Diarrhoea in ruminants with a focus on Cryptosporidiosis

Brigitte Duquesne, DVM
Technical Manager Europe
Neonatal calf diarrhoea (NCD) is the most important disease of neonatal calves and results in the greatest economic losses due to disease in this age group in both dairy and beef calves.
Calf scours

10 to 30% calves affected
(UK, 2010)

20% during the first 2 weeks of life
(FR, Creuse 2009)

>25% of the reasons for consultation on farm
(FR, Mayenne, 2014)
And neonatal diarrhea affecting small ruminants...

Dominant disease: 45% of the caprine holdings
(Poitou-Charentes, Fr – 2012)

High mortality: 30 to 50%
(Quebec, 2000)
How much is calf scours costing?

• Loss of a calf = price of a heifer to replace + input costs per died calf: semen and breeding costs, feeding the dam while she carried the calf to term and labor through gestation and calving, resources invested in the calf itself (labor, vet)

• And, long-term financial impact of scours if the heifers recover:
  - Increased age at first calving (>30 months)
  - Reduced ability to meet genetic potential
  - Increased chance of being culled from herd
NCD is a multifactorial disease

results from a combination of

- an adverse environment
- poor host immunity
- challenge from infectious agents
Aetiology

- 2 possible sources:
  - Faulty feeding
  - Infectious causes
Various studies detecting frequency of bovine enteric pathogens...

6 dairy farms, 382 calves (from 8 to 15 days)

<table>
<thead>
<tr>
<th>Jour 0</th>
<th>E. coli K99</th>
<th>5,8 %</th>
<th>Jour 7</th>
<th>Cryptosporidium</th>
<th>51,8 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus</td>
<td>9,9 %</td>
<td></td>
<td>Rotavirus</td>
<td>27,2 %</td>
</tr>
<tr>
<td></td>
<td>Coronavirus</td>
<td>31,6 %</td>
<td></td>
<td>Cryptosporidium</td>
<td>31,9 %</td>
</tr>
<tr>
<td></td>
<td>Salmonella spp</td>
<td>4,7 %</td>
<td></td>
<td>Rotavirus</td>
<td>12,6 %</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
<td>16,8 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jour 3</td>
<td>Cryptosporidium</td>
<td>23,0 %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
40 farms (suckling cows) 311 calves (from 4 to 10d)

<table>
<thead>
<tr>
<th>Jour 0</th>
<th>E. coli K99</th>
<th>6.1%</th>
<th>Jour 3</th>
<th>Cryptosporidium</th>
<th>84.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus</td>
<td>14.3%</td>
<td>Jour 7</td>
<td>Cryptosporidium</td>
<td>86.0%</td>
</tr>
<tr>
<td></td>
<td>Coronavirus</td>
<td>6.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmonella spp</td>
<td>0.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
<td>50.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Detection of *E. coli* K99, rotavirus, coronavirus, cryptosporidium among healthy (n=14) and diarrheic calves (n=46)

Results:

Diarrheic calves:

43 % Crypto +
46 % Rota +
Detection of enteropathogens in faecal samples from diarrhoeic and healthy calves younger than 90 days in a study comprising 75 dairy herds from south-east Sweden.

<table>
<thead>
<tr>
<th></th>
<th>Crypto only</th>
<th>Giardia only</th>
<th>Rota only</th>
<th>Corona only</th>
<th>Crypto+G</th>
<th>Crypto+Rota</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=146</td>
<td>7%</td>
<td>21%</td>
<td>17%</td>
<td>2%</td>
<td>3%</td>
<td>0,5%</td>
</tr>
<tr>
<td><strong>Healthy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=124</td>
<td>3%</td>
<td>21%</td>
<td>8%</td>
<td>0</td>
<td>2%</td>
<td>0</td>
</tr>
</tbody>
</table>
Enteropathogens isolated in subjects with neonatal enteritis

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Samples examined</th>
<th>% Positive samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>246</td>
<td>32%</td>
</tr>
<tr>
<td><em>Cryptosporidium parvum</em></td>
<td>297</td>
<td>31%</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>171</td>
<td>15%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>252</td>
<td>12%</td>
</tr>
</tbody>
</table>

Italy, Vicenza, 2012
Dairy farm, 101 calves

A. Barberio and al, Rivista di Medicina Veterinaria, vol 47, 2012
Aetiological agents of gastroenteritis in Belgian Blue calves

Vandeputte S, Detilleux J, Carel S, Bradfer B, Guyot H and Rollin F

The open Veterinary Science Journal, 2010, 4, 36-40

<table>
<thead>
<tr>
<th>Nbr of positive faecal samples</th>
<th>Diarrheic calves (N=28)</th>
<th>Non diarrheic calves (N=13)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>E Coli F5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>24</td>
<td>7</td>
<td>31</td>
<td>76</td>
</tr>
</tbody>
</table>
USA, 165 cattle farms - 2012

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Overall % positive</th>
<th>% positives among diarrheic calves</th>
<th>% positives among healthy calves</th>
<th>p-Value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine norovirus</td>
<td>29.1</td>
<td>44.7 (89/199)</td>
<td>16.3 (40/245)</td>
<td>0.042</td>
<td>2.0 (1.002–3.9) b</td>
</tr>
<tr>
<td>Cryptosporidium parvum c</td>
<td>15.1</td>
<td>33.7 (67/199)</td>
<td>0.0 (0/245)</td>
<td>0.0007</td>
<td>173.0 (8.9–3365.1)</td>
</tr>
<tr>
<td>Bovine coronavirus</td>
<td>20.9</td>
<td>31.7 (63/199)</td>
<td>12.2 (30/245)</td>
<td>0.0034</td>
<td>2.7 (1.4–5.1)</td>
</tr>
<tr>
<td>Bovine rotavirus group A</td>
<td>12.2</td>
<td>27.1 (54/199)</td>
<td>0.0 (0/245)</td>
<td>0.0025</td>
<td>79.9 (4.7–1369.5)</td>
</tr>
<tr>
<td>Nebovirus</td>
<td>0.9</td>
<td>21.6 (43/199)</td>
<td>1.6 (4/245)</td>
<td>0.0001</td>
<td>16.7 (4.0–68.8)</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>4.1</td>
<td>9.0 (18/199)</td>
<td>0.0 (0/245)</td>
<td>0.0056</td>
<td>80.6 (3.6–1803.7)</td>
</tr>
<tr>
<td>Bovine enterovirus</td>
<td>20.3</td>
<td>5.0 (10/199)</td>
<td>32.7 (80/245)</td>
<td>&lt;0.0001</td>
<td>0.113 (0.04–0.3)</td>
</tr>
<tr>
<td>Escherichia coli K99</td>
<td>1.8</td>
<td>4.0 (8/199)</td>
<td>0.0 (0/245)</td>
<td>0.0143</td>
<td>98.4 (2.5–3859.9)</td>
</tr>
<tr>
<td>Bovine torovirus</td>
<td>1.1</td>
<td>2.5 (5/199)</td>
<td>0.0 (0/245)</td>
<td>0.2404</td>
<td>10.4 (0.2–520.3)</td>
</tr>
<tr>
<td>Bovine viral diarrhea virus</td>
<td>0.5</td>
<td>0.5 (1/199)</td>
<td>0.4 (1/245)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clostridium perfringens tox B</td>
<td>0.0</td>
<td>0.0 (0/199)</td>
<td>0.0 (0/245)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

a Numbers in the parenthesis show number of positive feces/number of samples tested.
b Numbers in the parenthesis is 95% confidence interval of the estimated odds ratio.
c The bold letters indicate microorganisms detected only in feces from diarrheic calves.
Pathogenic agents: 4 most prevalent

- Bacteria
- E.Coli
- Rotavirus
- Coronavirus
- Viruses
- Parasites
- Cryptosporidium
Diagnosis?

- Confirmed etiological diagnosis needs faeces analysis

- Clinical diagnosis:
  - Key elements:
    - Age
    - Faeces
    - Symptoms
Incidence of the causes of diarrhoea according to the age of calves

Some helpful elements for the differential diagnosis ..... 

<table>
<thead>
<tr>
<th>Mean age of affected calves</th>
<th>Clinical signs</th>
<th>Probable aetiological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>Very liquid diarrhoea, yellow</td>
<td>Colibacillosis (ETEC = F5 E. coli)</td>
</tr>
<tr>
<td></td>
<td>Rapid and important dehydration (eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sunkness, diminished skin elasticity)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weakness, cold extremities</td>
<td></td>
</tr>
<tr>
<td>4-11 days</td>
<td>Mucoid diarrhoea</td>
<td>Rotaviruses, coronavirus, cryptosporidiosis</td>
</tr>
<tr>
<td></td>
<td>Hyperthermia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia, abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressive dehydration</td>
<td></td>
</tr>
</tbody>
</table>

The clinical diagnosis should be based on the clinical picture including:

- the age of the affected animals
- and associated clinical signs collated through a thorough physical examination
together with epidemiological data including:
  - the season
  - herd history.

In most situations, the clinical diagnosis requires confirmation by on-farm or laboratory tests.
Is a precise diagnosis indispensable?

• Not at the individual level: doesn’t affect the course of actions to take: urgent rehydration + supportive treatment

• BUT at the herd level → importance to know the infectious agents implicated to adapt treatment and preventive measures
Rapid test in farm

Huve Check®

- **Huve-Check® Crypto kit**
  Strips for detection of *Cryptosporidium parvum*

- **Huve-Check® Calf scours 4**
  Strips for detection of *Rotavirus*, *Coronavirus*, *E. coli F5* (K99), *Cryptosporidium parvum*
Rapid test in farm

- **METHOD**
  - Immunochromatographic strip test

- **ANALYSIS**
  - Detection of antigens specific to:
    - Coronavirus
    - Rotavirus
    - Cryptosporidium parvum
    - E. coli K99(F5)

- **SAMPLE**: Faeces
Focus on colibacillosis
Schematic of the distribution and concentration of Escherichia coli bacteria in the intestinal tract of a calf with undifferentiated diarrhea and a similarly aged calf without diarrhea. The figure indicates that the number of E coli in the large intestine of diarrheic and healthy calves is similar but that diarrheic calves have increased E coli numbers in their small intestine, particularly in the distal jejunum and ileum. (from Constable PD. Antimicrobial use in the reatment of calf diarrhea. J Vet Intern Med 2004a;18:8–17)
• *E coli* is the most important bacterial cause of diarrhea in calves during the first week of life
• distinct types of diarrheal disease are produced by different strains of this organism
• may be differentiated by serotyping based on antigenic differences in the O antigen of the LPS, in the flagellar or H antigens, and the fimbrial or F antigens.
→ Enterotoxigenic *E coli* (ETEC) which has two virulence factors (fimbrial adhesins): K99 (F5) and F41

→ Attaching and effacing *E coli* (AEEC)
Escherichia coli pathotypes

Associated with calves diseases

**ETEC** (Enterotoxigenic Escherichia coli)
Diarrhea (0-1 week /small intestine)

**EPEC** (Enteropathogenic Escherichia coli)

**STEC** (Shiga toxin producing Escherichia coli)
Hemorrhagic dysentery (1-6 weeks) colon

**ExPEC** (Extraintestinal Escherichia coli)
Septicemia (0-1 week) / systemic
Enterotoxigenic *E. coli* (ETEC)

- **ETEC:**
  Fimbrial antigens (F5 or F41 or both) enable them to attach to and colonize the villi of the small intestine of neonatal calves in the first days of life → these Ag = focus of immunologic protection.

Elaborate also a thermostable non-antigenic enterotoxin (Sta) that influences intestinal ion and fluid secretion.
Pathogenic bacteria contaminating the environment are ingested by susceptible animals and enter the intestinal tract (1). These bacteria possess fimbrial adhesins which mediate adherence to specific receptors on the intestinal epithelial cells (2). Resulting bacterial colonization is found mostly on the jejunal and or ileal mucosa. The adherent bacteria produce enterotoxins which stimulate water and electrolyte loss into the intestinal lumen (3), leading to dehydration and possibly death, and a decreased weight gain in surviving animals (4). (Source: Ecl, Univ Montreal)
AEEC: adherence to the intestine to produce so-called attaching and effacing lesions, with dissolution of the brush border and loss of microvillous structure at the site of attachment, a decrease in enzyme activity, and changes in ion transport in the intestine.
Pathogenic bacteria contaminating the environment are ingested by susceptible animals and enter the intestinal tract (1). Focal to extensive bacterial colonization of small and large intestine is observed (2). Bacteria produce their own specific receptor which is injected into the host epithelial cell via a syringe-like bacterial apparatus. A bacterial adhesin then mediates a very intimate attachment of the bacteria to the cell receptors and bacterial signals stimulate effacement of the microvilli, or brush border, and reorganization of the cell cytoskeleton (3). The adherent bacteria also stimulate epithelial cell degeneration, and infiltration of PMN's in lamina propria. These cell changes may lead to the appearance of diarrhea (4). *(Source: Ecl, Univ Montreal)*
Cattle, including calves, are one of the reservoirs for the verotoxic *E. coli* serotype O157:H7 (human hemorrhagic colitis and the hemolytic uremic syndrome)
Focus on cryptosporidiosis
What is Cryptosporidiosis?

Кρυπτός…

Photo credit: United States Environmental Protection Agency
Cryptosporidiosis

= parasitic zoonosis

• Pathogen = a protozoan: *Cryptosporidium Parvum*

  The most widespread - Can infect several mammal hosts including humans

  ➔ NOT HOST SPECIFIC
Non exhaustive list

- **C. parvum**: mice, cattle, humans, sheep, goats, pigs, horses
- **C. andersoni**: cattle
  - **C. meleagris**: turkey
  - **C. baileyi**: chicken
  - **C. hominis**: humans
  - **C. muris**: mice, humans
  - **C. felis**: cats, humans
  - **C. canis**: dogs, humans
  - **C. wairi**: guinea pig
- **C. nasorum Naso lituratus**: fishes
- **C. molnari Sparus aurata et Dicentarchus labrax**: fishes
- **C. serpentis**: different species of snakes
- **C. saurophilum**: lizards & snakes
History

• 1907: first reported by Tyzzer: C. muris
• 1955: Slavin identified the agent of turkey’s diarrhea
• 1970-1980: C. parvum associated with neonatal diarrhea (calves, piglets, lambs and kids)
• 1980-1990: Worldwide distribution - Serious human pathogen (AIDS) - Identified several new species (genomic studies)...
• 1993: Milwaukee- important epidemic: immunodeficient humans (origin: contaminated water)
DESCRIPTIVE EPIDEMIOLOGY of bovine cryptosporidiosis

Newborn calves / Prevalence (different studies, detection methods, surveys size)

Around the world (SANTIN and TROUT, 2008)

- **Oceania**
  - New Zealand: 21.8%

- **South America**
  - Brazil: up to 47%
  - Venezuela: 29.3%

- **North America**
  - Canada: 15 to 100%
  - USA: 35%–41%

- **Asia**
  - India: 40%
  - Japan: 93%
  - Korea: up to 100%

- **Africa**
  - Zambia: 42.8%
In Europe

LeFay et al. (2000)

- Finland: 76%
- Netherlands: 55%
- Spain: 52% - up to 58.5% (J. A. Castro-Hermida, 2006)
- Ireland: 44.4%
- Italy: 40%
- France: 43.4%
- Germany: 40-44%
- Hungary: 27%
- Great Britain: 23 to 32.9%
- Denmark: 17% (Santin (2004): from 86 to 84%, depending on the age)
- Portugal: 25.4% (Santin (2004))
Epidemiology

• No limited to a specific species
• Affected hosts: young animals (neonatal period)
• Season: calving period - when stabled
Prévalence d’excrétion d’oocystes de *Cryptosporidium* par tranche d’âge dans un élevage de bovins laitiers (*SANTIN et al.*, 2008).
Epidemiology

• Transmission: orally
  ingestion, licking water, plants, equipment...
  contaminated by wild animals, infected animals or healthy carriers

• Significant morbidity
• Mortality: 10 à 50% (>>>>>small ruminants)
• Immunity: resistant to subsequent infection after the initial episode.
Epidemiology

• Resistance:
  viability of the oocysts from 3 months (at 15°C) to more than 1 year (at 4°C) =>
  High prevalence
  Disinfection difficult
Pathophysiology

• Tropism: Gut
Pathophysiology

- Tropism: Gut
- Location: epithelial cells
Pathophysiology

- Tropism: Gut

- Location: epithelial cells: Intracellular, extracytoplasmic

hard to treat!
Pathophysiology

Tropism: Gut

• Location: epithelial cells:
  Intracellular, extracytoplasmic
  => hard to treat!

  Villous atrophy and epithelial cells loss

leads to a 

malabsorptive diarrhea
Upon necropsy, what will you see in the intestine?

Thick mucoid content
Life cycle of cryptosporidium

Key points
- Total duration: only 4 days
- All the stages of development inside the host
- 2 ways of reinfection
Villus

4 days
1. Ways of autoinfection

2. SPOROGONY

3. MEROGONY

4. GAMETOGONY
On the field....
« Signs » of Crypto?

– Age of calves: **2de week after birth**
– History of the farm (Hygiene, livestock buildings)
– Calving period (higher infection pressure in the second half)
– Recurrent diarrheal episodes
– High morbidity (anorexia - dehydration) Low mortality
– Symptoms: mucoid diarrhea

*But to confirm diagnosis*

=> faeces analysis
Treatment of calf diarrhea?
“an ounce of prevention is worth a pound of cure”.
Prevention?

Livestock buildings:
- different area: calving - grouping calves by age
- Isolation of sick - fallowing period
- well-being: air renewal, density, litter...

Appropriate hygiene and husbandry
- Disinfection of equipments

Vaccination of cows (Rota-Corona-Coli)
Early intake of colostrum of good quality
Treatment?

• Symptomatic: rehydration
  + to protect intestinal lining

• Curative?
Treatment of calves diarrhea?

• Several factors involved → therapy must often be started before an etiologic diagnosis has been established.
• Fluid and electrolyte therapy is most important
• Majority of cases of bacteremia and septicemia in neonatal calves are associated with *E coli* ➔ the chosen antibiotic should be effective against gram-negative bacteria
• Provide analgesia (NSAIDs) seems to help a faster recovery
Reduced and responsible use of Antibiotic

- Based on an accurate diagnosis
- Prescribed by a veterinarian
- The **effective** AB at the good **time**, the good **dosis** for the good **duration**
- Curative and/or metaphylactic use?....
Curative, metaphylactic use

Past! Hey kid! Wanna be a Superbug...?
Stick some of this into your genome...
Even penicillin won't be able to harm you...

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.
Majority of cases of bacteremia and septicemia in neonatal calves are associated with *E coli*

→ the chosen antibiotic should be effective against gram-negative bacteria

e.g. **Paromomycin:** *(Parofor ®70)* Parofor® is licensed for the treatment of gastrointestinal infections caused by *E. coli* sensitive organisms to paromomycin
Control of cryptosporidiosis

• Disinfectants that could be effective
  • ammonia 50% , hydrogen peroxide 3%
  • formalin 10%... (Chartier- Paraud 2010)
  • Keno™ cox (formule based on amines)
    (Naciri et al, 2011)
  • Neopredisan® 135-1 and Aldecoc® TGE (based
    Cresol) (SHAHIDUZZAMAN et al., 2010).

• But: efficacy in vitro ≠ on field
• Prolonged needed contact time
• Importance of practicing high pressure
  steam cleaning
Therapeutic agents and treatment strategies for cryptosporidiosis

- Have been pursued for over 40 years since Cryptosporidium was first identified in humans
- Paromomycin has been one of the most widely used agents to treat cryptosporidial infections in AIDS patients
Some tested molecules ....

- **Nitazoxanide** (WYATT et al., 2010)
- **Macrolides**
  - *Azithromycin* (WYATT et al., 2010 - PARAUD 2010).
  - *Tilmicosine* (PARAUD et al., 2010).
- **Cyclodextrin** (CASTRO-HERMIDA et al., 2004b).
- **Anti coccidian**
alternative therapies?

**Obionekk® ( Obione, France)**

- product containing activated charcoal and wood vinegar liquid
- efficacy in preventing cryptosporidiosis in goat kids in field conditions. *C. Paraud (2011)*

Same results: **Nekka-Rich (Japan)** has an anticryptosporidial effect in calves. *S.Watarai (2008)*

**Chitosan**

- synthesis from chitin (crustacean shells)
- in vitro inhibitory activities of Chitosan against C. parvum.

*K.Adjou (UMR -BIPAR Anses-ENVA,France)*
In veterinary medicine

Many molecules tested but only 2 with satisfactory results: Halofuginone lactate and Paromomycin

- Since 2000, only one licensed medication in a number of countries in Europe: **Halofuginone** (Halocur ®) (cryptosporidiostatic)

- **Paromomycin** (Parofor ®) Alongside antibacterial activity, published literature also supports that paromomycin has anti/protozoal properties and shows efficacy in the treatment of cryptosporidiosis in ruminants: calves (Fayer & Ellis, 1993), kids (Viu et al, 2000) and lambs (Mancassola & al, 1995 – Johnson & al 2000)
**Parofor®**: non-ruminating calves

**Indications**: Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin

**Dose**: 25-50 mg paromomycin sulphate /kg bodyweight/day for 3-5 days
Milk and milk replacer

**Withdrawal time**: Meat and offal: 20 days
Parofor®

- Active: Paromomycin sulphate 10%
  70 mg/g paromomycin
  = 100 mg paromomycin sulphate

Aminoglycoside with **Expanded spectrum**
Aminoglycosides: several groups based activity

- Narrow spectrum
  Streptomycin

- Broad spectrum
  Apramycin

- Extended spectrum
  Paromomycin (including antiprotozoic activity)
Parofor®

- Aminoglycoside with **Expanded spectrum**

**Bacterial &**

**Antiprotozoal spectrum:**

- *Cryptosporidium spp*
- Giardia
  
  (Alejandro Grinberg, 2002; E.H. Johnson, 2000; Viu et al.; 2000; Grinberg et al., 2002)
- Histomoniasis (poultry species)
- Leishmania (companion animals, human)
ACTIVITY: Bactericidal

1. Cell wall inhibitors
   - Block synthesis and repair
   - Penicillins
   - Cephalosporins
   - Vancomycin
   - Bacitracin
   - Monobactams/carbapenems
   - Fosfomycin
   - Cycloserine
   - Isoniazid

2. Cell membrane
   - Cause loss of selective permeability
   - Polymyxins

3. DNA/RNA
   - Inhibit replication and transcription
   - Inhibit gyrase (unwinding enzyme)
   - Quinolones (ciprofloxacin)
   - Inhibit RNA polymerase
   - Rifampin

4. Protein synthesis inhibitors
   - Site of action 50S subunit
     - Chloramphenicol
     - Erythromycin
     - Clindamycin
     - Oxazolidinones
   - Site of action 30S subunit
     - Aminoglycosides
     - Tetracyclines
     - Streptomycin
     - Amikacin

5. Metabolic products
   - Block pathways and inhibit metabolism
   - Sulfonamides (sulfa drugs)
   - Trimethoprim

- Tylosin, tilmicosin
- Paromomycin
- Colistin
- Enrofloxacin
- Amoxicillin
Mode of action: double

- binds to the 16 rRNA of 30S subunits of ribosomes
- binds passively to negatively charged portions of the outer membranes of gram-negative bacteria and displaces cell wall Mg\(^{2+}\) and Ca\(^{2+}\) that link lipopolysaccharide molecules
Pharmacodynamics

Concentration dependent antibiotic
A correct dose as a pulse = better

$C_{\text{max}}$

Concentration

Daily dose 1x/ day

Time

MIC
Pharmacokinetics

- Poorly absorbed from the GI Tract

- High concentrations in the gut lumen
- Completely safe
- Specific (enteric)
THANK YOU FOR YOUR ATTENTION