ANTIPARASITIC RESISTANCE
RECENT HISTORY AND FDA EXPERIENCE

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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
- U.S. regulatory experience
FDA-CVM

- Within FDA, the Center for Veterinary Medicine (CVM) regulates animal drugs (including antiparasitics), animal feed, and veterinary devices.
- We make sure an animal drug is safe and effective before approving it.
- We monitor the safety and effectiveness of animal drugs on the market.
Background

- Common gastrointestinal nematodes (roundworms) of grazing livestock
  - Haemonchus*
  - Trichostronglyus*
  - Ostertagia*
  - Cooperia
  - Strongylus vulgaris*
  - Cyathostomes
  - Parascaris equorum

*most pathogenic
Background

- Internal parasitism has a large impact on livestock owners

- Results in:
  - Weight loss
  - Decreased milk production
  - Decreased fertility
  - Increased susceptibility to other diseases
  - Death
## 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>Benzimidazoles</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>Imidothiazoles-tetrahydropyrimidines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>Sheep</td>
<td>1970</td>
<td>1979</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1974</td>
<td>1996</td>
</tr>
<tr>
<td>Macrocyclic lactones</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:
- Since 2003, resistance well-documented and widespread, mostly in Southeast U.S.
- First case of total antiparasitic failure in goats in U.S. 2004

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: 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.
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
Responsible use

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 antiparasitic 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
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!
CVM’S ARMS initiative

**Antiparasitic Resistance Management Strategy (ARMS)**

- CVM’s initiative to promote sustainable use of antiparasitic drugs in grazing livestock species
- Launched in September 2012
- 3-pronged approach:
  - Education
  - Research
  - Regulation
Final thoughts

- Ultimately, we want to ensure that approved antiparasitics remain effective for as long as possible.
- This should be a shared goal throughout the world for the benefit of animal and public health.
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.
Resources

- **CVM website:** [http://www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm](http://www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm)

- **Docket for public meeting:**
  [http://www.fda.gov/animalveterinary/resourcesforyou/ucm318015.htm](http://www.fda.gov/animalveterinary/resourcesforyou/ucm318015.htm)

- **Public meeting overview:**

- **Brochure:**

- **Antiparasitic Resistance and Grazing Livestock in the United States**

- **Veterinary Parasitology Special Issue Vol 204, Issues 1-2, Pages 1-80 (30 July 2014)**
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