

DIALYSIS FLUID QUALITY: AN IMPORTANT PART OF THE DIALYSIS PRESCRIPTION

Presented by Dr. Richard Ward

A Webber Training Teleclass, March 11, 2004

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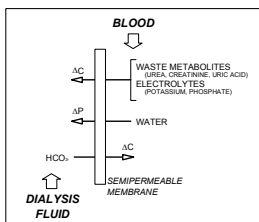


OVERVIEW

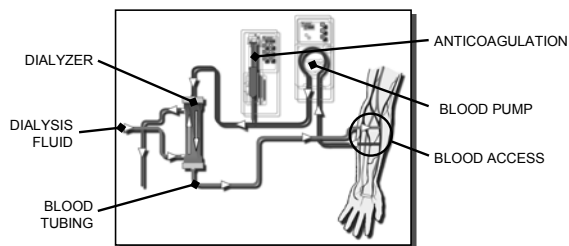
- WHAT IS THE ROLE OF DIALYSIS FLUID (DIALYSATE) IN HEMODIALYSIS?
- WHY IS THE QUALITY OF THE DIALYSIS FLUID IMPORTANT?
- WHAT ADVERSE OUTCOMES MAY BE RELATED TO CONTAMINATED DIALYSIS FLUID?
- HOW CAN SAFE LEVELS OF THESE CONTAMINANTS BE ASSURED?

HEMODIALYSIS

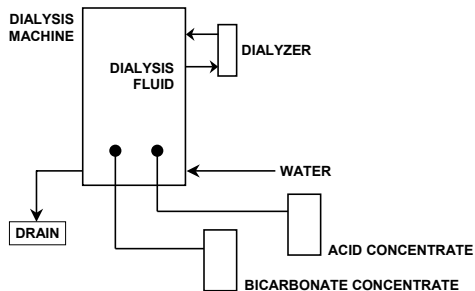
- REPLACES THE EXCRETORY FUNCTIONS OF THE KIDNEY
 - ✓ REGULATES WATER BALANCE
 - ✓ REGULATES ELECTROLYTE BALANCE
 - ✓ ELIMINATES WASTE PRODUCTS OF METABOLISM
- DOES NOT REPLACE ENDOCRINE AND METABOLIC FUNCTIONS OF THE KIDNEY



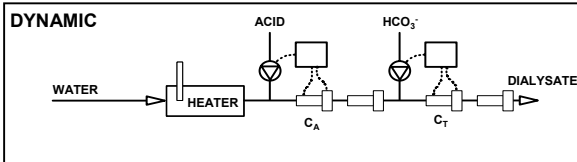
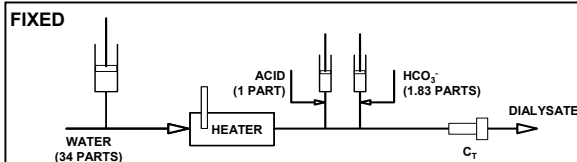
HEMODIALYSIS



PREPARATION OF DIALYSIS FLUID



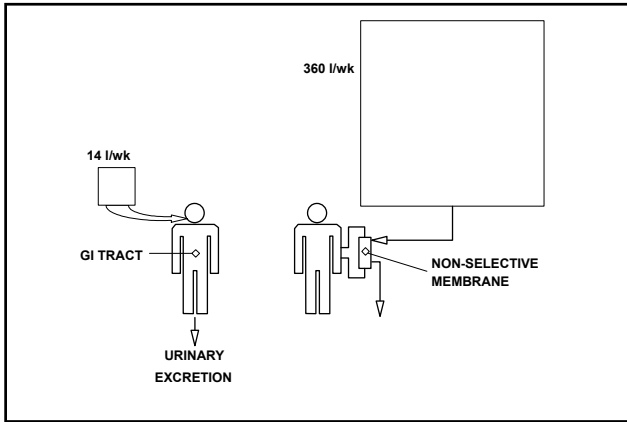
DIALYSIS FLUID PREPARATION



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TOXIC WATER CONTAMINANTS

CONTAMINANT	SOURCE	ADVERSE EVENT
ALUMINUM	MUNICIPAL WATER	ENCEPHALOPATHY, BONE DISEASE, ANEMIA
CHLORAMINES	MUNICIPAL WATER	HEMOLYSIS
FLUORIDE	MUNICIPAL WATER	FATAL ARRHYTHMIA, BONE DISEASE (?)
CYANOTOXIN	SOURCE WATER	LIVER FAILURE
NITRATES	SOURCE WATER	ANEMIA
ENDOTOXIN	DIALYSIS UNIT	PYROGENIC REACTIONS, CHRONIC INFLAMMATION
COPPER	DIALYSIS UNIT	HEMOLYSIS, NAUSEA, VOMITING
ZINC	DIALYSIS UNIT	HEMOLYSIS, NAUSEA, VOMITING
CALCIUM, MAGNESIUM	SOURCE WATER, MUNICIPAL WATER	NAUSEA, VOMITING

Progressive Dialysis Encephalopathy From Dialysate Aluminum

Vitor V. Rosta, MD, Friedrich K. Port, MD, Wilmar M. Rost, MD

Arch Intern Med—Vol 138, Sept 1978

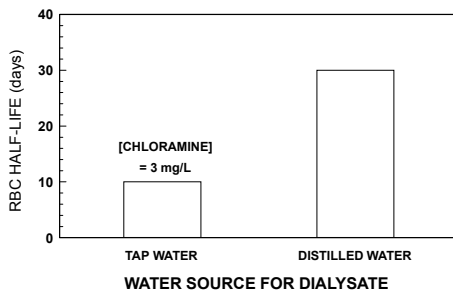
Dialysis Encephalopathy—Rosta et al 1275

- 8 CASES OF FATAL DIALYSIS ENCEPHALOPATHY OBSERVED IN 22 MONTHS (38% OF ALL PATIENTS).
- COINCIDED WITH ADDITION OF ALUMINUM SULFATE AND SODIUM ALUMINATE TO THE CITY WATER RESULTING IN DIALYSIS FLUID ALUMINUM CONCENTRATIONS OF 200 - 1000 µg/L (AVERAGE 675 µg/L), AND AN ESTIMATED LOAD OF ALUMINUM WITH EACH DIALYSIS TREATMENT OF 3 - 16 mg.
- THE OUTBREAK ENDED AFTER INSTALLATION OF DEIONIZER THAT REDUCED DIALYSIS FLUID ALUMINUM TO < 1 µg/L.

ANEMIA OR APPARENT ERYTHROPOIETIN RESISTANCE

- **CHLORAMINES**
 - OXIDIZES HEMOGLOBIN TO METHEMAGLOBIN
 - INHIBITS ANTIOXIDANT PATHWAYS
- **COPPER**
 - INHIBITS ANTIOXIDANT PATHWAYS
 - DECREASES RBC DEFORMABILITY
- **ZINC**
- **ALUMINUM**
 - DECREASES HEMOGLOBIN SYNTHESIS
 - INTERFERES WITH IRON METABOLISM

CHLORAMINE-INDUCED HEMOLYSIS



Kjellstrand C et al. Nephron 13:427, 1974

AAMI WATER QUALITY STANDARDS - RD62:2001

SUBSTANCES IN DIALYSATE		SUBSTANCES TOXIC IN DIALYSIS	
CALCIUM	2	ALUMINUM	0.01
MAGNESIUM	4	CHLORAMINES	0.10
SODIUM	70	FREE CHLORINE	0.5
POTASSIUM	8	COPPER	0.10
		FLUORIDE	0.20
TOXIC SUBSTANCES (SDWA)		NITRATE (as N)	2.0
ANTIMONY	0.006	SULFATE	100
ARSENIC	0.005	ZINC	0.10
BERYLLIUM	0.0004		
BARIUM	0.1	MICROBIOLOGICAL CONTAMINANTS	
CADMIUM	0.001	BACTERIA	200
CHROMIUM	0.014	ACTION LEVEL	50
LEAD	0.005	ENDOTOXIN	2
MERCURY	0.0002	ACTION LEVEL	1
SELENIUM	0.09		
SILVER	0.005		
THALIUM	0.002		

CHEMICAL CONCENTRATIONS IN mg/L, BACTERIA CFU/ml, ENDOTOXIN EU/ml

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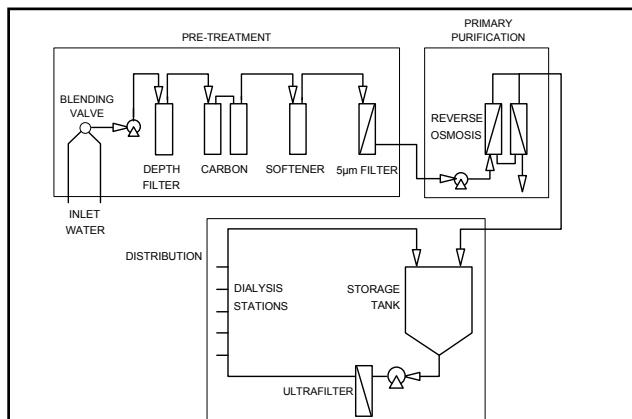
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WATER TREATMENT SYSTEM

- 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

PROCESS	CONTAMINANT
CARBON ADSORPTION	CHLORAMINES, ORGANICS
SOFTENER	CALCIUM
REVERSE OSMOSIS	IONIC CONTAMINANTS, BACTERIA, ENDOTOXIN
DEIONIZATION	IONIC CONTAMINANTS
ULTRAFILTRATION	BACTERIA, ENDOTOXIN



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 CHLORAMINE**

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

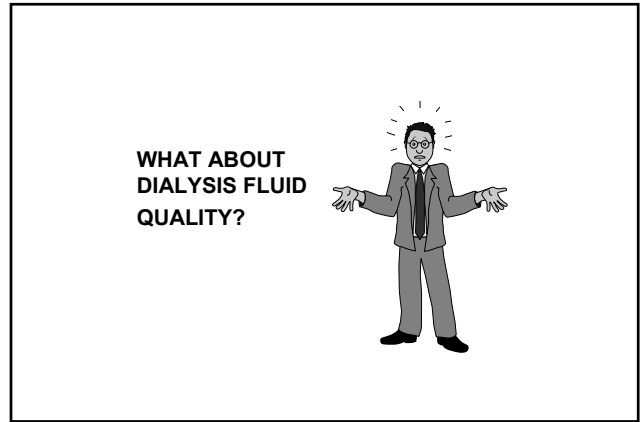
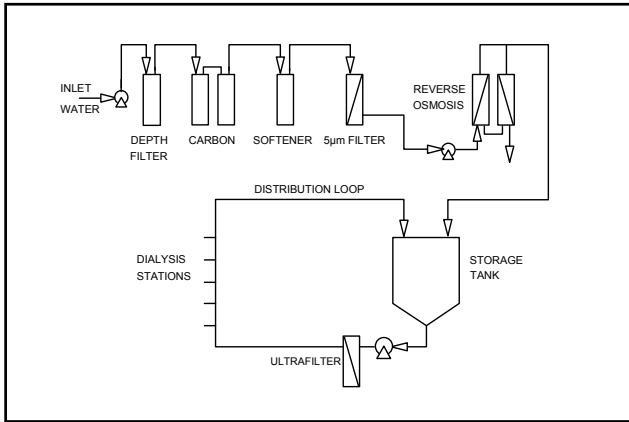
REVERSE OSMOSIS versus ION EXCHANGE

- **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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DIALYSIS FLUID QUALITY
AAMI RD52 - DIALYSATE FOR HEMODIALYSIS

PROPOSED LIMITS FOR CHEMICAL CONTAMINANTS

- SAME AS FOR WATER (RD62:2001)

PROPOSED LIMITS FOR MICROBIOLOGICAL CONTAMINANTS

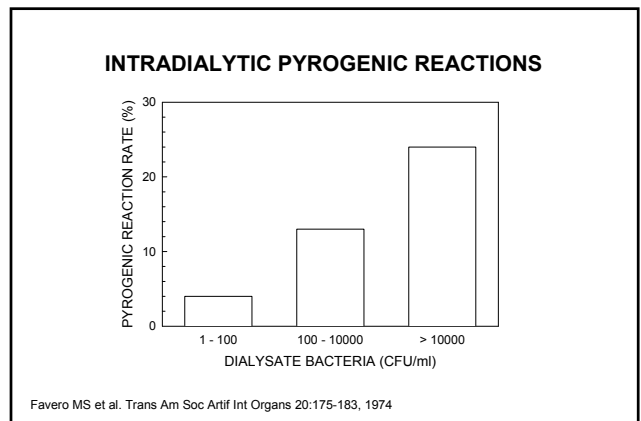
- BACTERIA: 200 CFU/ml
ACTION LEVEL: 50 CFU/ml
- ENDOTOXIN: 2 EU/ml
ACTION LEVEL: 1 EU/ml

DIALYSIS FLUID
DEFINITIONS OF MICROBIOLOGICAL QUALITY

	Bacteria (cfu/ml)	Endotoxin (EU/ml)
AAMI Recommended Practice (Proposed)	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

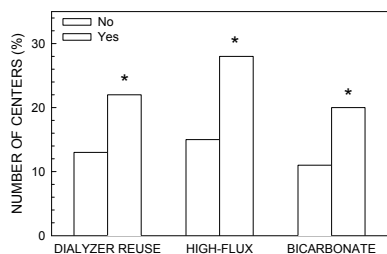


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INFLUENCE OF DIALYSIS PRACTICES ON PYROGENIC REACTIONS



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

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

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

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 > 10⁶ CFU/ml
P. aeruginosa, *Enterobacter cloacae* and *Candida parapsilosis*
Carr J. Hospital Infections Program, CDCP

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BIOMASS FROM DIALYSIS MACHINE TUBING

TUBING FROM	CFU/cm ²	TOTAL BACTERIA/cm ²
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

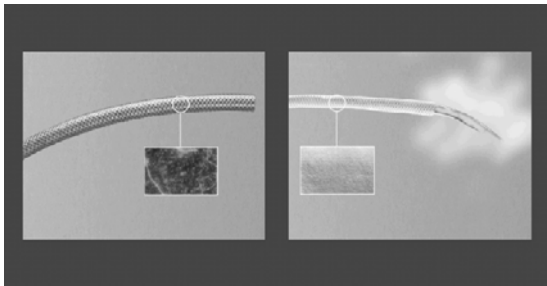
DESIGN TO LIMIT BACTERIAL PROLIFERATION

- 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.

NO MAN'S LINE



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
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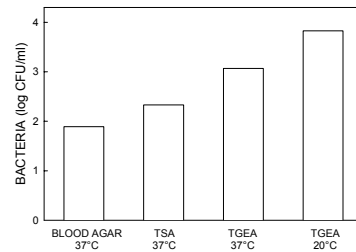
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ALTERNATIVES TO SPREAD-PLATE CULTURES

- **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

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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