NEONATAL PHYSIOLOGY

JON PALMER, VMD, DACVIM

NEW BOLTON CENTER, KENNETT SQUARE, PENNSYLVANIA

Neonatal Period

- Physiologic transition period
  - Full dependence on maternal physiology
  - Adaptation to independent life
- Period transition all organ systems
  - First 3 to 4 weeks of life

Physiologic Transitions

Counterintuitive Physiology

- Different from Adult Physiology
- Fetal Physiology

Renal Response to Hypovolemia

- Adult kidney
  - Producing concentrated urine
  - Maintain vascular volume
- Fetus
  - Concentrated urine
    - Increase fetal fluid osmolarity
    - Prevent reabsorption of the fluids
    - Draw fluid from the fetus
    - Negative effect on volemia

Renal Response to Hypovolemia

- Produces dilute urine
  - Decrease fetal fluid osmolarity
  - Enhance reabsorption of fetal fluids
  - Positive effect on volemia

Heart Rate Response To Hypoxemia

- Adult
  - Tachypnea and tachycardia
  - Deliver more oxygen to tissues
- Fetus
  - Bradycardia
  - Maximizing perfusion of fetal placenta
  - Increasing vascular tone - directing blood to vital organs
  - Increase in afterload
    - Increase cardiac work and thus oxygen demand
    - Decrease HR
      - New circulatory pattern
      - Requires no more oxygen

Species

Fluid Physiology

Fluid Physiology
Fetus/Neonate

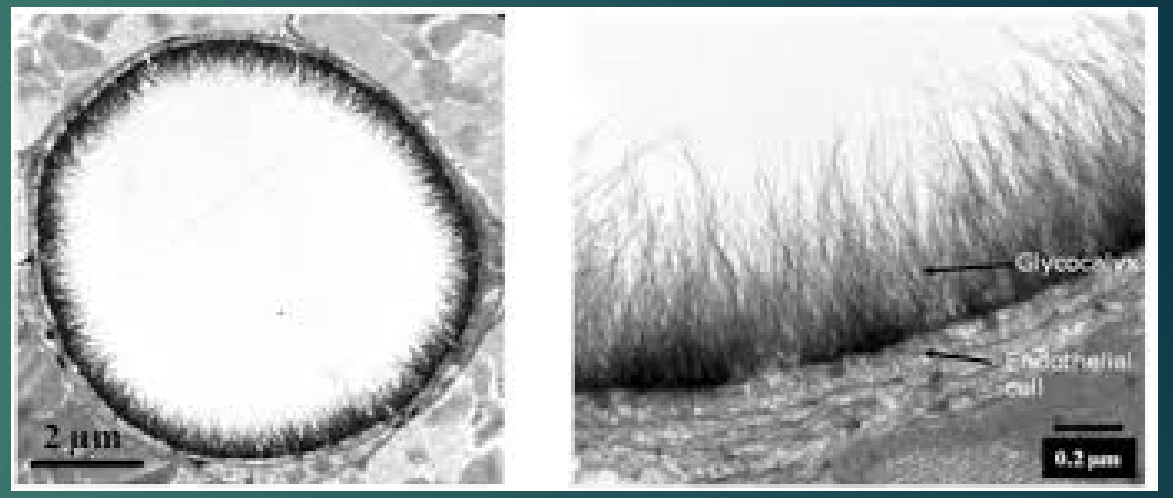
- Unique characteristics of Fetal/ Neonatal
  - Interstitium
  - Lymph flow
  - Capillary endothelial permeability
- Interstitium
  - Heterogeneous space
  - Dynamically controls its fluid content
  - Compliance 10X adult (fetal lamb)

Fluid Physiology
Fetus/Neonate

- Lymph flow
  - Volume of lymph 1 mL/kg in adult dogs
  - Thoracic duct lymph flow
    - Fetal lamb - 0.25 mL/minute/kg
    - 5x the adult rate
  - Lymph flow - subcutaneous
    - Puppies 2X adult dogs (per kg)
  - Pulmonary lymph flow
    - Newborn lambs and puppies > adults
  - Neonate – local/ whole body lymph flow > adult
    - Increased interstitial volume
    - Higher capillary permeability

Fluid Physiology Fetus/Neonate

- Capillary endothelial permeability
  - Filtration rate in fetal lambs vs adults
    - Fluid 5x
    - Proteins 15x
  - Why?
    - Poor precapillary tone
    - Higher capillary hydrostatic pressure
    - Higher filtration
    - The role of the glycocalyx?
  - Filtration related to hydrostatic pressure
    - Precapillary tone lambs – develops during 1st week
    - Doesn't develop in a uniform manner



From: http://www.hubrecht.edu

Fluid Physiology
At Birth

- Blood pressure increases - lambs
  - Last weeks – increases 20%
  - During labor – increases another 18%
  - At birth – increases another 12%
- Transmitted to capillaries
- Increased transcapillary filtration
  - Poor precapillary tone

Fluid Physiology
At Birth

- Other reasons for fluid shifts
  - Direct compression of the fetus
    - Increased venous pressure
  - Vasoactive hormones
    - Arginine vasopressin
    - Norepinephrine
    - Cortisol
    - Atrial natriuretic factor

Fluid Physiology

Neonates are Born Fluid Overloaded

- Fluid shifts
  - From fetal fluids / maternal circulation
  - Accumulating in the fetal interstitium
- ***All Neonates Are Born Fluid Overloaded***
- Rate of loss of this fluid - species variation
  - Foal – weeks
  - Other species
    - 10-15% body weight rapidly after birth
  - Important not to replace fluid loss
    - Poor outcomes with persistent fluid overload

Fluid Physiology
Consequences

- **Response to Hemorrhage**
- **Response to Volume Loading**
- **Response to Hypoxia**

Fluid Physiology
Response to Hemorrhage

- Perinatal blood loss
  - Rupture of umbilical vessels
  - Premature placental separation
  - Fetomaternal transfusion
  - Fetofetal transfusion
  - Internal bleeding

Fluid Physiology
Response to Hemorrhage

- 30% loss of blood
  - Adult dogs, cats, and sheep
    - With out fluid therapy - 24 to 48 hours
  - Fetus or neonate is shorter
    - Fetal sheep
      - 2x adults within 30 minutes
      - 100% blood volume within 3 to 4 hours

Fluid Physiology
Response to Hemorrhage

- Neonatal kittens and rabbits
  - Greater blood loss /kg before BP decrease
    - Translocation fluid and protein
    - From the interstitial space
  - Tolerate blood loss better than adults

Fluid Physiology
Response to Volume Loading

- Rapid intravascular infusions crystalloids
  - Fetal lambs - 6 to 7% retained at 30-60 min
  - Adults – 20% to 50% retained at 30-60 min
- Rapid transfer into the interstitial space
  - High interstitial compliance
  - High capillary filtration coefficient

Fluid Physiology
Response to Volume Loading

- Fluid Overload – lack of intravascular retention
  - Adults (dogs, sheep)
    - The adult clears the fluid load hours
    - Renin
    - Vasopressin
    - Atrial natriuretic factor

Fluid Physiology
Response to Volume Loading

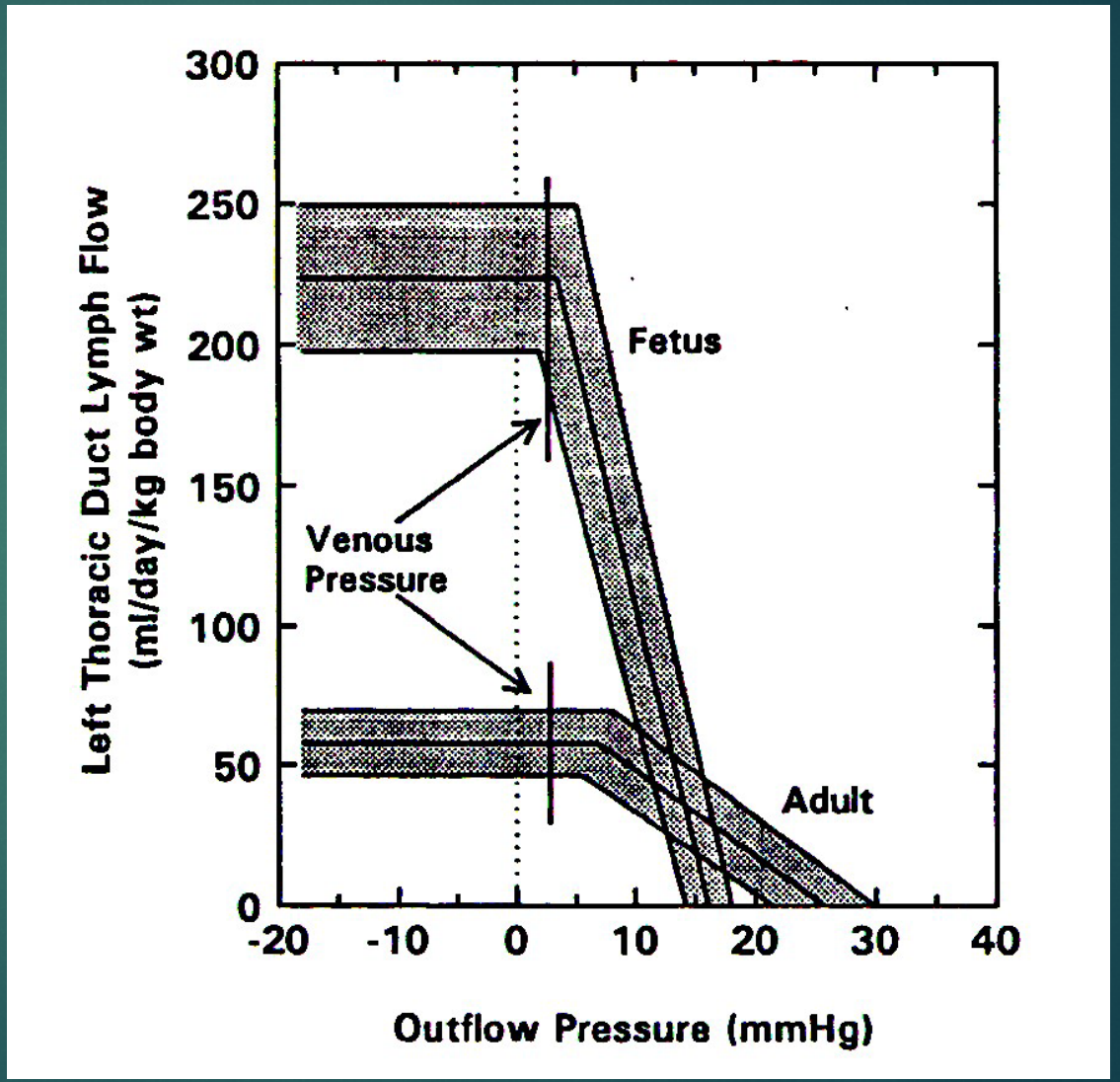
- Fluid Overload – lack of intravascular retention
  - Neonates (puppies, lambs)
    - 24 to 36 hr to clear fluid load
    - Volume load escapes vasculature space quickly
    - Escape volume sensors detection
    - No diuretic response
    - Urine flow rapidly returns to normal
      - Before clearing volume load

Fluid Physiology
Response to Volume Loading

- After fluid loading (fetal lambs, neonatal lambs)
  - Increase thoracic duct lymph flow
    - Increase by 3.5 times (max flow rate)
    - Angiotensin II augments lymph flow
  - Fluid therapy – rapid infusion
    - Increases CVP
    - Dramatic decrease in lymphatic flow
    - Result in edema

Thoracic Lymph Flow

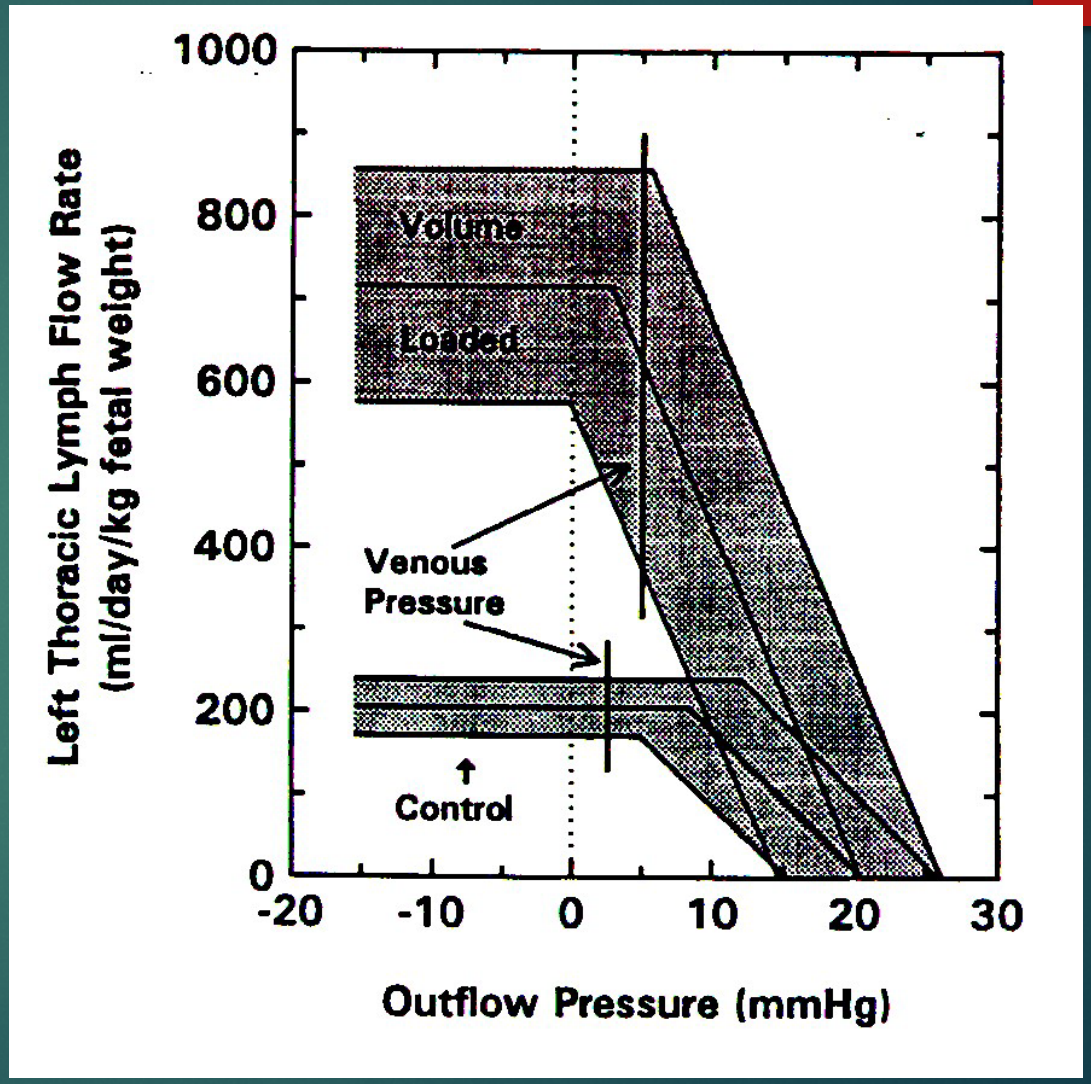
- Fetal lamb
- Adult sheep



From: Brace RA et.al.

Thoracic Lymph Flow

- Fetal lamb
- With large volume intravenous infusion
  - ↑↑ Lymph flow as much as 340%
  - Limited by CVP



From: Brace RA et.al.

Fluid Physiology
Response to Hypoxia

- Moderate/severe hypoxemia (fetal lambs)
  - Increases arterial and venous pressures
  - Poor precapillary tone
    - Increase capillary pressure
  - Greater fluid shift interstitial space
  - Leading to excessive fluid overload

Fluid Physiology
Response to Hypoxia

- All neonates
  - Fluid overloaded at birth
- With hypoxia/asphyxia
  - Greater degree of fluid overload
- ***Hypovolemic with concurrent fluid overload***

Renal Physiology

Renal Physiology
Renal Maturation At Birth

- Nephrogenesis is Complete, GFR adult levels in days
  - Lambs
  - Foals
  - Calves
- Nephrogenesis continues 2 + weeks
  - Puppies
- ??
  - Kitten
  - Kid

Renal Physiology
Neonatal Puppy Renal Function

- Low GRR
- Low renal plasma flow (RPF)
- Low filtration fraction (FF)
- Decreased tubular reabsorption
  - Amino acids
  - Phosphate
- Exaggerated proximal tubule natriuresis
  - Balanced by increased distal tubule Na reabsorption
- Low concentrating ability

Renal Physiology
Neonatal Cr & BUN Levels

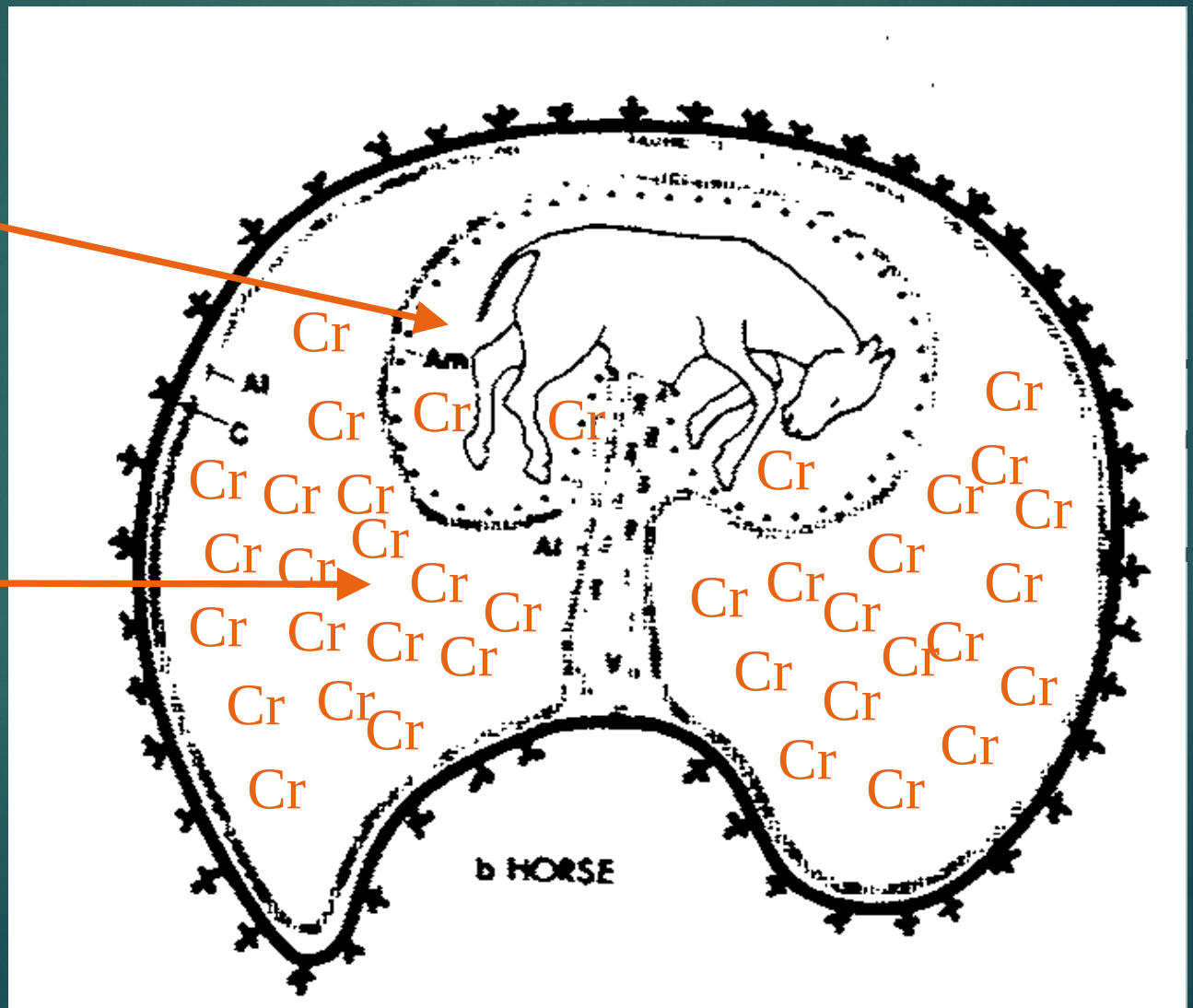
- BUN
  - Lower than adults
  - Dependent on nutrition
- Cr level at birth
  - Cr lower than adult
    - Puppy
  - Adult level at birth
    - Infant - increase first 48 hr then decreases
  - Higher Cr than adult at birth but rapid drop
    - Foals
    - Calves

Renal Physiology

Sea of Cr – Fetal Foal

Amnionic Cr
9 – 12 mg/dl

Allantoic Cr
120 – 180 mg/dl



Renal Physiology
Renal Perfusion

- Fetus - 3-5% of cardiac output
- Birth rapid increases to 15%
  - Increase in BP
  - Renal vascular resistance
    - Increases modestly
    - But less relative to other vascular beds

Renal Physiology
Renal Perfusion

- Autoregulation
  - Normal range for age
  - “Autoregulatory range” increases as BP increases
- Puppies
  - GFR/RPF increase in parallel with
    - Increases in BP
    - Decreased in VR
  - Not changed by inhibition of angiotensin
    - Until 6 weeks old
- Foal, calf and lamb
  - GRF becomes adult-like
  - Independent of increases in arterial BP

Renal Physiology
Neonatal Vasogenic Nephropathy

- Balancing BP and renal VR
  - Vital for proper renal function
- Neonatal Vasogenic Nephropathy (NVN)
  - Abnormal levels of vasoactive substances
  - Increased sympathetic tone
- Prostaglandins in neonates
  - Afferent arteriolar vasodilation
  - Counterbalancing endogenous vasoconstrictors
  - High PG activity is physiologically necessary
    - Maintain renal perfusion

Renal Physiology
NSAID

- Greater potential for adverse renal effects
  - Reduce GFR and RBF
  - Neonatal Vasogenic Nephropathy
  - Oliguria
  - Fluid overload
- Both COX 1 and COX 2 inhibition equally bad

Renal Physiology
Hypothermia

- Rabbits decreases temperature 2 C
  - Induce renal vasoconstriction
  - Decrease GFR
- Hypothermic neonates at risk
  - Environmental temperature at birth
    - Sympathoexcitatory response
  - Response occurs before a decrease in core temperature
  - Reversible with rewarming
  - Mediated by cutaneous cold-sensitive thermoreceptors
    - Not core temperature

Renal Physiology
Nephron Development

- Number of nephrons
  - Great variation in normal individuals
  - Linear relation with body weight
- Normal and compensatory renal growth
  - Primarily proximal tubular mass

Renal Physiology
Nephron Development

- Decrease nephron numbers
  - Intrauterine growth restriction
  - Perinatal asphyxia
  - Shock
  - Exposure of the fetus to maternal administration
    - NSAIDS
    - Glucocorticoids
    - Aminoglycosides
    - Beta lactam antibiotics

Renal Physiology
Tubular Function

- Immature at birth
  - Low carrier density
  - Short tubules
- Puppies
  - Urine specific gravity
    - Birth is limited (1.006 to 1.017)
    - Adult levels 12 weeks (8 weeks kittens)
  - Protein, glucose, amino acids in the urine
    - Neonate
    - Adult levels by 3 weeks

Renal Physiology
Tubular Function

- Large animal neonates urine specific gravity
  - Broad range within 24 hours
  - 1.001 to > 1.035
  - Herbivore Milk diet
    - Usg < 1.004
- Foal
  - First urine
    - 12 hours, Usg > 1.035
    - 24 hours Usg < 1.004

Renal Physiology
Sodium Story

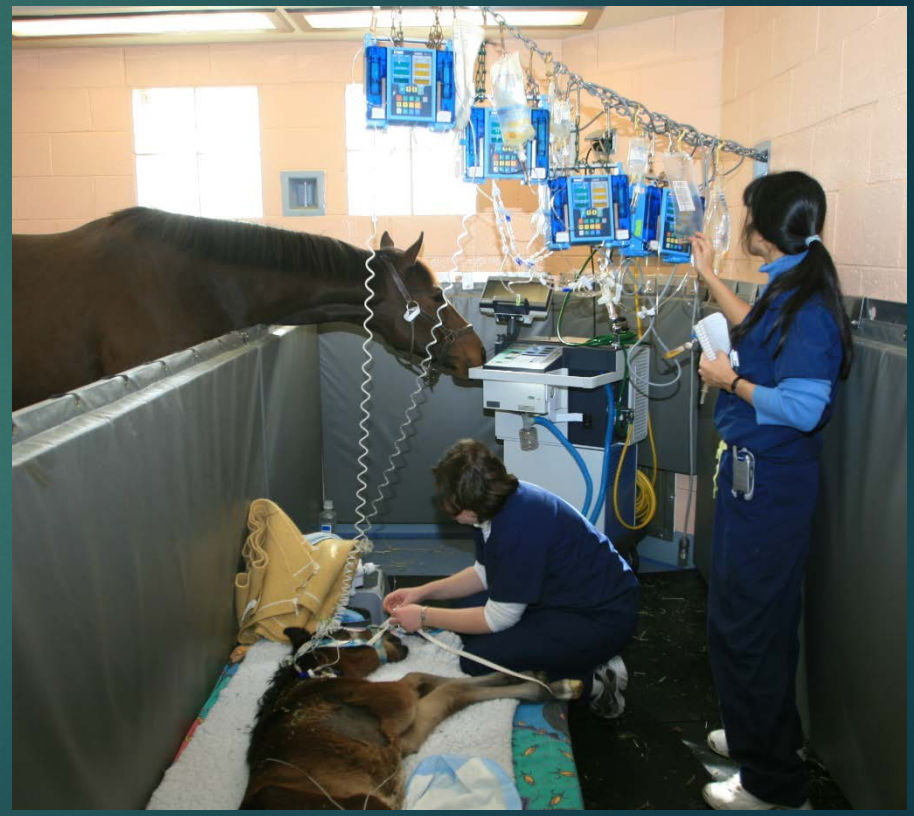
- Positive sodium balance needed for growth
  - Increase interstitium
  - Bone growth
- Fresh milk is sodium poor
  - Mare's milk – 9 to 14 mEq/L
  - 20% milk diet – 1.9mEq/kg/day
  - Growth requirement 1 mEq/kg/day

Renal Physiology
Sodium Story

- Immature kidney Na reabsorption
  - With sodium loading in dogs
    - Proximal tubule – 64% adult dog: 48% puppy
    - Distal tubule – 26% adult dog: 51% puppy
    - Total – 91% adult dog: 98% puppy
- Upregulation distal tubular Na transporters

Renal Physiology
Sodium Story

- Slow to respond to Na load
  - Species dependent
  - Predisposes to Na overload
  - Problem in critically ill neonatal foals
- Crystalloid fluid therapy
  - Na overload
  - Fluid overload
  - Limited urine dilution
    - Puppies
    - Neonatal Vasogenic Nephropathy



Cardiovascular Physiology

Cardiovascular Physiology
At Birth

- Increase in
  - Arterial blood pressure
  - Heart rate
  - Cardiac output
    - 4X higher than adult (lamb)
- Regional changes blood flow
  - Initially retains low-resistance–high-flow system
  - Renal 3% to 15% at birth

Cardiovascular Physiology
Neonatal Changes

- Puppies
  - SBP 61±5 birth to 139±4 at 4 wk
  - HR 204±3 at birth to 123±6 at 4 wk
- Large animal neonates
  - Studies confounded by restrain artifacts
  - Clinical experience – low BP/VR to high BP/VR
    - Most make a rapid transition
    - A few neonates retain the low BP/VR maintain excellent perfusion
    - Critically ill neonates more likely delay transition

Cardiovascular Physiology
Neonates

- BP cannot be used as surrogate for perfusion
- Absolute BP numbers - Dangerous therapeutic goals

Cardiovascular Physiology
Autonomic influence heart rate

- Puppies, kittens
  - Sympathetic innervation functionally incomplete
    - Puppies – less chronotropic response
  - Lack of vagal tone - minimal response to atropine
    - Puppies < 14 days
    - Kittens < 11 days
    - Atropine not effective in neonatal resuscitation
- Clinical observations in foals, calves, crias, lambs and kids
  - Autonomic cardiac control at birth
  - Calves, crias
    - Intubation my induce dangerous bradycardia

Cardiovascular Physiology
Resetting baroreflex

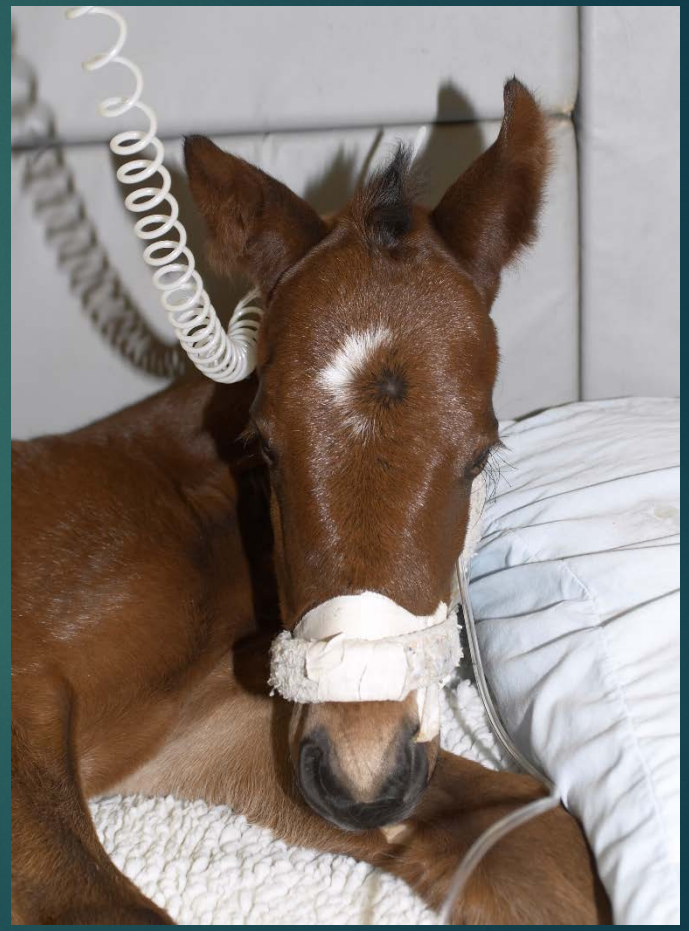
- Baroreflex sensitivity changes with maturation
  - Resets - shifts toward higher pressures
  - Shifts during fetal life
  - Shifts immediately after birth
  - Shifts during postnatal period
  - Paralleling BP increases
- Resetting complex
  - Peripheral resetting
    - Level of the baroreceptor
  - Central resetting
    - Sympathetic or parasympathetic activity

Cardiovascular Physiology
Resetting baroreflex

- Puppies
  - Baroreceptor reflex absent until 4 days of age
- Large animal neonates
  - Most make rapid transition
  - Some critically ill neonates
    - Retain the fetal baroreceptor set point
      - Apparent inappropriate bradycardia
      - Low BP
      - But good perfusion

Cardiovascular Physiology
Autonomic Dysregulation

- Critical neonates
  - Transient but requires careful management
  - Not respond adrenergic support
  - Not vagally mediated
    - Not respond to atropine
  - May respond to oxygen therapy



Cardiovascular Physiology
Ductus Arteriosus, Foramen Ovale

- Functional closure
  - 50% by 24 hr
  - 90% by 48 hr
- Anatomic closure
  - Within weeks
  - Until they – powerful survival tool

Cardiovascular Physiology
Ductus Arteriosus, Foramen Ovale

- Pulmonary hypertension
  - Hypoxemia
  - Sepsis
- Consequences of Pulmonary hypertension
  - Adult – Hypoxia Ischemia
  - Neonate – Hypoxia without ischemia

Gastrointestinal Physiology

Gastrointestinal Physiology
Development

- Small intestine - first 10 days of life
  - Increases 80% in length
  - Increase 30% in diameter
  - Maturation is incomplete until after weaning
- Macromolecules transport
  - IgG, cytokines, trophic hormones, others
    - Gastric acid secretion not occur during transport period
      - At least 24 hours
      - Rat - acid secretion not occur until weaning
        - 18 days after birth

Gastrointestinal Physiology Development

- Macromolecules transport
  - Fetal intestinal epithelial cells
    - Transport macromolecules
      - Some species neonatal epithelial cells
    - Life span 3 weeks
      - Lambs – 5 days after birth
      - Calves – 14 days
      - Pigglets – 21 day
    - Transport slows by 6-12 days
  - Nonselective pinocytosis some species
    - Reason for frequent translocation of bacteria?

Gastrointestinal Physiology
Development

- Trophic signals
  - Luminal
    - Amnionic fluid
    - Colostrum
    - Fresh milk
    - Food
    - Nutrients
    - Microbes

Gastrointestinal Physiology
Development

- Trophic signals
  - Circulation/ local
    - Peptide growth factors
    - Gut origin peptide hormones
    - Steroid and thyroid hormones
  - Neural inputs
    - CNS
    - Enteric Nervous System

Gastrointestinal Physiology
Development

- Importance of luminal nutrition
  - "Trophic feeding"
    - Growth and metabolism of mucosal cells
    - Release of local growth factors
    - Release of gut hormones
    - Activate neural pathways (ENS)

Gastrointestinal Physiology
Development

- Fresh colostrum
- Fresh milk
- Mucosal barrier and immune function
- Establish normal flora
  - Flora is trophic
  - Discourages establishment of pathogens

Confused?