Dilemmas in Fluid Therapy

The Goldilocks Principle

Jon Palmer, VMD, DACVIM
Chief, Neonatal Intensive Care Service
New Bolton Center, University of Pennsylvania, USA

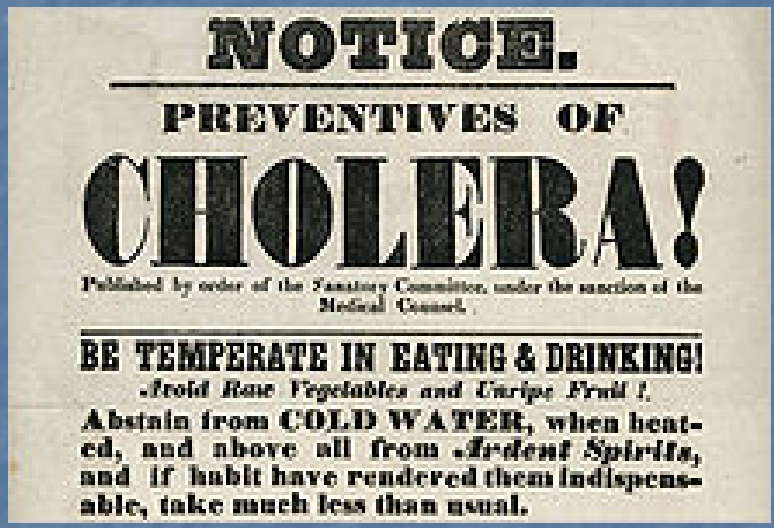
Online Lecture Notes

PDF files of slides

iveccs15.NICUvet.com

Pandemic
“Indian Cholera”

- 1831-1832
  - 23,000 victims in Britain
  - Began in Russia
  - Arrived in London Dec
  - Over by May
- Standard care
  - Blood-letting
  - With or without emetics



NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Council.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit!

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

William O'Shaughnessy

- 22-year old
- Recent medical graduate
  - Edinburgh University 1829
  - Denied license to practice London
- Unemployed
  - Clinical Chem lab in London
  - Analyzed blood Cholera victims
    - At request of medical board
    - Blood dark – oral fluids could correct
- Presented findings to medical community
  - Board of Health
  - Westminster Medical Society
- He suggested oral, colonic or IV fluids
  - Had been tried in Russia - unsuccessfully

Thomas Latta

- Scottish physician, in Leith
- Read paper/letters, heard talks
- Tried new therapy
  - First tried enteral fluids
    - "...injecting copiously into the larger intestine ..."
  - Then Latta said: 'having no precedent to direct me, I proceeded with much caution' – IV fluids
  - Critically ill woman
    - Moribund
    - Unresponsive to all other treatments
    - Revived in 30 minutes – began to talk

Thomas Latta

- Left Hospital
  - Left for 6 hrs.
  - House Officer took over care
  - Patient relapsed – died
- Tried on other patients
  - 3 of 15 survived
  - Lancet – “a favorable result”
  - Later report 25 of 156 survived
- Medical Society Hearings
  - “New treatment” tried on a few of 23,000 victims
  - Renounced new treatment as malpractice
- Thomas Latta – died within a year (TB)

William O'Shaughnessy

- Joined the civil service – India
- Medical marijuana
  - Tetanus cases
  - Rabies
- Telegraph system
  - Using rivers in India
- Knighted
- IV fluids not used again for half a century

FEAST Study

- Fluid Expansion As Supportive Therapy
  - NEJM 364(26):2483, 2011
- Justify modernizing hospitals
  - All fluid therapy in wards
- Pediatric patients - fluid resuscitation
  - Poor perfusion (1st hr. total, 2nd hr. total)
    - 20 ml/kg boluses saline (20 ml/kg, 5 ml/kg)
    - 20 ml/kg boluses albumin (20 ml/kg, 4.5 ml/kg)
    - No boluses (1.2 ml/kg, 2.9 ml/kg)
  - Severe sepsis
    - 40 ml/kg bolus saline
    - 40 ml/kg bolus albumin

FEAST Study
Poor Perfusion Group

- Children – 60 d to 12 yr – 3000+
  - Severe febrile illness
  - Impaired consciousness
  - Respiratory distress
  - Impaired perfusion
    - Capillary refill time of ≥ 3 sec
    - Lower limb temperature gradient
    - Weak pulse volume
    - Severe tachycardia

FEAST Study

- Poor perfusion group
  - 51% moderate to severe acidosis
  - 39% lactate > 5 mmol/l
- Poor perfusion group deaths by 48 hr
  - 10.6% albumin bolus group
  - 10.5% saline bolus group
  - 7.3% no bolus group
  - RR bolus vs no bolus
    - 1.45; 95% CI, 1.13 to 1.86; P = 0.003

FEAST Study

- No benefit from bolus fluid infusion
- Bolus fluids increased risk of death
  - No subgroup benefited
    - Hypotension
    - Severe metabolic acidosis
  - Increased mortality all subgroups
    - All physiological derangement
    - All microbial pathogen
  - Deaths not associated fluid overload
    - Cardiovascular death
    - Early use of vasopressors?

Fluid-Bolus Resuscitation

- Patients with compensated shock
  - Harmful? Mechanisms?
  - Interruption catecholamine responses
    - Rapid increase in plasma volume
    - Reperfusion injury?
  - Transient hypervolemia/hyperosmolality
    - Exacerbate capillary leak
    - Harmful edema
- Bolus-fluid resuscitation in compensated shock
  - If no clinical fluid deficit
  - Practice with caution

Septic Shock
Volume Resuscitation

- Immediate positive effect
  - Increased perfusion
  - Patient “looks better” but ...
- Rapid infusion – adverse effects
  - Fluid responder
    - CO increases
    - Vasodilatation
    - BP unchanged (perfusion?)
  - Increased shear stress
    - Increases NO

Septic Shock
Volume Resuscitation

- Increased cardiac filling pressure
  - Increased right atrial pressure
  - Increase natriuretic peptide
    - cGMP-mediated vasodilatation
    - Cleaves endothelial glycocalyx
    - Endothelial barrier injury
- Capillary leak
  - At 3 hr. < 5% crystalloid intravascular
  - Increased tissue edema
  - Myocardial dysfunction

Once Shock Reversed

- Positive fluid balance = increased mortality
  - Acute load
  - Rapid unload – diuresis
- Patients who rapidly unload live
  - Less severe disease?
  - Can we influence outcome?
- Dilemma
  - Initially fluids are helpful in shock
  - But once reversed – harmful
- Restrictive fluid strategy
  - Early use inopressors
  - Reverse severe vasodilatory shock

Fluid Therapy

- Timing
  - Fluid substitution
    - Electrolyte mix
  - Volume substitution
    - Resuscitation shock
      - Timely
      - Adequate
- Bolus Therapy
  - Timing
  - Positive effects
  - Negative effects

Are Fluid Boluses Needed?

- Clinical guess
  - Clinicians can't guess correctly
    - Clinical examination
    - Hemodynamic indices (e.g. CVP)
  - 50% improve outcome
  - 50% cause harm

Are Fluid Boluses Needed? ProCESS

- Protocol-based Care for Early Septic Shock
  - NEJM 5/14
  - 1341 patients with septic shock
    - Protocol-based EGDT
      - CVP, inotropes, blood transfusions
    - Protocol based standard therapy
    - Usual care
  - Resuscitation strategies differed significantly
    - Monitoring: CVP, O_2 etc.
    - Intravenous fluids, vasopressors, inotropes and blood transfusions

Are Fluid Boluses Needed? ProCESS

- No differences despite intense monitoring/ aggressive Rx
  - 90 day mortality
  - 1-year mortality
  - Need for organ support
- Similar findings
  - Australasian Resuscitation in Sepsis Evaluation (ARISE)
  - Protocolised Management of Sepsis (ProMISe)
- Goldilocks Principle
  - “Just Right”
  - Without available cues
- “Targeted Fluid Minimization” - TFM
  - Following initial resuscitation in septic shock
  - Using “fluid responsiveness”

Type of Fluid

- Saline vs balanced crystalloids
- Crystalloids vs colloids
- Plasma (albumin)

Saline vs Balanced Crystalloids

- Saline vs Balanced Crystalloids
  - Hyperchloremic acidosis
    - Renal vasoconstriction
    - Decreased renal artery
      - Flow velocity
      - Blood flow
      - Cortical tissue perfusion
    - Reduced GFR
      - Salt and water retention
  - Greater interstitial edema
- Chloride-restrictive strategy
  - 1533 ICU patients
  - Significant decrease in AKI

Which Balanced Crystalloid?

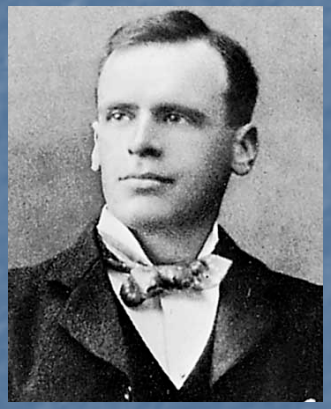
- Sydney Ringer 1880s
  - Ringer's lactate - USA
- Alexis Hartmann 1920s
  - Hartmann' solution - UK
- Normosol-R, PlasmaLyte
  - Formulations – "balanced"
    - Lactate, acetate, gluconate
  - Gluconate
    - Not metabolized
    - Diuresis

Colloids vs. Crystalloids

What's the Evidence?

Classic Compartment Model

- Intracellular fluid compartment
- Extracellular fluid compartment
  - Intravascular
  - Interstitial
- Ernest Starling 1896
  - Semipermeable membrane
  - Hydrostatic and oncotic pressure gradients
  - Principal determinants of transvascular exchange



25 Years Ago - Promise

Assumptions:

- Plasma volume 20% of the extracellular fluid
  - Volume equivalence for resuscitation hypovolemia
  - 20 ml colloid to 100 ml crystalloid
- Transfusion of hyperoncotic colloid solutions
  - Absorb fluid from the interstitial fluid
  - Increase intravascular volume

Colloid and Crystalloid Solutions

- Colloids in theory
  - More effective in expanding intravascular volume
    - Stays within the intravascular space
    - Maintain colloid oncotic pressure
  - 1:5 ratio of colloids to crystalloids
- Crystalloids
  - Inexpensive
  - Available
- But significant interstitial edema
  - Occur with both types of fluids

Major Studies

- Saline versus Albumin Fluid Evaluation (SAFE)
- Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)
- Scandinavian Starch for Severe Sepsis/Septic Shock (6S)
- Synthetic Colloids vs Crystalloids
- Crystalloid versus Hydroxyethyl Starch Trial (CHEST)
- Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL)

Type of Fluid
Colloid vs Crystalloids

- HES:crystalloid all studies volume used
  - Approximately 1:1.3 (not 1:5)
  - But colloids retain fluids = negative outcome
- Reversal of shock
  - No difference volume or speed
- Toxicity of HES
  - Coagulopathy
  - Kidney injury – tubular uptake
  - Hepatic failure in the HES group
  - Severe persistent pruritus
  - Tissue storage of HES

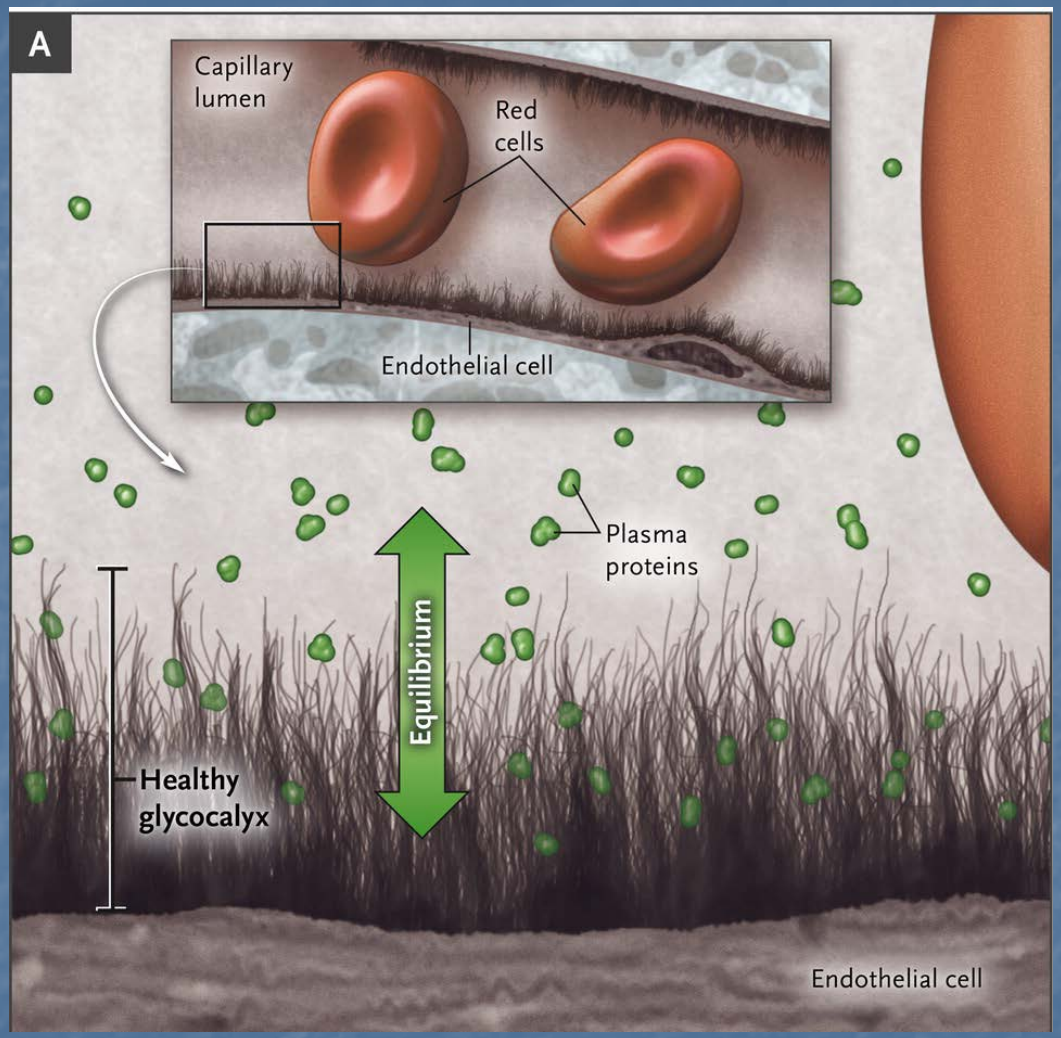
Type of Fluid
Colloid vs Crystalloids

- Human regulations
  - Do not use critically ill
  - Do not use sepsis
- Research misconduct
  - Joachim Boldt
    - Scientific fraud
    - 87 reports retracted

Why don’t colloids work as expected?

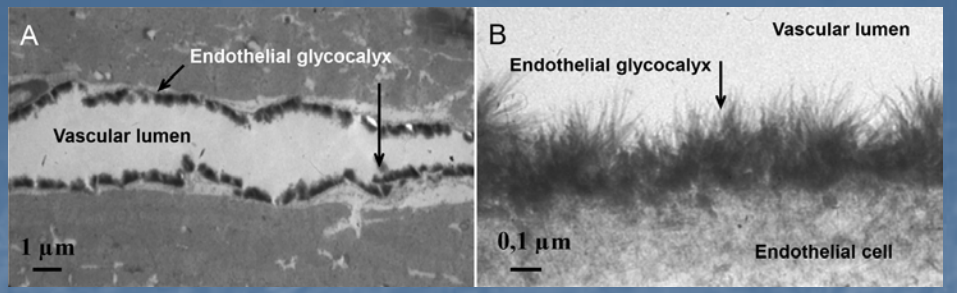
Changing Beliefs

Increased Understanding



Myburgh JA, Mythen MG. Resuscitation Fluids. **N Engl J Med 2013;369:1243-51.**

EGL barrier

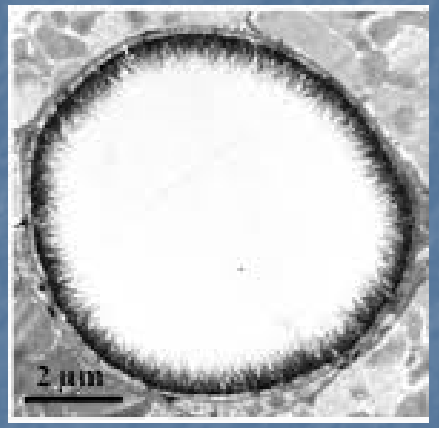


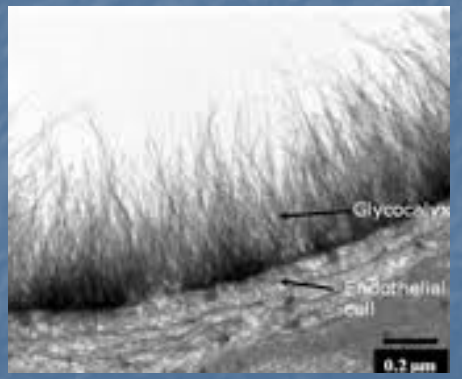
Best Practice & Research Clinical Anaesthesiology 28 (2014) 227-234.

- Endothelial glycocalyx
  - Carbohydrate-rich layer
  - Proteoglycans and glycoproteins
  - Bound plasma proteins, mainly albumin
- Hydrostatically forced fluid
  - Forces albumin and other osm particles into web
  - Forms a gradient with more caught outside
  - Any protein making it through washed into interstitium
  - Layer of fluid on luminal side of endothelium – protein free
  - Forms oncotic gradient
  - Not effected by interstitial protein content

Fluid Type and the EGL

- Transvascular fluid filtration
  - Depends on endothelial glycocalyx
    - If intact with normal capillary pressures
      - Crystalloids freely pass
      - Colloids are held back
    - If damaged neither are held back
- Intravascular hypovolemia
  - Low capillary pressures
  - No filtration crystalloids or colloids
- Damage EGL – loss of filtering ability
  - Hypervolemia
  - Rapid fluid administration
  - Sepsis (inflammatory mediators, TNF)
  - Ischaemia/Reperfusion

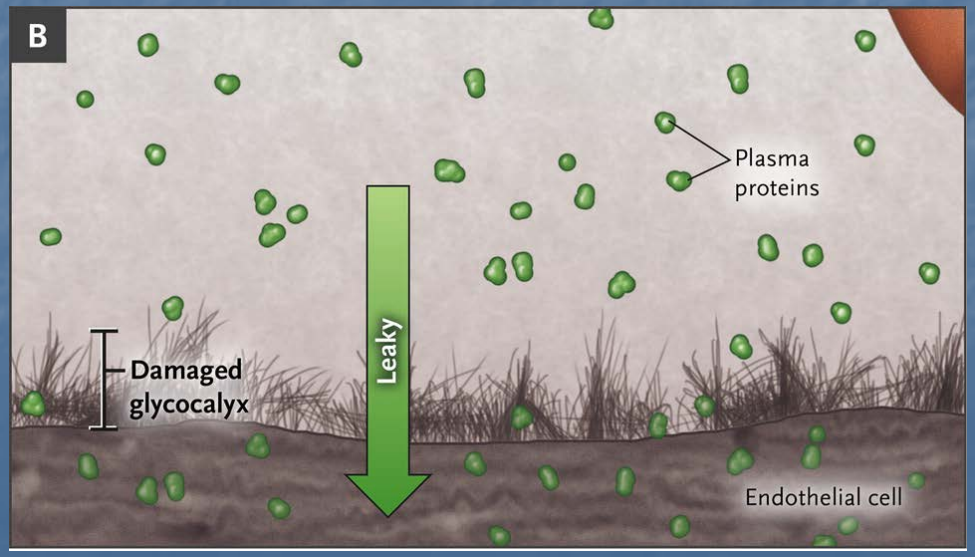




From: http://www.hubrecht.eu

EGL – Damage by Hypervolemia

- Theory
  - Volume sensed by atria
  - Release natriuretic peptides (ANP)
  - Which activates metalloproteinases



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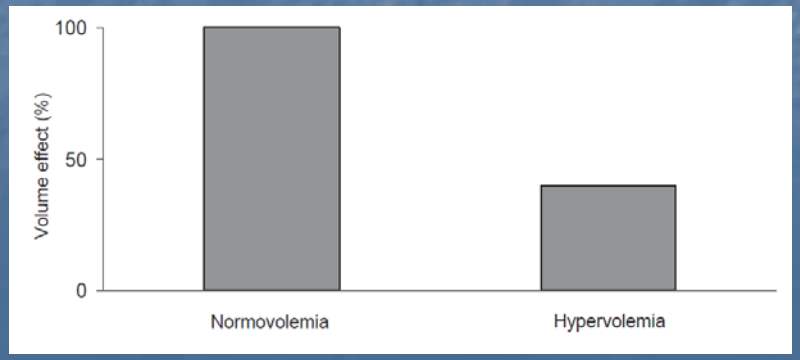
EGL – Damage by Hypervolemia

- Studies
  - Acute blood loss
    - Add HES or albumin to maintain normovolemia
    - Almost 100% retained
  - Hypervolemia – HES or albumin
    - Infuse same volume without loss
    - 60% colloid escapes into interstitium
    - Glycocalyx is decreased



Fluid Type
Crystalloids vs Colliods

- Depend on state of endothelial glycocalyx
- Colloid increases intravascular volume
  - Resuscitation from hemorrhage
- No difference intravascular volume
  - Sepsis
  - Inflammatory states
  - Trauma
  - Hypervolemia

Endothelial Glycocalyx "Capillary Leak"

- Normovolemia
  - Endothelial glycocalyx healthy
  - Colloids remain intravascular
  - Crystalloids leak
- Hypervolemia (fluid therapy)
  - Endothelial glycocalyx damaged
  - Colloids and crystalloids leak
- Hypovolemia
  - Colloids and crystalloids remain intravascular
- Sepsis
  - Endothelial glycocalyx damaged
  - Colloids and crystalloids leak with fluid therapy

Fluid Type
Albumin

- Saline versus Albumin Fluid Evaluation (SAFE) 2004
  - 7000 patients – overall no differences
  - Septic patients – trend increased survival
- Albumin Italian Outcome Sepsis (ALBIOS) study 2014
  - No benefit from maintaining normal albumin level
  - Reduced mortality in Septic Shock subgroup
- Role in glycocalyx functioning
  - Albumin level important for normal filtering
- Transcapillary escape rate of albumin (TCERA)
  - Index of 'vascular permeability'
  - Normal TCERA - 5% per hour
  - Septic shock - 20% or more
  - Low albumin
    - Increased escape?
    - Catabolism?

COP Paradox

- Traditional Starling
  - Great importance to the COP of plasma
- But clinical studies show
  - No difference between the COP of plasma
    - Septic and non-septic patients
  - COP does not influence pulmonary transcapillary filtration
    - In patients with pulmonary edema
  - Not found to be a determinant of outcome
    - In intensive care cases

COP Paradox

- Rx albumin vs HES vs saline
  - Transiently raised plasma COP with albumin, HES
  - Not change fluid balance
  - Not change development of edema
- Fluid type in patients with acute lung injury
  - Colloids worsened thoracic compliance
  - Type of fluid used does not affect pulmonary edema
- Properties other than the effect on COP contribute to the capillary ‘sealing’ effect of albumin

COP Paradox
"Capillary Leak"

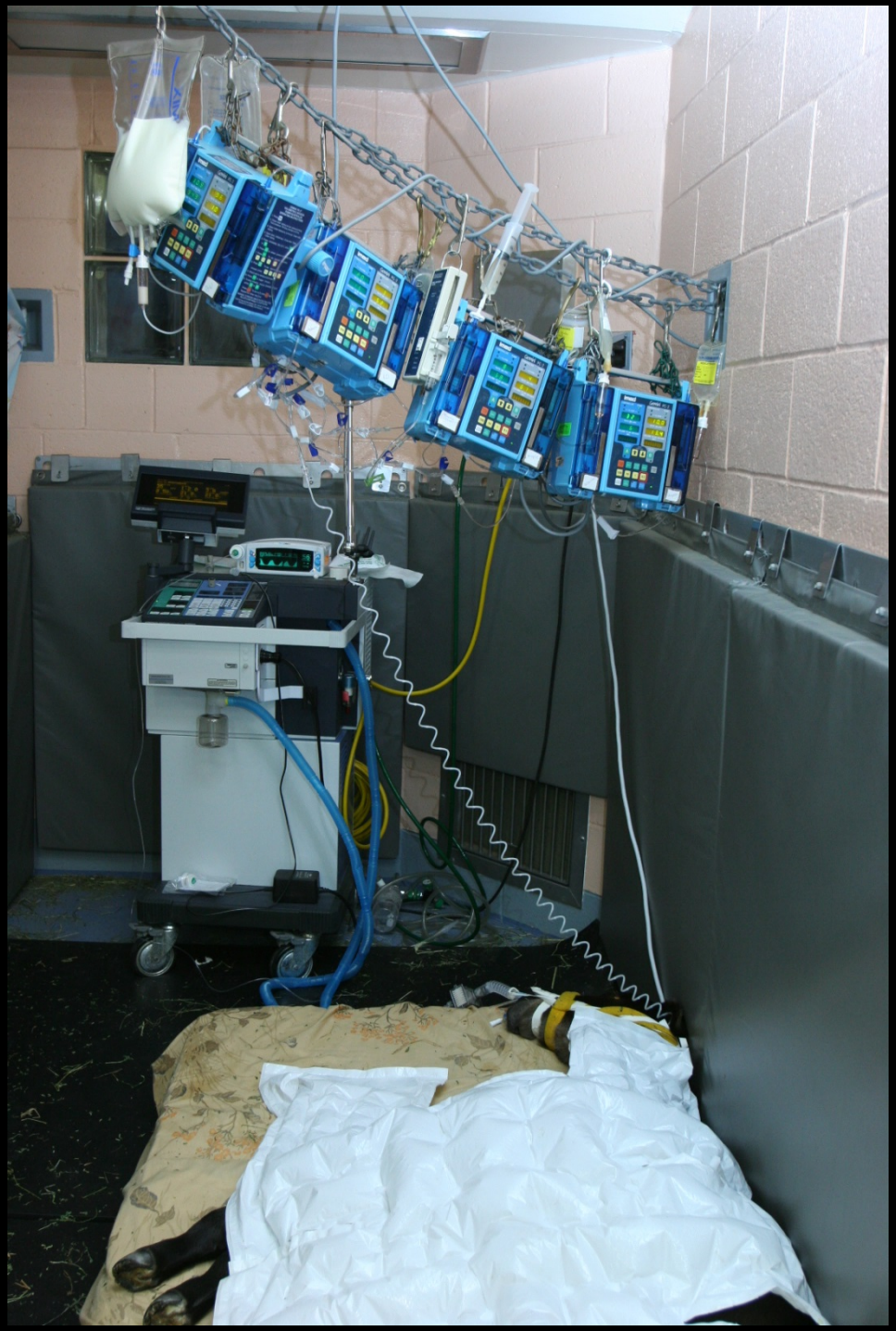
- If capillary pressure is normal
  - Colloid infusion
    - Preserves plasma COP
    - Increases capillary pressure
    - Increases capillary filtration
  - Crystalloid infusion
    - Lowers plasma COP
    - Increases capillary pressure
    - Increases capillary filtration more than colloids
  - Colloids normal individual
    - Keep vascular volume higher than crystalloids

COP Paradox "Capillary Leak"

- If low capillary pressure – shock
  - Infusion of colloid
    - Increases plasma volume (inside EGL - lumen)
  - Infusion of crystalloid
    - Increases vascular volume (lumen and EGL)
    - Results is 1:1.3 ratio colloid:crystalloid volume?
  - Capillary filtration
    - Close to zero in both cases
  - Effect on volemia is equal – no clinical difference
- COP of plasma/ colloid
  - Not help volume resuscitation

Colloids

- Only indicated for intravascular hypovolemia
  - Without inflammation
- No better than crystalloids
  - For hypoperfusion
  - For capillary hypotension/vasodilation
  - Any time disruption of EGL
- Should not be used as a fluid preload
  - Neither should crystalloids
- Not helpful in cases with low COP



Fluid Therapy
Critical Patients

- Primarily used to treat hypoperfusion
  - Loosely connected to hypovolemia
  - Ideally use physiologic endpoint
- No reliable clinical guides to endpoint
- Old idea of treating shock
  - More is better and faster please!
  - No longer tenable
- Goldilocks principle
  - Not too little!
  - Not too much!

Fluid Therapy
Critical Patients

- Past focus on short-term goals
  - Rapid correction of hypovolemia
  - Emergency resuscitation
  - Clinically immediately rewarding but ...
- Potential longer-term consequences
  - Contribution to organ failure
  - Long term mortality/morbidity

Fluid Therapy
Things I Try to Do

- Bolus fluids but not too much
  - No good stall side guide
- Stop high rates fluids early
  - Before legs warm
  - Give IV nutrition
    - In as small a volume as practical
  - Na restriction in neonates
  - Cl restriction

Fluid Therapy
Things I Try to Do

- Watch weight increases as gauge?
  - Confounding factors
- Fluid restriction
  - If good perfusion
  - Signs fluid overload
    - Edema
    - Weight gains
- No good clinical guides
  - Too much vs too little
  - Be well aware of possible harm
- Type of fluid
  - Crystalloids
  - Plasma

Goldilocks Principle

Getting it “Just Right”

No Jelly Belly