Equine Perinatology

Gastrointestinal and respiratory problems

http://nicuvet.com

Infectious Gastrointestinal Problems of the Neonate

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Gastrointestinal Problems

- Most common problems of neonatal foals
- Range from mild to life threatening
- Infectious diarrheas
  - Most important herd problems
  - Often high morbidity
    - Once begin, every new born foal at great risk
    - It may return and become a farm problem year after year
  - Variable mortality
  - Costly to treat
    - Economically
    - Human resources
  - Our knowledge of etiologies incomplete
    - Multiple pathogens often present

Enterocolitis

- Foals with diarrhea may have
  - Simple GI upset with the problem confined to the lumen
  - Significant intestinal inflammation
    - Leading to widespread systemic inflammation
- Foals with enterocolitis
  - May develop systemic inflammation
  - May develop metabolic complications and mutliorgan failure
    - Acidosis
    - Hypovolemic shock
    - Hypotension
  - May develop systemic infections
    - Bacteremia
      - Secondary infections
      - Secondary pathogens
    - Secondary sites of infection/inflammation
      - Pneumonia
      - Hepatitis
      - Nephritis
      - Physitis

Infectious Causes of Foal Diarrhea

- **Clostridial enteritis**
  - ***Clostridium difficile***
  - ***Clostridium perfringens***
- ***Salmonellosis***
- ***Escherichia coli***
  - **Part of a systemic infection**
  - **Rarely a primary enteritis – opportunist**
- **Others?**
  - ***Aeromonas hydrophila***
  - ***Streptococcus durans***
  - ***Clostridium sordelli***
  - ***Bacteroides fragilis***
  - **Others???**
- ***Viral***
  - ***Rotavirus***
  - ***Coronavirus***
  - ***Adenovirus***
  - ***Others??***
- ***Other?***
  - ***Cryptosporidium parvum***

Clostridial enteritis

- Clostridia can be found in clinically healthy foals
- Pathogenesis depends on
  - Host,
  - Pathogen
  - Environmental factors
- Epidemiology is complex
  - Limited colonization common causing no disease
  - Critical number that causes clinical disease varies with strains
  - Diagnosis often made by toxin gene detection
    - Toxin gene PCRs – soft diagnosis but easy
    - If target toxin gene not present – still could be clostridial infection
      - Enterotoxin gene most common PCR target – many strain lack
  - Culture of *Clostridia spp* is not enough to make a diagnosis
    - Best diagnosis is finding toxin gene and positive culture
- Signs
  - Diarrhea (hemorrhagic *C. perfringens* Type C)
  - Colic
  - Tachypnea
  - Depression

Clostridial enteritis

- **Onset usually < 36 hr, < 24 hr**
  - Often as soon as meconium passes
  - 6-12 hr old
  - Herd outbreak on breeding farm
    - First few foals born OK
    - Then first clinic cases begin at 24-36 hr
    - Soon every foal born develops enteritis between 6 and 12 hr
    - As soon as meconium passed enteritis
- **Clinical lab as expected**
  - Leukopenia, neutropenia, lymphopenia
  - Left shift
  - Hyperfibrinogenemia
  - Low Na, K, Cl, HCO_3, hypoproteinemia
  - Often IgG OK – still give plasma

Clostridial enteritis

- **Therapy**
  - **Specific therapy**
    - **Metronidazole**
      - **Vancomycin?**
  - **Supportive therapy**
    - **Intensive fluid therapy**
      - **Continuous fluids best but bolus therapy can be successful**
        - **Inotrop/pressor therapy rarely needed**
      - **Electrolyte replacement therapy**
    - **Plasma therapy – independent of passive transfer**
      - ***C perfringens* type C and D antitoxin?**

Clostridial enteritis

- **Therapy**
  - **Antidiarrheal therapy**
    - **Di-tri-octahedral smectite (Biosponge)**
      - **Absorb toxins??**
    - **Bismuth subsalicylate**
    - **Other antidiarrheals**
- **Outcome**
  - **With early intensive therapy mortality 5-10%**
    - **Farm problem – labor intensive and expensive therapy**
    - **Likely to occur next breeding season on same farm**
  - **Mortality higher with *C. perfringens* Type C**
  - **Varies with outbreak to certain extent**

Clostridial enteritis

- **Prevention**
  - Good hygiene
  - Strict isolation protocols
  - Vaccination??
    - *C perfringens* type C and D toxoid ??
      - Safety and efficacy???
- **Spores**
  - Virtually impossible to eliminate
  - Reduce numbers with good hygiene
    - Cleaning (scrubbing) remove all organic material
    - Disinfection (bleach or other disinfectant)

Salmonellosis

- Endemic enterocolitis in foals of all ages
- Herd problem
  - Endemic strains, often multiple strains in individual cases
  - Breeding farms
    - Endemic strains
      - Long time resident mares resistant
      - Transient mares susceptible
    - New mares may introduce new strains
    - Wildlife's role
    - In feed, pellets
      - Calcium source
      - Contaminated feed mills
    - Density of housing
  - All ages
    - Neonates, sucklings
    - Weanlings, yearlings
  - With stress
    - Diet changes
    - Housing, grouping changes

Salmonellosis

- Clinical signs range widely
  - Localized enteritis
    - Diarrhea – occasionally hemorrhagic
    - Fever
    - Colic
    - Dehydration
      - Hyponatremia, hypokalemia, azotemia, acidosis
    - Depression
    - Not suckling

Salmonellosis

- Systemic signs
  - Hypotensive shock
  - Multiorgan dysfunction
  - Secondary sites of infection
- Other foci with or without enteritis
  - Bacteremia – not localized
  - Physitis, synovitis, osteomyelitis
  - Vertebral body abscesses
  - Nephritis
  - Hepatitis
  - Pneumonia/pleuritis
  - Uveitis

Salmonellosis

- **Therapy**
  - Aggressive fluid therapy
  - Close attention to K and HCO_3 replacement

  - Systemic antimicrobials
    - Often multiply resistant
    - Aminoglycosides??
      - Amikacin
      - Gentamycin
    - Cephalosporins, potentiated beta lactams
      - Especially with aminoglycoside
    - Others
      - Inopenum – only when resistance pattern is known
    - Not antimicrobials routinely used on the farm
      - Should do antibiogram on outbreak isolates

Salmonellosis

- **Therapy**
  - **Plasma transfusions**
    - **Not for protein replacement**
    - **For antibodies but also other immunomodulators**
      - **IgG level should not be trigger**
  - **Other symptomatic antidiarrheal therapy**

Rotavirus

- **Epidemiology**
  - Clinical signs when 5 to 35 days old
    - Most subclinical
  - Wide range of severity in clinical signs
  - Numbers game – severity depends on:
    - Exposure dose
      - Depends on environmental contamination
      - More and younger foals infected higher shedding rate
      - Shedding heavier from clinical vs subclinical cases
    - Host resistance factors
      - Age
      - Passive immunity
      - Mare's exposure history
      - Population density
      - Other concurrent infections
    - > 90% exposed before reach training
      - Most subclinical

Rotavirus

- **Clinical Signs**
  - Mild to severe diarrhea
  - Association with gastroduodenal ulcer syndrome????
- **Pathogenesis**
  - Maldigestion and malabsorption
  - Villous atrophy, compensatory crypt cell proliferation
    - Decrease in fluid absorption/ increase in secretion
    - Maldigestion, lactose enter the colon
    - Fermentation increase osmotic fluid retention
    - Less Cl/HCO3 exchange in ilium
      - Less buffer for VFA absorption colon
      - Osmotic diarrhea
- **Diagnosis**
  - Viral particles easily detected – rapid test in practice
  - Finding virus ≠ cause of diarrhea
    - Infection universal in young horses
    - Not always cause of problem

Rotavirus

- Control
  - Good husbandry
  - Decreasing environmental contamination
    - Cleaning/ disinfection
      - Virus can survive for months in the environment
    - Population control
  - Increase herd immunity
    - Rotavirus vaccines
    - Bring mares onto farm early
      - To expose them to all the endemic flora

Therapy

- Antimicrobials
- Fluid Therapy
  - What
  - How
  - How much
- Plasma – why?
- Antidiarrheals
- Management – isolation
- Owner/farm manager control?

Bacteremia in Foals with Diarrhea

- J Vet Intern Med 2008;22:1203–1209
- 50% (66 of 133 foals) bacteremic at admission
  - 75 isolates from the 66 samples
- Multiple isolates
  - 7 % (9 foals).
- 57% Gram-negative, 43% Gram-positive
  - Enterococcus spp. (22 isolates, 29%)
  - Pantoea agglomerans (13 isolates, 17%)
- IgG at admission not associated
- Survival not associated
- Bacteremia common but not associated with prognosis

Antimicrobials

- Aminoglycosides
  - Amikacin
    - 30 min Peak >60 (MIC < 16 S; >32 R), 23 hr trough < 2
    - Dose < 1 week – 30-35 mg/kg
    - Dose 2-4 weeks – 20-25 mg/kg
  - Gentamycin
    - 30 min Peak >40 (MIC < 4 S; >8 R), 23 hr trough < 2
    - Dose < 1 week – 20-25 mg/kg
  - Effectiveness depends on high peak then dropping to trough
  - Toxicity
    - Not dropping to tough
    - Length of therapy
    - Toxicity not associated with high peak
      - Higher peak better killing but not more toxicity
- B-lactams
  - Penicillin derivatives
  - Cephalosporins
    - Ceftiofur IV
      - 10 mg'kg QID – slow infusion over 20 min
      - CRI – 1.5 mg/kg/hr (3 hr aliquots)
  - Carbapenems – Imipenem
- See website for other options/doses: NICUvet.com

Fluid Therapy

- New ideas
- General Principles
- Different clinical situations
  - Hypoperfusion with and without fluid loss
- Fluid therapy changes the endothelial glycocalx
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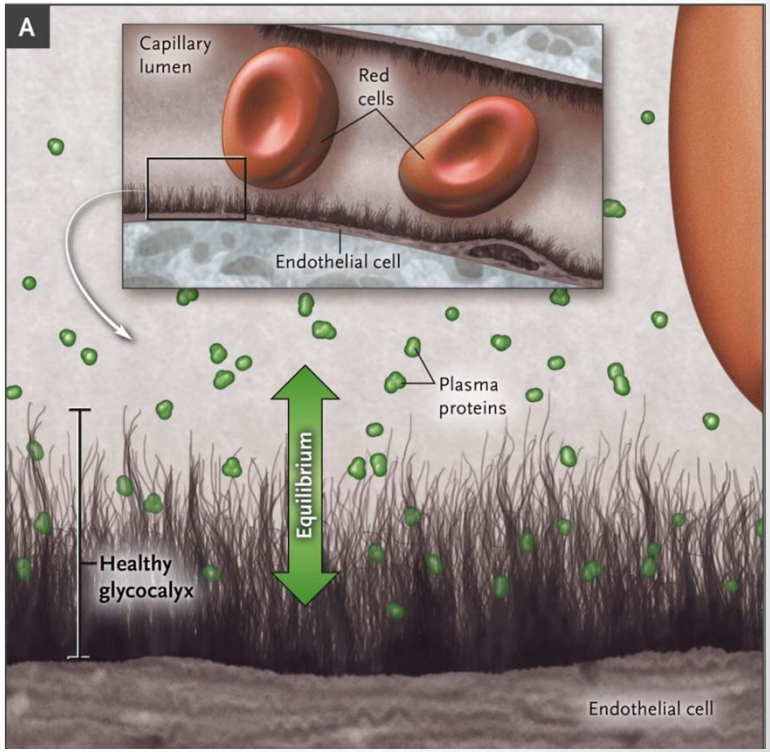
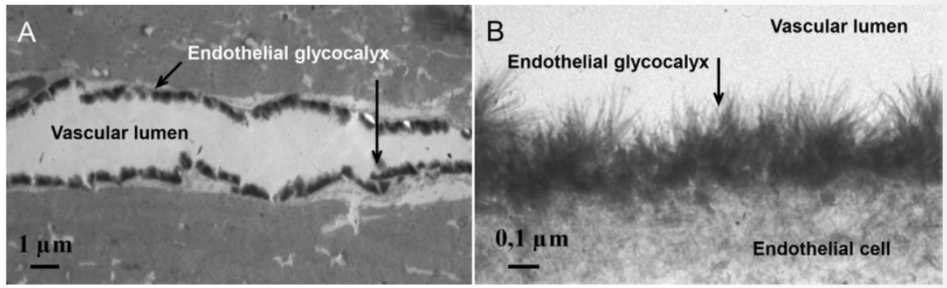


Myburgh JA, Mythen MG. Resuscitation Fluids. **N Engl J Med 2013;369:1243-51.**

Endothelial Glycocalyx

- Complex, multicomponent
- Functions
  - Molecular sieve
  - Lubrication layer
    - RBC motion
  - Inhibitor of inflammation
  - Shear sensor
    - Plasma flow-induced fluid shear strain



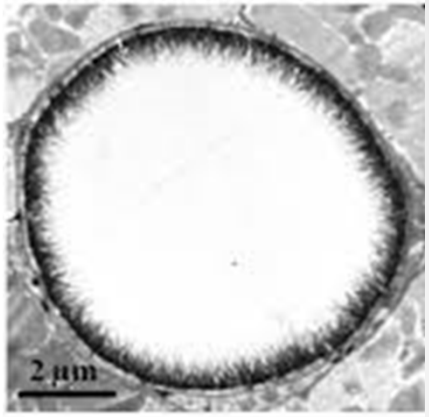
- Hydrostatic forces push fluid through glycocalyx
  - Forces albumin and other osm particles into web
  - Forms a gradient with more caught outside
  - Any protein making it through washed into interstitium
  - Forms oncotic gradient
  - Not effected by interstitial protein content

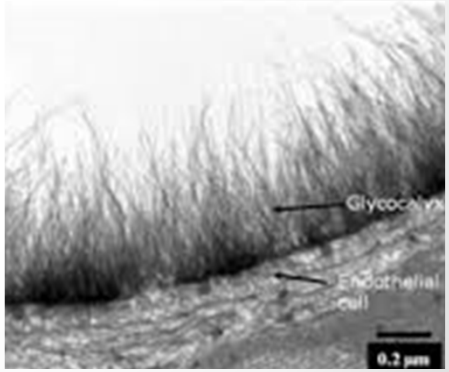
Endothelial Glycocalyx

- **Molecular sieve**
  - Fence-like meshwork
  - Size exclusion of plasma molecules
  - Semipermeable filter to large solutes
- **Soluble components caught in meshwork**
  - Albumin

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)
  - Ischemia/Reperfusion

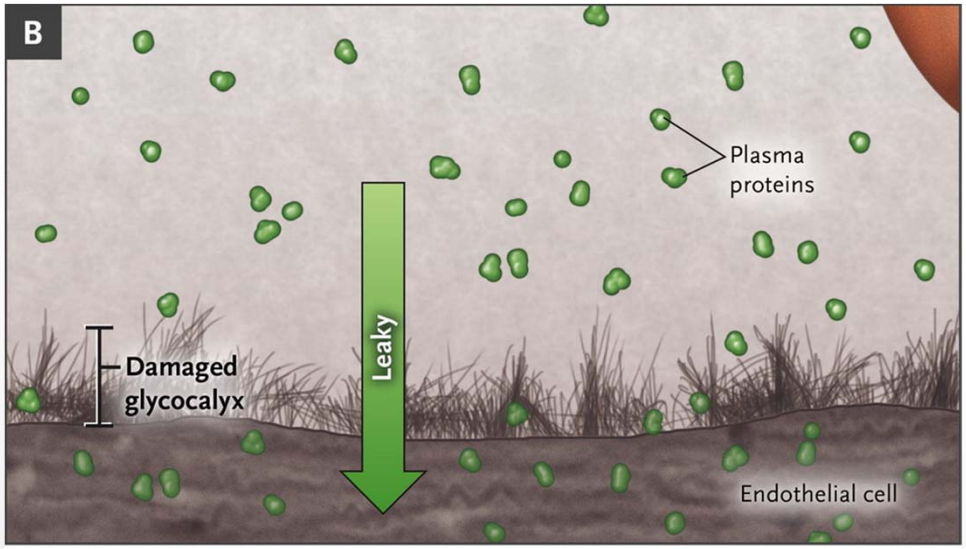




From: http://www.hubrecht.eu

EGL – Damage by Hypervolemia

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



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Fluid Type
Crystalloids vs Colliods

- Depend on state of endothelial glycocalyx layer
- Colloid increases intravascular volume
  - Resuscitation from hemorrhage
- No difference intravascular volume
  - Sepsis
  - Inflammatory states
  - Trauma
  - Hypervolemia
- Crystalloids and colloids will have the same effect

Albumin

- **Albumin within the Endothelial Glycocalyx Layer**
  - Determinant of its filter function
  - Works as long as plasma albumin at least ½ normal
  - Congenital analbuminaemia/ acquired hypoalbuminaemia
    - Other proteins become important
- **Albumin**
  - In health - about 40% intravascular
  - In inflammation
    - Intravascular albumin will decrease
    - Extravascular proportion will increase
  - Transcapillary escape rate of albumin (TCERA)
    - Index of 'vascular permeability'
    - normal 5% per hour
    - 2x during surgery
    - > 20% per hr in septic shock

Endothelial Glycocalyx "Capillary Leak"

- **Normovolemia**
  - Endothelial glycocalyx layer 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 Therapy How Much?

- **Vasogenic shock vs fluid loss leading to shock**
  - **Hypovolemia vs dehydration**
  - **With diarrhea volume needed indicated perfusion and ongoing diarrhea**
- **Bolus therapy**
  - **10-20 ml/kg bolus**
  - **Bolus effect**
    - **Time to return to pre-bolus vascular volume**
      - **Adult – 3 hr < 5% of infused volume intravascular**
      - **Neonate – 0.5-1 hr < 6-7 % of infused volume intravascular**
    - **Needed but effect short-lived**
    - **Increases interstitial fluid volume**

Fluid Therapy How Much?

- How to tell if you have given enough?
  - Clinical clues lie
  - Signs of too much fluids
    - Warm legs
    - Good pulses
    - All the clues we previously used to tell if we had corrected dehydration
  - But need to keep up with loss from diarrhea
  - But need to maintain CO
- Rescue vs maintenance

Septic Shock
Volume Resuscitation

- **Immediate positive effect**
  - **Increased perfusion**
  - **Patient "looks better" but …**
- **Rapid infusion – adverse effects**
  - **Fluid responder**
    - **CO increases**
  - **Increased shear stress**
    - **Increases NO**
    - **Vasodilatation**

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

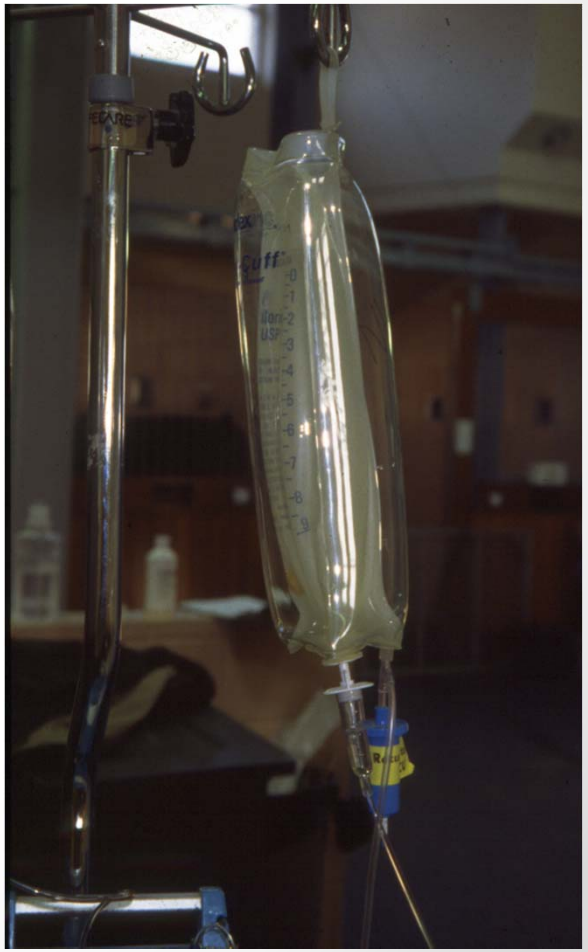
- **Positive fluid balance = increased mortality**
  - Acute load
  - Rapid unload – diuresis
- **Patients who rapidly unload live**
  - Less severe disease?
  - Can we influence outcome?
- **Dilemma**
  - Initially fluids are helpful in shock
  - But once shock reversed – harmful
- **Restrictive fluid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

Fluid Therapy

- **Timing**
  - **Fluid type**
    - **Electrolyte mix**
    - **Which fluid mix?**
  - **Volume – how much?**
    - **Resuscitation shock**
      - **Timely**
      - **Adequate**
      - **But harmful!**
- **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



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
- Losses from diarrhea
  - Need fluids to keep up with
  - But these fluids are harmful

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?
    - But enteritis GI Na loss
    - Need to keep up with
      - Balanced fluids, NOT hyponatremic fluids
  - Cl restriction
    - Don't use saline

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
  - With diarrhea
    - Balanced fluids
  - When diarrhea resolves
    - Mare's milk diet ideal
    - Sodium restriction (3-4 mEq/kg/day) if continued IV fluids
  - Chloride restriction
    - Don't use saline

Goldilocks Principle

Getting it "Just Right"

Plasma Therapy

- IV plasma administration
  - Should be considered in all critically ill foals
  - IgG level should not be a deciding factor
  - If available and affordable it should be given
  - If the foal is septic
    - Plasma can supply many helpful factors
    - IgG, acute phase proteins, C-reactive protein, albumin, etc
    - Opsonins, compliment, clotting factors, protease inhibitors, etc.
- IgG measurement
  - May reflect passive transfer
  - May reflect IgG catabolism
    - Specific
    - Nonspecific
  - Is quantitative and not qualitative
    - High level does not mean useful antibodies are present
- Important source of albumin

Antidiarrheals

- **Bismuth subsalicylate**
  - Mechanism – NOT coating
    - Block PG?? – flunixin
    - But don't use flunixin
  - Nonspecific binding and a reduction in bioavailability??
- **Kaolin/pectin?**
- **Activated charcoal**
  - Can bind endotoxin and reduce its absorption
  - May bind other toxins
- **Di-tri-octahedral smectite (Biosponge)**
  - Can bind endotoxin and reduce its absorption
  - Neutralize toxins of *C difficile* and *C perfringens* in vitro???
    - Location and concentration of Clostridial exotoxins
    - Luminal neutrolization not likely to be effective
- **Probiotics/ prebiotics**
  - Yeast *Saccharomyces boulardii* for use in enteric clostridiosis
    - Suggested not to use because of "open gut"
  - All neonatal foals up to several weeks – enterocyte pinocytosis

General Therapy

- Gastric acid blockers – should not be used
  - With hypovolemia – stomach does not produce acid
    - Ulcers not caused by acid in these cases
    - Ulcers secondary to hypoperfusion, trauma
  - When acid production is blocked
    - Allow GI colonization of pathogen
    - Translocation and bacteremia more likely
- Sucralfate – has many actions
- Antiendotoxin therapy
  - Flunixin
  - Polymyxin B
- Nutritional support