Antimicrobial strategy for respiratory disease

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Knowledgeable use of antimicrobials in horses is essential in the antimicrobial-resistant world in which we live and work. We all know the gold standard, but what should we do when we need empirical treatment, if we can't perform culture and sensitivity for practical and/or economic reasons?!

Firstly, we need to know our region. This means that we require contemporary data of local pathogens and their antimicrobial sensitivity patterns (aka antibiograms).

Secondly, we need to know that just because a client thinks we should provide antimicrobials in a febrile horse, we know we shouldn't if it is likely a viral infection &/or the horse is improving. At least, we can decide to watch for 12-48 hours and reassess the patient. Thirdly, we must recognise the likelihood of a certain bacterial species causing certain clinical signs in the horse. Fourthly, we use our knowledge of what antimicrobials are empirically helpful against distinct bacterial pathogens in choosing an antimicrobial. Finally, we need to be ready to firmly advocate for our patients [and indeed humanity (through us not being responsible for the exacerbation of antimicrobial resistance)] and perform culture and sensitivity on samples including nasal swabs, guttural pouch lavage, tracheal lavage fluid and pleural fluid. Remember that if you have diagnosed pleuropneumonia through ultrasonographic examination, then after pleurocentesis, we need to collect and submit pleural fluid samples for both aerobic and anaerobic culture.

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How to manage and pharmacologically treat allergic respiratory disease

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"Allergic respiratory disease" can have two different presentations in the horse, anaphylaxis (1) and Equine Asthma (2, 3).

Anaphylaxis, also known as anaphylactic or allergic shock, is an acute, severe allergic response that affects the entire body. This reaction is characterized by narrowing of the airways, resulting in dyspnea, and can also be accompanied by non-respiratory signs like hives or cardiovascular shock. In severe cases, swelling of the upper airways (throat, laryngeal edema) and/or lower airways (bronchospasm, primary or secondary pulmonary edema) can obstruct air passage to a potentially life-threatening degree. Immediate therapeutic action is indicated and depending on the severity and presentation may include pharmacological and physical intervention (1): Epinephrine (1 : 1000), 3 - 5 ml/450-500 kg slowly IV in 20-30 ml NaCl (also IM or SQ in less severe cases); holding the head of the patient high; applying ice-cooling; lidocaine spray, epinephrine 2% or phenylephrine spray (0.1%, 20 - 30 mL) locally to decrease swelling; furthermore NSAIDs, such as flunixin, 1.1 mg/kg i.v. BID, steroids, such as dexamethasone, 0.05 - 0.2 mg/kg IV SID, antihistamines, such as Ceterizin 0.2-0.4 mg/kg PO, q12h; and if pulmonary edema is present, furosemide (1 mg/kg IV slowly, repeat after 30 minutes if necessary) may be used; in severe cases of upper airway obstruction, tracheostomy can be life-saving and O_2 insufflation (10 - 20 ml/kg/min.) may be given by nasal tube or tracheostomy; in severe allergic shock, crystalloid and colloid fluids may be indicated for cardio-vascular support.

While anaphylaxis is rare and poorly documented in the horse, Equine Asthma is very common in some regions and its clinical manifestations and management are well-described. However, the exact etiology and pathogenesis, particularly the role of allergy in Equine Asthma, are still unclear. Nevertheless, this syndrome is commonly regarded as an "allergic respiratory disease" in the broader sense (i. e. a hypersensitivity to external "normal" stimuli). This concept is indeed helpful to explain to owners of affected horses that pharmacological treatment is only symptomatic, and the condition should be treated and controlled by avoiding or decreasing external triggers. Apart from "summer-pasture associated Equine Asthma" (prevalent in some regions with hot, humid climates and suspected outdoor "allergens"), most affected horses are hypersensitive to indoor stable environments, specifically irritants and potential allergens from hay dust and bedding. The best documented potential allergens in indoor environments are of fungal origin (i. e. mold spores, amplified by non-specific irritants like endotoxin and B-glucans), but currently no proven allergen testing and desensitization protocols exist. Accordingly, management changes directed at improving stable air hygiene to decrease dust exposure (e. g. steaming of hay; replacing by haylage, hay cubes or pelleted feeds; pasture with grass as roughage etc.) are the most important aspects of Equine Asthma therapy.

Despite measures to improve air hygiene, or when these cannot be fully instituted, many horses still require medical therapy to control clinical signs. Systemic and aerosolized formulations are available for various medications, and choice will depend on clinical presentation, availability local regulations, and veterinarian/owner preferences. In severe exacerbations, bronchodilators can provide relief of airway obstruction. Muscarinic receptor antagonists, like hyoscine butylbromide (0.2 - 0.3 mg/kg IV), also known as scopolamine

butylbromide (brand name Buscopan), is only short-acting but highly effective, and can also be used diagnostically to demonstrate reversibility of bronchospasm induced signs. It is well tolerated and does not have the side-effects and risks of atropine. B-agonist bronchodilators can be administered by inhalation (e. g. Salmeterol or Albuterol) or orally (Clenbuterol, 0.8 -3.2 µg/kg PO q12h; gradual increase of dose; drug tolerance with prolonged use). Bronchodilators should not be used as the sole treatment and are often combined with corticosteroids given systemically (e. g. prednisolone 0.5-2 mg/kg or dexamethasone, 0.03 - 0.1 mg/kg) or by inhalation (e. g. fluticasone, budesonide, beclomethasone, ciclesonide). Ciclesonide (brand name Aservo EquiHaler) provides the best documented therapeutic efficacy with the least systemic effects and is registered for the treatment of severe Equine Asthma in many countries. Further options include sodium cromoglycate, a mast cell stabilizer, for horses with mastocytic mild-moderate Asthma, and supplementation with polyunsaturated omega-3 fatty acids as an adjunct treatment. Mucolytic agents are often used, but evidence for efficacy, at least as a sole medication, is lacking. Non-steroidal anti-inflammatory drugs, leukotriene-receptor antagonists and antihistamines do not appear to be helpful in Equine Asthma therapy.

Further reading

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All dosages must be checked for correctness and accordance with local regulations and recommendations.

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Understanding the risk of intra-articular medication in racehorses

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Intra-articular medication is widely used in the treatment of joint injury and joint disease in horses. Medications such as corticosteroids are very effective for treating soft tissue inflammation and reducing pain. However, in racehorses a high proportion of joint injury and joint disease results from damage to the subchondral bone due to the repeated loads generated on joint surfaces in galloping horses. Fortunately, fractures arising from the subchondral bone are relatively uncommon, however subchondral bone injuries that remain confined to the joint surface are very common. The inflammation and pain associated with such injuries can be managed with intra-articular medication, but these medications have no ability to reverse subchondral bone damage. Therefore medication potentially allows horses that have developed microdamage to continue to race and train exposing them to the risk of exacerbation of existing injuries. It has been found that racehorses undergoing local injection of corticosteroids suffer a higher rate of musculoskeletal injury for seven weeks post injection and the injury and fracture rate is higher following injection on multiple occasions. Clinicians have advocated radiographing joints prior to treatment to mitigate the risk of subsequent injury. While this approach has merit, radiographs are relatively insensitive for detecting subchondral bone injury. The use of advanced imaging will increase the detection of subchondral bone injury however no imaging method developed to date can detect microdamage so we are always ignorant to the level of subchondral bone injury at the time of treatment. It is therefore prudent to use intra-articular medication sparingly and to make sure owners and trainers are fully aware of the risks involved.

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Chris leads the Equine Limb Injury Prevention Program at the University of Melbourne Equine Centre a multidisciplinary research program funded by Racing Victoria, the Victorian State Government and the University of Melbourne, combining microstructural analysis, histopathology, biomechanics, epidemiology and mathematical modelling, dedicated to developing preventative training and management protocols for racehorses.

Chris trained as a specialist equine surgeon at the University of Sydney, Australia, gaining Fellowship of the Australian and New Zealand College of Veterinary Scientists in Equine Surgery by examination in 1995. He also completed a PhD in Carpal disease of racing horses at the University of Sydney in 1998 before moving to work at the Animal Health Trust in Newmarket, England in 1996. From 1999 to 2004 he ran his own surgical referral practice at the Newcastle Equine Centre in Australia and has worked at The University of Melbourne since 2004 as a Specialist surgeon and researcher.

He has published over 70 peer reviewed papers and contributed to 12 book chapters. He has been awarded over $13million in research grants. He regularly presents educational lectures on injury prevention to trainers in Australia and has also presented to trainers and racing veterinarians in England, Ireland, Wales, Hong Kong, Singapore, Korea, Brazil, and Uruguay.

Rational Antimicrobial Use and Resistance

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Knowledgeable and rational use of antimicrobials in horses is essential in the antimicrobial-tolerant and antimicrobial-resistant world. The tenets in the previous lecture on strategies of antimicrobial use in equine respiratory disease hold true for use of antimicrobials in other organ systems. The use of topical disinfectants such as chlorhexidine have a place in management of skin wounds and infections.

Important questions to answer are how do we treat horses, achieve client compliance and avoid antimicrobial-tolerance and antimicrobial-resistance? Steps should be taken to ensure clients can not obtain antimicrobials unless prescribed specifically by their veterinarian. Unverified internet sales appear to be an international crisis. Client education is key, as we all understand that client-determined administration and brief, inconsistent exposure to an antimicrobial may prime bacteria to become tolerant and eventually resistant. Veterinarians need to be more aware and engaged in surveillance of antimicrobial resistance in equine pathogens, especially in their practice region, as well as staying abreast of national and international trends. Such knowledge will allow us to ascertain if resistance is increasing and whether previously unrecognised resistance is occurring. Veterinarians must be vigilant about particular classes of antimicrobials being over-represented in resistance patterns and whether a definitive type of resistance is associated with particular outbreaks.

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Addressing acute diarrhea in horses

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There are multiple causes of acute diarrhea in adult horses. In other species, diarrhea may not be considered an emergency. However, in horses, acute diarrhea can lead to fast dehydration, endotoxemia, systemic inflammatory response syndrome (SIRS) and death. Therefore, all horses with acute diarrhea should be considered risk patients and should be closely monitored.

The causes of diarrhea differ by geographic localization and age of the patient. Acute diarrhea can be caused by infectious agents such as Salmonella spp, Clostridium spp, Equine coronavirus, Neorickettsia risticii (Potomac Horse fever), Lawsonia intracellularis and encysted small strongyles (Cyathostomes). Non-infectious causes include administration of NSAIDs, exposure to toxins such as cantharidin, hoary alyssum, and arsenic, sand accumulation as well infiltrative diseases such as alimentary lymphoma or inflammatory bowel disease (which can also present as chronic diarrheas or weight loss). Some of these infectious organisms are contagious. Thus, horses should be isolated until the contagious causes of diarrhea are ruled out or a cause can be stablished. In our hospital, isolation is mandatory for horses that show up with diarrhea, neutropenia, or fever (2 out of these 3 signs).

There are multiple mechanisms for diarrhea: malabsorption, increased osmolarity of the GI content, increased secretion of water and electrolytes into the lumen, inflammation of the GI or altered GI motility. In adult horses, diarrhea results almost exclusively from disorders of the large intestine (although small intestine may be involved at the same time). This is less true in foals. Regardless of the mechanism, most of the treatment focuses on patient maintenance.

Clinical signs:
Aside from diarrhea, the clinical signs are typically those of dehydration and endotoxemia. Horses may show lethargy, anorexia, tachycardia, tacky mucous membranes that might be congested. Fever and colic are not uncommon. Some cases develop ileus and acute laminitis.

Diagnosis:
A definitive diagnosis is difficult to obtain in horses. A definitive diagnosis is not achieved in > 50% of the cases. Clinical signs are too similar between etiologies and are rarely pathognomonic. A proper history is critical to differentiate infectious (other horses infected, history of fever, travel, etc.) from non-infectious (NSAID administration, feeding on ground, potential exposure to toxins, etc.).

- Fecal samples (and blood for some pathogens) should be submitted whenever possible for culture, PCR, and/or toxin identification.
- Bloodwork is useful to assess acid base status, electrolyte abnormalities, dehydration, and overall organ function. Marked neutropenia and toxic changes in neutrophils are common.
- Abdominal ultrasonography may show fluid in the large colon/cecum, thickening of the wall and free fluid.
- Abdominal radiographs are useful to assess the presence of sand/gravel.

Treatment:
Treatment is aimed at correcting dehydration and electrolyte imbalances as well as the causative agent when identified.

Restoring fluid balance:

- Fluid therapy is typically administered IV in severe cases, but enteral fluid administration can also be performed using a small nasogastric tube. Both routes allow for electrolyte supplementation.
- Oncotic pressure: Low albumin is not uncommon in these cases. Hydroxyethyl starch solutions or plasma can be used to correct these. Hydroxyethyl starch solutions can cause coagulation abnormalities if administered >20 ml/kg or for multiple days.

Anti-endotoxin treatment:

- DTO smectite (Biosponge®) or activated charcoal can be administered via NGT to decrease endotoxin absorption from the GI.
- Polymixin B (6,000 IU IV q 6-8h) can be used to bind circulating endotoxin. This drug is expensive and can be nephrotoxic.

Analgesia:

- NSAIDs can be used to provide analgesia. However, they should be use cautiously as they are nephrotoxic and can cause mucosal damage of the colon.
- Butorphanol or other opioids can be added to the pain management plan.

Treating the underlying cause:

- In many cases, empirical treatment is selected based on regional incidence of disease.
- Systemic antibiotics are typically recommended in the case of Clostridium spp., *Neorickettsia risticii and Lawsonia intracellularis*. Broad spectrum administration in horses with other causes of diarrhea can worsen GI dysbiosis. Administration of systemic antibiotics to all neutropenic horses remains controversial.
- *Clostridium* spp: Metronidazole, 15 mg/kg PO q8h. IV formulations are available, but their price restricts its use in adult horses. Per rectum administration can be used in cases of ileus, doubling the dose to 30 mg/kg is recommended. Anorexia and increased liver enzymes are common after administration. Ataxia may be seen if the protein is low; more common with IV formulaitons.
- *Neorickettsia risticii* and *Lawsonia intracellularis*: Oxytetracycline IV (6.6 mg/kg IV q 12-24h for 3-5 days). Lawsonia may require longer treatment. Improvement is seen within 24h. Oxytetracycline is nephrotoxic and should be given after the patient is hydrated. or twice daily for 5 days (dilute in fluids or give slowly). If given fast, it can cause collapse and death. Thus, in the case of sick animals, it is best to use diluted in sterile water.

Isolation: *Salmonella* spp, Equine coronavirus and *Lawsonia intracellularis* cases should be isolated until no longer shedding. This may require prolonged isolation (min 3 weeks)

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Alternatives to antimicrobial use in the uterus

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The global use of antibiotics over the last several decades has resulted in significant antibiotic resistance being observed. With a serious concern of antibiotic resistance resulting in the inability to treat common bacterial infections in the future practitioners are looking for alternative therapies for treating routine infections. Historically multiple non-antibiotics have been used for the successful treatment of uterine infections. A few of the more common ones are dilute povidone Solution (titratable iodine 1%, 15 mls povidone solution in 1 liter of saline or LRS), hydrogen peroxide (1% solution as infusion or used in lavage) and tris-EDTA (50 mM tris with 3.5 mM EDTA as a lavage or infusion). Recently there has been a surge in new alternatives to antibiotics for treating uterine infections such as ozone, anti-microbial peptides or platelet rich plasma. However, the practitioner needs to use caution when deciding if alternatives to antibiotics will be better than traditional therapy with antibiotics. The first major decision that needs to be determined is the safety and efficacy ideally reported both in vitro and in vivo for the compound to be used. The clinical case you are treating should be evaluated to determine if the clinical case supports consideration of treatment with non-antimicrobials. For example a post breeding antibiotic infusion in a "normal" mare likely would benefit with non-antibiotic replacement as compared to antibiotic infusion. However a mare diagnosed with a uterine infection via endometrial culture and cytology may still require antibiotic treatments. In the end as you consider alternative antibiotic treatments you must consider as the practitioner are you doing the right thing for the horse and your client.

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Bisphosphonates - Is their use worth the problems?

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In the early to mid-noughties bisphosphonates (BPs) were hailed by many equine clinicians as a useful group of drugs that could treat or prevent a wide host of troublesome skeletal issues. In the intervening years sentiment has changed dramatically and use of these compounds is now considered contraindicated in all but older horses with specific degenerative conditions. Bans on their use have been imposed by many racing jurisdictions and severe penalties exist for violation of embargos. However, knowledge of the pharmacological and physiological effects of these drugs in the horse is wanting and there may be a call for a more rational, science-based review of their use in equine medicine.

Not all BPs are equal. Firstly, they can be classified into two broad groups: those that contain an amine group (so-called nitrogen-containing BPs) and those that do not. The effect of these different groups on the metabolism of cells is fundamentally different. This is mirrored in their pharmacological properties. Nitrogen-containing BPs (such as Pamidronate and Zoledronate) are many times more potent at inhibiting osteoclastic resorption of bone than non-nitrogen containing products (e.g. Tiludronate and Clodronate). Furthermore, the range of pharmacological effects varies between groups and there is some evidence that the analgesic properties of non-nitrogen-containing BPs may be the greater of the two. Secondly, the potency of BPs at inhibiting bone resorption and range of other effects varies greatly between different products, depending on molecular subgroup substitutions.

Much of the discussion about the effects of BPs in the horse and nearly all of the concerns regarding potential complications of these drugs in this species has been inferred from studies on laboratory animals and data from human clinical practice. In fact, only one study has demonstrated that one of the BPs licensed for use in horses (Tiludronate) inhibits bone resorption in the horse (as determined by serum concentrations of a marker of type I collagen degradation, CTX-1) and then only for a short duration [1]. More recently it was found that while Clodronate (the only other BP licensed for use in horses) administered to a group of Thoroughbreds at a standard clinical dose did not increase plasma concentration of CTX-1 above that of a saline placebo administered to a control group, it did decrease concentration of type 5 acid phosphatase, which may be a more sensitive indicator of osteoclastic activity [2]. Conversely, others have found that Tiludronate and Clodronate administered at clinical dose rates do not appear to impact bone structure or cellular activity in horses [3,4]. Only one study reports the effect of nitrogen-containing BPs in horses and this did demonstrate that Zolendronate resulted in a profound and prolonged inhibition of bone resorption [5]. These findings suggest that concerns over the clinical use of BPs currently licensed for use in the horse, namely that they may interfere with bone development and homeostatic repair mechanisms, may not be as significant as some claim. On the other hand, the off-label use of nitrogen-containing BPs is clearly a potential concern.

In the absence of profound inhibition of bone resorption, the beneficial clinical effects reported from the BPs licensed for use in horses may be due to their analgesic or anti-inflammatory properties. Bisphosphonates are used in human medicine to manage pain arising from tumours that have metastasised to bone.

The pharmacological mechanism by which BPs affect analgesia and whether this property is more profound in bone than other tissues remains undetermined. If these drugs do preferentially impact bone pain they may been beneficial in the management of pain associated with subchondral bone disease, which is prevalent in racehorses.

Several studies have documented prolonged detection times of BPs in horses, which are measured in times of months and years. While pragmatic measures can be used to manage evidence of BP administration in legitimate cases, clinicians considering clandestine use of these products should be aware of the fact that evidence of their administration to a horse can be detected for such protracted periods.

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Chris studied Veterinary Science at the University of Bristol, UK, in the early nineteen eighties. He received further training in Equine Surgery at the Royal Veterinary College, UK and was awarded a PhD for research into the causes of racehorse fractures in 1991. He subsequently worked as a Senior Lecturer at the Philip Leverhulme Equine Hospital, University of Liverpool, where he developed specialist skills in equine surgery. He gained further clinical experience at several equine referral centres in the United Kingdom and Australia before joining the Hong Kong Jockey Club as Head of Veterinary Clinical Services in 2003. He was appointed to a new role in the Club as Director, HKJC Equine Welfare Research Foundation/ Chief Advisor, Mainland Veterinary Engagement in 2019.

Chris has a particular interest, and specialist qualifications, in surgery and orthopaedics. He has published over 80 scientific papers about fatigue damage in bone and its role in racehorse fractures, among other topics. He also cares deeply about helping to provide opportunities for young colleagues to further their clinical skills, with a focus on Mainland China.

Chris is a Fellow of the Royal College of Veterinary Surgeons, UK and holds positions as Adjunct Professor at the College of Veterinary Medicine and Life Sciences, City University, Hong Kong, Special Professor at the School of Veterinary Medicine and Science, University of Nottingham, UK, and Guest Professor at Inner Mongolia Agricultural University.