Dialysis Water, The Essential Basics February 27, 2003

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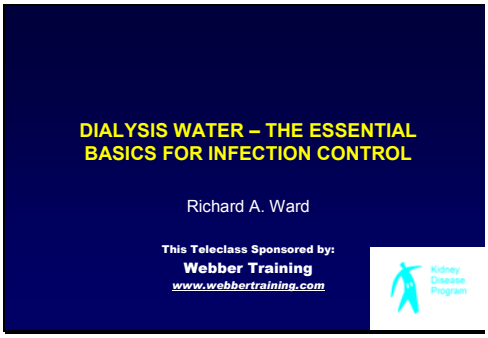

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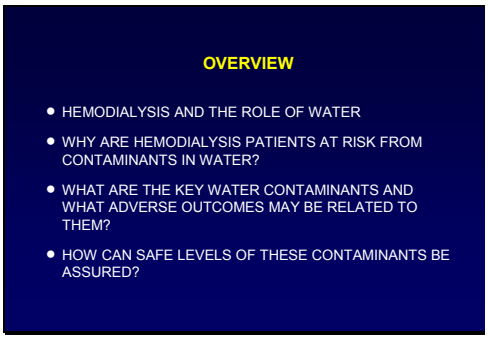

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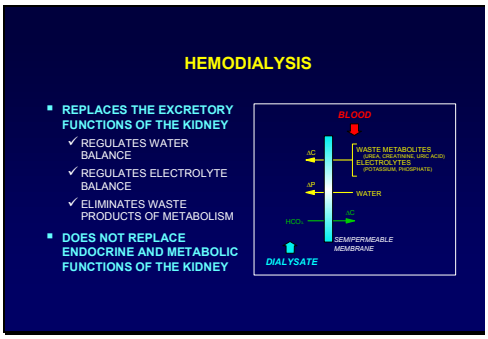

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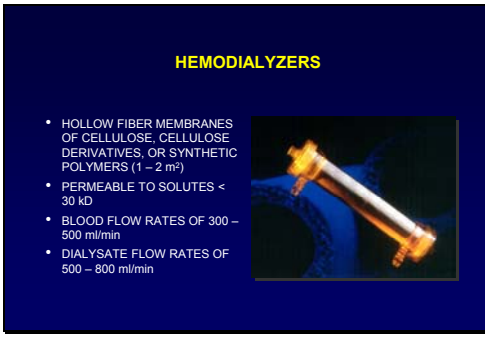

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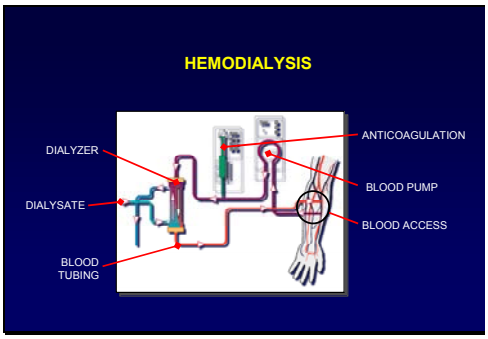

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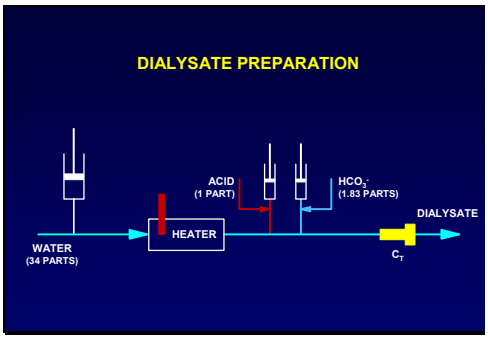

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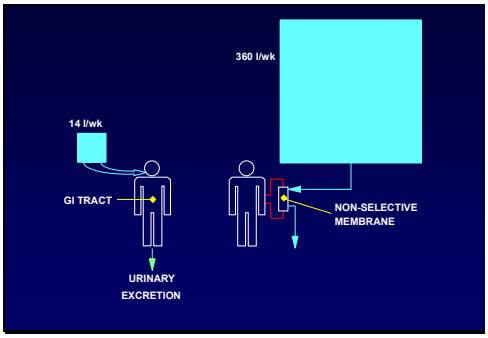

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TOXIC WATER CONTAMINANTS

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

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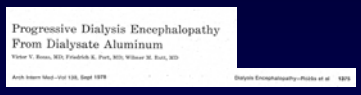
Progressive Dialysis Encephalopathy From Dialysate Aluminum

- 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 DIALYSATE 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 DIALYSATE ALUMINUM TO < 1 μg/L.

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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

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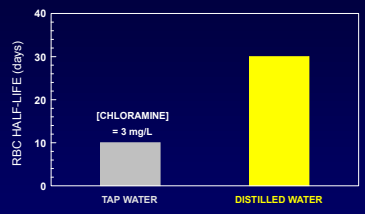
CHLORAMINE-INDUCED HEMOLYSIS



WATER SOURCE FOR DIALYSATE

Kjellstrand C et al. Nephron 13:427, 1974

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CHLORAMINE-INDUCED HEMOLYSIS

YEAR	PLACE	PTS Tx	CAUSE
1970	MINNEAPOLIS	?	WATER TREATMENT SYSTEM
1974	MADRID	?	?
1981	SYDNEY	13	MUNICIPAL WATER
1984	LOS ANGELES	25	WATER TREATMENT SYSTEM
1984	SAN DIEGO	10	WATER TREATMENT SYSTEM
1987	PHILADELPHIA	41	WATER TREATMENT SYSTEM
1989	SEOUL	24	MUNICIPAL WATER
1996	RAMAT-GAN	?	WATER TREATMENT SYSTEM
1996	LONDON	0	MUNICIPAL WATER
1998	DURHAM	1	?

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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
TOXIC SUBSTANCES (SDWA)		FLUORIDE	0.20
ANTIMONY	0.006	NITRATE (as N)	2.0
ARSENIC	0.005	SULFATE	100
BERYLLIUM	0.0004	ZINC	0.10
BARIUM	0.1		
CADMIUM	0.001	**MICROBIOLOGICAL CONTAMINANTS**	
CHROMIUM	0.014	BACTERIA	200
LEAD	0.005	ACTION LEVEL	50
MERCURY	0.0002	ENDOTOXIN	2
SELENIUM	0.09	ACTION LEVEL	1
SILVER	0.005		
THALIUM	0.002		

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

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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

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PURIFICATION PROCESSES

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

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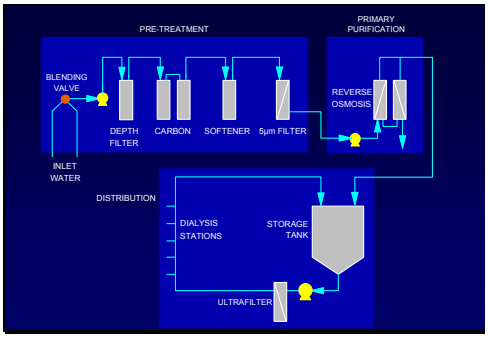

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PRE-TREATMENT

- **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**

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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 MUNICPAL WATER
  - HIGH pH IN THE MUNICIPAL WATER

  UNDER THESE CIRCUMSTANCES, CARBON ADSORPTION MAY NEED TO BE SUPPLEMENTED; FOR EXAMPLE, BY INJECTION OF METABISULPHITE

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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 Al 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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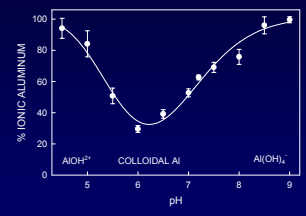
EFFECT OF pH ON ALUMINUM IN WATER



Parkinson IS et al. J Clin Pathol 34:1285-1294, 1981

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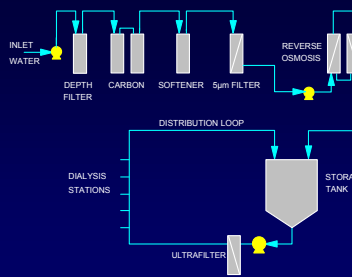

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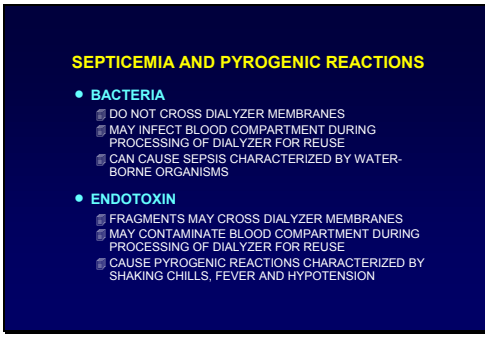

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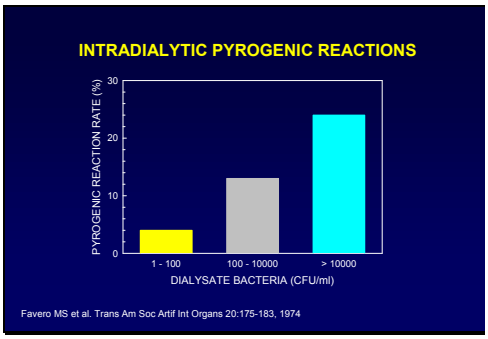

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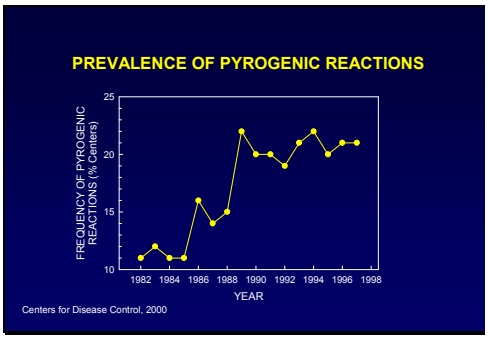

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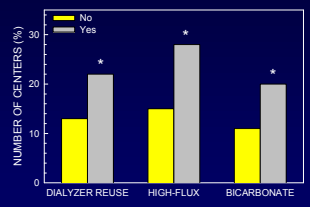
INFLUENCE OF DIALYSIS PRACTICES ON PYROGENIC REACTIONS



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

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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

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AAMI REQUIREMENTS MICROBIOLOGICAL QUALITY OF WATER FOR DIALYSIS

- **BACTERIA: < 200 CFU/ml.**
  - ACTION LEVEL: 50 CFU/ml
  - CULTURING CONDITIONS: TRYPTIC SOY AGAR OR EQUIVALENT FOR 48 hours AT 35 - 37°C
- **ENDOTOXIN: < 2 EU/ml.**
  - ACTION LEVEL: 1 EU/ml
  - LIMULUS AMEBOCYTE LYSATE ASSAY

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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

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RISK OF DEVELOPING DIALYSIS-ASSOCIATED AMYLOIDOSIS WITH CONTAMINATED DIALYSATE

	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 DIALYSATE: 550 CFU/ml
STANDARD DIALYSATE: 65 CFU/ml

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

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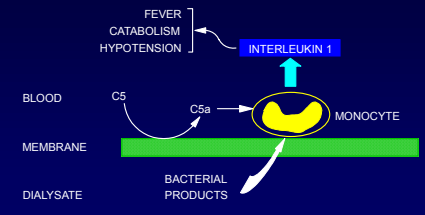
INTERLEUKIN HYPOTHESIS



Henderson LW et al. Blood Purif 1:3-8, 1983

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POTENTIAL ADVANTAGES OF WATER AND DIALYSATE 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

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DEFINITIONS OF DIALYSATE 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

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

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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
DIALYSATE PATH	12	3.2 x 10^5
DIALYSATE	0	0

N = 3

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

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CONTROL OF BACTERIA, ENDOTOXIN AND OTHER CYTOKINE-INDUCING SUBSTANCES

- DESIGN TO MINIMIZE 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
  - IF A STORAGE TANK IS USED
    - MINIMUM SIZE NEEDED TO ENSURE TURN-OVER OF WATER
    - TIGHT-FITING LID WITH A HYDROPHOBIC 0.2 mm FILTER AIR VENT
    - CONICAL BOTTOM WITH DRAIN AT LOWEST POINT
    - ADEQUATE DISINFECTION MECHANISM

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CONTROL OF BACTERIA, ENDOTOXIN AND OTHER CYTOKINE-INDUCING SUBSTANCES

- INCLUDE BACTERIAL CONTROL DEVICES
  - ULTRAFILTERS,
  - ON-LINE DISINFECTION WITH HOT WATER, OZONE, OR ULTRAVIOLET IRRADIATION
- DISINFECT REGULARLY
  - DISINFECTION SCHEDULES SHOULD BE DESIGNED TO **PREVENT**, NOT ELIMINATE, CONTAMINATION WITH BACTERIA AND BIOFILM
- MONITOR FREQUENTLY
  - USE SENSITIVE CULTURING METHODS FOR BACTERIA
  - USE LIMULUS AMEBOCYTE LYSATE ASSAY FOR ENDOTOXIN

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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.

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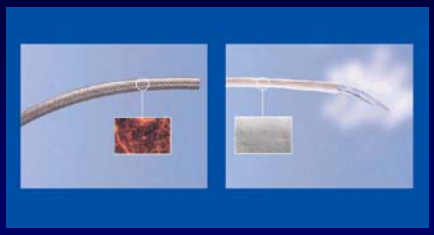
NO MAN'S LINE



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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

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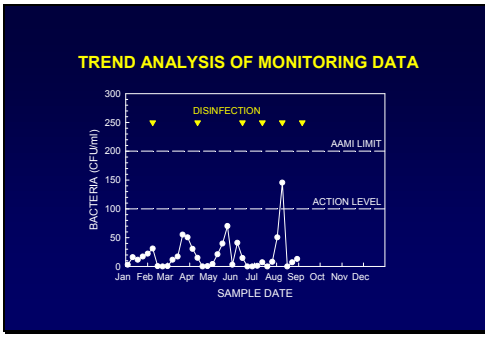

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