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The Battle Against Bugs

There's an "anti" for almost everything. Here's a rundown on our arsenal of equine disease-fighting drugs and their proper uses.

Humans have been waging war against the soldiers of disease for hundreds of years, long before fabled scientist Antonie van Leeuwenhoek first discovered these tiny organisms under a microscope. In fact, in March 2015 a team of biologists and medieval scholars at the University of Nottingham uncovered a 10th century recipe for antibacterial eye ointment. After recreating the salve, they confirmed their predecessors in the laboratory were on to something—the concoction was effective against today's methicillin-resistant *Staphylococcus aureus* (MRSA), bacterial species that earned their name because of broad resistance to most modern drugs.

Indeed, the battle with pathogens, or agents of disease, continues today, but current mainstays of the human-led arsenal in the disease wars are an array of "anti" drugs, which include antimicrobials (more commonly called antibiotics), antivirals, antiparasitics, and antifungals. These are designed to fight enemies that use guerrilla-type tactics against the horse's immune system—targeting its weaknesses and adapting quickly to changes in the environment.

The Enemy
Different pathogens cause similar signs of disease. Bacteria, viruses, and fungi, for instance, can all cause nasal discharge, while bacteria, parasites, protozoa, and viruses can all cause diarrhea. However, each pathogen is a unique organism carrying its own strengths and weaknesses into battle. Recognizing the ploys of each—and applying proper treatment—can mean a more successful outcome.

Bacteria are single-celled organisms classified according to cellular shape and structure. They reproduce by a process called binary fission, in which one cell divides into two. Some bacteria produce toxins that damage host cells. In the case of Gram-negative bacteria (generally -associated with more virulent infectious disease than Gram-positive and more resistant to treatment) such as *Escherichia coli* or *Salmonella*, the cell membrane itself becomes toxic to the host when it breaks down during bacterial death. Common bacterial pathogens in horses include *Salmonella*, *Streptococcus equi* (the causative agent of strangles), *Clostridium tetani* (responsible for tetanus), and *Rhodococcus equi* (causes foal pneumonia).

Viruses are much smaller and simpler than bacteria. A virus is essentially a piece of DNA or RNA (genetic material) wearing a protein coat. It invades a host cell, using it as a base of operations and as raw material for reproduction. Once inside, a virus breaks down components of the host cell, using them for its own membranes and structures and begins replication by duplicating its own genetic material. Examples of equine viruses include West Nile virus; Eastern, Western, and Venezuelan encephalitis viruses; equine herpesvirus; and rabies virus.

Fungi are more complex than bacteria or viruses. Fungi can be single-celled or multicellular, reproduce through spore formation, and often form complex filamentous structures. They can be direct pathogens (meaning they cause disease in healthy animals) or opportunistic (causing disease in animals with already weakened immune systems), and in horses they can cause skin and hoof diseases, such as ringworm and thrush, or systemic diseases, such as guttural pouch mycosis.

Protozoa are single-celled organisms with a more complex cell structure than bacteria, but less complex than fungi. One of the more common protozoal diseases in horses is equine protozoal myeloencephalitis (EPM).

Helminth is a general term for worms. Parasitic worms fall into several categories, including nematodes (e.g., roundworms and strongyles), trematodes (flukes), and cestodes (tapeworms).

The Arsenal
Practitioners use a broad assortment of veterinary weaponry to take down these enemies:

Antimicrobials (antibiotics) either kill bacteria or inhibit their reproduction. Some antimicrobials target structures within the bacterial cells, while others target the cell membranes. Antimicrobials that kill bacteria outright are called bactericidal. Those that inhibit bacterial reproduction, controlling cell numbers in a "static" fashion to help the body fight infection, are called bacteriostatic. Penicillin is a classic bactericidal antimicrobial.

Antivirals target viral DNA or RNA.

Antifungals target fungal metabolism, usually by inhibiting the production of cellular chemicals important to the fungi.

Antiprotozoals are typically antimicrobials that also work against protozoa, often in a static manner.

Anthelmintics interfere with the parasite cell integrity, neuromuscular coordination, or ability to defend against the host's (e.g., the horse's) immune system.

Antitoxins do not target the bacterial organism itself, but are biologically derived products that counteract specific toxins the organism produces by binding and neutralizing them. An example is tetanus antitoxin.

Antibody products, like antitoxins, are biologically derived. Antibodies are harvested from the blood of horses with high levels of immunity against specific diseases, and veterinarians usually use them to combat and/or prevent disease in foals that have not received sufficient infection-fighting antibodies from their dams.

The War
Selecting the appropriate "anti" depends on both the organism and your strategy for eliminating or attenuating it, say both Scott Weese, DVM, Dipl. ACVIM, professor of pathobiology at the University of Guelph's Ontario Veterinary College, and Andrew Peregrine, BVMS, PhD, DVM (Hons), Dipl. EVPC, ACVM, MRCVS, associate professor of parasitology at Guelph.

Antibiotics, which can come in injection, topical, or tablet form, either kill bacteria or inhibit their reproduction.

Photo: Anne M. Eberhardt/The Horse

For instance, "antibiotics have a specific target," says Weese. "It might be that they attach to part of the bacterial wall, and when the bacterium grows, the antibiotic disrupts that. Or it might be that the antibiotic gets into a bacterial cell and disrupts the machinery when it reproduces (the bacteriostatic described)."

"In the antiparasitic world," says Peregrine, "we only use three drug classes: macrocyclic lactones, benzimidazoles, and tetrapyrimadines (pyrantel pamoate)." As a parasite becomes resistant to one drug within a class, that resistance tends to carry over to all drugs within that class. With limited drug classes available, resistance is a real concern in the fight against helminth parasites.

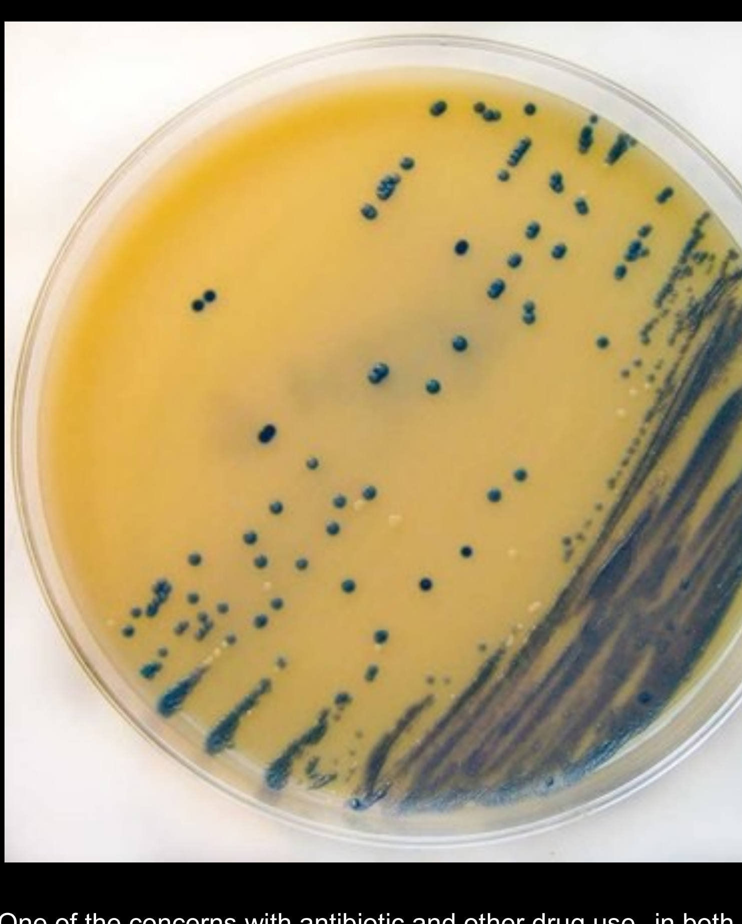
"Two (of the classes, macrocyclic lactones and tetrapyramidines) work on the nervous systems of parasites," he continues. "The benzimidazoles work on metabolic processes." Because these drugs produce a slower kill, Peregrine says their use is less likely to cause drug-induced impaction with roundworms (ascarids) than a rapid kill in horses with heavy burdens.

These specific mechanisms of action emphasize the importance of diagnostic testing to identify the cause of disease rather than just treating with the first drug at hand and hoping for the best.

The Resistance Movement
For every weapon developed, the enemy finds means of evasion. Resistance has become a major concern for veterinarians as we've become reliant on the "antis," even beyond parasite resistance. "Bacteria develop different ways to evade those killing mechanisms," says Weese.

Anyone who has turned on a television, fired up a computer, or opened a newspaper or magazine in the past decade or two has heard of these multi-drug-resistant bacteria.

From a horse owner standpoint, says Weese, the key concern is about pathogens developing resistance in the horse and becoming more difficult to treat. However, there is also concern about veterinary use of drugs that might cause antibiotic resistance in pathogens that also affect people, such as *Staphylococcus*, rendering these drugs less effective.



One of the concerns with antibiotic and other drug use--in both horses and humans--is that pathogens, such as methicillin-resistant *Staphylococcus aureus* seen here, can develop resistance against the very drugs designed to fight them.

Photo: Wikimedia Commons/Nathan Reading

Weese points out the risks of drugs impacting normal resident bacterial populations, as well: "The greater the drug hits the normal population, the greater the chance of something resistant developing."

In horses, disrupting normal bacterial flora with antibiotics can have significant and even catastrophic results. However, as Weese points out, even drug-induced colitis (inflammation of the colon) does not occur merely as the result of antibiotic use. "The drug has to screw up the normal bacterial population, but something else has to be there (a pathogenic bacterium) to cause disease," he says, adding that this likelihood becomes "slightly more complicated with resistance." When there is a drug-resistant population, the impact is "more driven by how much of the flora the drug disrupts."

Despite the prevalence of antimicrobial resistance among various pathogens, Weese points out that scientists know relatively little about the mechanisms, transfer across bacterial generations, and impacts of drug resistance in equine infections.

Pathogens develop resistance differently to different types of drugs, says Weese. In some cases bacteria can become resistant quickly if they have pre-existing mutations (making them likely to be resistant upon initial exposure), or they mutate during treatment to become resistant. He points out that this can happen with any animal in any situation, regardless of pre-exposure or drug type. In other instances the bacterial population develops resistance when it acquires a new gene. The mode of resistance development determines how quickly it occurs and to what extent.

However, curtailing drug use might not reduce resistant populations. "Generally we think if we stop using a drug, resistance will disappear over time," says Weese, who cautions that this might not be the case if the resistance is part of that bacterium's genome and the bacterium is a normal inhabitant of the horse. "If there is no cost to the bacterium to maintain that resistance, it might just keep it."

While antibiotic-resistant bacteria such as MRSA monopolize health news headlines, the overuse of antiparasitic drugs remains an important issue. This promotes development of resistant populations in horses and other species and renders current anthelmintics ineffective. "When I first came to North America," says Peregrine, "the most extraordinary talk I heard was about heartworm; people were saying ivermectin resistance will never arise. I heard the same thing about roundworms (ascarids) in horses." Researchers have identified ivermectin-resistant populations of both species in recent years.

Battle Strategies
In a nutshell, use the right weapon for the job. Antibiotics won't work against viruses (the reason your physician won't prescribe an antibiotic for your cold), and anthelmintics don't fight bacteria. But even within categories it's important to choose the right "anti." For example, penicillin, while highly effective against various anaerobic bacteria (those not needing oxygen for survival) such as *Clostridium*, is almost useless against a Gram-negative bacterium such as *Salmonella*.

Similarly, if a horse is infected with highly ivermectin-resistant roundworms, all the ivermectin in the world might not get the job done. At low levels of resistance, large doses of ivermectin might be effective, but this approach can contribute to increasing ivermectin resistance.

"Our antibiotics aren't smart enough to just go where they're told. "

Dr. Scott Weese

Weese cautions that sometimes both horse owners and veterinarians have tunnel vision when it comes to what they're trying to treat. "Our antibiotics aren't smart enough to just go where they're told," he explains. "So if you're treating pneumonia, (remember that) the antibiotic also goes to the skin, GI tract, etc. The antibiotics are being used for the lungs but the drug is going everywhere."

He adds that because antibiotics don't just treat the one disease-causing organism, it's possible to inadvertently contribute to resistance among the trillions of bacterial species you'd consider out of the line of fire.

Appropriate timing of the targeted, correct treatment also influences outcome and resistance development.

"The drugs themselves don't make the parasites resistant," says Peregrine, adding that inappropriate deworming methods are more to blame. "If you are treating all animals every time, that's probably the worst type of selection pressure you can apply," meaning that you're killing off any remaining susceptible parasites in horses that don't need to be and, thus, enabling survival and perpetuation of parasites with natural resistance to these drugs.

He cautions that any development of new antiparasitic drugs will not be enough to eliminate the drug-resistant parasite problem; instead, owners and veterinarians need to continue focusing on treating only the most heavily affected animals to preserve the remaining effectiveness of the weapons we have.

Another problem Peregrine sees in antiparasitic strategies is underdosing. "There is a lot of evidence that underdosing strongly selects for parasites with resistant genes," he says.

Operational Intelligence
Weese cautions against basing drug use decisions on fear or hype. For instance, he says, "It's easy to have a knee-jerk response of 'Don't use antibiotics,' while there are some situations where antibiotics are used (advisedly) to prevent disease, and the flip side—having to treat existing disease, and often with more important drugs—isn't always good.

In other words, while it's tempting to try to minimize resistance by only bringing out the antimicrobial arsenal in the face of an invasion, in certain cases it might be better to use a drug less important in human medicine to prevent disease in animals, thus saving the "big guns" (and delaying resistance against them) for human use.

And even though veterinarians have decades—even centuries!—of experience in battling these bugs, Weese says there's plenty left to learn: "We still don't understand a lot about optimal dosing and treating different sites (e.g., the lung vs. the skin). We overestimate how much we know."

For now, diagnostic measures such as fecal egg count reduction testing for parasites, which allows monitoring their response to anthelmintic drugs; viral diagnostic testing (respiratory swabs); and bacterial or fungal culture and sensitivity testing can help veterinarians select the proper "anti" drug to kill the pathogen at hand and effectively treat your horse.