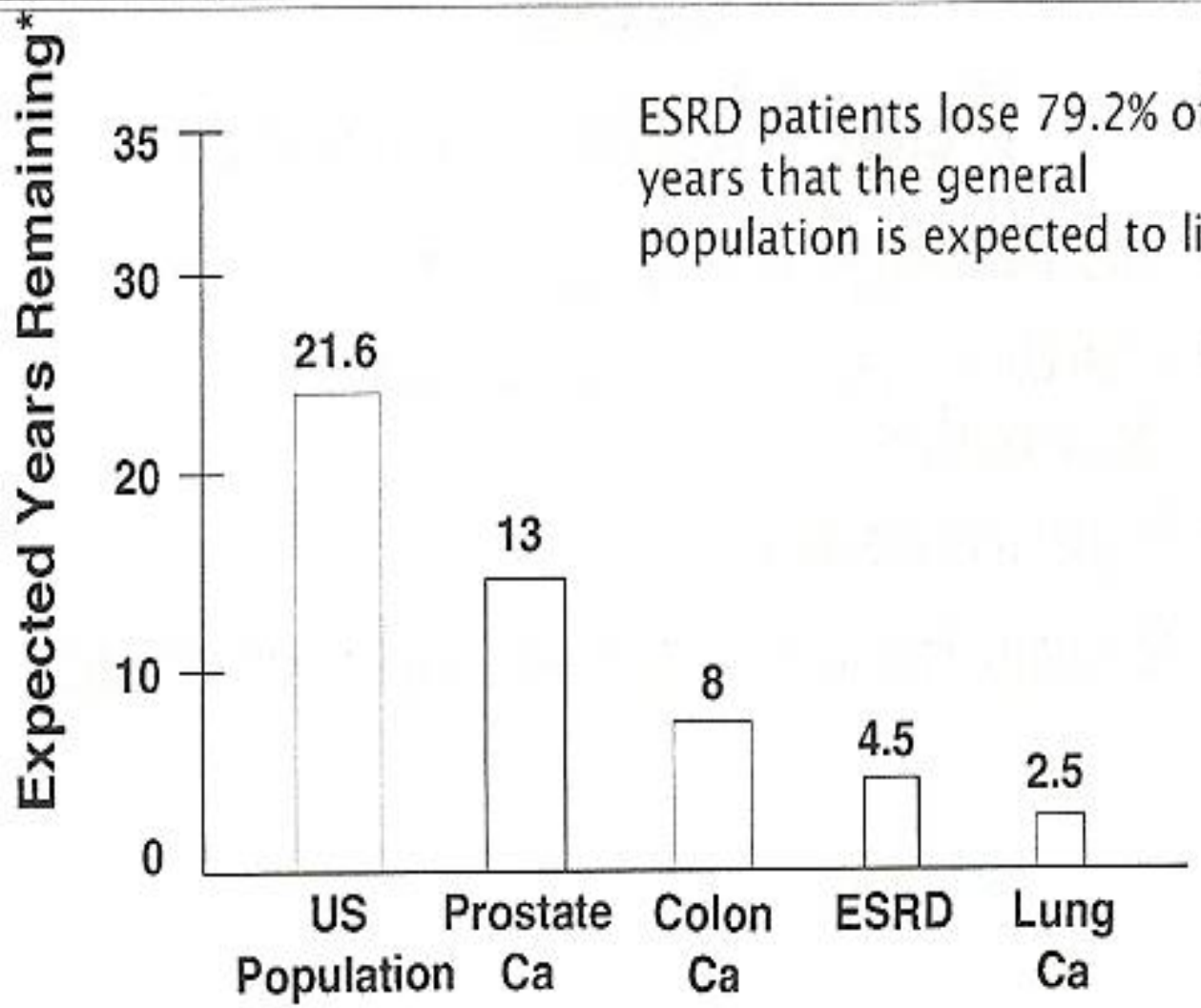
Hemodialysis

Ιωάννης Γ. Γριβέας,MD,PhD

athens-NEPHROLOGY

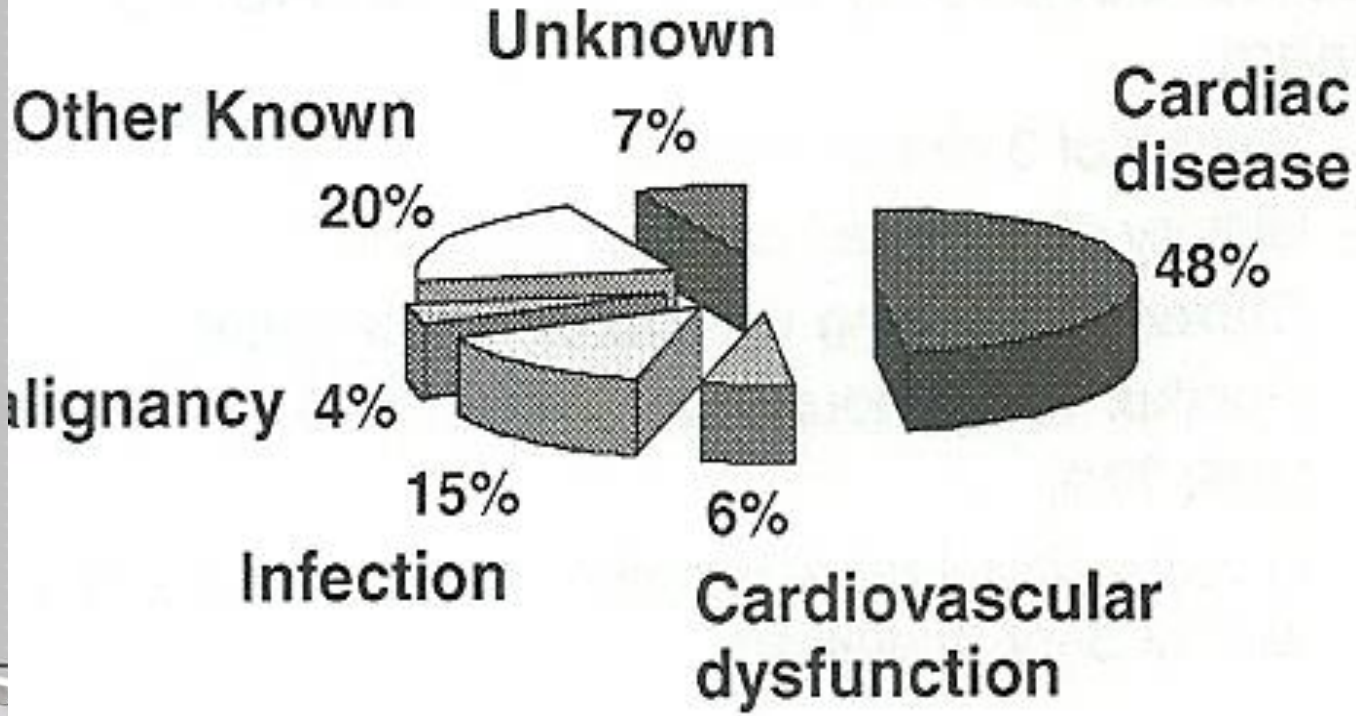
Survival in ESRD



*Based on adult, age 59 years
Ca=Cancer

USRDS 2005

Cause of Death in ESRD



Source: USRDS

Mortality Risk Factors Not Related to Dialysis

- Comorbid Conditions: DM (42%)
  - 10y survival lower in DM (4 vs 11-14%)
  - CAD, LVH
    - Enhanced CAD with Dialysis due to HTN, Metabolic abnormalities (Ca, Phos), LVH with anemia, hyperlipidemia
- Underlying renal disease, age, country, race, *nutrition*, inflammation, anemia, late referral, fractures, dialysis adequacy

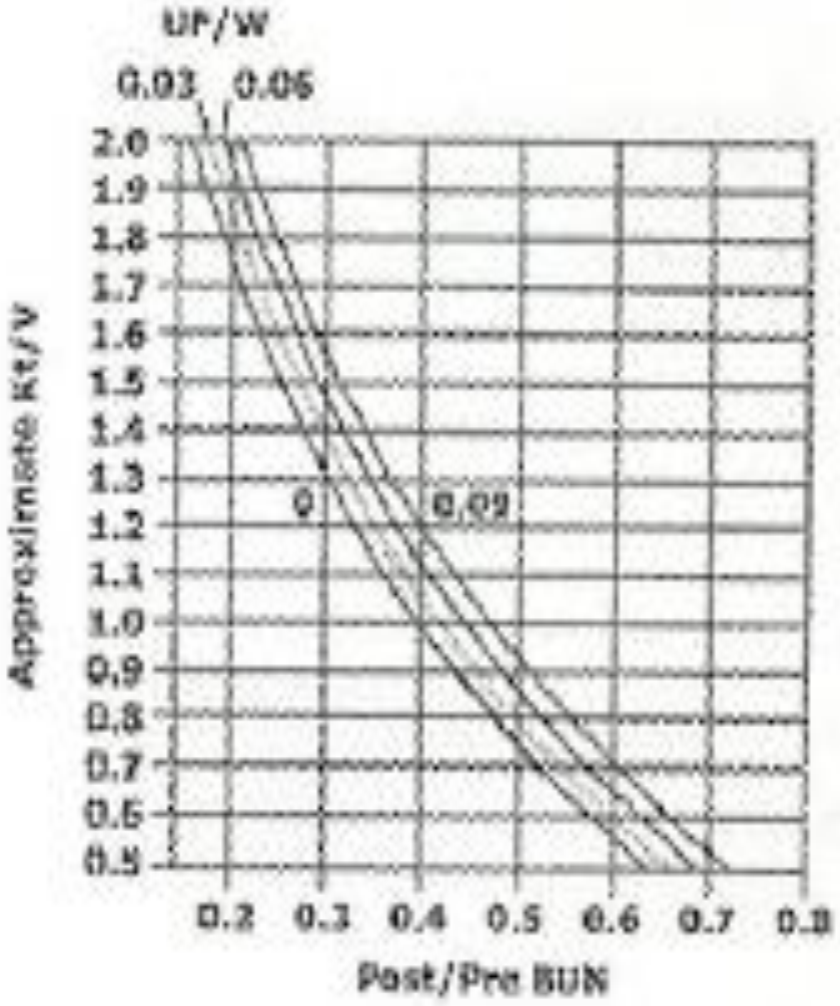
NCDS and Kt/V

- Landmark 1981 study showing that time-averaged urea and PCR were important determinants of morbidity and mortality.
  - Urea reflects Kt/V and dietary protein intake
  - Kt/V "acceptable" at 1.0 - *Increased Mortality*
- Kt/V allows urea kinetic modeling (clearance and generation (PCR~Protein Intake)

Calculating Kt/V

- Computer Models; pre- and post-HD weight, UF volume, Hct, pre- and post-HD BUN
- Statistical Models:
  - URR=(1-[post BUN/pre-BUN])
  - More complex models add urea generation during dialysis and changes in body water
    - Both raise post HD BUN
    - Different Pools
    - Single pool, nonequilibrated
      - Kt/V = ln(R-0.03+[4-3.5R) x UF/W

Nomogram

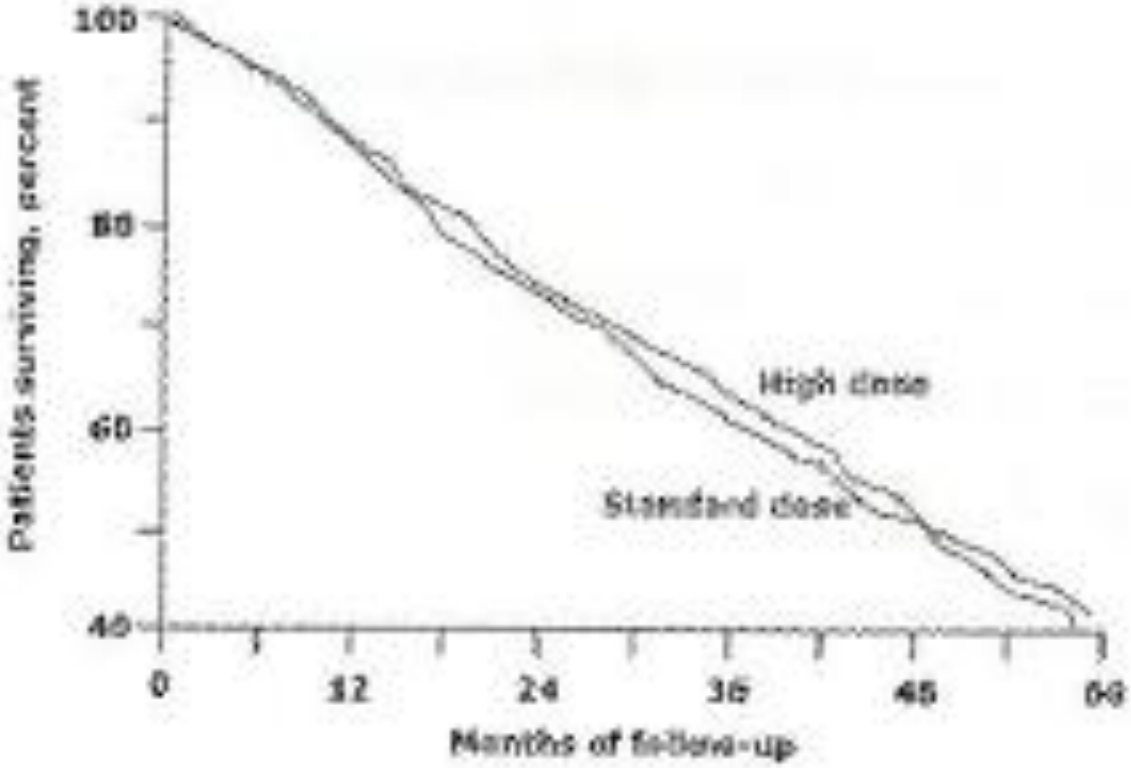


Data from
Daugirdas, JT.
J Am Soc
Nephrol 1993;
4:1205.

HEMO Study

- Prospective; 1846 pts - Primary Outcome-Death
- Secondary Outcomes-hospitalizations (non-access), first hospitalization for cardiac problem or death, infectious cause or death, and the first decline of >15% in albumin or death
- Results:
  - Good separation 1.32 (66.3) v 1.71 (75%)
  - No difference in death or secondary outcomes
  - No difference high vs low flux dialyzers (CV)
  - Subgroup analysis - if >3.7y of HD benefit of highflux (32%)
  - Women with high dose had 19% better survival
    - Men had 16% higher death rate with high dose

Survival Curves for High and Standard Dialysis Doses



Eknoyan, G, Beck, GJ, Cheung, AK, et al. N Engl J Med 2002; 347:2010.

Improved Survival with Longer Dialysis Session

- Effect of time independent of conventional markers is unclear:
  - DOPPS (Dialysis Outcomes and Practice Patterns Study) of 22,000 HD patients found >240 min. had lower mortality (RR-0.81). 7% lower risk of death with each 30min (Saran et al., KI 2006)
  - Similar findings in Australia (Marshall et al., KI 2006)
- ?Better Control of Fluids and HTN

So, independent of URR is longer time beneficial? (nocturnal HD, Tassin France)

K/DOQI-Adequacy

- K/DOQI: If GFR <2 mL/min;
  - Single Pool Kt/V of 1.2 or 65% URR is minimally adequate dose
  - Target recommended dose 1.4 or 70% URR
- If Below Target:
  - Assess Fistula (recirculation)
  - Treatment time
  - Method of obtaining BUN
  - Patient specific variables: Qb, hypotension,etc

Our Patient: Increased risk of death in some studies with high URR (>75%); low body volume and poor nutrition (Chertow et al., KI 1999)

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(Chertow et al., KI 1999)

Complications

- Hypotension
- Hypertension
- Dialyzer reactions
- Infection and pyrogen reactions
- Air embolism
- Vascular access bleeding
- Seizures
- Hemolysis
- Arrhythmias
- Muscle cramping

1. Hypotension During Hemodialysis (IDH)

Interventions that may be Effective

- Decrease fluid gains (salt intake)
- Increase treatment time
- *Increase dialysate sodium*
- Raise dry weight
- *Lower dialysate temperature*
- Administer midodrine
- Stop eating during dialysis
- Supplement L-carnitine

Causes of hypotension in HD patients

- Medications
- Autonomic dysfunction
- Sepsis
- Endogenous vasodilators
- Underestimation of "dry weight"
- Cardiac causes
  - Reduced diastolic filling
    - Atrial fibrillation
    - Tachycardia
    - Left ventricular hypertrophy
  - Ischemia
  - Pericardial effusion

L-Carnitine Supplementation

- Carnitine deficiency is common in hemodialysis patients
- Facilitates fatty acid entry into mitochondria; cofactor for fatty acid utilization as energy substrate
- Randomized, placebo-controlled trial of 82 patients found reduction in IDH (Ahmad et al, Kidney Int 1990)
- Mechanism underlying effect is not known

Sodium modeling

- As solutes are removed from the extracellular compartment, plasma osmolality falls
- Plasma osmolality decreases relative to the intracellular compatment
- Fluid moves into the intracellular compartment at the same time that it is being removed from the vascular compartment

Sodium modeling

- Sodium modeling helps to maintain the plasma osmolality as ultrafiltration takes place.
- The plasma osmolality is gradually decreased over the course of the treatment
  - Linear
  - Stepwise

Cool temperature dialysis

- Cool temperature dialysate induces vasoconstriction, which helps to maintain BP
- Disadvantage: Patients may complain of feeling cold.

Intradialytic blood volume monitoring

- Devices that prospectively monitor blood volume have been advocated for better volume management.
- The Crit-Line® is one such device that noninvasively monitors hematocrit by optical transmission.
- The CLIMB study compared conventional monitoring to Crit-Line® monitoring to test the hypothesis that Crit-Line® monitoring would decrease morbidity associated with ultrafiltration.
- There was no difference in hypotensive events between the two groups.
- There was a higher mortality and hospitalization rate in the Crit-Line® group.

Reddan *et al*, J Am Soc Nephrol 16: 2162-2169, 2005

Sequential UF/HD

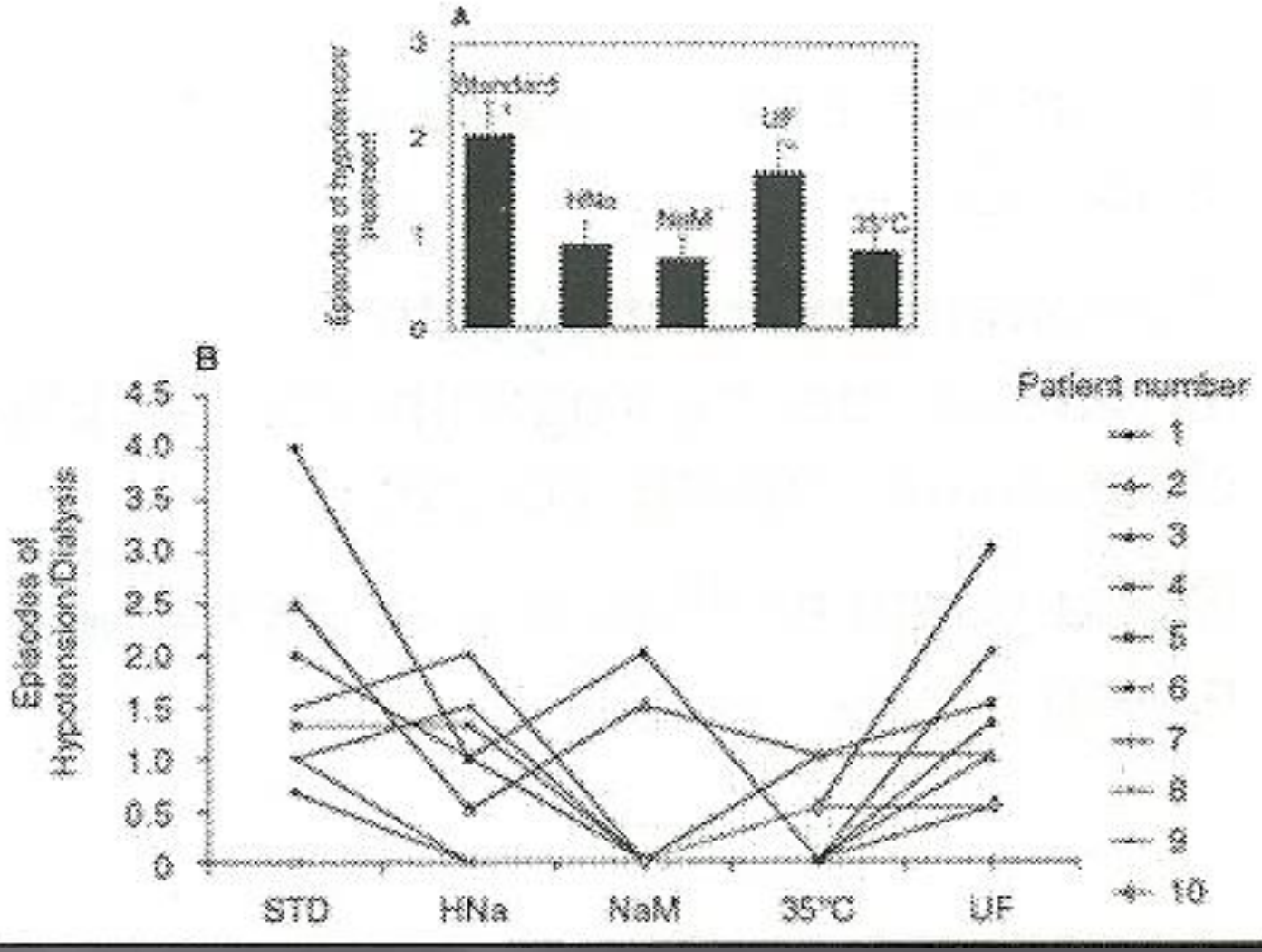
- Isolated UF followed by HD is often referred to as "sequential."
- Isolated UF is iso-osmotic and therefore less likely to lead to hypotension.
- Isovolemic hemodialysis can be performed after isolated UF.
- Disadvantage: Total treatment time is longer.

Which treatment works best to reduce hypotension in HD?

- Dheenan and Henrich (Medical College of Ohio)
  - Single center study
  - 10 stable chronic outpatients
  - Single-blinded, crossover study design of five different protocols
    - High sodium dialysate (144 mEq/L)
    - Sodium modeling (152 mEq/L → 140 mEq/L in the last half hour)
    - Sequential (One hour of isolated UF followed by 3 hours of isovolemic dialysis)
    - Cool temperature dialysis (35° C)
    - Standard dialysis (dialysate sodium 138 mEq/L)

Dheenan and Henrich, KI 59: 1175-1181, 2001

Number of hypotensive episodes per HD treatment



2. Chest Pain During Dialysis

Causes of Dialysis-Associated Chest Pain

- Myocardial ischemia or infarction
- Hemolysis
- Dialyzer Reaction
- Air embolism
- Pulmonary thromboembolism

Hemolysis

- Rare with current equipment and monitoring devices
- Manifestations
  - chest pain/tightness, back pain, dyspnea
  - hyperkalemia, fall in hematocrit
  - port-wine appearance of blood in venous line
  - pink appearance of plasma in centrifuged blood

Causes of Hemolysis

- Hypotonic or over-heated dialysate (>55° C)
- Contamination of dialysate with formaldehyde, hydrogen peroxide, bleach, chloramine, nitrate, copper
- Blood pump malfunction or defective tubing

Dialyzer Reactions

- Broad group of events with multiple etiologies
- Type A - anaphylactic
  - occur early in treatment, 1st 15-20 minutes
  - ethylene oxide was frequent cause in past but less frequent now with better removal of ETO by manufacturer
- Type B - milder, complement activation?
  - Occur any time during dialysis, usually 1st hour
  - back pain, chest pain

Management of Type A Reactions

Immediate: Stop Dialysis and Treat with Epi, steroids, antihistamines

Subsequent:

Increase volume of saline for dialyzer rinsing

- Replace ETO-treated dialyzer with dialyzer sterilized by other methods
- Use biocompatible membrane
- Switch heparin type
- Avoid combination of PAN dialyzer & ACE I
- Consider latex allergy

Management of Type B Reactions

Immediate:

- Can continue dialysis
- Symptoms resolve without specific intervention
- Oxygen, saline, diphenhydramine often used

Subsequent:

- Use biocompatible membrane
- Reuse may help (without bleach)

This is what our patient had - "first use" syndrome

Air Embolism

- Rare but need to be aware!
- Multiple potential sites for air to enter circuit
- Manifestations depend on patient position
  - Supine: dyspnea, chest pain, hypotension
  - Upright: loss of consciousness, seizure
  - Trendelenburg: lower extremity ischemia
- Signs
  - "foaming" of blood in venous line
  - "churning" sound with auscultation of heart
- Treatment
  - clamp venous line and turn off blood pump
  - position patient on left side, chest and head down
  - 100% Oxygen
  - Aspiration of air from ventricle

Pulmonary Embolism

- Not really a dialysis-associated complication and not particularly likely to occur *during* the dialysis session
- But the lore that "patients with ESRD do not develop pulmonary embolism" appears not to be true in current era
  - Tveit et al, AJKD 2002; Analysis of USRDS and NCHS data
    - Age-adjusted rates of hospitalization for PE greater in patients with ESRD than general population

3. Fever

Pyrogen-Reaction versus Infection

- Pyrogen reaction
  - Afebrile pre-dialysis, fever during dialysis
  - Blood cultures negative, no infection identified
  - Dialysis-associated fever can occur with use of infected catheter
  - More common with high-flux dialyzers

"Outbreak" of Pyrogen-Reactions or Infections

- Many possible sources
  - Inadequate disinfection of dialysis machines
  - Defect in water processing system
  - Bicarbonate concentrate (powder form eliminates this)
  - Reuse process
  - Mishandling of intravenous medications

Gram Negative Infection Outbreaks

Medication Contamination

- Serratia liquefaciens bloodstream infections from contamination of epoetin alfa at a hemodialysis center. N *Engl J Med 2001; 344:1491.*

WHO Contamination

- An outbreak of gram-negative bacteremia in hemodialysis patients traced to hemodialysis machine waste drain ports. Infect Control Hosp Epidemiol 1999 20: 746.

Reuse Procedure

- An outbreak of gram-negative bacteremia traced to contaminated O-rings in reprocessed dialyzers. Ann Intern Med 1993; 119:1072.

Infected HD Catheter Management

- Incidence of Catheter Related Bacteremia (CRB)

Author	#	CRB/1000d	CRB/yr
Marr,1997 (Annals)	102	3.9	1.4
Beathard, 1999(JASN)	387	3.4	1.2
Saad, 1999 (AJKD)	101	5.5	2.0
Jean, 2002 (Nephron)	129	1.1	0.4

Risk Factors for CRB

- Most Significant Risks (Single Study: Jean, Nephron, 2002 91:399)
  - Nasal Staph Aureus Carriage
  - Previous Bacteremia
  - Peripheral Vascular and CAD
  - Diabetes
- Others Include: Low albumin, High Ferritin, Immunosuppression, prior bacteremia, ?higher iron, low Hb, poor hygiene, catheter care

Treatment of CRB

- Antibiotics; broad spectrum typically for 3 weeks
- Salvage Rate: Prospective: 62 CRB (Marr; Ann Intern Med 1997; 127:275)
  - 24 Immediate Removal; 38 Left In
  - Only 12 (32%) of catheters left in were salvaged but no increase in complications
  - Catheter Exchange: Afebrile x 48h; stable w/o tunnel infection (Robinson-Kidney Int 1998; 53:1792, Tanriover-Kidney Int 2000; 57:2151.
    - 50% required removal within 48h
    - Guidewire Replacement; Ab x 3 weeks
    - 80% 90 day Infection Free Rate

Approach to CRB

Fever, Sx (BCs; Empiric Abx)

Stable? (BP; Comps)

NO

NO

Catheter Removal

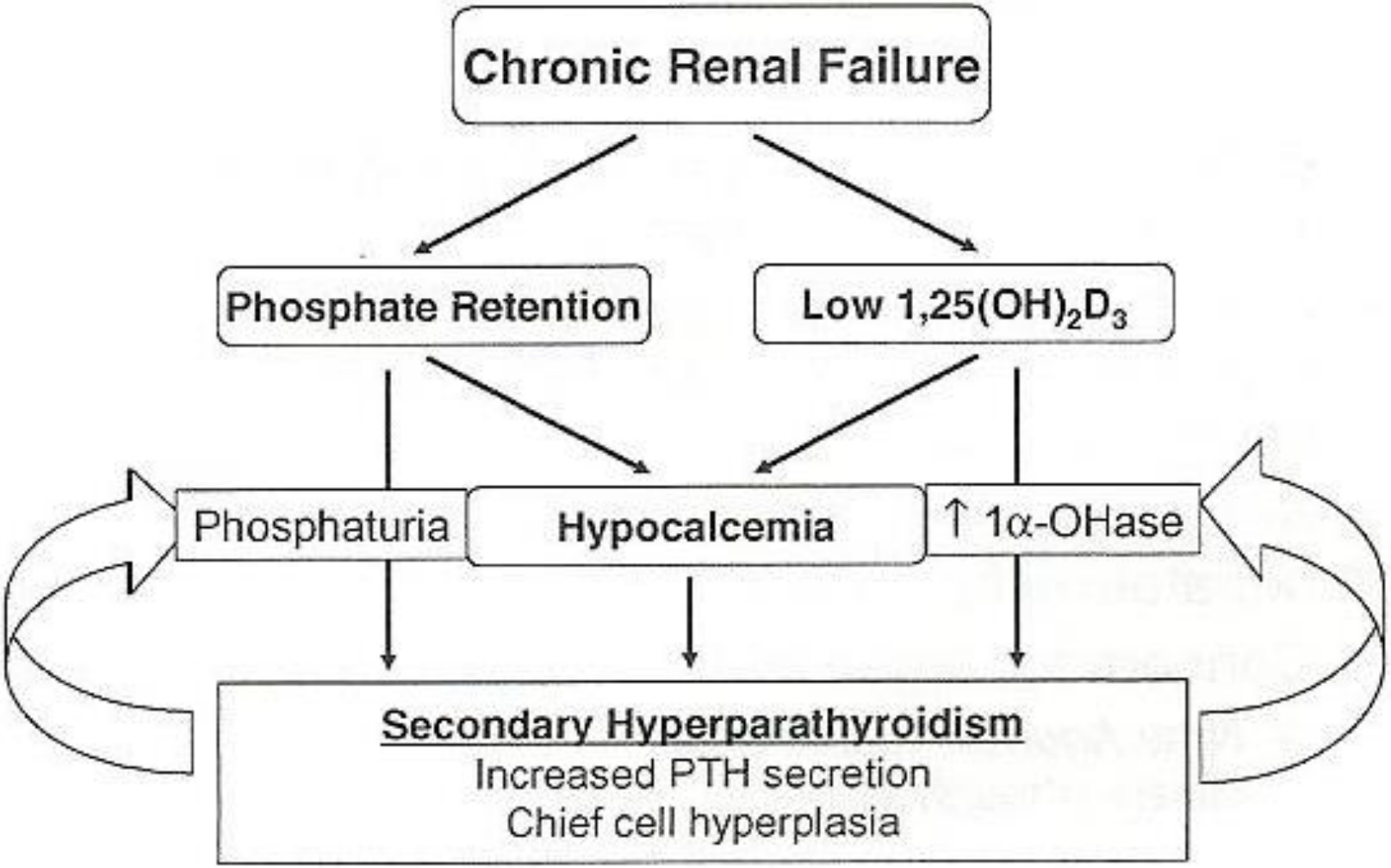
Afebx48h; Stable

Abx x 3 weeks
+/-Guidewire Change

Bone Disease in CKD

- **Osteitis Fibrosa**
  - PTH mediated high bone turnover
  - TREAT by suppressing PTH
- **Adynamic Bone**
  - Low bone turnover
  - Pathologically the same as osteoporosis
  - Usually due to low PTH
  - TREAT by:
    - avoid Calcium binders
    - Avoid Active Vitamin D
    - Use low Calcium bath
- **Osteomalacia**
  - Low bone turnover with large amounts of unmineralized osteoid
  - Usually due to Vitamin D deficiency
  - In past seen commonly due to Aluminum
  - Suspect in dialysis patients with low bone mass and frequent fractures
  - TREAT with Ergocalciferol with or without Active Vitamin D

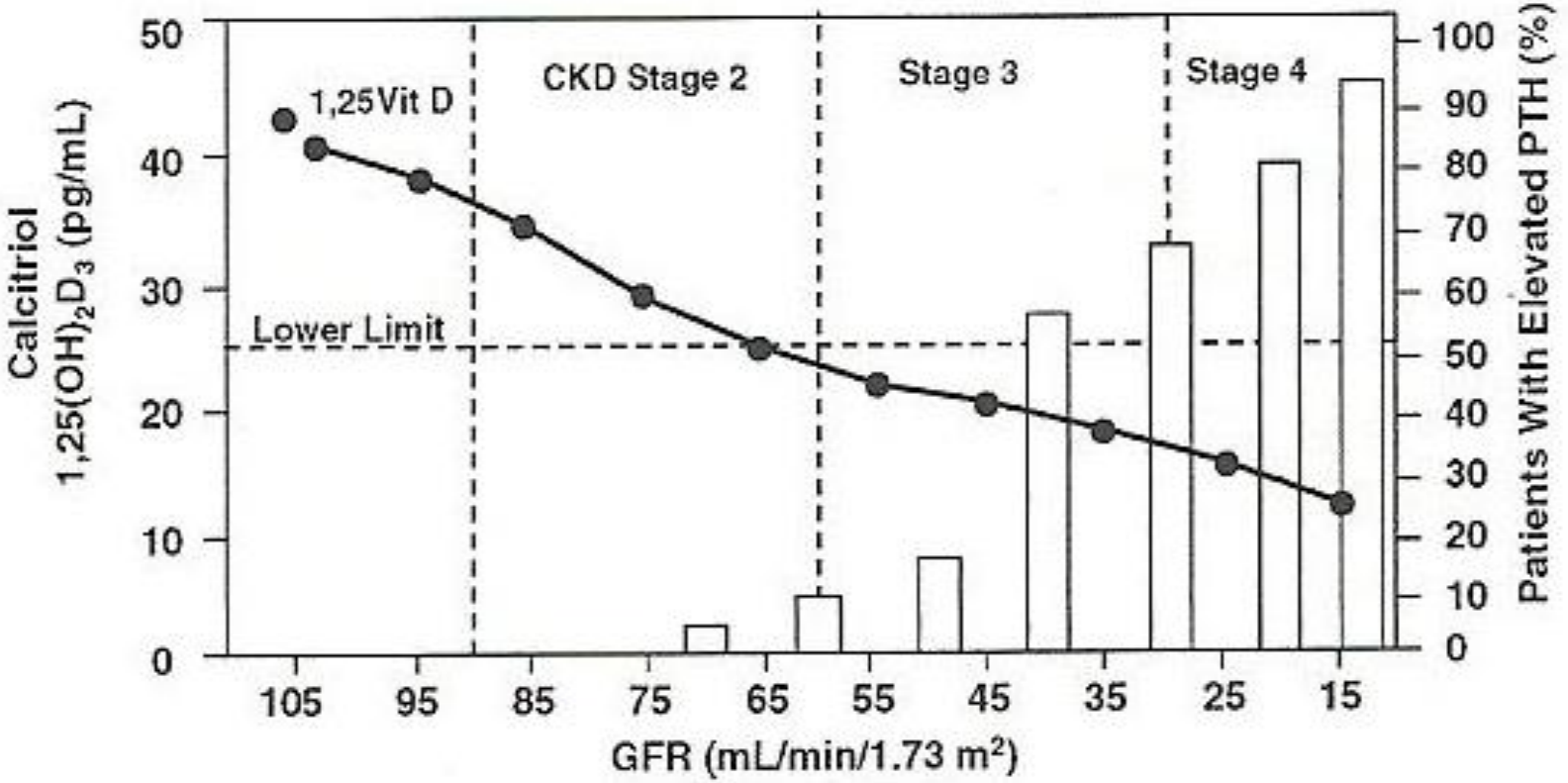
Pathogenesis of Secondary Hyperparathyroidism



Mortality with Disorders of Mineral Metabolism in ESRD

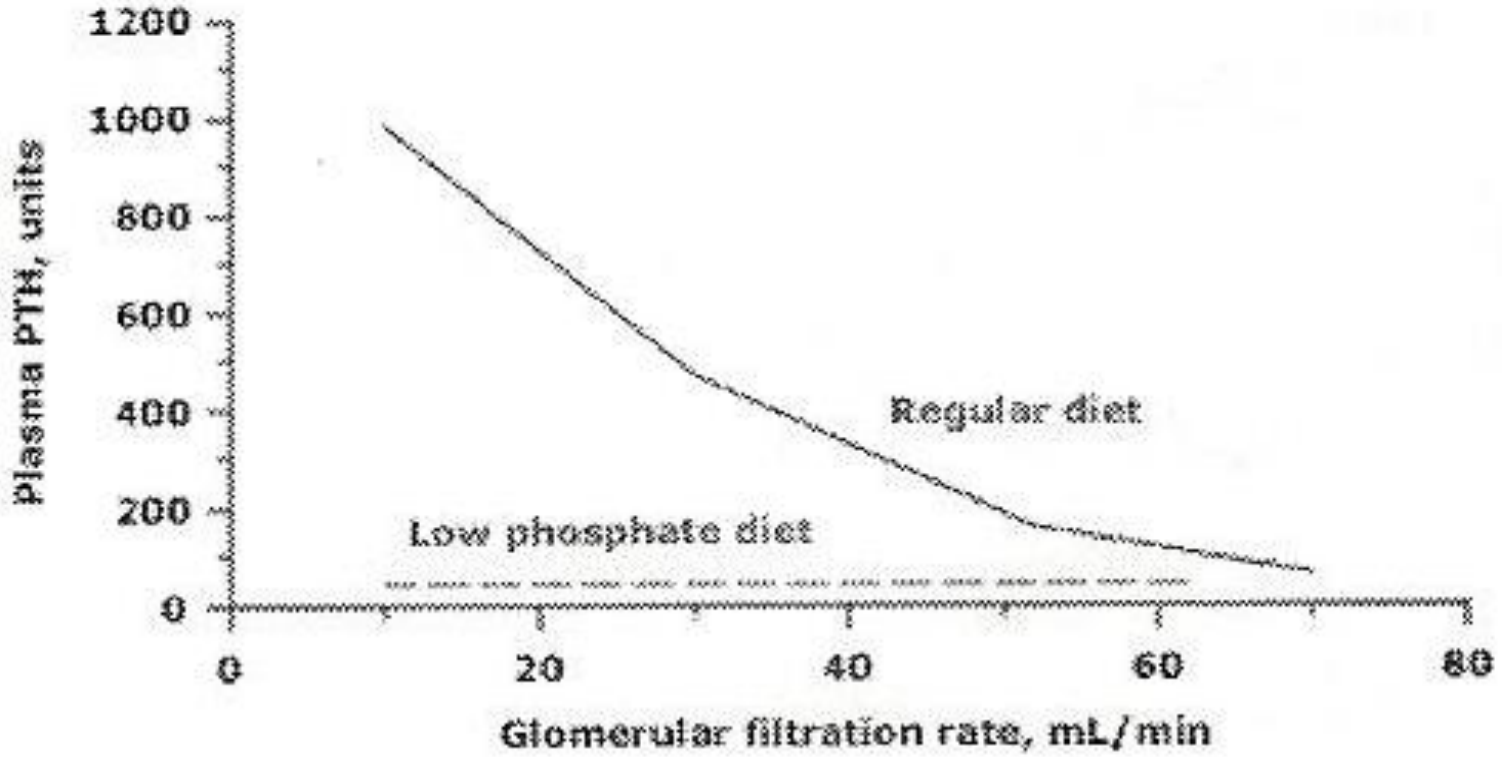
- Retrospective Analysis of >40,000 HD Pts: Block GA, et al., JASN 2004
  - Lowest Death Risk with:
    - Phosphorous 3-5 mg/dl
    - Calcium <8.0 mg/dl
    - Calcium x Phos product < 45-50
    - iPTH<600ng/L
- Similar findings in DOPPS+Others
- Prospective Studies: Phosphorous elevation correlated with increased mortality at baseline and as time dependent variable; Calcium and PTH only time dependent (Melamed et al., KI 2006; Kalantar-Zadeh et al., KI 2006)

Declining Calcitriol and Increasing PTH With CKD Progression



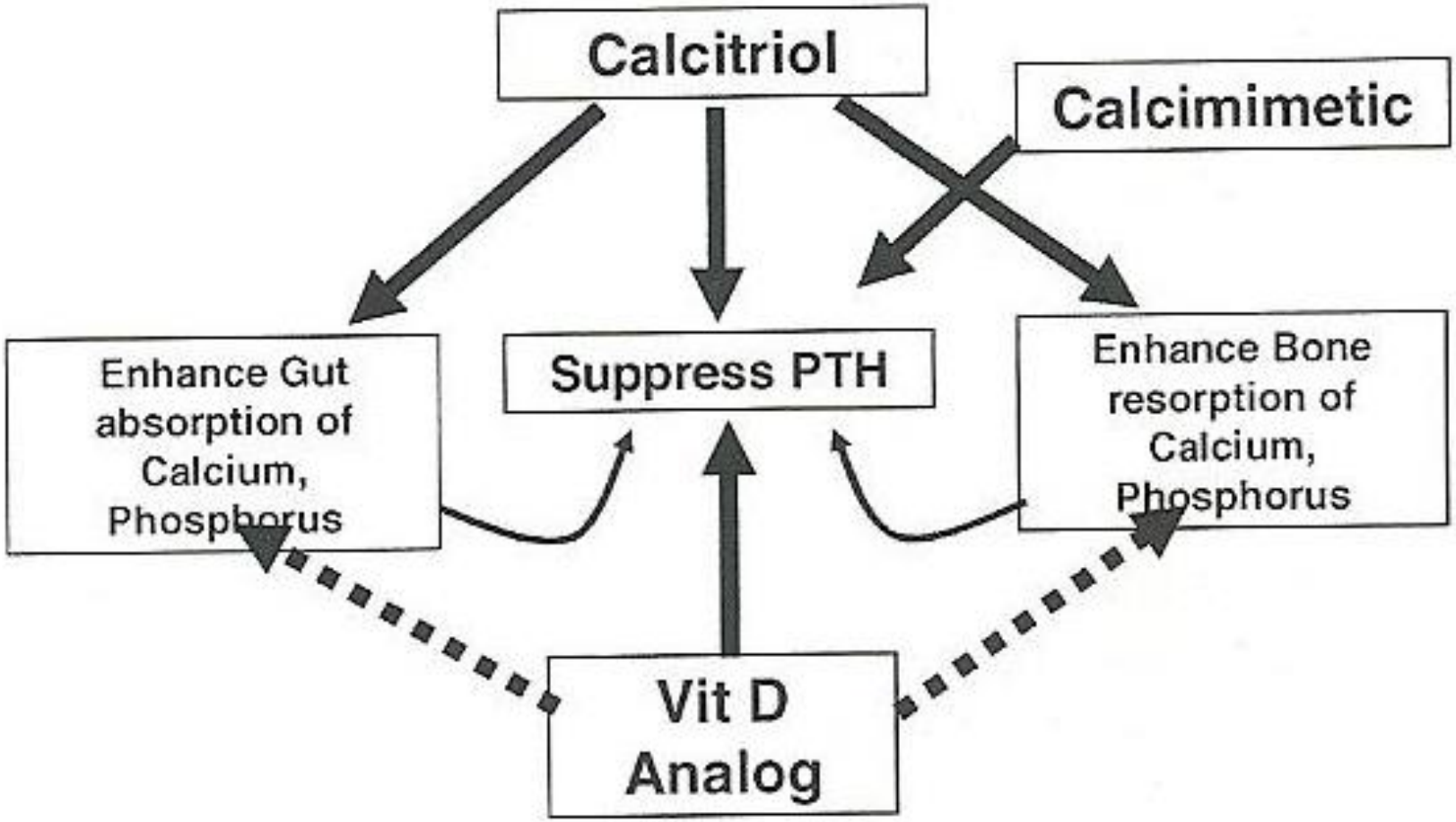
Kates et al. *Am J Kidney Dis.* 1997;30:809-813; Martinez et al. *Am J Kidney Dis.* 1997;29:496-502; Martinez et al. *Nephrol Dial Transplant.* 1996;11(suppl 3):22-28; St. John et al. *Nephron.* 1992;61:422-427.

Phosphate Restriction Prevents Hyperparathyroidism



Slatcpolsky, E, Caglar, S, Pennell, JP, et al, J Clin Invest 1971; 50:492.

Vitamin D Actions in Humans



Treatments-Phosphorous

- Control Serum Phosphorous - Dietary! *But* Malnutrition risk in HD
  - Binders (Calcium based, Sevelamer, Lanthanum)
    - "Treat to Goal Study" - Sevelamer vs Calcium (Chertow, KI 2002)
      - Similar Phos control; less hypercalcemia, low PTH levels, lower LDL, and less coronary artery calcification with Sevelamer, Lower CRP (US)
    - CARE Study (calcium acetate Renagel Eval) found better phos control with calcium acetate (Quinibi, KI 2004)
    - DCOR (Dialysis Clinical Outcomes Revisited); no difference in mortality at 3y as of 11/05 (still not published)
- Limit Total Calcium from binders to <1500mg/d (Calcium carbonate has 500mg/1250 and acetate has 167/667)

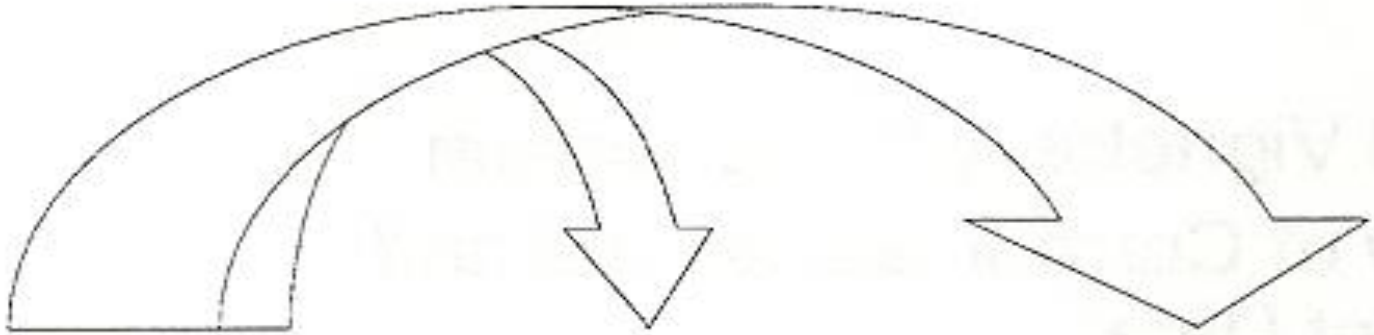
Treatments-Vitamin D

- Retrospective analyses show improved survival with Vit D in dialysis patients and paricalcitol was better than calcitriol (Teng M., et al, NEJM 2003)
- Three Choices (US); calcitriol, paricalcitol, doxercalciferol
  - All increase serum calcium, analogues may be better than calcitriol
    - 1 randomized prospective trial (calcitriol vs paricalcitol); no difference in PTH, hypercalcemia or CaxP product (Sprague et al., KI 2003)

Treatments-Cinacalcet

- Calcimimetic; binds to CaSR
- 3 Prospective phase 3 studies have shown increased % of patients achieving K/DOQI endpoints
- Phase 2 study showed reduced risk for PTX, fracture and cardiovascular hospitalization.
  - No data on CV outcomes
- Monitor: Risk of hypocalcemia, N/V (self-limited)

CKD and CVD



CKD ⇒ **"Traditional" CVD Risk Factors** + **"Kidney" specific Risk Factors** ⇒ CVD

- Age
- Male gender
- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Physical Inactivity
- Menopause
- Family History of CVD
- LV Hypertrophy

- Anemia
- Proteinuria
- Elevated Ca.P Product
- Oxidative Stress
- Inflammation

Risk Factors

- CHOICE Study (Longenecker JASN 2002)
- Traditional Risk Factors at Initiation:
  - Diabetes (54%), low HDL (33%), HTN (96%), LVH (22%), advanced age (~60)
  - Other risk factors; anemia, homocysteine
- Unique Risk Factors: CKD alone, RRT, uremia, oxidant stress, calcium and mineral metabolism, abnormal nitric oxide

Prevention-2

- Homocysteine - large doses of folic acid were minimally effective (29.5 to 21.9 μmol/L)
- Calcium and Phosphorous
- Oxidative Stress - Vitamin E vs Placebo; lower CV endpoints (16 v 33%) at 1.5y (Boaz, M et al., Lancet 2000)
- Similar finding with n-acetylcysteine
- Fish oil - fewer MIs, no effect on cardiovascular events and death over-all (Svensson et al., JASN 2006)

LVH/CHF

CHF mortality 83% at 3 years (USRDS)

Prospective Study of 431 pts;

- 31% incidence at initiation; 7%/year (Harnett, JD., KI 1995)

K/DOQI - Baseline ECHO and repeat at dry weight; q 3 years thereafter or if symptoms

LVH in 75-80% of dialysis patients

- Major risk for morbidity; 2/3 die from CHF or sudden death
- Prevention: BP!, Anemia and ?ACEI/ARB

Consider: Valvular disease, AVF shunting, Anemia, Carnitine deficiency, Volume control

ACEI, B-blockers and digoxin are *under* utilized and literature supports reductions in onset of new CHF and death (Cice J Am Coll Cardio 2003).

•Our Patient - most likely LVH; probable diastolic dysfunction, consider use of β-blockers

Conclusions

- Clinical Vignette with Discussion
- Review of Current Guidelines and Relevant Data:
  - Survival/Dialysis Adequacy
  - Complications (Acute)
  - Bone Disease
  - Cardiovascular Disease

Dialyzer

Key facets of a dialyzer:

- Capacity for solute clearance
- Capacity for ultrafiltration of fluids
- Nature of dialyzer membrane (biocompatibility)

Ideal dialyzer:

- Low & middle molecular weight molecule clearance
- Vital solutes
- Adequate ultrafiltration
- Low adverse metabolic events
- Low blood volume compartment
- Low Cost
- Reliable
- Low Gibbs-Donnan effects - *in vitro* vs. *in vivo*

- Diffusive vs convective clearance >300Da
  - surface area, thickness, pore size, pore density, and potential to adsorb proteins
- Ultrafiltration co-efficient
- Hollow fiber vs. parallel plate
- Humoral activation pathway clotting vs complement
- Cellular activation pathway
- Reuse
- Types of membranes
  - Cellulosic, Coated, Synthetic
- Biocompatible membranes
- Classification of dialyzers: solute vs water flux

Dialyzer Clearance

Diffusive and convective. Small molecules move principally by diffusion

Mass solute transfer across a dialyzer or diffusive dialyzer clearance

$(K) = Q_b(C_a - C_v) / C_a$

For solutes not present in dialysate $K = Q_{do}(C_{do})/C_a$

Clearance varies with blood flow. Mass transfer coefficient is constant K_oA:

Mass transfer area coefficient $(K_oA) = \frac{Q_b \times Q_d}{Q_b - Q_d} \ln\left(\frac{Q_d(Q_b - K_d)}{(Q_b(Q_d - K_d)}\right)$

K_o (cm/min) may be thought of solute flux /unit area/unit of concentration gradient

K_oA is the most specific constant that describes the efficiency of a dialyzer for removal of a specific solute and represents maximum clearance

FACTORS AFFECTING CLEARANCE

Toxin related	Procedure related	
	LMW	HMW
Size	Dialysate	Flux
Charge	Q_b	Time
Protein binding	Q_d	area
Vol. Distribution	area	Q_b
	Time	Q_d
	Flux	Dialysate

C_a = conc. arterial
C_v = conc. venous
C_{do} = conc dialysate
Q_{do} = flow dialytsate

Water Permeability

Measured by ultrafiltration co-efficient K_{UF}

ml/hr/mmHg of TMP, measured in vitro using bovine blood. Taken from linear part of curve

Directly related to Pore size (power 4) and also size of membrane

Solute and Water permeability do not necessarily correlate
Porosity (i.e. total area of pores) and depth of pores determines small solute transfer whereas pore size affects water flux
Also HMW molecules can adsorb to hydrophobic microdomains, increasing local concentrations

Flow rate

Flow limited mass transfer is part of clearance characteristics

- Resistance/turbulence, Non linear flow
- Boundary layers & streaming effects increased K_oA, maintaining countercurrent gradient
- For hollow fibre dialyzers K_{urea} increases between Q_b 200-300ml/min, and rises less steeply to 400-500ml/min
- Solute removal: Sigdell/Tersteegen dialysate flow max 2 x blood flow
- Recirculation: $R = C_s - C_a / C_s - C_v$. Best C_s is from arterial port where $Q_d = 0$ $Q_b = 50$ml/min. Alternatives, saline/hematocrit or cold bolus/temp probe
- Mismatch of blood/dialysate
- Optimize flow for individuals

Sigdell & Tersteegen Nephron. 1995;71(4):401-6.

Time

- Solute clearance increased with time
- Diminishing returns
- Volume homeostasis and intra-dialytic complications
- Tassin experience
  - 6-8h, BP control, volume control, larger molecule clearance, Phosphate control, best survival, less disparity between prescribed and delivered dialysis
  - Kt/V 1.67 10y survival 88% (35y) 64% (65y) (Cellulosic)
- Daily dialysis experience
- Time as an independent variable?
- Guidelines: Minimum dialysis time 2.5h X 3

Charra et al Journal of Nephrology (2003);16:S64.
Chan et al KI (2002); 61:2235

The problem with V

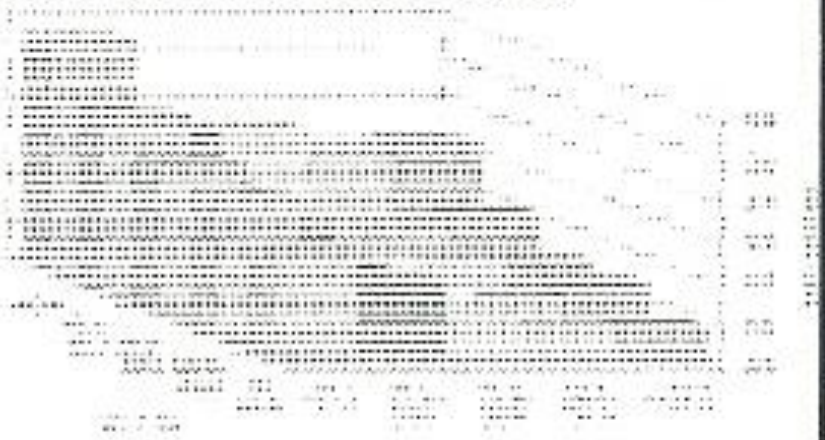
Anthropometric formulas (Watson) vs. kinetic modeling (9-13% lower) vs. bioimpedence vs. dilution

V is an independent predictor of mortality. V predicts low body mass and patients with low body mass on dialysis are more likely to die.

Kt/V assumes that smaller people require less total treatment (Kt) to achieve adequacy. However the survival curve is J shaped

Lowrie et al in a large retrospective study demonstrated that Kt is a predictor of survival and that Kt against survival generates a linear curve not a J curve

Conclusion: In patients with BMI below 24, consider targeting Kt > 50L/*Rx*



Lowrie et al KI (1999); 56:729

Dialysate composition

Sodium: options similar to plasma Na, hyponatric, sodium modeling

- 130-135. Used historically Prevents HTN, thirst, wt gain, but high dialysis dysequilibrium, hypotension & cramps interdialytic
- 140-144
- >145. Sodium modeling. May reduce symptoms but increased thirst, IDWG, hypertension.
- tailored to patient's plasma Na

Potassium:

- 1-2% of 3000-3500mEq is in ECF. Rate largely dependent on predialyisis K.
- Setting K tends to be empirical.
- Evidence that arrhythmias occur in first half of HD during greatest change. Highest sudden death in patients in lowest K bath.
- Consider stepwise approach.

Calcium:

- 60% plasma Ca is not protein bountPositive intradialytic calcium balance. Achieved with 3.5mEq/L or 7.0mg/dL)
- 2.5-3.0 to prevent hypercalcemia.
- Cardiac contractility/BP/QT dispersion

Dialysate composition

Magnesium:

•Magnesium flux unclear since 1% only is in plasma, 60% is ionic. Most centres use 1mEq/L

Buffers: Acetate- standard for 20y until high flux dialyzers

•Acetate toxicity (nausea, vomiting, headache, fatigue, hypoxemia)

•Bicarbonate. Proportioning systems (single patient) mixes bicarbonate and divalent ions in acid.

•Rarely varied from 30-35

•Can support pathogen growth. Membrane filters on dialysate

Chloride: Major anion. Defined by cation prescription

Glucose:

•Most dialysate used physiological 200mg/dL. Dialysis imposed glucose clamp. Affects K+ removal, dialysis dysequilibruim, post dialysis fatigue

Dialysate temperature

- Dialysate usually maintained between 36.5 and 38C
- Heat generation during HD. Response to heat generation
- Role of pyrogens
- Evidence that dialysate temperature determinant of intradialytic BP, improved contractility, venous tone, complement activation
- Isothermic dialysis

Ultrafiltration Rate

•Definition of dry weight: lowest weight a patient can tolerate without signs or symptoms of hypovolemia. Can be measured but usually determined clinically

•Hematocrit monitoring maybe of use in assessing dry weight

•Achieving dry weight should be accomplished gradually over a number of dialysis treatments (usually over 4 to 12 weeks, but it may require as long as 6 to 12 months) until evidence of fluid overload is in abeyance. May take longer in diabetics

•goal to render the patient euvolemic and normotensive. This includes counseling the patient on sodium and fluid restriction, adequate ultrafiltration, and the use of diuretics in patients with RKF (residual kidney function)

•Study of USRDS cohorts when adjusted for comorbidity, showed that weight gain between dialyses of more than 4.8% (ie, 3.4 kg in a 70 kg person), a reflection of excessive sodium and water intake, is associated with increased mortality

•Some patients require longer time to achieve fluid removal

•Hypotension induced by overzealous UF rate contributes to loss of RKF and coronary, cerebral ischemia and short dialysis times.

Alternatives to the standard 3x weekly prescription

Nocturnal slow dialysis 8h 3 x wkly
Daily short dialysis 2.5-3h 6 x wkly

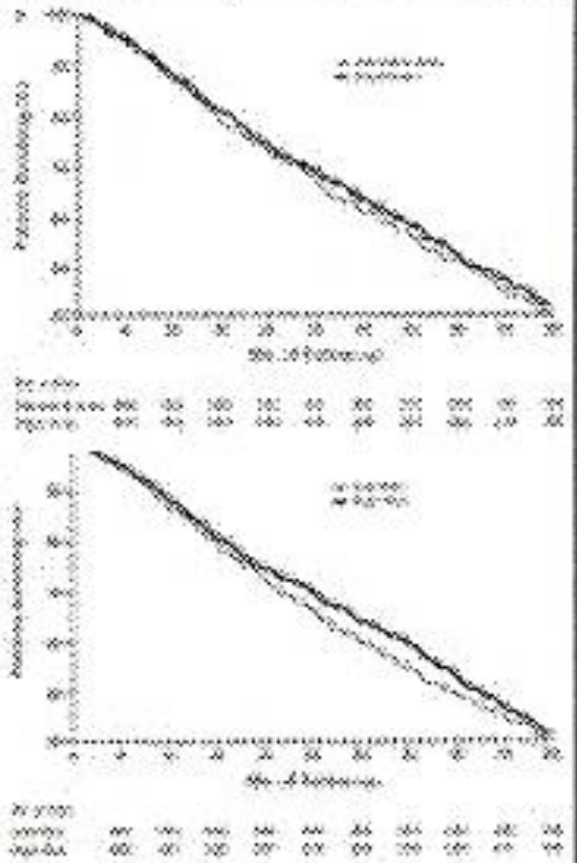
Small prospective controlled study showing improved (8-10h vs 4h 3x wkly) : Pre-dialysis BP, cardiac LVMI, cardiac FS, phosphate control, increased Hb, decreased Epo resistance, reduction in tablets / anti-hypertensives, reduction in PTH with nocturnal dialysis

Many other non-controlled studies showing improved nutrition, total body nitrogen, QoL, BP control, fluid balance and mortality.
In Tassin France, mortality on >64y was 55% over 10y

Hemo study

1846 patients. Prospective 3x a week dialysis, study period 5y. 2x2 factorial design HD dose & membrane flux

1. High dose, high flux
2. High dose, low flux
3. Low dose, high flux
4. Low dose low Flux



- Prescribed equilibrated eKt/V 1.05, (spKt/V 1.25) vs eKt/V 1.45, (spKt/V 1.65)
- Achieved eKt/V 1.16 (sp 1.32) (URR 67%) vs 1.53 (sp1.71) (URR 75%) respectively

β_2-M clearance was 3 vs 34 ml/min

- Primary (death) and secondary outcomes were no different between groups
- Patients on HD for >3.7y had lower mortality with high flux dialyzers (RR 0.68 $P = 0.01$)
- Sub- analysis: high flux lead to fewer hospitalizations or death from cardiac disease, and women had lower mortality with higher dose

Annual mortality rate in USA 20-22%

Several large observational studies indicate increasing spKt/V to 1.7 will lead to improvements in mortality

Eknoyan et al NEJM (2002) 347:2010

Formal Urea Kinetic Modeling

Recommended by K-DOQI, RPA

- Used to prescribe individual hemodialysis treatment
- Checks for errors in dosage
- Approximately take into account residual renal function
- Permits calculation of nPCR (an independent risk factor)

Measure delivered Kt/V by single pool differential equation:

$d(V \times C)/dt = G - (K + K_r) \times C$ (accumulation = generation - loss)

Where G = generation of urea, C = conc urea, V = volume distribution urea, K = urea mass cleared by dialyzer

Incorporate residual renal function as urea clearance $(K_r) = (U_{urea} \times V)/(P_{urea} \times t)$

Corrected $Kt/V = Kt/V_d + 5.5 \times K_r/V$

Complex formulae to derive V(kinetically derived) and G requiring C_o, C_t, C_{o2}, weights pre, post and pre(2), interdialytic interval

Measure prescribed Kt/V using K from: $K_oA = \frac{Q_b \times Q_r}{Q_b - Q_r} \ln\left(\frac{Q_r(Q_b - K_d)}{(Q_b(Q_r - K_d)}\right)$

Protein catabolic rate (PCR) = 9.35G + 0.29V

nPCR = PCR/nBWT (V/0.58)

nPCR enables longitudinal analysis of nutritional status

Urea kinetic modeling

Single Pool Kt/V: = -ln(R - 0.008 x t) + (4 - 3.5 x R) X UF/W

Double Pool (Equilibrated) Kt/V = single pool Kt/V - 0.6 x K/V + 0.03

$R = C_t/C_o$, UF = UF volume (L), W = post weight (Kg)

Kt/V Daugirdas - single pool

Kt/V Lowrie

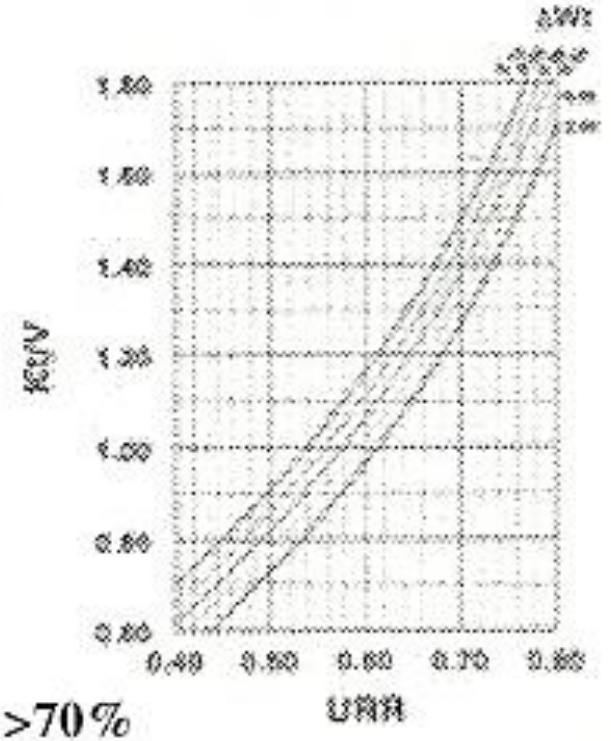
eKt/V Daugirdas double pool

URR = 100 X (1 - C_t/C_o)

UKM (3 and 2 urea samples)

Kt

Relationship between standard weekly Kt/V and intermittent Kt/V



Guidelines: for patients on 3x weekly HD with K_r < 2ml/min/1.73m², targeted spKt/V = 1.4, or URR >70%

Daugirdas et al (1993) JASN 4:1205