Antimicrobial Therapy in Horses
Case-Based presentation

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DipACVIM

“Shadow”
7 yr, American Saddlebred, Gelding
Show horse, pleasure riding. Current light work schedule.
Current vaccination for West Nile Virus, EEE, WEE, PHF, Influenza, EHV1 and Tetanus.
Ivermectin q8wks for parasite control.
Diet: 5lbs 12% sweet feed BID, free choice grass hay
Housing: Stall, limited individual pasture turnout

“Shadow”
2004: R eye trauma – corneal laceration & perforation, subsequent blindness & ptosis bulbi
Intermittent bilateral forelimb lameness associated with foot conformation (club foot L fore) and sole bruising
1gm Phenylbutazone q24h for 6 days prior to presentation
No abnormalities noted by the owner the evening prior to presentation

“Shadow”
8am: No abnormalities noted, exercise (light riding), groomed, stall confined and fed normal ration.

Referred to VTH
Examination at 6pm
HR 72, RR 42, Temp 101.4
MM purpie, tongue cyanotic, CRT 3s
Bilateral serous nasal discharge
Depressed, sweating
Decreased GIT motility all quadrants
Profuse watery diarrhea
Shifting weight in all limbs, increased digital pulses all limbs
Decreased jugular fill
Increased thirst, decreased appetite

Treatment: Procaine penicillin IM 20000 IU/kg, Gentamicin IV 6.6 mg/kg, lactated Ringer’s solution 7L IV

Referring Vet Examination
HR 110, RR 60, Temp 101.5 F
MM injected with a toxic line, CRT 3s
Sunken L eye, prolonged skin tent test
Skin and distal extremities cold to touch
Decreased digital pulses in all limbs
Decreased gut sounds all quadrants, no gastric reflux, no abnormalities on rectal examination
Profuse watery diarrhea

Treatment: Procaine penicillin IM 20000 IU/kg, Gentamicin IV 6.6 mg/kg, lactated Ringer’s solution 7L IV
Abdominal ultrasound:
- left dorsal colon wall thickness 0.2mm
- right dorsal colon wall thickness 0.4mm
- fluid filled colon and small intestine

Nasogastric intubation:
- no reflux

Additional Diagnostic tests:
- Blood culture, PHF titer, Fecal salmonella cultures (5 x q24h)
- Clostridium perfringens & difficile enterotoxin (feces): negative

Problem list:
- azotemia
- dehydration
- hypochloremia, hyponatremia, hypocalcemia,
  hyperphosphatemia
- hypoalbuminemia
- leukopenia, neutropenia
- diarrhea
- suspected decrease in blood pressure & peripheral perfusion
- laminitis

Differential diagnosis:
- Phenylbutazone associated right dorsal colitis
- PHF
- Salmonella
- Clostridial colitis
- Endotoxiaemia

Treatment
- Lactated Ringer's solution IV 120ml/kg/day (2.7L/hr) + Calcium gluconate
- Potassium Penicillin 22 000 IU/kg IV q 6h
- Gentamicin 6.6mg/kg IV q24h
- Metronidazole 20mg/kg PO q12h
- Polymyxin B 5000 IU/kg IV loading dose, then 1000 IU/kg IV q 12h
- Pentoxyflumine 8.5 mg/kg PO q 8h
- Omeprazole 4mg/kg PO q 24h
- Biosponge 120mls PO q12h
- Sand bedding
- Free choice grass hay and water (16L plain, 16L 10gm/L NaCl/KCl)
Day 2
HR 60, RR 18, Temp 99.3
MM dark pink, cyanotic tongue
20L water consumed in 12h
Minimal appetite
Profuse watery diarrhea
PCV 42%, TP 5.6 g/dL
Obel grade 2 laminitis score
Additional treatments:
Ice feet q6h
Aspirin 8.5 mg/kg PO q48h

Day 3
HR 64, RR 30, Temp 99.6
MM pink and moist, tongue pink
Depressed
Profuse watery diarrhea
PCV 34%, TP 4.2 g/dL
Obel grade 3 laminitis score
Oxytetracycline 6.6mg/kg IV q12h
Lactated Ringer’s solution
60ml/kg/day
Senior feed 1lb q 12h

Day 4-5
HR 52-60, RR 30, Temp 99.6, MM pink and moist
Depression, inappetance
PCV 35%, TP 5.2 g/dL

Results of Diagnostic tests
Blood culture: negative
PHF titer: low titer

“Shadow”
Euthanasia elected by owner: cost, guarded prognosis for athletic activity, insurance.

Gentamicin
- Concentration dependent agent with post antibiotic effect
- Dose rate = \( V_d \times (\text{desired plasma concen.}) \)
  - \( V_d = 0.3 \text{ l/kg}(0.02\text{mg/ml}) \)
  - foal \( V_d \times (10\times\text{MIC for Klebsiella}) \)
  - \( = 6\text{mg/kg QD IM} \)

K Penicillin
- \( t_{1/2} = 1\text{hr.} \)
- 22,000 IU/kg QID IV
- Time dependent antibiotic objective is to stay above the MIC for the entire interdosing interval
- Intermediate to short post antibiotic effect (PAE)
Metronidazole

- Effective vs. anaerobic bacteria and protozoa (*Giardia* and *Trichomonas spp.*)
- $V_d = 1-2 \text{ l/kg}$
- $t_{1/2} = 3-4 \text{ hrs.}$
- Concentration dependent antimicrobial
- Dose 20 mg/kg TID PO

**Results:** Horses may be infected with a number of heterogeneous isolates of *C. diff.* Toxigenicity and antimicrobial susceptibility vary and metronidazole-resistant strains may be associated with severe disease.

Polymixin B

- PMB was found to decrease *in vivo* endotoxin-induced TNF activity
- Compared with baseline values 5,000 U of PBM/kg should inhibit 75% of endotoxin induced TNF activity for 12 hours
  (Parviainen, 2001)

**Post mortem examination**

**Stomach:** focal area (8x8.5 cm) of hemorrhage and edema in the non glandular portion adjacent to the margo plicatus

**Intestinal contents:** watery and foul smelling

**Jejunum, cecum, large colon, small colon:** diffuse edema and congestion yellow-green mucus coating

**Lung:** left dorsal cranial lobe: 3 nodules (5mm diameter), white and firm on section

**Forelimbs:** lamellae thickening, P3 rotation

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Sample</th>
<th>Salmonella Result</th>
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<tbody>
<tr>
<td>1</td>
<td>Feces</td>
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<tr>
<td>2</td>
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<tr>
<td>5</td>
<td>Large colon</td>
<td><em>Salmonella agona</em></td>
</tr>
<tr>
<td>5</td>
<td>Small colon</td>
<td><em>Salmonella agona</em></td>
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</table>
Salmonella

Gram-negative, flagellated facultatively anaerobic bacilli

Possessing 3 major antigens:

* H (flagellar): phase 1/phase 2
* O (somatic): surface of outer membrane, determined by specific sugar sequences on cell surface
* Vi: superficial antigen overlying the O antigen, present in only a few serovars (S typhi)

Cell envelope contains complex LPS

2449 serotypes

Pathogenesis:

1) ability to invade cells
2) complete LPS coat
3) ability to replicate intracellularly
4) elaboration of toxin(s)

Equine Salmonellosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Serovar</th>
<th>Cases</th>
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<tr>
<td>New Bolton Center 2004</td>
<td>S. newport</td>
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<td>Spain 2003</td>
<td>Salmonella Enteritidis and Mucor</td>
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<td>Virginia Tech 2001</td>
<td>S. agona</td>
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<td>Purdue 1999</td>
<td>S. typhimurium</td>
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<td>Victoria (AUS) 1997</td>
<td>Salmonella heidelberg</td>
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<td>Michigan 1996</td>
<td>S. typhimurium</td>
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<tr>
<td>ISU 1996</td>
<td>S. infantis</td>
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<td>Wisconsin-Medison 955</td>
<td>S. anatum</td>
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<tr>
<td>Venezuela</td>
<td>Salmonella abortusequi</td>
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<tr>
<td>UC Davis 1994</td>
<td>Salmonella cholerae suis var. ohio</td>
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<tr>
<td>UC Davis 1991</td>
<td>S. krenfield</td>
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<tr>
<td>Liebert (GER) 1991</td>
<td>S. typhimurium var. Copenhagen</td>
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<tr>
<td>California TB Farm 1990</td>
<td>S. ohio</td>
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Biosecurity at VTH

- SOP’s established and strictly adhered to:
  - “Yellow Dot” status is reserved for patients at high risk for acquiring infections due to poor immune status. The biosecurity status may be changed to “green dot” as the patient’s condition improves.
  - Examples: critically ill, immuno-compromised, unvaccinated (non-infectious, neonatal animals < 30d of age), Failure-of-passive-transfer foals, neonatal patients or those requiring intensive care.

- “Green Dot” Status is reserved for patients with no historical, physical or laboratory evidence of contagious disease.
  - Examples: Patients presenting for elective surgical procedures, non-infectious disease work-ups, minor trauma, or ancillary diagnostics.

- “Red Dot” status is reserved for patients known or suspected to have highly contagious diseases. Patients should be placed directly into LA-ISO after being examined.
  - Examples: Patients with a previous history of salmonellosis, those exhibiting clinical signs which include a fever, leukopenia, and/or diarrhea. Other equine examples: strangles, cryptosporidiosis, food/fiber animal examples: salmonellosis, tuberculosis, Johne’s disease, cryptosporidiosis, all calves with diarrhea, caseous lymphadenitis.
“Johnny”

- Use- trail riding, jumping. Recent transport from MO to VA. Housed at boarding stable with 2 horses.
- De-worming & Vaccination current (?)
- 3 days prior to presentation @ VTH; inappetance, fever (103.8F), loose feces. Owner tx w/ PBZ (1gm QD x2)
- AHS visit - pcv 34%, WBC + chem WNL (fibrinogen 400),
- Tx; oxytetracycline (6.6 mg/kg q 12 hr), flunixin (1mg/kg q 12 hr)

“Johnny” Part II

- VTH- T 103F, HR 64, RR 16, diarrhea, depression...PCV 51%, WBC 7.4 w/ 19% bands, BUN 29, Cr 2.7, Na 123, Cl 86, bid gas pH 7.19, HCO\textsubscript{3} 15, UA- bld + protein.
- Tx; Oxytet., metronidazole, pentoxifylline, flunixin, omeprazole, biosponge, LRS + bicarb.
- Ensuing 72 hrs; leukopenia....normal, diarrhea...normal, TP 4.5....normal, pH acidosis....7.34, PCV 32%, urine GGT/Cr=19,
“Johnny” Part II
• Discharged after 7 days on doxycycline.
• BAR, temp 98.7F, HR 36, RR 8, PCV 32%
• Salmonella cultures (x5) negative
• Gram (-) obligate intracellular bacterium w/ tropism for monocytes.
• Incubation period +/- 10 to 18 days
• Infection of enterocytes in SI and LI = diarrhea.
• Oxytetracycline, doxycycline, erythromycin + rifampin

Pentoxifylline
• $V_d = 1.15+/-0.30$
• $t_{1/2} = 0.38+/-0.23$
• Suggested dose 10mg/kg BID PO results in comparable serum levels as in humans
• Note: if a decrease in clinical response is experienced increasing the total daily dose to 30mg/kg (either BID or TID dosing) (Liska,2006)

Pentoxifylline
• Methylxanthine derivative.
• Beneficial effects include: improved hemodynamics, inhibition of platelet aggregation, > erythrocyte and leukocyte deformability, > prostacycline release, inhibition of endothelial cell activation and altered leukocyte adhesion.
• Effects attributed to inhibition of cellular phosphodiesterase with > cAMP concentration.

Ceftiofur
• 99% protein bound (clinically significant)
• Binds to acute phase proteins ($\alpha_1$-antitrypsin) which carries bound drug to sites of inflammation
• Time dependent antimicrobial

Oxytetracycline
• $V_d = 0.34-0.95$ l/kg in horses
• $V_d = 2.2-4$ l/kg in foals
• $t_{1/2} = 6$ hrs. (IV)
• Dose 7-10 mg/kg IV QD or EOD (long post antibiotic effect)

Doxycycline
• Semi-synthetic tetracycline.
• Good bioavailability, $t_{1/2} = 10-12$ hrs.
• CNS penetration and good gm(+) activity.
• Dose; 10 mg/kg BID per os
**“Imperial”**

- 4 month old miniature colt
- Weaned at 2 months and constantly shown since. Vaccines (?) and daily 'strongid'. Moved to owners farm 2 weeks prior (w/ 3 others). Depressed, febrile and anorectic- wt loss noted. Ventral edema w/ intermittent loose feces.
- rDVM tx= chloramphenicol, metronidazole, ranitidine, omeprazole, probios, panacur x5

**“Imperial”**

- rDVM labs- WBC 14.7 (mature neut), fibrinogen 500, Tot prot. 2.1, albumin 0.7, globulin 1.4, Ca 7.0. Treatment for 1 week w/o improvement.
- Presentation @VTH; T 98F, HR 50, RR- rapid shallow, CRT <2, ventral edema ++, loose feces, depressed....
- Labs: lymphocytosis, panhypoproteinemia TP 2.9, albumin 0.9, globulin 2.0, fibrinogen 300; Ca 7.6, phos 5

**“Imperial”**

- DDx; acute bld loss, GI ulceration, protein losing enteropathy (parasites etc), peritonitis, glomerulonephritis, R equi infection...
- Thoracic US- WNL, rads- mild interstitial, Trach asp- mild mixed inflammation, culture= B bronchiseptica. Abdominal US- very thick SI (0.5cm diameter), (minimal free abd fluid), gastric endo- slight hyperkeratosis, Sheathers (-),

**“Imperial”**

- Tx: plasma (2x 500ml), azithromycin (10mg/kg PO q24 x5 then EOD) flunixin (1.1mg/kg IV BID), omeprazole (4mg/kg QD), SMZ-TMP (25mg/kg PO BID), dexamethasone (0.1mg/kg PO QD) nutrition consult.
- More Labs: Lawsonia intracellularis PCR (-), serology 1:120 (+). Salmonella (x5) negative

**Progress**

- following plasma- TP +/- 4.0, edema resolved over 72 hrs, appetite ++, day 6 abdominal US – SI wall thickness much improved, dex discontinued, discharged on day 12 w/ azithromycin (2 weeks), SMZ-TMP, omeprazole.
- 2 weeks post discharge gaining weight and doing well. (** owners recalled that 2 weeks prior to shipping mini’s- trailer used to transport pigs!)

**Azithromycin**

- Bioavailability =56% in 6 healthy foals
- BAL concentrations 15-170X serum
- PELF concentrations 1-16X serum
- 10mg/kg QD PO for 5 days then reduced to every other day (suggested)
- (Jacks, 2001)
Potentiated Sulfas

- $t_{1/2} =$sulfamethoxazole 3.5-5 hrs.
- $t_{1/2} =$sulfadiazine 3-4 hrs.
- $t_{1/2} =$trimethoprim 2-3 hrs.

BID PO dosing is necessary to attain therapeutic plasma concentrations of trimethoprim (Dowling in Bertone, 2004)

“Imperial”

Lawsonia intracellularis

- Obligate intracellular bacteria: proliferative enteropathy in swine, dog, rabbit, sheep, deer & horse. Transmission fecal-oral (equine?) tropism for crypt epithelial cells: normal villus structure lost & replaced w/ undifferentiated crypt cells. Minimal inflammatory response. AB’s – macrolides, doxycycline, chloramphenicol

“lil appy”

- 7 day old Appaloosa colt
- Two day hx of lameness and lethargy. Mare purchase 2 months prior: unknown vaccination and anthelminthic hx. Foaling unattended and colt discovered under fence unable to rise.
- rDVM – colostrum, ceftiofur. Foal did well until 2 days ago.

“lil appy”

- Arthrocentesis of rt tarsocrural joint- cloudy w/ 46.6 nucleated cells (neutrophils) & protein 2.8
- Joint flushed + amikacin (IA)
- Abdominal US - umbilicus normal, increased hyperechoic peritoneal fluid (52.2 nucleated cells + protein 4.4) All fluids submitted for culture.
- Tx: Kpen, amikacin (25mg/kg IV QD), flunixin, omeprazole, plasma (1 L), IV balanced fluids
- Colt improved over 24 hr, stood, suckled, temp 101F

“lil appy”

- Radiographs of tarsus & carpus- adequate calcification, no signs of osteomyelitis, septic physis. Thoracic rads & UA = WNL
- Day 3- patent urachus! Confirmed w/ US (Also noted absence of hyperechoic peritoneal fluid!)
- Surgical resection of urachus + abdominal & joint lavage (cell ct 16.1 & protein 2.7)
- Regional perfusion of rt pelvic limb (kpen-22,000 iu/kg QD) for 3 days
- Culture results (peritoneal & synovial) = Listeria monocytogenes
“lil appy”
- Sensitivity: amikacin, chloro, enrofloxacin, erythromycin, gentamicin, penicillin, tetracycline, smz-tmp.
- CBC; persistent leukocytosis (27.5) w/ lymphopenia, fibrinogen 300.
- Mare’s milk and fecal culture- (-) for Listeria.
- Colt discharged on day 10 w/ smz-tmp (20mg/kg BID PO), flunixin (0.5mg/kg QD PO) omeprazole (4mg/kg QD PO)

Amikacin
- Concentration dependent aminoglycoside
- Once daily dosing is safer than more frequent administration while being as effective
- Dose 10mg/kg in horses
- Dose 25mg/kg in foals
(Papich, 2005)

“lil appy”
- *Listeria monocytogenes*; gram (+), commonly affects ruminants, fowl, man.
- Clinical; septicemia (neonates), abortion, neurologic dz,
- In horses; depression, diarrhea, pneumonia, neurologic (seizures)
- Caused by ingestion (environment, feces, silage)

Prognosis favorable w/ early diagnosis & prompt, appropriate treatment

“Darla”
- 35 day old QHx filly
- Intermittent coughing +/- 7 days with increased resp. rate. Appetite decreased but still suckling. No previous issues and adequate PT at birth.
- Presentation; BAR, temp 102F, HR 96, RR 40, wt.94 lbs. Lung sounds diffusely bilat. (no crackles or wheezes); cough easily elicited, mild bilateral ocular discharge, all other systems WNL

Prognosis favorable w/ early diagnosis & prompt, appropriate treatment

“Darla”
- Labs; CBC= leukocytosis (16,000), neutrophilia, fibrinogen 700, Chemistry glucose 187, otherwise- WNL.
- Thoracic radiographs and US; multiple areas of consolidation (abcessation) bilateral. Diffuse nodular- interstitial pattern w/ cranioventral consolidation.
- Tracheal aspirate; marked neutrophilic septic inflammation. Cultures submitted.

Use of Thoracic ultrasound to screen foals for *R equi* at affected farms
Slovis N, McCracken J. Proceedings AAEP, December 2005

Grade 1 pulmonary abscess
Grade 6 cavitated pulmonary abscess
Left lateral thorax of foal with *R. equi* pneumonia. Diffuse nodular opacities greatest near hilus (lymphadenopathy?)

“Darla”
- Hx and initial findings suggestive of *Rhodococcus equi* infection.
- Treatment: clarithromycin (7.5mg/kg PO BID), rifampin (5mg/kg PO BID) omeprazole, albuterol (MDI- 2 ‘puffs’ BID), beclomethazone (1 ‘puff’ BID 3 days), ‘Equioxx’ (0.2ml PO QD) ophthalmic ointment,
- Day 3; cultures confirmed *R. equi*, WBC-11,000, fibrinogen 500.
- Discharged after 2 weeks; continue AB tx & rDVM closely monitor.

Clarithromycin
- Oral bioavailability =57.3% +/- 12.0%
- 7.5 mg/kg BID PO provides serum, pulmonary epithelial lining and bronchovascular cells of foals above MIC for *R. equi* isolates during entire 12 hr period
- Determined in 6 healthy foals
- (Womble, 2006)

Rifampin
- Bioavailability is 40 – 70%, lower bioavailability if fed with feed
- t½ =17 hrs. in foals, 6-8 hrs. in adults
- Dose 5mg/kg BID PO
- Emerging resistance especially if used as a monotherapy (Takai, 1997)

“Jordan”
- 13 yr old AQH mare, pleasure horse, trails…
- One week prior, discharged from VTH following colic sx (rt dorsal displacement) - All cultures (salmonella, & toxins: C difficile & perfringes (-) PHF titers (-), Discharged w/ flunixin & omeprazole PO.
- Currently- inappetance, diarrhea (profuse, watery), lethargy, dark toxic mm.
- Biopsy (colon) from previous visit- edema, pmn infiltrate, (I/R event?)

“Jordan”
- Physical exam; T 99.6, HR 52, RR 16 CRT> 3 w/ dark ‘injected’ mm.
- Labs; PCV 60%, TP 3.9, WBC 12.3 (PMN 8.5 w/ 7% bands) fibrinogen 200, glucose 235, BUN 58, Cr 3.3, Na 109, Cl 80, albumin 1.9, Bld gas- met acidosis (bicarb 19.8, pH 7.2)
- US- rt. Dorsal colon- 0.4cm
- DDX; salmonellosa, rt dosal colitis, clostridium, PHF…….
“Jordan”
- Initial Tx; balanced fluids (+ bicarb & cmpk) at 2x maintenance. K pen, gent., metronidazole, pentoxifylline, flunixin, polymixin B (6000 IU/kg BID) biosponge, omeprazole, ice feet.
- Day 2- mare BAR & physical parameters improved (mm still injected), diarrhea, ventral edema, adm. 4 L plasma
- Immunology; + for C difficile A/B

“Jordan”
- Day 3/4; BAR, diarrhea frequency less, TP still 3.9, PCV 37%, WBC 4.7, fibrinogen 400
- Nutrition consult; formulated to maximize protein absorption- 3.5lbs alfalfa-grass mix BID, 1 lb ‘senior’ (Purina) q 5hrs. ½ lbs alfalfa pellets q 6hrs.

“Jordan”
- Days 5-12; all parameters improve, CBC improves (10.3, no left shift, TP 5.5, fibrinogen 300); Chemistry & bld gas normalizes, feces formed (loose), appetite good, drinking, (kpen & gent D/C day 10), doxycycline (10mg/kg BID PO) continue metronidazole, flunixin, pentoxifylline, omeprazole….
- Discharged day 15 (flunixin 0.5mg/kg q24)

“Blazin”
- 2 day old AQH colt
- Presented for depression, ill thrift and lack of suckling.
- Initial exam; alert, responsive, T 102F, HR 104, RR 28, CRT 2 sec, dehydrated, auscultation- GI ‘watery’, joints- thorax- umbilicus NAF.
- Initial labs; PCV 39%, WBC 1.5, bands 15%, lymphs 0.46, bld gas- met acidosis pH 7.28, HCO3 19, Chem- albumin 2.9, Ca 10.6

“Blazin”
- Condition quickly deteriorates (colic & diarrhea)
- More samples- bld & fecal culture (+ salmonella PCR), sheathers, urine, PT (snap)
- Immunology- C perfringes- enterotoxin (+). C difficile A & B (-), rotavirus (-)
- Initial Tx; K pen, amikacin, metronidazole, esomeprazole 40mg IV q24, flunixin (1mg/kg q12) ‘Plasmalyte’ + bicarb & dextrose, biosponge.

Clostridium difficile
- Gram- positive, anaerobic, spore-forming rods.
- Ubiquitous, soil, commensal bacterium of intestine. Resistant to most AB’s.
- Produces several toxins; enterotoxin (toxin A) & cytotoxin (toxin B).
- Most commonly associated w/ diarrhea/colitis. Notoriously unpredictable (sever disease to asymptomatic shedding)
- Susceptibility to metronidazole & vancomycin. Increased resistance to metronidazole noted.
“Blazin”
• Next 48 hrs; CBC improves- PCV 29.5%, WBC 7.15 (9% bands) lymphs 2.1, TP 5.9, Chemistry- respectable, bld gas- better.
• Foal is BAR, suckling, diarrhea resolving. Salmonella cultures pending- PCR (-)
• Discharged; metronidazole, naxcel 2.2mg/kg IM BID), biosponge.

Clostridium perfringens
• Gram-positive, anaerobic, spore forming
• Found in soil and GI tract of most vertebrates.
• Foals with C perfringens – associated enterocolitis that are < 3 days often have bloody diarrhea but dz is sporadic.
• Reports suggest that > 90% of foals at 3 days of age shed organism in feces.