Managing Resistance to Anthelmintics

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What are the anthelmintics?

Kill or control:
Nemat helminthes (roundworms)
Platy helminthes (flatworms)

CLASSES
- Benzimidazoles
- Levamisole
- Macrocyclic lactones
  - Avermectins
  - Milbemycins
- Amino acetonitrile derivative
- Spiroindoles
  (Ops, piperazine, closantel)

What is resistance?

- Greater frequency of individuals in a population able to tolerate doses of a compound than in a normal population of the same species.
- Efficacy is less that 90% (or 95% in sheep).
Anthelmintic Resistance

- R Mechanisms specific to drug class
- Appear to be target site related
- Mendelian inheritance - chromosomal genes (sexual reproduction)
- Parasite species specific
- Can infect other hosts within host range eg.
  - donkeys ➔ pasture ➔ horses,
  - goats ➔ pasture ➔ sheep

Antimicrobial Resistance

- Range of resistance mechanisms
- Genetic transfer of R factors between bacterial species occurs
- Transfer of organisms between host species eg.:
  - pigs ➔ humans
  - humans ➔ dogs

Ivermectin-resistant *Trichostrongylus*: sheep ➔ faeces ➔ humans

Tricladendazole-resistant *Fasciola*: cattle ➔ faeces ➔ snails ➔ water plants ➔ humans
<table>
<thead>
<tr>
<th>Hosts</th>
<th>Resistant parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>Haemonchus</td>
</tr>
<tr>
<td>Goats</td>
<td>Teladorsagia</td>
</tr>
<tr>
<td>Cattle</td>
<td>Trichostrongylus</td>
</tr>
<tr>
<td></td>
<td>Ostertagia</td>
</tr>
<tr>
<td></td>
<td>Cooperia</td>
</tr>
<tr>
<td></td>
<td>Fasciola</td>
</tr>
<tr>
<td>Dogs</td>
<td>Dirofilaria</td>
</tr>
<tr>
<td></td>
<td>Ancylostoma</td>
</tr>
<tr>
<td>Horses</td>
<td>Cyathosominae</td>
</tr>
<tr>
<td>Donkeys</td>
<td>Parascaris</td>
</tr>
<tr>
<td>Pigs</td>
<td>Oesophagostomum</td>
</tr>
<tr>
<td>Camel ?</td>
<td></td>
</tr>
</tbody>
</table>
## Resistance in scour worms

### % of farms with <95% FECR

<table>
<thead>
<tr>
<th>Drug</th>
<th>NZ (Waghorn et al 2006)</th>
<th>Spain (Alvarez-Sanchez)</th>
<th>Australia (Playford et al 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>BZ</td>
<td>LEV</td>
<td>ML (IVM)</td>
</tr>
<tr>
<td>NZ</td>
<td>41</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>Spain</td>
<td>13</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Australia</td>
<td>88</td>
<td>84</td>
<td>25-76</td>
</tr>
</tbody>
</table>

Note: in some regions resistance is CRITICAL
Measuring resistance

• In vivo
  • FECR
  • Problems with interpretation

• In vitro
  • Development of freeliving stages
  • But: Time delay, validation

• Molecular
  • PCR
  • Lack of knowledge of mechanisms

CAGACGAAACTTTCTGTATT
CAGACGAAACT*CTGTATT
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CAGACGAAACTACTGTATT
A case study – ivermectin resistance

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>New drug class with outstanding in potency and spectrum</td>
</tr>
</tbody>
</table>
| 1990 | Outcomes:  
|      | • Some parasite species are virtually eradicate  
|      | • In others, eg. *Trichostongylus*, resistance is rare.  
|      | • *Ostertagia (Teladorsagia)* and *Haemonchus* develop resistance in 2 to 5 years, IVM-R appears to be a dominant phenomenon. |
| 1995 | More potent and persistent chemicals of the same class (eg. moxidectin) followed IVM on to the market - resistance quickly developed to those compounds too. |
To manage resistance we need to understand the risk factors

Activities that allow resistance genes: to be selected and reach the next worm generation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worm biology</td>
<td>Presence of R gene at some level</td>
</tr>
<tr>
<td>Survive treatment</td>
<td>Underdosing allows marginally R individuals to survive</td>
</tr>
<tr>
<td></td>
<td>Low level daily dosing in horses</td>
</tr>
<tr>
<td>High treatment frequency</td>
<td>More opportunities for selection</td>
</tr>
<tr>
<td>Few organisms in the environment (low refugia)</td>
<td>Most worms in the metapopulation are selected</td>
</tr>
</tbody>
</table>
# Guide to managing resistance

<table>
<thead>
<tr>
<th>Factor</th>
<th>Principles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worm biology</td>
<td>inherent property of the parasite species</td>
</tr>
<tr>
<td></td>
<td>Do not import resistance- quarantine treat</td>
</tr>
<tr>
<td>Not surviving treatment</td>
<td>Give full doses of effective* compounds</td>
</tr>
<tr>
<td></td>
<td>Oral or injection preferred</td>
</tr>
<tr>
<td></td>
<td>Use short acting drugs not long acting preps</td>
</tr>
<tr>
<td>Reduce treatment frequency</td>
<td>Use non chemical control such as:</td>
</tr>
<tr>
<td></td>
<td>Pasture rotation to prevent reinfection</td>
</tr>
<tr>
<td></td>
<td>Select animals for immunity</td>
</tr>
<tr>
<td></td>
<td>Improve immunity with nutrition</td>
</tr>
<tr>
<td>Organisms in the environment (high</td>
<td>Use targeted treatment – monitor for infection and treat at threshold</td>
</tr>
<tr>
<td>refugia)</td>
<td>Leave some animals untreated</td>
</tr>
<tr>
<td></td>
<td>Do not ‘treat and move’</td>
</tr>
<tr>
<td>Intermediate hosts</td>
<td>Control other hosts to break life cycle</td>
</tr>
</tbody>
</table>

* Quality, storage, rotation between classes. Prescription
Some approaches

• Using mathematical models to understand
• Better diagnosis
• Targeted treatment
• Combination therapy
• Rotational systems, especially for the tropics
• Advice and decision support
Mathematical models

- Need information on parasite pop. Dynamics
- Outputs are burdens, resistance frequency etc.
- Can ask ‘What if?’

Sangster and Dobson 2002
Better diagnosis of resistance

log drug concentration

proportion responding

susceptible

resistant
Targeted treatment

Treat when pathology appears

Treat when burden reaches threshold
Combination therapy

Components:
• High efficacy (no resistance)
• Independent action
• Similar half life
• Coadministration

Sangster and Dobson (2002)
Rotational grazing management

- In warm and moist environments larvae become infective in 5 days
- In these conditions larvae die in 60 days on pasture
- 15 cells grazed for 4 days - achieves zero transmission

Zero grazing forage systems (Chandrawathani et al 2004)
Advice and decision support
Sheep worms — summer-autumn worm control

Rob Woodgate, Veterinary Officer, Albany and Brown Besier, Principal Veterinary Parasitologist, Albany

Background
Resistance by sheep worms to drenches in Western Australia is rapidly reaching a crisis point. There are worms resistant to white (bimimidazole or BZ – e.g. Valbazen, Panacur, Alben, Fenbendazole, Nemadet, Oxfen, Fencore, etc.) and clear (levamisole or LEV – e.g. Nilverm, Levamisole, Ripercol, etc.) drenches on virtually all farms. Worms on about 60 per cent of farms tested show resistance to BZ/LEV combination drenches (containing a white and clear drench, e.g. Combi, Salvo, Scanda, etc.). Of most concern, testing between 2002 and March 2004 showed resistance on about 60 per cent of properties to the macrocyclic lactone group of drenches (the MLs - active ingredients ivermectin, abamectin and moxidectin) in the brown stomach worm (Ostertagia circumcincta).

What is the answer?
Since 2001, Ag Department officers have monitored worm levels in weaners, ewes and dry sheep on more than 20 properties (“dorm farms”) throughout the State. This has included 6 key IPM’s sites (as part of the national Integrated Parasite Management – sheep project funded by Australian Wool Innovation Ltd) since 2004. The work involves collecting on-farm worm and management data at locations covering all major sheep producing regions (from Northampton and Moora in the north to Albany and Esperance in the south). The program is aimed to provide good worm control while reducing the selection pressure for drench resistance.

On results to date the following approach is recommended:

- Weaner and hogget sheep: give a single, fully effective* summer drench after the pasture
Plenty to chew on:
- Better measurement of resistance
- Understand the risk factors and minimise them
- Lower chemical use (use combinations)
- Break the life cycle
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