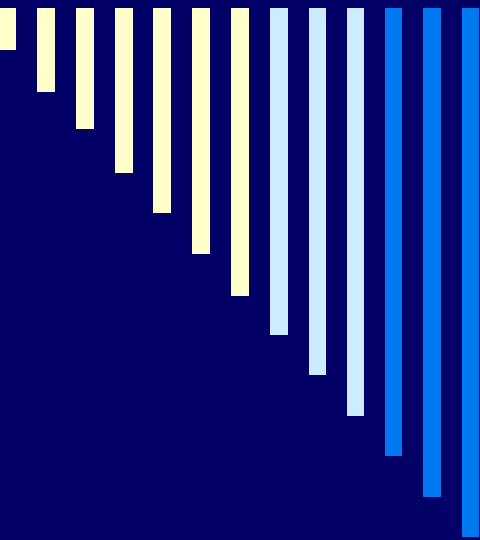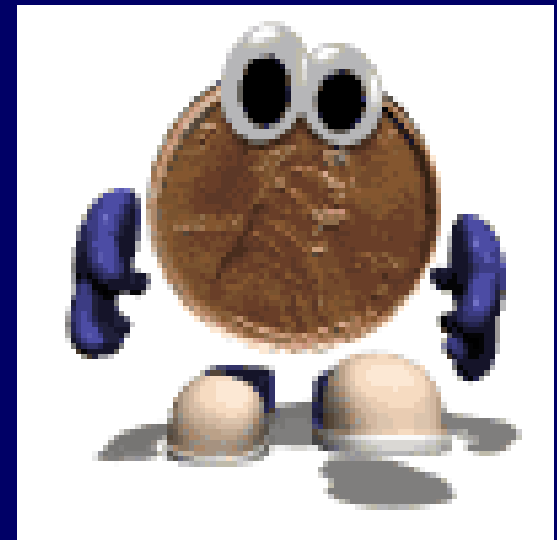# Anti-Coagulation in Today's Hemodialysis World

Wayne Carlson
Minntech Renal Systems

HEPARIN ECONOMICS PRE-2008 (BC)

➢ Heparin was relatively inexpensive

> ➢ Could be used in priming, during treatments, and in post-treatment rinse without incurring major expense

> ➢ Costs ≈ $.03 - $.08/1000u ml

HEPARIN ECONOMICS IN 2008 & NOW (AC)

➢ Heparin recall begins in Jan. 2008

➢ Baxter stopped manufacturing heparin
  ➢ Only one US manufacturer still making heparin – APP Pharmaceuticals

➢ 6 - 7 fold increase in price

➢ Cost escalated to ≈ $.19 - $.56/1000u ml

➢ Typical prescribed heparin dose decreases

ACTIONS OF HEPARIN

➢ Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots

➢ Heparin does not dissolve previously formed clots, but it does forestall their enlargement and prevent new clots from forming

ACTIONS OF HEPARIN

➢ Heparin may be the most important medication used in hemodialysis

➢ It allows the patient's blood to flow through the extracorporeal circuit

➢ During the course of on dialysis treatment a patient's blood will contact approximately 650m^2 of tubing and membrane material
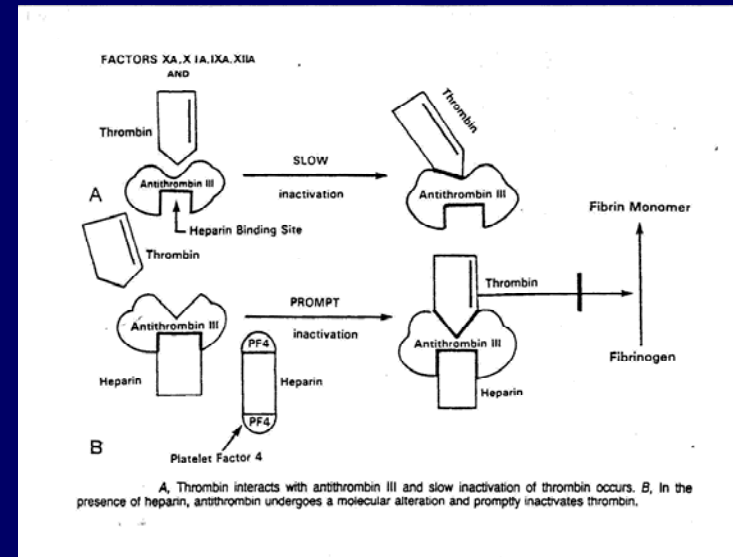
CLOTTING CASCADE

➢ Exposure to foreign materials activates the clotting cascade
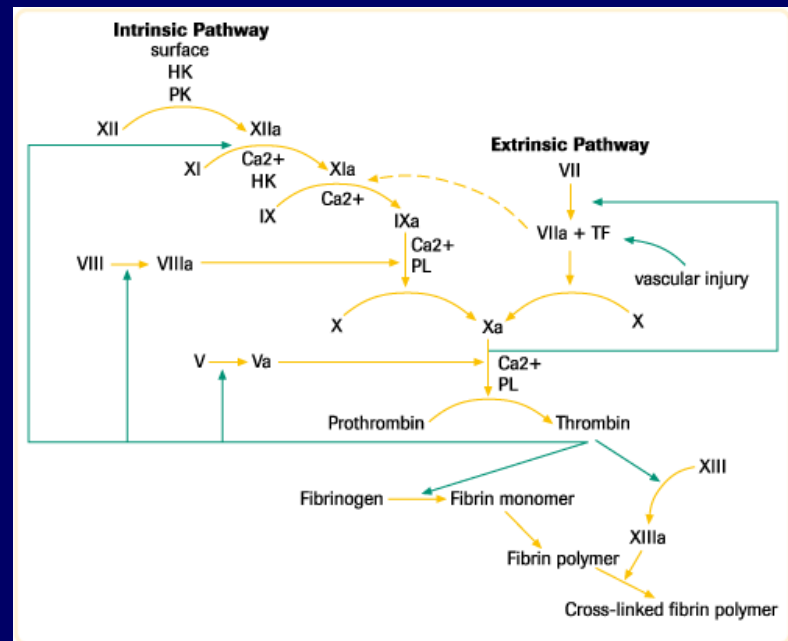
HEPARIN – MECHANISM OF ACTION

➢ Primarily affects the intrinsic clotting system

➢ Heparin binds to the lysine site on Antithrombin (AT)

➢ Heparin produces a conformational change in AT

➢ Heparin/AT-complex binds to thrombin

➢ Mechanism Of Action (MOA)
  ➢ Directly inhibits the thrombin activated conversion of fibrinogen to fibrin
  ➢ Blocks the activation of factor IX and neutralizes factor X by activating factor X inhibitor

A, Thrombin interacts with antithrombin III and slow inactivation of thrombin occurs. B, In the presence of heparin, antithrombin undergoes a molecular alteration and promptly inactivates thrombin.

HEPARIN AND DIALYSIS

> Most dialyzers currently in routine clinical use require anticoagulation to prevent the clotting that reduces blood compartment volume
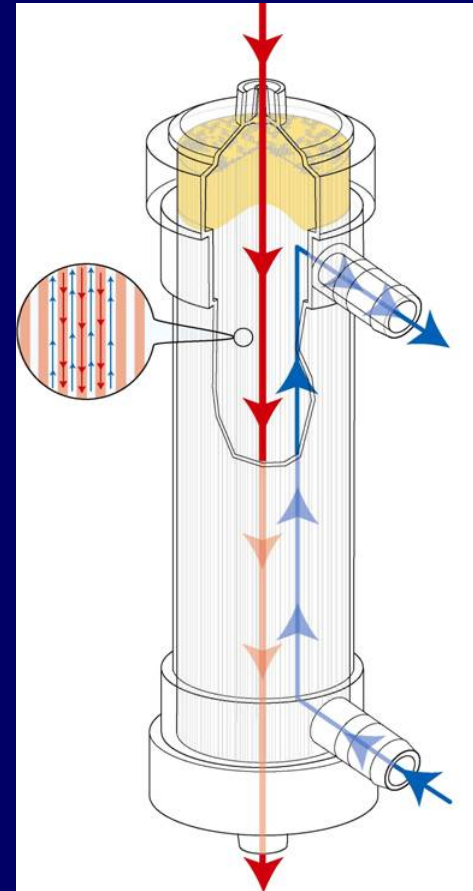
ACTIONS OF HEPARIN

➢ Too much heparin can induce hemorrhage

➢ Too little heparin and the clotting mechanism resumes, causing clots to form in the dialyzer

➢ As fibers are lost due to clotting, the efficiency of the dialyzer decreases

➢ Reduced surface area translates to reduced clearance

HEPARIN MODELING

➢ Original heparin administration scheme was empirical

➢ Anti-coagulation was more art than science

➢ Late 70's Frank Gotch and others developed pharmacodynamic models for determining individual heparin doses, based on serial measurements of coagulation times over several dialysis treatments

➢ Implementation of these models are time consuming and expensive, particularly after passage of the Clinical Laboratory Improvement Amendments of 1988 that effectively prohibited manual determination of coagulation times

HEPARIN MODELING

- Components of Heparin Modeling
  - Sensitivity
  - Elimination Constant
  - Infusion rate
  - Response

- Tools
  - Activated clotting time

- Calculation
  - $I_R = R_d K/S$

- Target Range
  - 1.5 - 2 x baseline clotting time

- Example
  - Baseline = 80 seconds
  - Target range = 120 - 160 seconds
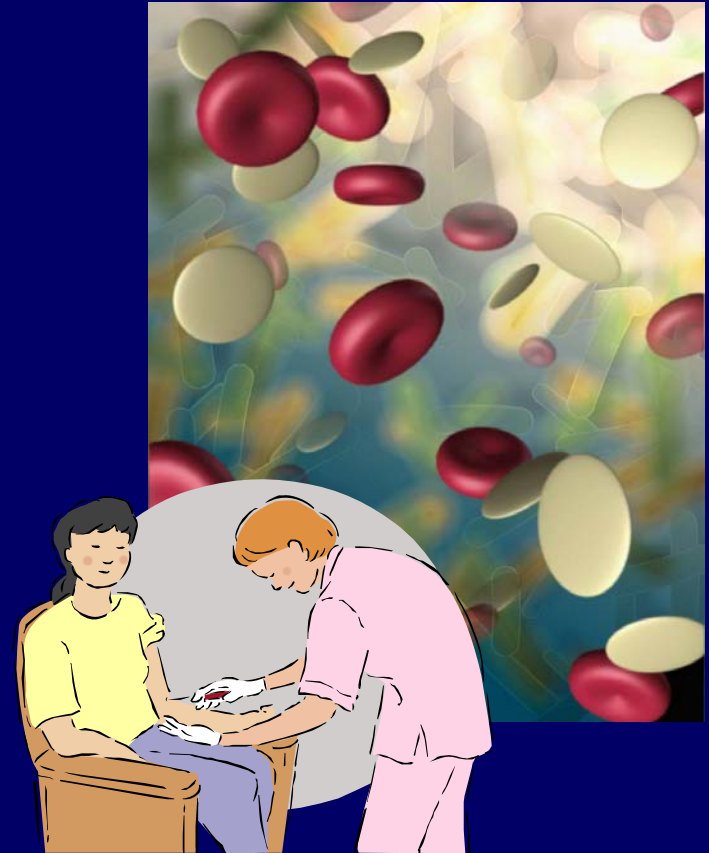
CLIA (Clinical Laboratory Improvement Amendments) of 1998

➢ CLIA requires that any laboratory testing of human specimens be performed in a certified laboratory that incorporates quality control, proficiency testing, and calibration verification in its testing program

Ward, R, Aronoff, G,Anticoagulation Strategies During Hemodialysis
Procedures, Principles and Practices of Dialysis (pp 70-78)Lippinicott, Williams & Wilkins 1994

ALTERNATIVE HEPARIN MODEL

➢ From AANA Contemporary Nephrology Nursing: Principles and Practice. 2nd Ed. 2006

➢ Pre-Dialysis Bolus (Loading Dose)
  ➢ 50 to 100 u/kg*

➢ Maintenance dose
  ➢ Continuous dose about 1,000 u/hr*

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* Lazurs, J.M., Denker, B., & Owen, W. (1996). Hemodialysis. In B. Brenner (Ed.), *The kidney* (5th ed.) (pp. 2424-2506). Philadelphia: W.B. Saunders Co.

MORE BANG FOR YOUR BUCK!!!

- ➢ Maximize effectiveness of delivered heparin
  - ➢ Route
  - ➢ Timing
  - ➢ Delivery

- ➢ Minimize factors that promote coagulation
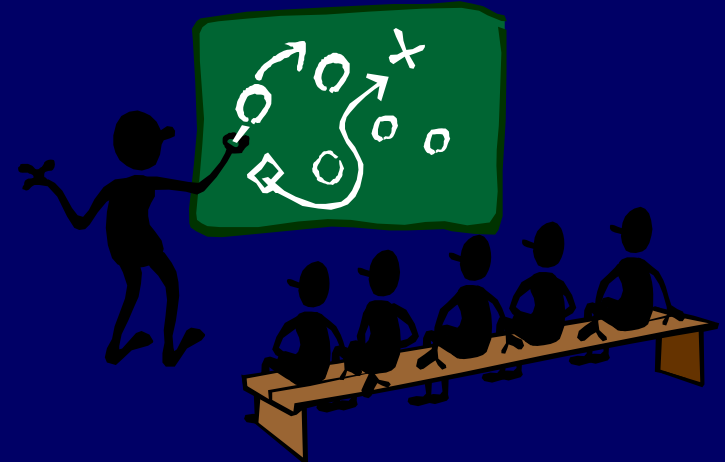
Strategy

➢ Route and Timing

  ➢ Loading dose administered through catheter or last needle placed

 ➢ Allow loading dose to recirculate for 3 – 5 minutes before initiating dialysis

Lazurs, J.M., Denker, B., & Owen, W. (1996). Hemodialysis. In B. Brenner (Ed.), *The kidney* (5th ed.) (pp. 2424-2506). Philadelphia: W.B. Saunders Co.

Strategy
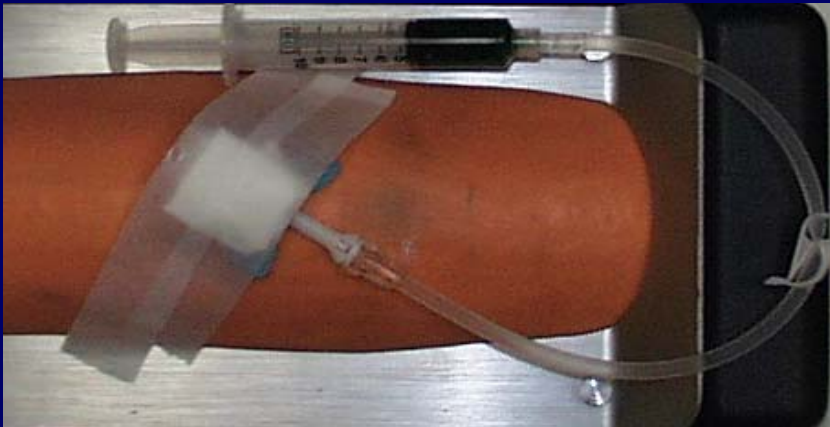
➤ Delivery

  ➤ Loading dose aspirated or followed by NS to ensure that <u>ALL</u> heparin is circulating

  ➤ Maintenance heparin line primed with heparin and heparin pump turned on <u>before treatment initiated</u>
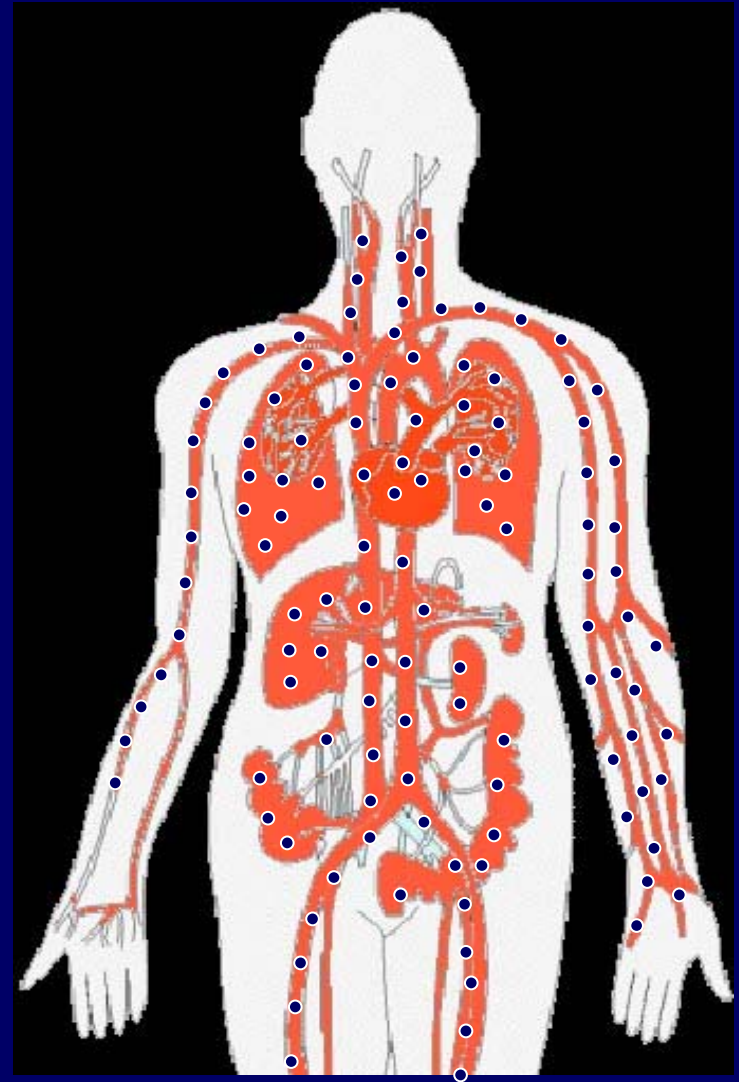
IMPORTANCE OF LOADING DOSE

➢ It is important to aspirate and flush the heparin loading dose or follow the loading dose with saline to ensure delivery to the patient
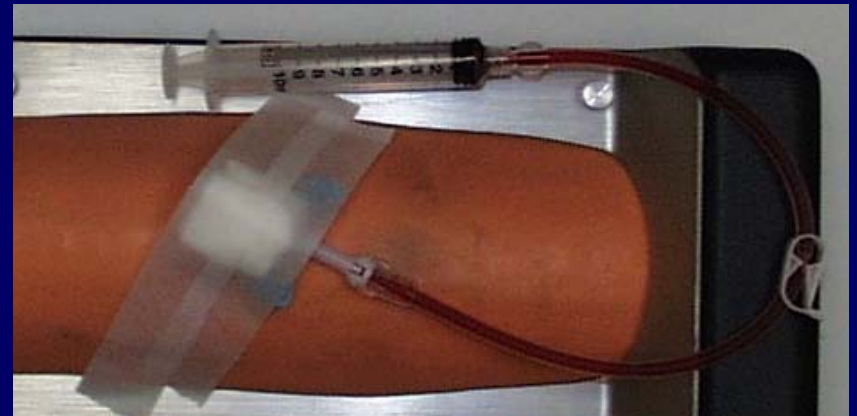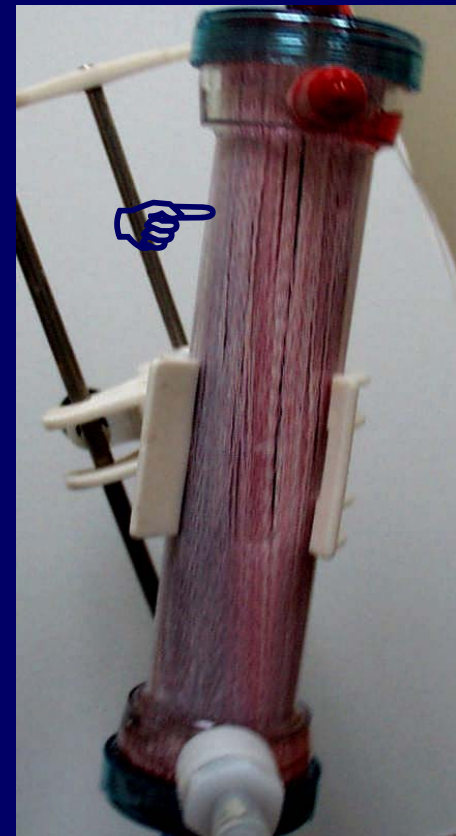
Heparin Loading Dose

➢ It will take 3 to 5 minutes for a measurable portion of the heparin to reach the arterial access

IMPORTANCE OF PRE-DIALYSIS BOLUS

➢ If you do not wait 5 minutes before patient connection, part of the hemodialyzer clots at the very beginning of the treatment and the entire treatment becomes suboptimal

LOADING DOSE ONLY HEPARINIZATION

- A large enough dose of heparin is delivered at the initiation of dialysis to anticoagulate the patient for the entire treatment

- Effective for treatments of short duration

- Is much less effective as the length of dialysis treatments increase

- Half-life of heparin is 90 – 110 minutes

INTERMITTENT BOLUS HEPARINIZATION

➢ Loading dose administered

➢ Small bolus' administered hourly

➢ Associated with periods of under and over anticoagulation
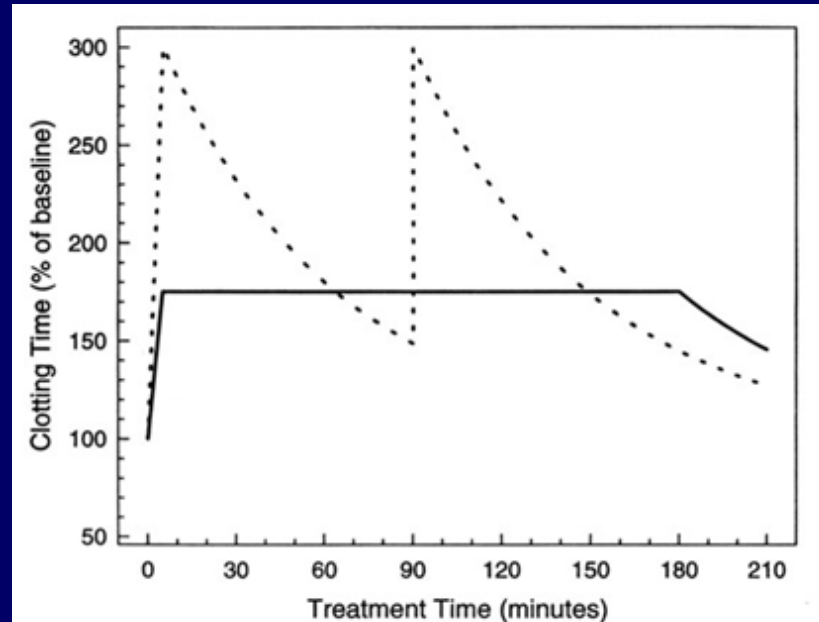
➢ Requires an attentive caregiver

CONTINUOUS HEPARINIZATION

- ➢ Loading dose administered

- ➢ Continuous injection of heparin delivered via a heparin pump

- ➢ Pump shut off at some point before the end of the treatment

INTERMITTENT vs CONTINUOUS INFUSION

Figure 6.2. Idealized anticoagulation profiles during hemodialysis. The solid line shows the clotting time profile obtained with a loading dose and constant infusion of heparin; the broken line shows the profile obtained with a loading dose and midtreatment bolus of heparin. (Reprinted with permission from Ward RA. Heparinization for routine hemodialysis. Adv Renal Replacement Ther 1995;2:362–370.)

IMPORTANT QUESTIONS TO ASK

➢ Was the heparin line primed before the initiation of dialysis?

➢ Was the heparin pump turned on at initiation of dialysis?

➢ Was the heparin line unclamped?

➢ Was the heparin pump calibrated and in working order?

➢ Was the heparin pump shut off at the prescribed time?

HEPARINIZED SALINE

➤ Theory: Heparinized-saline prime might inhibit the activation of thrombin & block the formation of fibrin on the membranes

➤ The results of using heparinized-saline for priming the dialyzer have been mixed

➤ Heparin is anionic (carries a negative charge) and will attach to positively charged membranes.

  ➤ Few membranes carry a positive charge

➤ Heparin will not inhibit platelet attachment to the membrane

STRATEGY

➤ Minimize Factors that Promote Coagulation
- ➤ Air
- ➤ Blood Flow
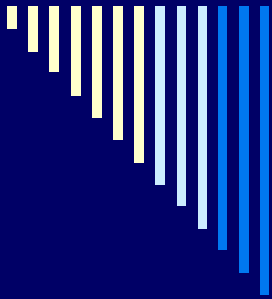
IMPACT OF AIR ON COAGULATION

➢ Promotes clotting at air/blood interface

➢ Eliminate ALL air from arterial line before attaching to the dialyzer

➢ Prime dialyzer from bottom to top

➢ Keep arterial end of dialyzer down until after recirculation of saline begins

➢ Recirculate at a speed that does not pull-in air

AIR IS DEATH TO A DIALYZER

➤ Air infused and remaining in the dialyzer fibers will promote clotting and a decrease in dialyzer efficiency
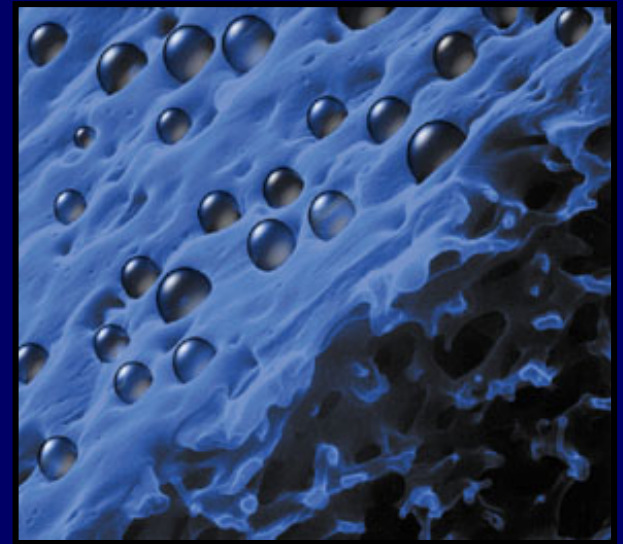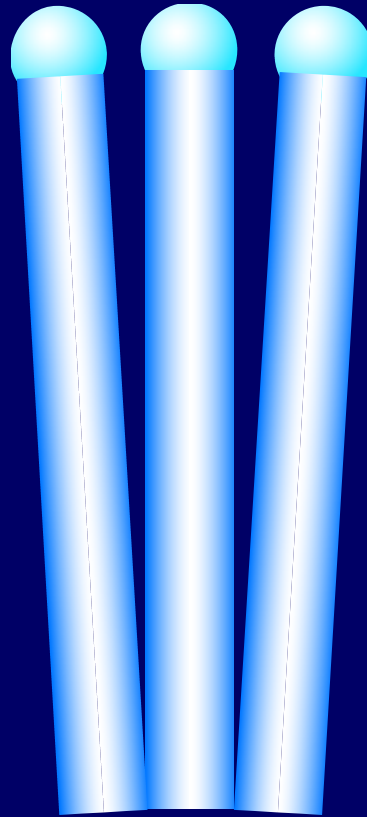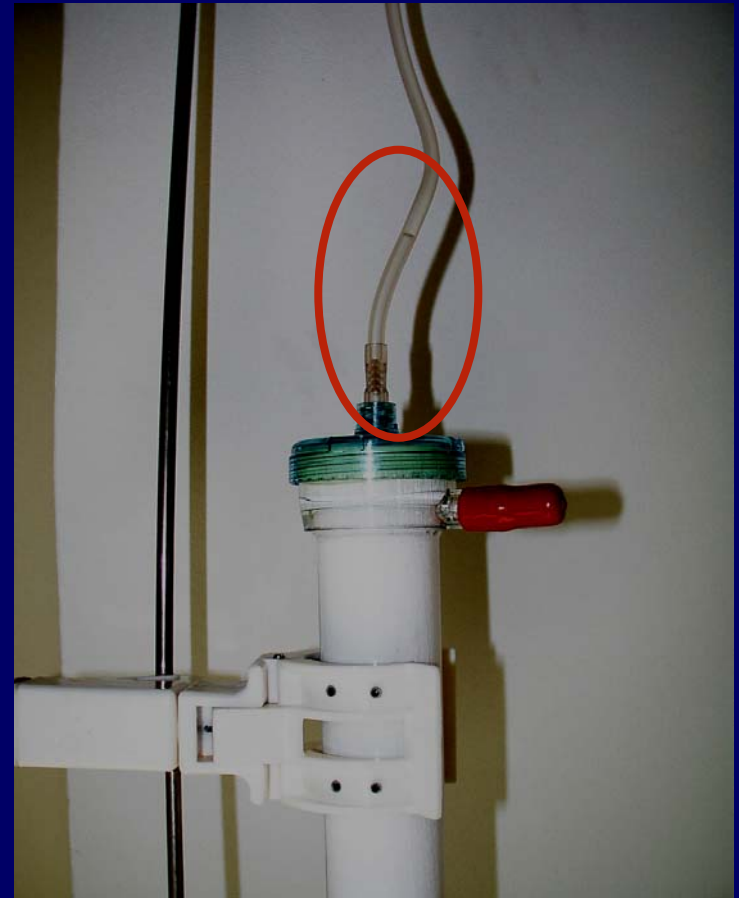
PRE-RUN PRIMING & RINSING

➢ Fully prime and then clamp the heparin maintenance line

> ➢ If the line is not primed at the appropriate time, air may be infused into the dialyzer if the arterial drip bulb/chamber is located pre-pump
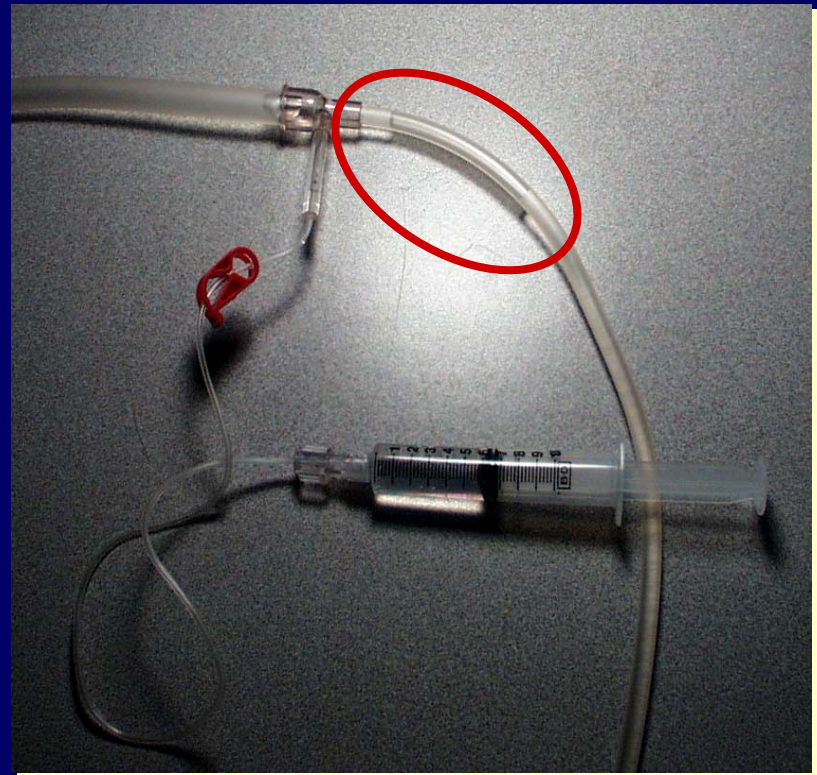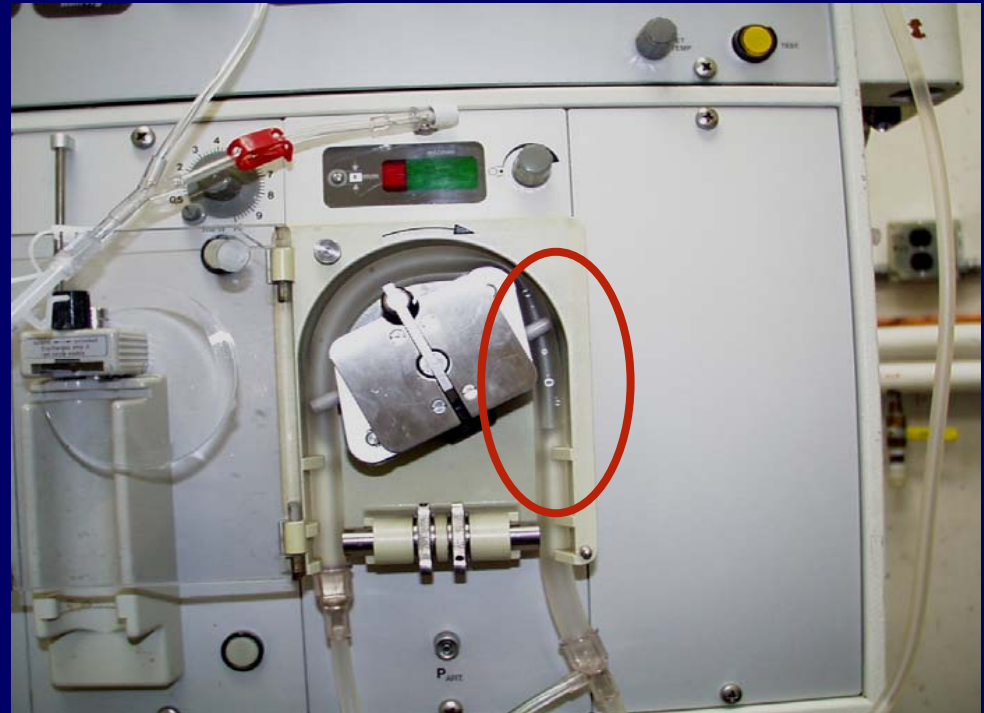
PRE-RUN PRIMING & RINSING

➢ Fully prime the arterial or venous bloodline before connecting it to the dialyzer

  ➢ If the bloodline is not fully primed before connecting it to the dialyzer, air will be infused into the fibers

PRE-RUN PRIMING & RINSING

➢ Air can become trapped in the blood pump header segment, be purged out during patient treatment and become lodged in the arterial header of the dialyzer

PRE-RUN PRIMING & RINSING

➢ Not positioning the dialyzer vertically allows air to migrate to the highest point in the dialyzer headers, occluding fibers and possibly reducing the membrane surface area

RUN MANAGEMENT

➢ Ensure the dialyzer is positioned vertically at all times

  ➢ This will reduce the possibility of air migrating to the highest point in the dialyzer header, possibly occluding active fibers and reducing the membrane surface area

POST-TREATMENT RECIRCULATION

➢ Inject remaining heparin

➢ Recirculate at maximum pump-speed

➢ If there is no heparin, recirculate <u>anyway</u>

➢ Prevents additional clotting before reprocessing

SODIUM CITRATE RINSE

➢ One facility is studying the effect of post-treatment recirculation of the dialyzer using sodium citrate in the extracorporeal circuit and is experiencing favorable results

CITRATE DIALYSATE

REGULAR 29% CITRATE 78%

SUCCESSFUL HEPARIN-FREE DIALYSIS TREATMENTS

➤ Citrate dialysate can be used for heparin-free dialysis of patients with antibodies to heparin.[1,2]

➤ Where heparin anticoagulation is contraindicated, citrate dialysate can be used for dialysis of patients with acute renal failure who are at risk of bleeding. In most cases, citrate dialysate reduces or eliminates the need to flush the extracorporeal circuit with saline.[2]
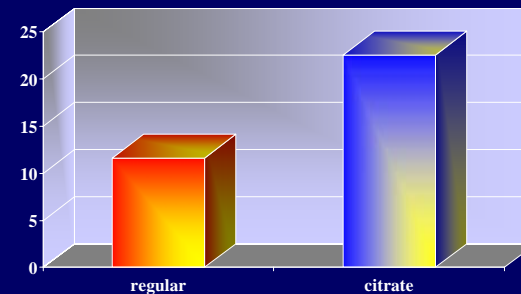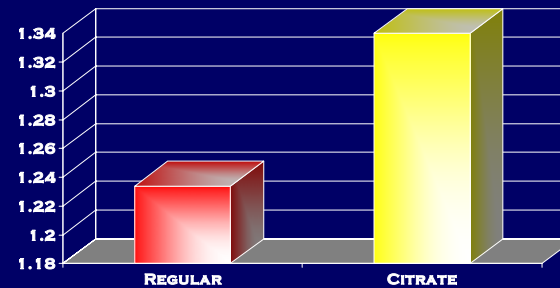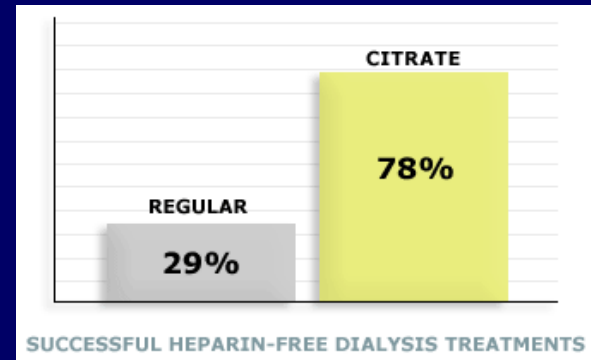
1) Pinnick RV, Wiegmann TB, Diederich DA. Regional citrate anticoagulation for hemodialysis in the patient at high risk for bleeding. *N Engl J Med.* 308(5):258-261, 1983.

2) Ahmad S, Callan, R, Cole JJ, Blagg CR. Effect of citrate-containing dialysate on dialyzer reuse. Abstr. *J Am Soc Nephrol.* 11:A0919, 2000.

CITRATE DIALYSATE

➢ No adjustment in the dialysis system is required; simply substitute citrate concentrate for the A concentrate normally used

➢ Additional staff training is unnecessary

➢ There is no need to perform additional patient monitoring beyond ordinary measures. No blood tests are needed

SUMMARY

➢ Dialysis practice BC relied on heparin to compensate for bad practice

➢ Current economics require close attention to best practice to maximize return on heparin investment

➢ The effectiveness of heparin protocols are not dependent on any one factor

➢ Anticoagulation strategy includes delivery of heparin and elimination of air from the extracorporeal circuit

➢ Alternative strategies are producing positive outcomes