FLUID PREPARATION





AAMI WATER QUALITY STANDARDS - RD62:2001

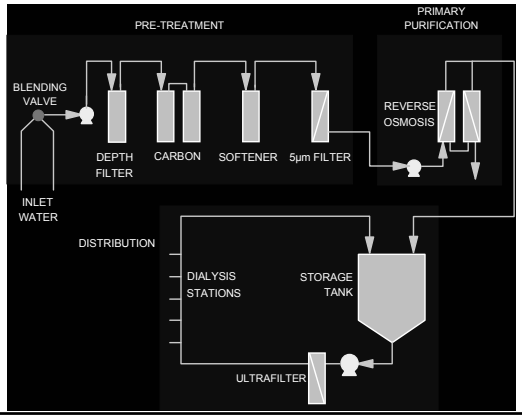
SUBSTANCES IN DIALYSATE	
CALCIUM	2
MAGNESIUM	4
SODIUM	70
POTASSIUM	8
TOXIC SUBSTANCES (SDWA)	
ANTIMONY	0.006
ARSENIC	0.005
BERYLLIUM	0.0004
BARIUM	0.1
CADMIUM	0.001
CHROMIUM	0.014
LEAD	0.005
MERCURY	0.0002
SELENIUM	0.09
SILVER	0.005
THALIUM	0.002

SUBSTANCES TOXIC IN DIALYSIS	
ALUMINUM	0.01
CHLORAMINES	0.10
FREE CHLORINE	0.5
COPPER	0.10
FLUORIDE	0.20
NITRATE (as N)	2.0
SULFATE	100
ZINC	0.10
MICROBIOLOGICAL CONTAMINANTS	
BACTERIA	200
ACTION LEVEL	50
ENDOTOXIN	2
ACTION LEVEL	1

CHEMICAL CONCENTRATIONS IN 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

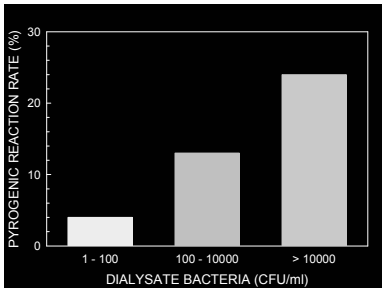
DEFINITIONS OF MICROBIOLOGICAL QUALITY

	Bacteria (cfu/ml)	Endotoxin (EU/ml)
AAMI Recommended Practice	200	2
ERA-EDTA Best Practice Guidelines	100	0.25
Ultrapure	0.1	<0.03
Sterile	10^{-6}	<0.03

SEPTICEMIA AND PYROGENIC REACTIONS

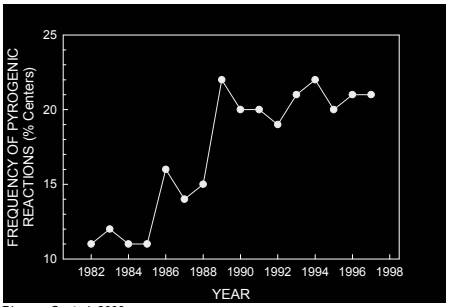
- **BACTERIA**
  - DO NOT CROSS DIALYZER MEMBRANES
  - MAY INFECT BLOOD COMPARTMENT DURING PROCESSING OF DIALYZER FOR REUSE
  - CAN CAUSE SEPSIS CHARACTERIZED BY WATER-BORNE ORGANISMS
- **ENDOTOXIN**
  - FRAGMENTS MAY CROSS DIALYZER MEMBRANES
  - MAY CONTAMINATE BLOOD COMPARTMENT DURING PROCESSING OF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

INTRADIALYTIC PYROGENIC REACTIONS



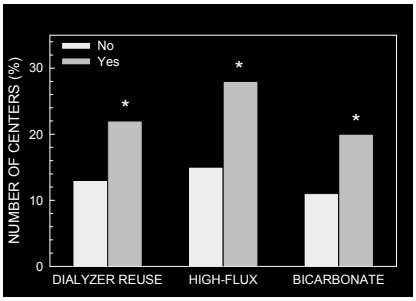
Favero MS et al. Trans Am Soc Artif Int Organs 20:175-183, 1974

PREVALENCE OF PYROGENIC REACTIONS



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

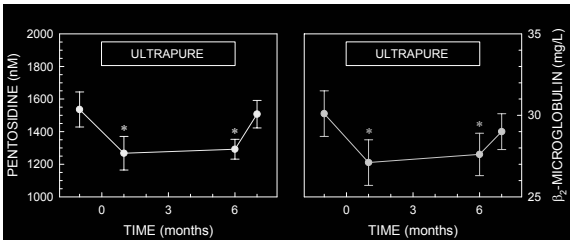
INCORRECT GERMICIDE CONCENTRATION	5/10
INAPPROPRIATE GERMICIDE	2/10
USE OF TAP WATER TO CLEAN OR RINSE DIALYZERS	3/10
USE OF MULTIPLE GERMICIDES	1/10
USE OF WATER NOT MEETING AAMI STANDARDS	10/10

Arduino MJ et al. Dial Transplant 22:652-656, 1993

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 β_2-MICROGLOBULIN AMYLOIDOISIS, ATHEROSCLEROSIS, AND MALNUTRITION

EFFECT OF WATER QUALITY ON INFLAMMATION AND β_2-MICROGLOBULIN



Furuya R, et al. Blood Purif 23:311-316, 2005

RISK OF DEVELOPING DIALYSIS-ASSOCIATED AMYLOIDOSIS WITH CONTAMINATED DIALYSIS FLUID

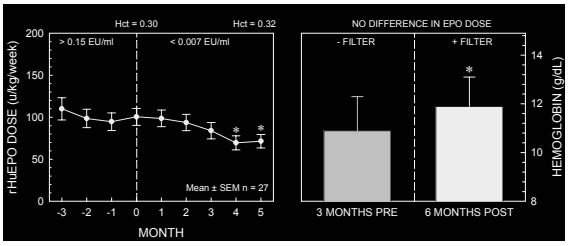
	ODDS RATIO (95% CI)
β_2-MICROGLOBULIN AMYLOIDOSIS	3.308 (1.45 – 6.35) p = 0.031
BONE CYSTS	1.85 (1.00 – 3.42) p = 0.047
CARPAL TUNNEL SYNDROME	2.86 (1.35 – 6.07) p = 0.006
ARTHROPATHY	9.04 (2.06 – 39.6) p = 0.004

N = 89
10 YEAR FOLLOW-UP

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

Schiffl H et al. Nephrol Dial Transplant 15:840-845, 2000

EFFECT OF IMPROVED WATER QUALITY ON ANEMIA CORRECTION

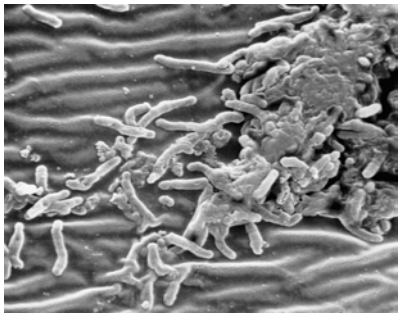


Matsuhashi N and Yoshioka T. Nephron 92:601-604, 2002

Rahmati MA et al. Int J Artif Organs 27:723-727, 2004

POTENTIAL ADVANTAGES OF WATER AND DIALYSIS FLUID OF HIGH MICROBIOLOGICAL PURITY

- LESS INFLAMMATORY STIMULUS
- REDUCED INCIDENCE OF β_2-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

	CFU/cm^2	TOTAL BACTERIA/cm^2
TUBING FROM		
WATER PATH	23	1.4 x 10^5
BICARBONATE PATH	17	1.54 x 10^5
DIALYSIS FLUID PATH	12	3.2 x 10^5
DIALYSIS FLUID	0	0

N = 3

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

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

CULTURING CONDITIONS	
TECHNIQUE	MEMBRANE FILTER, SPREAD PLATE
MEDIUM	TRYPTIC SOY AGAR OR EQUIVALENT
TEMPERATURE	35 - 37°C
TIME	48 hours
ENDOTOXIN MEASUREMENT	
TECHNIQUE	LIMULUS AMEBOCYTE LYSATE ASSAY

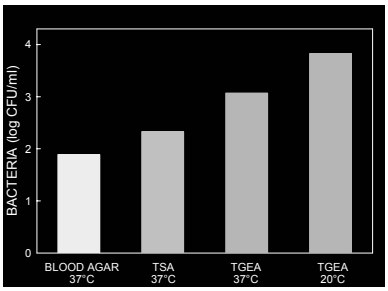
SAMPLE COLLECTION

- 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 INOT 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

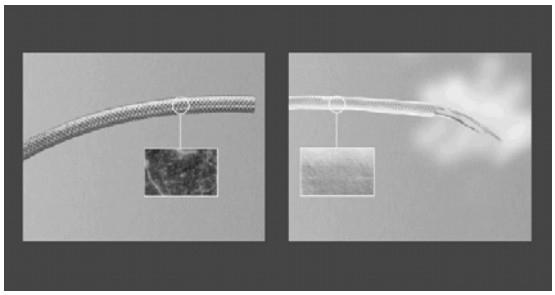
- **CALIBRATED LOOP**
  - STANDARD TECHNIQUE IN CLINICAL LABORATORIES
  - SAMPLE VOLUME IS TOO SMALL FOR REQUIRED SENSITIVITY
  - SPECIFICALLY PROHIBITED FOR DIALYSIS APPLICATIONS
- **PADDLES**
  - CONVENIENT FOR ON-SITE TESTING
  - REQUIRE A MAGNIFIER AND LIGHT-SOURCE FOR ACCURATE ENUMERATION OF COLONIES
  - MAY GIVE AN APPARENT FALSE NEGATIVE WITH HEAVILY CONTAMINATED SAMPLES
- **MEMBRANE FILTRATION**
  - VERY SENSITIVE
  - REQUIRES FILTRATION SYSTEM AND LARGE SAMPLE VOLUMES

EFFECT OF CULTURE CONDITIONS ON COLONY COUNT IN DIALYSATE



Ledebo I, Nystrand R. Artif Organs 23:37-43, 1999

NO MAN'S LINE



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 x 10^9 CFU/ml (*Pseudomonas sp.*).
- Tubing was cleaned with 3% citric acid at 20°c for 5 minutes before disinfection for 40 minutes.

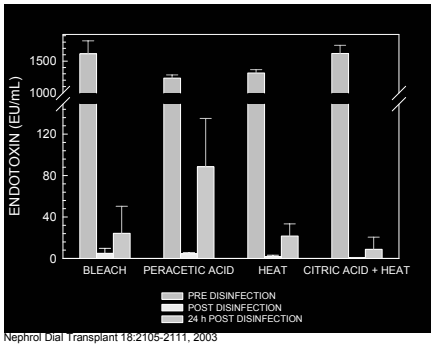
Marion-Ferey K, et al. J Hosp Infect 53:64-71, 2003

EFFECTS OF CLEANING AND DISINFECTION ON BIOFILM

CLEANING	DISINFECTION	BIOFILM (Δ%)		RESIDUAL	
		THICKNESS	COVERAGE	CFU/cm^2	EU/cm^2
-	BLEACH (0.3%, 20°C)	50	58	22	354
CITRIC ACID	BLEACH (0.3%, 20°C)	60	65	< 1	22
-	ACTRIL (3%, 20°C)	19	15	8.6 x 10^3	470
CITRIC ACID	ACTRIL (3%, 20°C)	54	68	2.1 x 10^3	70
-	CITRIC ACID (3%, 90°C)	0	7	3.6 x 10^5	2618
-	WATER (90°C)	0	7	9.1 x 10^4	1400
CITRIC ACID	BLEACH (3% 20°C)	67-100	98	18	27

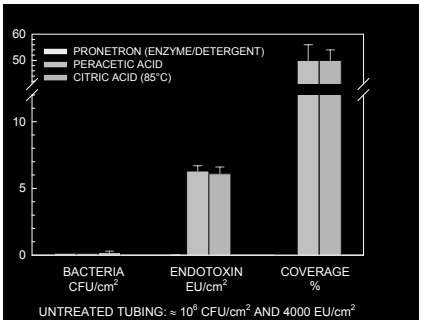
Marion-Ferey K, et al. J Hosp Infect 53:64-71, 2003

EFFECT OF ACID CLEANING ON DISINFECTION



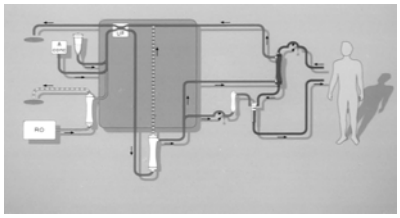
Cappelli G et al. Nephrol Dial Transplant 18:2105-2111, 2003

EFFECT OF CLEANING WITH ENZYMES AND



Marion K, et al. Blood Purif 23:339-348, 2005

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 β_2-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.