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Anthelmintic resistance in equine parasites—Current evidence and knowledge gaps

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ABSTRACT

Anthelmintic resistance is becoming increasingly prevalent among equine nematode parasites. The first reports documenting resistance were published in the 1960s, just a short time after introduction of the first modern anthelmintics phenothiazine and thiabendazole. Several factors are known to influence development of resistance, but evidence specific to equine parasites is limited. Most current knowledge and applications have been extrapolated from research with trichostrongylid parasites of sheep. The number of cyathostomin species co-infecting horses adds to the complexity of investigating drug resistance but, given their apparent limited biological diversity, viewing these in a unispecific context remains a pragmatic approach. Factors affecting resistance development in cyathostomins include parasite seasonality, life span and fecundity, host immunity, and the existence of encysted stages. Further, parasite refugia have been shown to play a vital role in resistance development in other parasites, and likely is also important in equine parasites. Specific genetic factors for drug resistance and possible modes of inheritance have been identified for trichostrongylid nematodes, but it is widely accepted that several more remain undiscovered. Current evidence with equine and ruminant parasites suggests that fitness is not significantly compromised in drug resistant strains. Attempts to develop *in vitro* and molecular assays for diagnosing anthelmintic resistance in equine nematodes have had only limited success, standardized guidelines are sorely needed for performing the fecal egg count reduction test in horse populations. Taken together, this review illustrates the complexity of understanding anthelmintic resistance in equine nematodes, and emphasizes the need for further research.

1. Introduction

Control of helminth parasite infection in horses is considered an essential aspect of routine management in equine establishments. Over the past 50 years, a number of broad spectrum endoparasiticides have been available for control of these parasites. Many (*e.g.*, thiabendazole, dichlorvos) have been withdrawn for commercial reasons, but anthelmintic resistance has been reported for all of the drug classes that are currently marketed (Table 1). Cyathostomin resistance to benzimidazoles and tetrahydropyrimidines is highly prevalent, especially as

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Table 1
Equine endoparasiticides in the United States, initial market appearance and first published report of anthelmintic resistance involving equine parasites in the United States.

Equine endoparasiticide	Initial market appearance (USA)	Initial resistance report (USA)
Phenothiazine	1940	Cyathostomins (Drudge and Elam, 1961)
Piperazine	1955	Cyathostomins (Drudge et al., 1988)
Benzimidazoles	1961[a]	Cyathostomins (Drudge and Lyons, 1965)
Tetrahydropyrimidines	1976[b]	Cyathostomins (Chapman et al., 1996)
Macrocyclic lactones	1984[c]	*Parascaris equorum* (Craig et al., 2007)

[a] Thiabendazole.
[b] Pyrantel pamoate.
[c] Ivermectin.

documented in the southeastern USA (Kaplan et al., 2004). Benzimidazole resistance has been reported world-wide in cyathostomins (reviewed by Kaplan, 2004), and recent European studies have documented signs of pyrantel resistance as well (Traversa et al., 2009; Nielsen et al., 2013b).

Of further concern are recent reports of an apparent reduction of cyathostomin egg reappearance periods (ERP) following treatment with ivermectin or moxidectin (Lyons et al., 2008a, 2011). Sangster (1999) has suggested that a shortening of the ERP is the first indication of developing anthelmintic resistance. This hypothesis is alarming in light of two recent studies in which shortened ERPs following ivermectin or moxidectin treatment were associated with survival of luminal, fourth-stage cyathostomin larvae in juvenile horses (Lyons et al., 2009, 2010).

In addition to cyathostomins, populations of *Parascaris equorum* that are resistant to ivermectin and moxidectin have been reported from multiple locations around the world (Boersema et al., 2002; Hearn and Peregrine, 2003; von Samson-Himmelstjerna et al., 2007; Schougaard and Nielsen, 2007; Lind and Christensson, 2009; Veronesi et al., 2010; Nareaho et al., 2011; Laugier et al., 2012). A study in central Kentucky also reported a lack of efficacy by pyrantel pamoate against *P. equorum* (Lyons et al., 2008b), illustrating the potential for ascarids to develop resistance to other drug classes as well.

Over the past decade, the pharmaceutical industry has developed and marketed three new drug classes for controlling nematode parasites in other domestic animals. These are emodepside (cyclo-octadepsipeptide class), monepantel (amino-acetonitrile derivatives), and derquantel (spiroindoles). However, it remains unknown whether these classes are safe and effective in horses, which will ultimately determine their suitability for the equine market. Historically, the macrocyclic lactones remain the drug class most recently introduced for equine use, but ivermectin was first marketed about 30 years ago (Table 1). Because no new equine anthelmintics are imminent, it is critical that further development of resistance be delayed as much as possible.

The increasing prevalence of anthelmintic resistance has fostered recommendations for surveillance-based approaches to parasite control and reduced frequency of anthelmintic treatment (Herd et al., 1985; Kaplan and Nielsen, 2010). Over the past 20 years, the practice of selective therapy has been promoted, *i.e.*, treating only those animals with egg counts that exceed a predetermined threshold value (Gomez and Georgi, 1991; Kaplan and Nielsen, 2010). Contemporaneously, the introduction of prescription-only restrictions on anthelmintics in Denmark appears to have stimulated veterinary involvement in equine parasite control and increased the routine use of fecal egg counts (Nielsen et al., 2006). Since 2006, a European Union directive has led to implementation of similar, restrictive legislation in other European countries.

A survey performed in the United States in 1998 determined that equine parasite control depended predominantly on frequent anthelmintic treatment, performed year-round, with little or no use of fecal surveillance (Anonymous, 1998). However, this trend appears to be changing recently as many U.S. veterinary practices have adopted surveillance-based control programs. The American Association of Equine Practitioners (AAEP) has published updated guidelines for parasite control (Nielsen et al., 2013a) which espouse surveillance and decreased use of anthelmintics. These attempts to establish a more sustainable approach to parasite control have highlighted the need for applied research to generate evidence supporting various control recommendations (reviewed by Nielsen, 2012).

The objective of this article is to review current information about anthelmintic resistance in equine parasites. Special emphasis will be given to the unique biology of cyathostomins, factors affecting the development of resistance, and methods for detection of resistance. Within each topic, we will identify gaps in the scientific knowledge required to make substantial advances in sustainable parasite control.

2. Important factors associated with parasite and host biology

For theoretical considerations of the development and management of anthelmintic resistance, it would be far simpler to consider the cyathostomins as a single species. Computer models of resistance selection have been developed for single nematode species in other hosts (Leathwick et al., 1992; Barnes et al., 1995), but complications grew exponentially when the number of parasite targets was increased, and as potential interactions approached infinity (Dobson et al., 2011). Regrettably, our current knowledge of cyathostomin biology is insufficient to determine whether a simplistic, "unispecific" approach would be valid.

Various aspects of cyathostomin biology are discussed herein from the perspective of their impact on resistance.