ANTIPARASITIC RESISTANCE
RECENT HISTORY AND RESPONSIBLE USE

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Overview

Antiparasitic resistance is a global issue for grazing livestock

- Defining antiparasitic resistance
- Brief history of antiparasitic resistance in North America and globally
- Methods for slowing the development of antiparasitic resistance on a farm
Common gastrointestinal nematodes (roundworms) of grazing livestock

- Haemonchus*
- Trichostronglyus*
- Ostertagia*
- Cooperia
- Strongylus vulgaris*
- Cyathostomes
- Parascaris equorum

*most pathogenic
Internal parasitism has a large impact on livestock owners. Results in:
- Weight loss
- Decreased milk production
- Decreased fertility
- Increased susceptibility to other diseases
- Death
# Background

- **Major antiparasitic drug classes**

<table>
<thead>
<tr>
<th>Antiparasitic Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazoles</td>
<td>Thiabendazole, albendazole, fenbendazole, oxfendazole, oxibendazole</td>
</tr>
<tr>
<td>Imidazothiazoles</td>
<td>Levamisole</td>
</tr>
<tr>
<td>Tetrahydropyrimidines</td>
<td>Morantel tartate, pyrantel</td>
</tr>
<tr>
<td><strong>Macrocyclic lactones</strong></td>
<td>Ivermectin, doramectin, eprinomectin, moxidectin</td>
</tr>
<tr>
<td>Piperazines</td>
<td>Piperazine</td>
</tr>
<tr>
<td>Isoquinolones</td>
<td>Praziquantel*</td>
</tr>
</tbody>
</table>
Defining antiparasitic resistance

**Definition:**

- Ability of a parasite to survive treatment with an antiparasitic drug that is generally effective against the same parasite species at the same dose and against the same stage of infection.

- Due mostly to gene mutations in the parasite which are passed to subsequent generations of parasites
Measuring antiparasitic resistance

Fecal egg count reduction test:
Egg reduction < 90% post-treatment indicates antiparasitic resistance
### First global reports of antiparasitic resistance (Kaplan 2004)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Host</th>
<th>Year of initial drug approval *not necessarily in US</th>
<th>First published report of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzimidazoles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiabendazole</td>
<td>Sheep</td>
<td>1961</td>
<td>1964</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1962</td>
<td>1965</td>
</tr>
<tr>
<td><strong>Imidothiazoles-tetrahydropyrimidines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>Sheep</td>
<td>1970</td>
<td>1979</td>
</tr>
<tr>
<td>Pyrantel</td>
<td>Horse</td>
<td>1974</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Macrocyclic lactones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Sheep</td>
<td>1981</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1983</td>
<td>2002</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>Sheep</td>
<td>1991</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1995</td>
<td>2003</td>
</tr>
</tbody>
</table>
Antiparasitic resistance: North America

Small ruminants:

- The HOT (Haemonchus, Ostertagia [Teladorsagia], Trichostrongylus) complex is the primary concern
- Since 2003, resistance well-documented and widespread, mostly in Southeast U.S.

First case of TOTAL antiparasitic failure in U.S. in goats: 2004
Antiparasitic resistance: North America

Cattle:

- 2009 data confirmed resistance to macrocyclic lactones across 9 states
- Cooperia spp. resistance becoming a problem
Antiparasitic resistance: North America

Horses:

- Resistance in small strongyles to benzimidazoles is high throughout the country.
- Overall equine nematode resistance to antiparasitics in U.S. uncertain.
## Antiparasitic resistance: South America

### Cattle:

<table>
<thead>
<tr>
<th>Country</th>
<th>Antiparasitic class</th>
<th>Route of administration</th>
<th># of farms with antiparasitic resistance</th>
<th>Nematode species/genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>ML, BZ</td>
<td>Injectable, oral</td>
<td>16</td>
<td>Cooperia spp., Ostertagia ostertagi</td>
</tr>
<tr>
<td>Brazil</td>
<td>ML</td>
<td>Injectable</td>
<td>23</td>
<td>Cooperia spp., Haemonchus spp., Oesophagostomum spp.</td>
</tr>
</tbody>
</table>
Antiparasitic resistance: South America

Sheep in Argentina:

<table>
<thead>
<tr>
<th>Region</th>
<th>Farms with resistance detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buenos Aires</td>
<td>7/32</td>
</tr>
<tr>
<td>Corrientes</td>
<td>19/20</td>
</tr>
<tr>
<td>Entre Rios</td>
<td>5/10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flock size</th>
<th>Farms with resistance detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>3/7</td>
</tr>
<tr>
<td>100 – 500</td>
<td>6/29</td>
</tr>
<tr>
<td>500 – 1000</td>
<td>2/6</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>16/19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># treatments per year</th>
<th>Farms with resistance detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>14/41</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>21/25</td>
</tr>
</tbody>
</table>
Antiparasitic resistance: Europe/Asia

- In general, antiparasitic resistance in Europe is relatively low, however:
  - 2007 report of resistance to all 3 major anthelmintic classes in Scotland (Sargison, et al 2007); other sporadic reports elsewhere

- Reports of antiparasitic resistance in India, Middle East
  - 2015 report from India demonstrating resistance in sheep to levamisole and albendazole (Manikkavasagan, 2015)
Antiparasitic resistance: Australia/New Zealand

- Cattle: in the North Island of NZ, a reduction in FEC of > 95% was demonstrated in only 7% of beef cattle farms (4/61) for albendazole, levamisole, ivermectin.

- Sheep: very serious growing problem:
  - 2000, 40% sheep farms in Western Australia had avermectin-resistant *T. circumcincta*
  - 2005, 60%
  - 2012, estimated 80% of farms
Antiparasitic resistance: Africa

- First case of ivermectin resistance in sheep reported by Van Wyk in South Africa in 1987
- Reports of antiparasitic resistance from other African countries
  - Primarily from Kenya and South Africa
  - Mainly in sheep
  - *Haemonchus contortus*
Parasitologists are uncertain of the current prevalence and distribution of antiparasitic resistant parasites in the U.S. in livestock species, particularly beef cattle and horses.

KEY: you only find antiparasitic resistance when you look. Many countries don’t have the personnel, infrastructure, or tools to look for resistance.
History of U.S. antiparasitic use

- **Recent history:**
  - Ivermectin and other macrocyclic lactones (MLs) were highly effective when first approved in 1980s/1990s
  - Producers became heavily dependent on drugs for control of parasites, resistance has spread
Factors contributing to antiparasitic resistance

- **Parasite factors**
  - Genetics, biology

- **Management factors**
  - Treating too frequently
  - Under-dosing

- **Drug factors**
  - Sub-therapeutic drug levels after initial therapeutic level
Need for a change in the way veterinarians and producers view parasites:

From parasite elimination to parasite control
Evaluating parasitism

- Weight loss/body condition score
- Diarrhea scores
- Poor coat
- Bottle jaw
- Fecal egg counts
- Age of animal/susceptibility risks
Evaluating parasitism: FAMACHA
Responsible management

- Weigh/weight tape animals to ensure proper dosing
- Follow label directions for adequate administration
- Quarantine new livestock, if possible
- Reduce grazing density on pastures, if possible
- Cull chronic poor-doers, if possible
- Avoid deworming the entire herd: Use Targeted Selective Treatment (TST)
Refugia

The proportion of the total parasite population that is not selected for anthelmintic treatment

- Those parasites that are in "refuge" from the drug
- Therefore have no selection pressure to develop resistance
- A benefit of refugia is to maintain a proportion of susceptible parasites on the farm

- Farmers taught to evaluate health of goats and only treat when needed based on:
  - FAMACHA, bottle jaw, body weight, diarrhea scores
- Results showed that farms that used TST did not suffer losses at a higher rate than farms treating all animals.
  - TST is feasible and effective for resource-poor farmers
  - TST helps reduce use of antiparasitics
Role of education

- In the U.S., many veterinary schools are starting to emphasize parasite management and vets are becoming more aware of the emergence of resistance in the U.S.
- This is where collaboration and communication play a vital role
  - Both locally and globally!
Final Thoughts

- Global antiparasitic resistance has a large impact on animal welfare and economies, both locally and nationally.
- Education is key in spreading the word about responsible use of antiparasitic drugs.
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